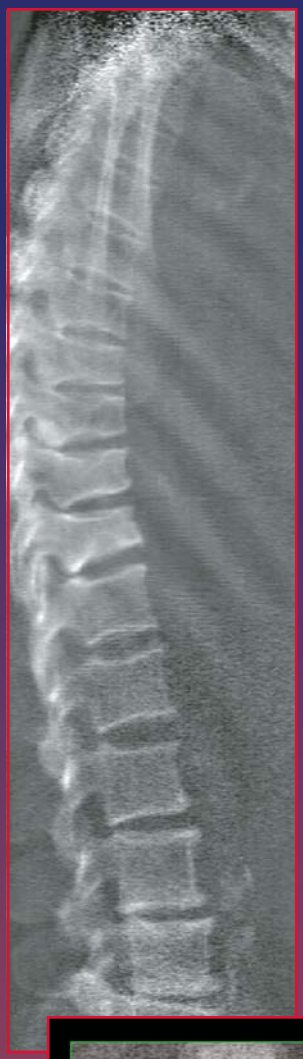
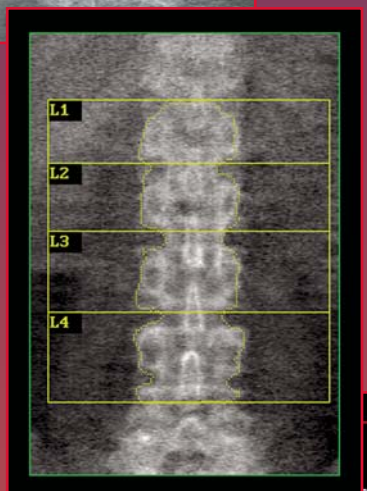


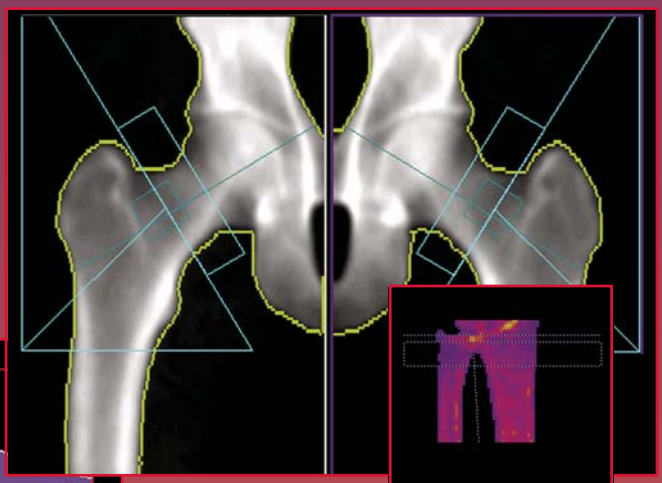
Bone Densitometry in Clinical Practice

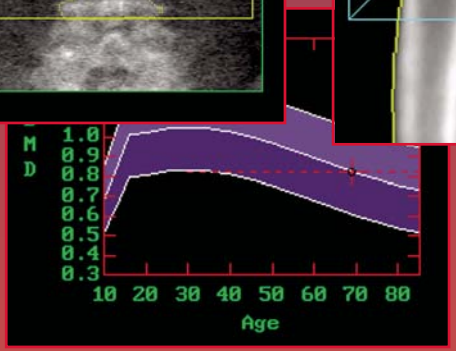
Application and Interpretation

Second Edition

Sydney Lou Bonnick, MD, FACP







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Humana Press

Bone Densitometry in Clinical Practice

Bone Densitometry in Clinical Practice

Application and Interpretation

Second Edition

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FOREWORD

The second edition of Dr. Sydney Lou Bonnick's text *Bone Densitometry in Clinical Practice* is an expansion of her highly regarded first edition, which has provided the bone densitometry community with simply the best, most accurate, and most precisely written resource in our field. Dr. Bonnick has applied her very careful and exact scientific approaches to expand and improve on her widely regarded initial text. In addition to the chapters in the first edition on the science of bone densitometry and its clinical application, this text has new chapters and a CD-ROM that come at a very critical time in our field.

The clinical use of bone densitometry is increasing exponentially as more professional societies have endorsements and guidelines on the application of bone densitometry in the assessment and management of osteoporosis. The recent endorsement of population screening by the US Preventive Services Task Force (USPSTF) has now provided governmental validation to this technology, whose proper use Dr. Bonnick has pioneered. In a new chapter, Dr. Bonnick compares the similarities and differences in the recent guidelines from the USPSTF and the National Osteoporosis Foundation, American Association of Clinical Endocrinologists, American College of Obstetrics and Gynecology, and the North American Menopause Society.

In another very important new chapter, Dr. Bonnick provides the data and concepts behind different fracture risk models. All who treat patients should study this chapter. The chapter provides reasoning behind the prevention of early postmenopausal bone loss rather than waiting until individuals have established osteoporosis before pharmacological intervention. Lifetime fracture risk, which calculates the lifetime risk for fragility fracture as a function of the bone mineral density (BMD) or *T*-score at the menopause and suggests that the risk is greater the lower the BMD at the menopause in untreated patients, may never be directly validated by 30-plus years of observation. Yet, to the extent that there is consistency in these predictive models, lifetime risk provides the clinician with reason to consider interventions in "osteopenic" women in the early menopausal years.

Dr. Bonnick's chapter on the very difficult issue of T-score discrepancies between both central and peripheral densitometers in diagnosing osteoporosis and the role that inconsistent reference population databases play in contributing to these discrepancies should be studied by those who want to see resolution to the problem of misclassifications by World Health Organization (WHO) Criteria. T-score discrepancies only create confusion as well as potentially lead to under- or overtreatment in the postmenopausal population.

Finally, Dr. Bonnick's chapter on BMD reporting is a summation of all the knowledge that she emphasized should be included in a BMD report as one of the original International Society of Clinical Densitometry (ISCD) certification course faculty. At the current time, there is great diversity in style and content in reporting densitometry results and often frank misinterpretation of the data. When the reports are interpreted competently, they are an invaluable aid in the management of patients. Yet until we achieve some standardization of reporting, the densitometrist is the one who will make each BMD

report meaningful in the context of individual patient data. Dr. Bonnick provides these key reporting guidelines.

Once again, *Bone Densitometry in Clinical Practice* should be read by all physicians and technologists who are involved in the application of bone densitometry. The management of osteoporosis is truly moving into primary care. It must, because osteoporosis constitutes an enormous health care issue for both the female and male populations. Hence, primary care physicians who either order or perform bone densitometry should read this text. The subspecialists who will manage the more complex osteoporotic cases should read it as well. Bone densitometry and its proper use and interpretation are a common thread between all of us, primary care and specialists alike. Yet, its value is only as good as the quality of performing BMD measurements and the interpretation of the machine output.

Once again, I have the privilege of contributing this foreword. In the first edition, I commented on how much I have learned from Dr. Bonnick's knowledge in this area. I continue to learn from her exceptional command of this entire subject. Likewise, by studying this text, so will you.

Paul D. Miller, ***MD, FACP***
Founding President
International Society for Clinical Densitometry
Colorado Center for Bone Research
Lakewood, Colorado

PREFACE

Bone densitometry is a fascinating field of medicine. Even in its earliest phases of development, densitometry incorporated aspects of imaging, physics, quantitative analysis, statistics, and computer technology that were applied in the diagnosis and management of multiple disease states. This extraordinary combination of attributes, however, left densitometry without a well-defined niche in clinical medicine. Imaging has traditionally been the purview of the radiologist. Quantitative analysis is more familiar to the pathologist. Metabolic bone disease has been the concern of the internist, rheumatologist, or endocrinologist, and occasionally the nephrologist and orthopedist. And of course, physics, statistics, and computer technology have been left to those hardy soles who enjoy such things.

In 1988, when X-ray-based densitometers began to rapidly replace isotope-based densitometers, the door was opened for any medical specialty to perform densitometry. And yet, without a well-defined niche, without a specialty to champion the technology, there were no physicians who, by specialty training, were immediately expert in the utilization of the technology.

In 1983, when I began working with dual-photon absorptiometry, the manufacturers provided a 4-hour inservice at the time of machine installation along with a brief operator's manual and the promise of technical support whenever it was needed. There were no ongoing programs of continuing education in the performance of densitometry or in the interpretation of the data that it generated. There was no supply of trained densitometry technologists. Conferences on osteoporosis were infrequent and lectures on densitometry were decidedly rare. As a clinical tool, densitometry was viewed with skepticism. None of the notable fracture trials had yet been published. Indeed, these would not come for approximately 10 years. Clinicians, unable to noninvasively measure bone density in the past, saw little need for the ability to do so. The one disease in which densitometry seemed most applicable, osteoporosis, was largely viewed as an unalterable component of aging, making the measurement of bone density superfluous.

Certainly much has changed in recent years. With the ability to measure bone density, many disease states are now known to be characterized, at least in part, by demineralization. Suddenly, it is not only osteoporosis for which the technology can provide information crucial to disease management. And osteoporosis itself is certainly no longer viewed as unassailable. The fracture trials are published. Therapeutic and preventive efficacy of several drugs has now been documented. And the disease itself is now defined based on the measured level of bone density. Although the technology is still properly viewed as a quantitative analytical technique, imaging with densitometry is progressing so rapidly that the time has come when some aspects of skeletal radiography are being superseded by morphometric densitometry.

In 1990, Dr. Paul Miller and I independently began teaching courses in bone densitometry for the physician and technologist. The physicians who attended these courses came from all specialties. The technologists were RTs, MRTs, RNs, PAs, and nursing assistants. With the publication of the first edition of *Bone Densitometry in Clinical*

Practice in 1998, I hoped to reach many more physicians and technologists who wished to become proficient in the application and interpretation of bone densitometry. In 2002, my technologist, Lori Lewis, and I published *Bone Densitometry for Technologists*. This volume was intended solely for technologists, regardless of background, who work in the field of densitometry. Although much of the requisite information and skill in densitometry are common to physicians and technologists alike, the unique demands placed on the densitometry technologist made such a volume both appropriate and necessary. It is time now to update and expand the original text for physicians with this second edition of *Bone Densitometry in Clinical Practice*.

Our concerns in 2004 are somewhat different from those of 1998. There are few locales in which bone densitometry is not available. Many physicians, clinics, and hospitals own densitometers. The number and types of devices have proliferated at a remarkable rate. It is rare to encounter a physician who does not yet know that fracture risk can be predicted with a single bone mass measurement. But accompanying this success are new concerns and even controversies. Should every woman have a bone density measurement, and if so, when? Can World Health Organization Criteria for the diagnosis of osteoporosis in postmenopausal Caucasian women be used to diagnose osteoporosis in women of other races or men of any race? Should the diagnosis of osteoporosis be restricted to bone density measurements of the proximal femur? Can peripheral skeletal sites be used to diagnose osteoporosis? How should an individual's risk of fracture be expressed? Can or should bone densitometry be used to determine efficacy of therapeutic agents in the treatment of osteoporosis? None of these concerns are esoteric. They go straight to the heart of how and when we use densitometry and interpret the data in the care of our patients. Whether you are new to the field or have worked in densitometry for 20 years, the issues are the same. And all of us must ensure that quality control procedures are instituted and followed, precision studies are done and data are properly interpreted.

The expansion of *Bone Densitometry in Clinical Practice* from the first edition reflects these concerns. Chapter 1 is a review of densitometry technologies that spans the earliest attempts in the late 1800s to quantify bone density in the mandible to the modern technologies of DXA, QCT, and QUS. Chapter 2 looks at the unique aspects of gross skeletal anatomy in densitometry and aspects of bone physiology relevant to the interpretation of bone density data. Chapter 3, which deals with statistics, is intended as an overview only. Although most clinicians are familiar with such statistical concepts as the mean, standard deviation, and significance, there are few if any areas of clinical medicine in which the application of statistical principles has assumed such a prominent role as in bone densitometry. This chapter has been expanded from the first edition to deal with statistical concepts needed to "test the test," such as sensitivity, specificity, and likelihood ratios, as well as the concepts of linear regression and regression to the mean. As the reader will find, an understanding of these concepts becomes imperative when one considers patient selection indices for densitometry, discussed in Chapter 8 and even the diagnosis of osteoporosis, discussed in Chapter 9. Chapter 3 is not intended to replace a review of more thorough statistical texts, but it is intended to ease the pain that the contemplation of such texts can engender. Chapter 4 reviews issues of machine quality control that are often underappreciated in clinical settings, but that profoundly affect the validity of the data generated by the densitometers. Chapters 5 and 6 continue to provide the necessary foundations of information for the densitometrist. Chapter 5 addresses the differences in bone density measurements among the various manufacturers and the attempts at stan-

dardization of bone density measurements among manufacturers when bone density is measured at the same skeletal site. Chapter 6, in which articles of interest from the medical literature have been abstracted, has been expanded from the first edition. In this chapter, the effects of diseases, drugs, and various procedures on bone density are reviewed.

Five of the last seven chapters in this edition of *Bone Densitometry in Clinical Practice* are new, as are the appendices that follow. Chapters 7 and 8 deal with clinical guidelines for selecting patients for densitometry measurements. Chapter 7 discusses and compares the recent guidelines from major organizations. Chapter 8 deals with the various questionnaires and indices that have been developed to help patients identify themselves as candidates for bone mass measurements. These indices are deceptively simple in their final form, belying the very complex development process behind them. Consequently, the initial skepticism with which most of these indices have been met is understandable. Nevertheless, they are extremely useful in many circumstances. Chapters 9, 10, and 11 deal with the specific densitometry applications of diagnosis of osteoporosis, fracture risk prediction, and monitoring changes in bone density. Diagnosis and fracture risk prediction are separate entities at present and both remain the subject of some controversy, as noted above. Chapter 11, which deals with monitoring changes in bone density, is similar to the chapter on precision that appeared in the first edition. This chapter has been updated and expanded, however, and also includes a discussion of the statistical concept of regression to the mean and its relevance to monitoring bone density. In Chapter 12, the challenge of bringing all this information to bear on the interpretation of the numerical densitometry data is addressed. Although it is one of the shorter chapters in the book, its importance should not be underestimated. The reality is that an inadequate or unread report will negate the expertise of the densitometrist and technologist, as well as the promise of the technology. Finally, in Chapter 13, the technical specifications of densitometry devices currently approved for use in the United States are listed. These specifications may change without notice, so the reader is encouraged to contact the manufacturer directly if more information is desired.

The appendices are an attempt to pull together reference information in a convenient location to enable the physician to refer to the information quickly, without searching the text. Reference databases for NHANES III and from the major manufacturers of central DXA devices will be found here as well as recent Medicare reimbursement data for densitometry. The CD-ROM that accompanies this book contains several files that the densitometrist should find useful in everyday practice, as well as a study guide that can be completed for continuing education credit.

In a few circumstances in *Bone Densitometry in Clinical Practice*, data has been presented from published abstracts, rather than from peer-reviewed, published articles. This was done in the interest of providing information rapidly. The reader should be cautioned that data presented in abstract form might change slightly when it is finally published in a peer-reviewed journal. Some data presented in abstract form are never published in a peer-reviewed journal for a variety of reasons.

Bone densitometry is an extraordinary clinical tool. It provides a safe, non-invasive window to the skeleton. Through that window a physician can obtain vital clinical information that enhances the management of the patient that cannot currently be obtained in any other way. So to whom in medicine does densitometry belong? To no one specialty in particular and to every specialty in general as long as the physician and technologist

are committed to learning the unique aspects of this technology and the proper interpretation of the data that it generates. The technology itself is superb. Bone density can be measured with superior accuracy in virtually every region of the skeleton. The machines are capable of the finest precision of any quantitative technique in use in clinical medicine today. But the machines will perform only to the level of the expertise of those who operate them. And the data that they generate will only be as useful as the clarity of the interpretation that is provided by the densitometrist. It is hoped that this volume will be useful in helping the densitometrist fulfill the potential that the technology holds for contributing to the highest quality of patient care and disease prevention and management.

Sydney Lou Bonnick, *MD, FACP*

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I would also like to thank those authors and publishers who allowed us to reproduce their work in the interest of continuing education.

And a special word of thanks to my editor, Paul Dolgert of Humana Press. Thank you for waiting.

Dedication

To Mom and Dad
I love you.

CONTENTS

Continuing Medical Education

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30 Hours

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Faculty and Disclosure

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Faculty for CME activities are expected to disclose to the activity audience any real or apparent conflict(s) of interest related to the content of the material they present. The following relationships have been disclosed:

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Intended Audience

This book is designed for physicians and technologists involved in the application of bone densitometry.

Overall Goal

The overall goal of this activity is to update the scientific knowledge and skills of physicians and technologists who utilize and interpret bone densitometry as part of patient management, in particular the management of patients who are at risk for or who have osteoporosis.

Learning Objectives

Upon completion of this continuing medical education activity, participants should have improved overall knowledge, skills, and attitudes concerning the use of bone densitometry. Specifically, the objectives are to:

1. Review the most clinically relevant aspects of interpreting bone density data.
2. Familiarize the physician with the resources found in the second edition of *Bone Densitometry in Clinical Practice*.
3. Emphasize the potential pitfalls in interpreting and reporting densitometry results.
4. Familiarize the physician with current recommendations and standards for patient selection for testing and for densitometry reporting.

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1 Densitometry Techniques

CONTENTS

Clinical densitometry is relatively new but densitometry itself is actually quite old. It was first described more than 100 years ago in the field of dental radiology as dentists attempted to quantify the bone density in the mandible *(1,2)*. With today's techniques, bone density can be quantified in almost every region of the skeleton. The extraordinary technical advances in recent years have expanded the realm of densitometry from that of a quantitative technique to that of an imaging technique as well. But even the oldest techniques remain both viable and valuable with computer modernization. Densitometry technologies have evolved as the understanding of relevant disease processes has increased. In a complimentary fashion, the understanding of the disease processes has increased as the technologies have evolved.

PLAIN RADIOGRAPHY IN THE ASSESSMENT OF BONE DENSITY

The earliest attempts to quantify bone mineral density (BMD) utilized plain skeletal radiography. When viewed by the unaided eye, plain skeletal radiographs can only be used in an extremely limited fashion to quantify bone density. Demineralization becomes visually apparent only after 40% or more of the bone density has been lost *(3)*. If demineralization is suspected from a plain film, a great deal of demineralization is presumed to have occurred. A more precise statement cannot be made. Plain radiographs have been used for qualitative and quantitative skeletal morphometry. Plain radiographs were also used to assess bone density based on the optical densities of the skeleton when compared to simultaneously X-rayed standards of known density made from ivory or aluminum. With the advent of the photon absorptiometric techniques, most of these early methods as originally performed have fallen into disuse. Nevertheless, a brief review of these techniques should enhance the appreciation of the capabilities of modern testing and provide a background for understanding modern technologies.

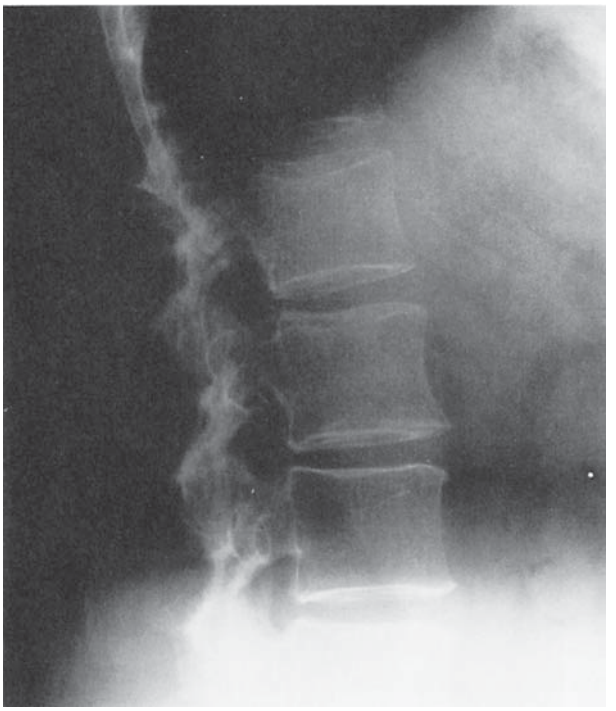

Fig. 1-1. Quantitative spine morphometry. The vertebrae on this lateral lumbar spine X-ray demonstrate marked accentuation of the vertical trabecular pattern and thinning of the cortical shell. This is a Grade 2 spine.

QUALITATIVE MORPHOMETRY

Qualitative Spinal Morphometry

Qualitative morphometric techniques for the assessment of bone density have been in limited use for more than 50 years. Grading systems for the spine relied on the appearance of the trabecular patterns within the vertebral body and the appearance and thickness of the cortical shell *(4)*. Vertebrae were graded from IV down to I as the vertical trabecular pattern became more pronounced with the loss of the horizontal trabeculae and the cortical shell became progressively thinned. The spine shown in Fig. 1-1 demonstrates a pronounced vertical trabecular pattern. The cortical shell appears as though it was outlined in white around the more radiotranslucent vertebral body. These vertebrae would be classified as Grade II.

The Singh Index

The Singh Index is a qualitative morphometric technique that was similarly based on trabecular patterns, but based on those seen in the proximal femur *(5)*. Singh and others noted that there was a predictable order in the disappearance of the five groups of trabeculae from the proximal femur in osteoporosis. Based on the order of disappearance, radiographs of the proximal femur could be graded 1 through 6 with lower values indicating a greater loss of the trabecular patterns normally seen in the proximal femur. Studies evaluating prevalent fractures demonstrated an association between Singh Index

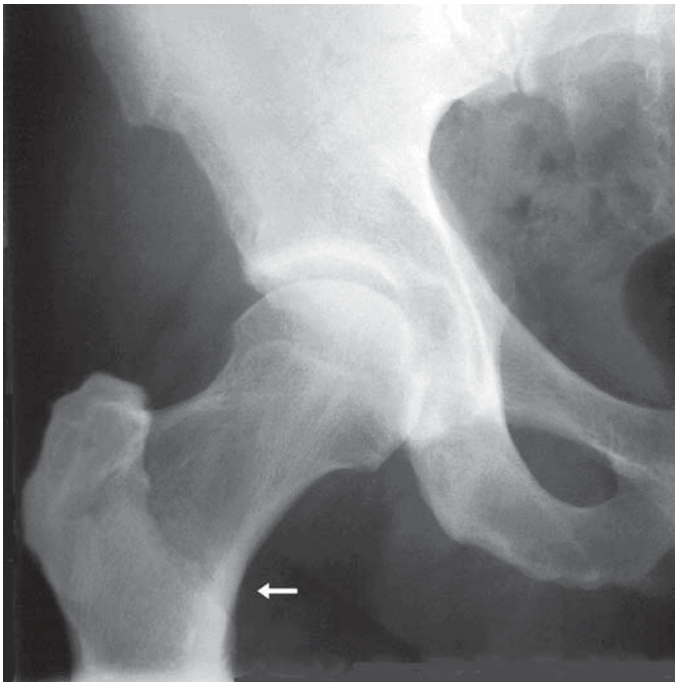

Fig. 1-2. The Singh Index and *calcar femorale* thickness. A Grade 2 Singh Index would be assessed based on having only remnants of the principle compressive trabecular group visible. This is indicative of osteoporosis. The arrow points to the *calcar femorale*, which measured 4 mm in thickness. Values less than 5 mm are associated with hip fracture. This patient had experienced a contralateral hip fracture.

values of 3 or less and the presence of fractures of the hip, spine, or wrist. Figure 1-2 shows a proximal femur with a Singh Index of 2. Only the trabecular pattern known as the principle compressive group, which extends from the medial cortex of the shaft to the upper portion of the head of the femur, remains. This patient was known to have osteoporotic spine fractures as well as a contralateral proximal femur fracture. Later attempts to demonstrate an association between Singh Index values and proximal femur bone density measured by dual-photon absorptiometry (DPA) were not successful *(6)*.

Both of these qualitative morphometric techniques are highly subjective. In general, the best approach to their use required the creation of a set of reference radiographs of the various grades of vertebrae for spinal morphometry or proximal femurs for the Singh Index to which all other radiographs could be compared.

QUANTITATIVE MORPHOMETRIC TECHNIQUES

Calcar Femorale Thickness

A little known quantitative morphometric technique involved the measurement of the thickness of the *calcar femorale*. The *calcar femorale* is the band of cortical bone immediately above the lesser trochanter in the proximal femur. In normal subjects, this thickness is greater than 5 mm. In femoral fracture cases, it is generally less than 5 mm in thickness *(7)*. The arrow, seen in Fig. 1-2 is pointing to the *calcar femorale*. This

patient had previously suffered a femoral neck fracture. The thickness of the *calcar femorale* measured 4 mm.

Radiogrammetry

Radiogrammetry is the measurement of the dimensions of the bones using skeletal radiographs. Metacarpal radiogrammetry has been in use for almost 50 years. As originally practiced, the dimensions of the metacarpals were measured using a plain radiograph of the hand and fine calipers or a transparent ruler. The total width and medullary width of the metacarpals of the index, long, and ring fingers were measured at the midpoint of the metacarpal. The cortical width was calculated by subtracting the medullary width from the total width. Alternatively, the cortical width could be measured directly. A variety of different calculations were then made such as the metacarpal index (MI) and the hand score (HS). The MI is the cortical width divided by the total width. The HS, which is also known as the percent cortical thickness, is the MI expressed as a percentage. Measurements of the middle three metacarpals of both hands were also made and used to calculate the six metacarpal hand score (6HS). Other quantities derived from these measurements included the percent cortical area (%CA), the cortical area (CA), and the cortical area to surface area (CA/SA) ratio. The main limitation in all of these measurements is that they were based on the false assumption that the point at which these measurements were made on the metacarpal was a perfect hollow cylinder. Nevertheless, using these measurements and knowledge of the gravimetric density of bone, the bone density could be calculated. The correlation[1] between such measurements and the weight of ashed bone was good, ranging from 0.79 to 0.85 *(8,9)*. The precision of metacarpal radiogrammetry varied depending on the measurement used.[2] The measurement of total width was very reproducible. The measurement of medullary width or the direct measurement of cortical width was less reproducible because the delineation between the cortical bone and medullary canal is not as distinct as the delineation between the cortical bone and soft tissue. Precision was variously reported as excellent to poor, but in expert hands it was possible to achieve a precision of 1.9% *(10)*.

Although metacarpal radiogrammetry is an old technique and somewhat tedious to perform, it remains a viable means of assessing bone density in the metacarpals. Metacarpal radiogrammetry demonstrates a reasonably good correlation to bone density at other skeletal sites measured with photon absorptiometric techniques *(11)*. The technique is very safe as the biologically significant radiation dose from a hand X ray is extremely low at only 1 mrem.

Radiogrammetry can also be performed at other sites such as the phalanx, distal radius, and femur *(12–14)*. Combined measurements of the cortical widths of the distal radius and the second metacarpal are highly correlated with bone density in the spine as measured by DPA *(12)*.

[1] Correlation indicates the strength of the association between two values or variables. The correlation value is denoted with the letter *r*. A perfect correlation would be indicated by an *r* value of +1.00 or –1.00.

[2] Techniques are compared on the basis of accuracy and precision, which can be described using the percent coefficient of variation (%CV). The %CV is the standard deviation (SD) divided by the average of replicate measurements expressed as a percentage. The lower the %CV, the better the accuracy or precision. *See* Chapters 3 and 11 for a detailed discussion of precision and accuracy.

Today, plain films of the hand and forearm can be digitized using flatbed optical scanners and radiogrammetry performed with computerized analysis of the digitized images. Using such a digital radiogrammetry (DXR) system, Bouxsein et al. *(15)* evaluated the utility of metacarpal radiogrammetry in predicting fracture risk and the correlation between metacarpal DXR-BMD and BMD measured by other techniques at other sites. The authors used a case-cohort approach to identify three groups of 200 women based on their having experienced a hip, wrist, or spine fracture during the first 5 years of the Study of Osteoporotic Fractures *(16)*. DXR-BMD of the metacarpals was strongly correlated with distal and proximal radial BMD measured by single-photon absorptiometry (SPA)[3] (r = 0.68 and 0.75, respectively). The correlation with femoral neck and lumbar spine BMD measured by dual energy X-ray absorptiometry (DXA)[3] was more modest (r = 0.50 and 0.44, respectively). Metacarpal DXR-BMD predicted spine and wrist fracture risk as well as SPA BMD measurements of the distal or proximal radius or heel or DXA posterior–anterior (PA) lumbar spine or femoral neck. The increase in risk for wrist fracture was 1.6 for each SD decline in DXR-BMD and 1.9 for spine fracture. Although femoral neck BMD was the strongest predictor of hip fracture risk, metacarpal DXR-BMD predicted hip fracture risk as well as the other BMD measurements with an increase in risk of 1.8 for each SD decline in BMD. This type of DXR system is available commercially from Sectra Pronosco in Denmark as part of a PACS[4] system.

The Radiologic Osteoporosis Score

The radiologic osteoporosis score combined quantitative morphometry from three skeletal sites *(14)*. Developed by Barnett and Nordin, this scoring system utilized radiogrammetry of the femoral shaft and metacarpal as well as an index of biconcavity of the lumbar vertebrae. In calculating what Barnett and Nordin called a peripheral score, the cortical thickness of the femoral shaft divided by the diameter of the shaft and expressed as a percentage was added to a similar measurement of the metacarpal. A score of 88 or less was considered to indicate peripheral osteoporosis. The biconcavity index was calculated by dividing the middle height of the third lumbar vertebra by its anterior height and expressing this value as a percentage. A biconcavity index of 80 or less indicated spinal osteoporosis. Combining both the peripheral score and biconcavity index resulted in the total radiologic osteoporosis score, which indicated osteoporosis if the value was 168 or less.

RADIOGRAPHIC PHOTODENSITOMETRY

Much of the development of the modern techniques of SPA, DPA and DXA actually came from early work on the X-ray-based method of photodensitometry *(17)*. In photodensitometry, broad beam X-ray exposures of radiographs were obtained and the density of the skeletal image was quantified using a scanning photodensitometer. One such early device at Texas Woman's University is shown in Fig. 1-3. The effects of variations in technique such as exposure settings, beam energy, and film development were partially compensated by the simultaneous exposure of a step wedge of known densities on the film. An aluminum wedge was most often used, but other materials such as ivory were also employed *(13)*. This technique could only be applied to areas of the

[3] This technique is discussed later in this chapter.
[4] Picture Archiving and Communications System.

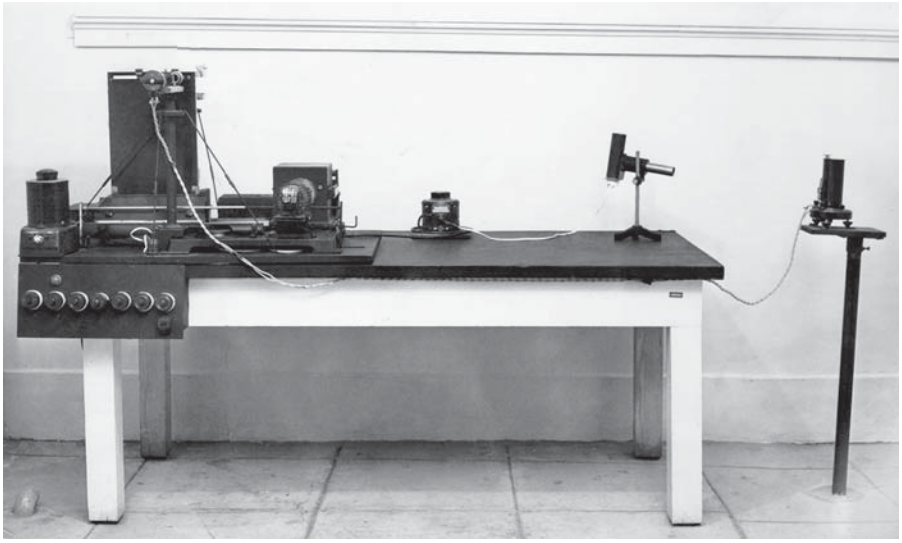

Fig. 1-3. A radiographic photodensitometer at Texas Woman's University from the early 1950s.

skeleton in which the soft tissue coverage was less than 5 cm such as the hand, forearm, and heel. This restriction was necessary because of technical limitations from scattered radiation in thicker parts of the body and "beam hardening" or the preferential attenuation of the softer energies of the polychromatic X-ray beam as it passed through the body. Photodensitometry was also used in cadaver studies of the proximal femur *(18)*. Such studies noted the predictive power for hip fracture of the density of the region in the proximal femur known as Ward's triangle[5] 30 years before studies using the modern technique of DXA in 1993 *(19)*. The accuracy of such measurements was fairly good with a %CV of 5%. The correlation between metacarpal photodensitometry and ashed bone was also high at 0.88 *(8)*. This was a slightly better correlation than seen with metacarpal radiogrammetry. The precision of photodensitometry was not as good, however, ranging from 5 to 15% *(20)*. In this regard, the 6HS was superior *(4)*. Radiation dose to the hand was the same for metacarpal radiogrammetry and radiographic photodensitometry. In both cases, the biologically significant radiation dose was negligible.

Radiographic photodensitometry was developed and used extensively by researchers Pauline Beery Mack and George Vose *(21)*. Many of the original studies of the effects of weightlessness on the skeleton in the Gemini and Apollo astronauts were performed by Mack and her colleagues at Texas Woman's University *(22)*. The photodensitometry hand film of one of the Gemini astronauts is shown in Fig. 1-4.

RADIOGRAPHIC ABSORPTIOMETRY

Radiographic absorptiometry (RA) is the modern-day descendent of radiographic photodensitometry *(23,24)*. The ability to digitize high resolution radiographic images

[5] Ward's triangle was first described by F.O. Ward in *Outlines of Human Osteology*, London, Henry Renshaw, 1838. It is a triangular region created by the intersection of three groups of trabeculae in the femoral neck.

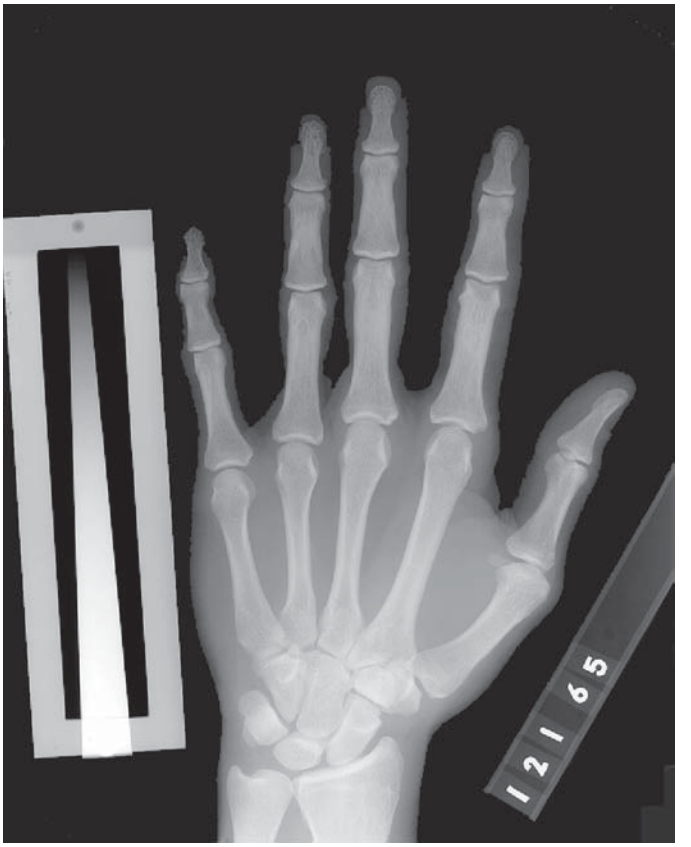

Fig. 1-4. A radiographic photodensitometry hand film taken in 1965 of one of the Gemini astronauts. The Texas Woman's University aluminum wedge is seen next to the little finger.

and to perform computerized analysis of such images largely eliminated the errors introduced by differences in radiographic exposure techniques and overlying soft tissue thickness. In an early version of RA, two X-rays of the left hand using nonscreened film were taken at slightly different exposures. Standard X-ray equipment was used to perform the hand films. The initial recommended settings were 50 kVp at 300 mA for 1 second and 60 kVp at 300 mA for 1 second. The exact settings varied slightly with the equipment used and were adjusted so that the background optical density of each of the two hand films matched a quality control film. An aluminum alloy reference wedge was placed on the film prior to exposure, parallel to the middle phalanx of the index finger. After development, the films were sent to a central laboratory where they were digitized and analyzed by computer. The average BMD in arbitrary RA units of the middle phalanxes of the index, long, and ring fingers was reported. Figure 1-5 illustrates the X-ray appearance of the hand and aluminum alloy reference wedge.

In cadaveric studies, the accuracy of RA for the assessment of bone mineral content of the middle phalanges was good at 4.8% *(25)*. The authors of this study noted that very thick soft tissue that might be seen in very obese subjects could potentially result in an underestimation of RA values. The correlation between the RA values and the ashed

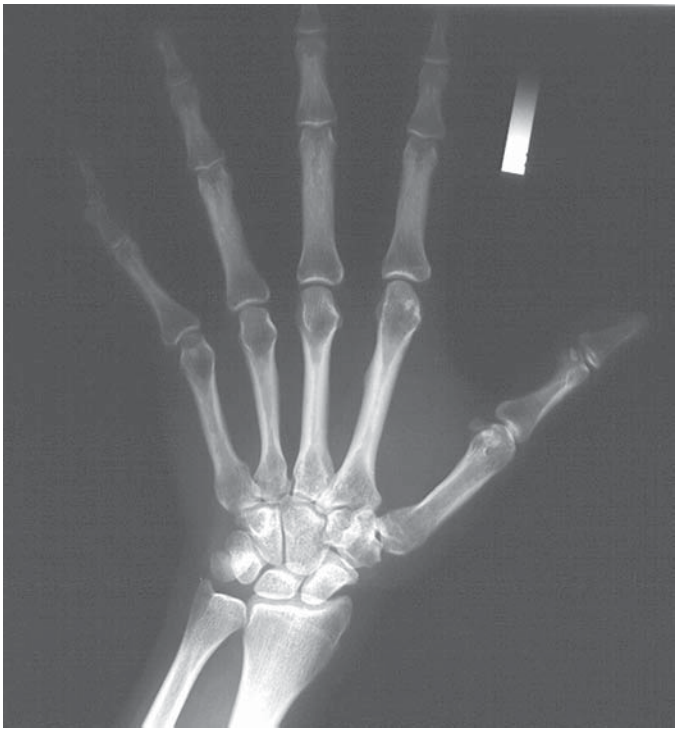

Fig. 1-5. A radiographic absorptiometry hand film. The small aluminum wedge, originally known as the Fel's wedge, is seen next to the index finger.

weight in the phalanges was excellent with $r = 0.983$. The short-term reproducibility of these measurements was also excellent at 0.6%.

The ability to predict bone density at other skeletal sites from hand RA is as good as that seen with other techniques such as SPA, DPA, DXA, or quantitative computed tomography (QCT) of the spine *(23,26)*. This does not mean that RA hand values can be used to accurately predict bone density at other skeletal sites. Although the correlations between the different sites as measured by the various techniques are correctly said to be statistically significant, the correlations are too weak to allow clinically useful predictions of bone mass or density at one site from measurement at another.

The utility of modern-day RA in predicting hip fracture risk was suggested by an analysis of data acquired during the first National Health and Nutrition Examination Survey (NHANES I, 1971–1975). During this survey, 1559 hand radiographs of Caucasian women were obtained with the older technique of photodensitometry using the Texas Woman's University wedge *(27)*. During a median follow-up of 14 years that extended through 1987, 51 hip fractures occurred. Based on radiographic photodensitometry of the second phalanx of the small finger of the left hand, the risk for hip fracture per SD decline in bone density increased 1.66-fold. These films were then re-analyzed using RA with some compensation for the differences in technique. This re-analysis yielded an increase in the risk for hip fracture per SD decline in RA bone density of 1.81-fold. Huang and colleagues *(28)* evaluated the utility of RA in the prediction of vertebral fractures. They followed 560 postmenopausal women, average age 73.7 years, for an

average of 2.7 years in the Hawaii Osteoporosis Study. The risk for vertebral fracture in this study using RA was 3.41-fold for each SD decline in bone density.

RA systems are commercially available. The automated Osteogram® system from Compumed, Inc. consists of the computer hardware, software, and film cassette with hand template and reference wedge needed to perform RA of the phalanges. A film-less, self-contained system is also in development. The Metriscan™ from Alara Inc. is a self-contained device that utilizes storage phosphor technology in place of X-ray film to perform RA of the phalanges. Both systems are discussed in Chapter 13.

PHOTON ABSORPTIOMETRY TECHNIQUES

In radiology, attenuation refers to a reduction in the number and energy of photons in an X-ray beam. Attenuation, then, is a reduction in an X-ray beam's intensity. To a large extent, the attenuation of X rays is determined by tissue density. The difference in tissue densities is responsible for creating the images seen on an X ray. The more dense the tissue, the more electrons it contains. The number of electrons in the tissue determines the ability of the tissue to either attenuate or transmit the photons in the X-ray beam. The differences in the pattern of transmitted or attenuated photons creates the contrast necessary to discern images on the X ray. If all the photons were attenuated (or none were transmitted), no image would be seen because the film would be totally white. If all of the photons were transmitted (or none were attenuated), no image would be seen because the film would be totally black. The difference in the attenuation of the X-ray photon energy by different tissues is responsible for the contrast on an X ray, which enables the images to be seen. If the degree of attenuation could be quantified, it would be possible to quantitatively assess the tissue density as well. This is the premise behind the measurement of bone density with photon absorptiometric techniques. The earliest photon absorptiometric techniques employed radionuclides to generate photon energy. These radionuclide-based techniques have given way to X-ray-based techniques. The basic principles on which they operate however, remain the same.

Single-Photon Absorptiometry

Writing in the journal *Science* in 1963, Cameron and Sorenson *(29)* described a new method for determining bone density in vivo by passing a monochromatic or single-energy photon beam through bone and soft tissue. The amount of mineral encountered by the beam could be quantified by subtracting the beam intensity after passage through the region of interest from the initial beam intensity. In these earliest SPA units, the results of multiple-scan passes at a single location, usually the midradius, were averaged *(30)*. In later units, scan passes at equally spaced intervals along the bone were utilized such that the mass of mineral per unit of bone length could be calculated. A scintillation detector was used to quantify the photon energy after attenuation by the bone and soft tissue in the scan path. After the photon attenuation was quantified, a comparison to the photon attenuation seen with a calibration standard derived from dried defatted human ashed bone of known weight was made in order to determine the amount of bone mineral.

The photon beam and the detector were highly collimated or restricted in size and shape. The beam source and detector moved in tandem across the region of interest on the bone, coupled by a mechanical drive system. Iodine-125 at 27.3 keV, or americium-241 at 59.6 keV, were originally used to generate the single-energy photon beam although most SPA units subsequently developed in the United States employed only ^{125}I.

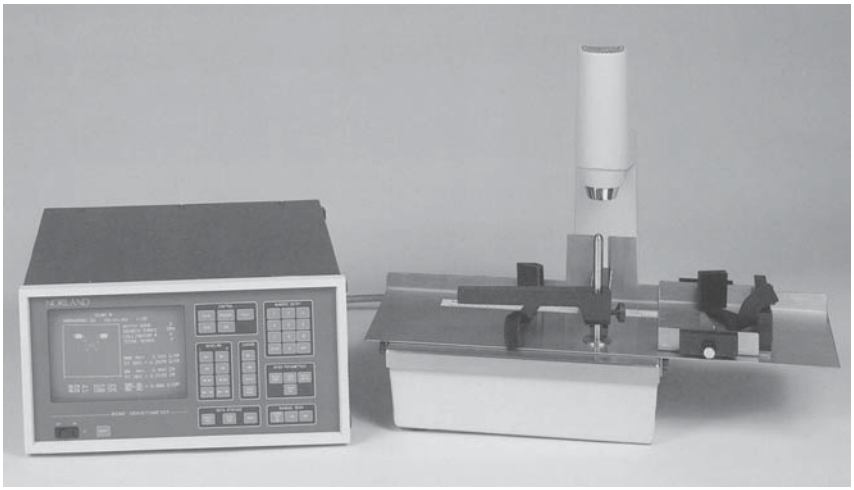

Fig. 1-6. An early Norland model 2780 single photon absorptiometer. This device utilized ^{125}I to generate photon energy. Photo courtesy of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

The physical calculations for SPA determinations of bone mineral were valid only when there was uniform thickness of the soft tissue in the scan path. In order to artificially create this kind of uniform thickness, the limb to be studied had to be submerged in a water bath or surrounded by a tissue-equivalent material. As a practical matter, this limited SPA to measurements of the distal appendicular skeleton such as the radius and later, the calcaneus. Figure 1-6 is a photograph of an old SPA device, the Norland 2780, that was in use in the 1980s.

SPA was both accurate and precise, although the parameters varied slightly with the site studied. For SPA measurements of the midradius, accuracy ranged from 3 to 5% and precision, from 1 to 2% *(29,31–33)*. Early measurements of the distal and ultradistal radius with SPA did not demonstrate the same high degree of precision primarily due to the marked changes in the composition of the bone with very small changes in location within the distal and ultradistal radius.[6] With later instruments that employed computer-enhanced localization routines and rectilinear scanning, SPA measurements of the distal and ultradistal radius approached a precision of 1% *(34)*. Accuracy and precision of measurements at the calcaneus with SPA were reported to be less than 3% *(32)*. The skin radiation dose for both the radius and calcaneus was 5 to 10 mrem *(32,33)*. The biologically important radiation dose, the effective dose, was negligible. Results were reported as either bone mineral content (BMC) in grams or as BMC per unit length (BMD/l) in grams per centimeter. The time required to perform such studies was approximately 10 minutes *(35)*.

SPA is rarely performed today, having been supplanted first by single-energy X-ray absorptiometry (SXA) and now DXA. The demise of SPA was due to improvements in ease of use and precision seen with SXA and DXA. SPA was an accurate technology that could be used to predict fracture risk. The ability to predict the risk of appendicular fractures with SPA measurements of the radius was convincingly established *(36–38)*.

[6] *See* Chapter 2 for a discussion of the composition of the radius and ulna.

SPA measurements of the radius were also good predictors of spine fracture risk and global[7] fracture risk *(36–40)*. Indeed, the longest fracture trials published to date, demonstrating the ability of a single bone mass measurement to predict fracture, were performed using SPA measurements of the radius.

Dual-Photon Absorptiometry

The basic principle involved in DPA for the measurement of bone density was the same as for SPA: quantifying the degree of attenuation of a photon energy beam after passage through bone and soft tissue. In DPA systems, however, an isotope that emitted photon energy at two distinct photoelectric peaks or two isotopes, each emitting photon energy at separate and distinct photoelectric peaks, were used. When the beam was passed through a region of the body containing both bone and soft tissue, attenuation of the photon beam occurred at both energy peaks. If one energy peak was preferentially attenuated by bone, however, the contributions of soft tissue to beam attenuation could be mathematically subtracted *(41)*. As in SPA, the remaining contributions of beam attenuation from bone were quantified and then compared to standards created from ashed bone. The ability to separate bone from soft tissue in this manner finally allowed quantification of the bone density in those areas of the skeleton that were surrounded by large or irregular soft tissue masses, notably the spine and proximal femur. DPA was also used to determine total body bone density. The development of DPA and its application to the spine, proximal femur, and total body is attributed to a number of investigators: B.O. Roos, G.W. Reed, R.B. Mazess, C.R. Wilson, M. Madsen, W. Peppler, B.L. Riggs, W.L. Dunn, and H.W. Wahner *(42–47)*.

The isotope most commonly employed in DPA in the United States was gadolinium-153, which naturally emitted photon energy at two photoelectric peaks, 44 keV and 100 keV. At the photoelectric peak of 44 keV, bone preferentially attenuated the photon energy. The attenuated photon beams were detected by a NaI scintillation detector and quantified after passage through pulse-height analyzers set at 44 and 100 keV. The shielded holder for the ^{153}Gd source, which was collimated and equipped with a shutter that was operated by a computer, moved in tandem with the NaI detector in a rectilinear scan path over the region of interest. A point-by-point calculation of bone density in the scan path was made. Figure 1-7 is an intensity-modulated image of the spine created with an early DPA device.

DPA bone density studies of the lumbar spine were performed with the photon energy beam passing in a posterior to anterior direction. Because of the direction of the beam, the vertebral body and the posterior elements were included in the scan path. The transverse processes were eliminated. This resulted in a combined measurement of cortical and trabecular bone, or an integral measurement, that included the more trabecular vertebral body surrounded by its cortical shell and the highly cortical posterior elements. The results were reported as an areal density in g/cm^2. The BMD of the proximal femur was also an areal density that was acquired with the beam passing in a posterior to anterior direction. Figure 1-8 shows an early DPA device with the patient positioned for a study of the lumbar spine.

[7] Global fracture risk refers to the risk of having any and all types of fractures combined. This is in contrast to a site-specific fracture risk prediction in which the risk for a fracture at a specific skeletal site is given, such as spine fracture risk or hip fracture risk.

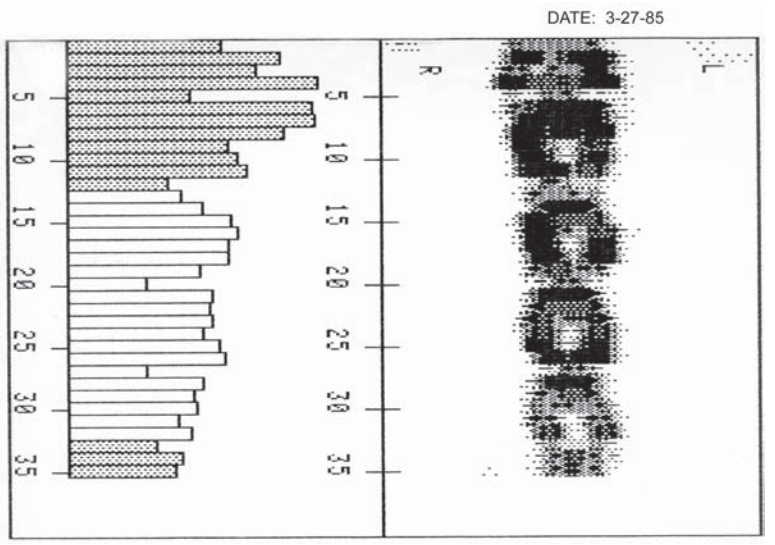

Fig. 1-7. A dual-photon absorptiometry posterior–anterior spine study obtained on a device as shown in Fig. 1-8. The spine image is upside down. The histogram on the left was used to place the intervertebral disc space markers. The shortest bar in the vicinity of the disc space was identified and the marker was placed there.

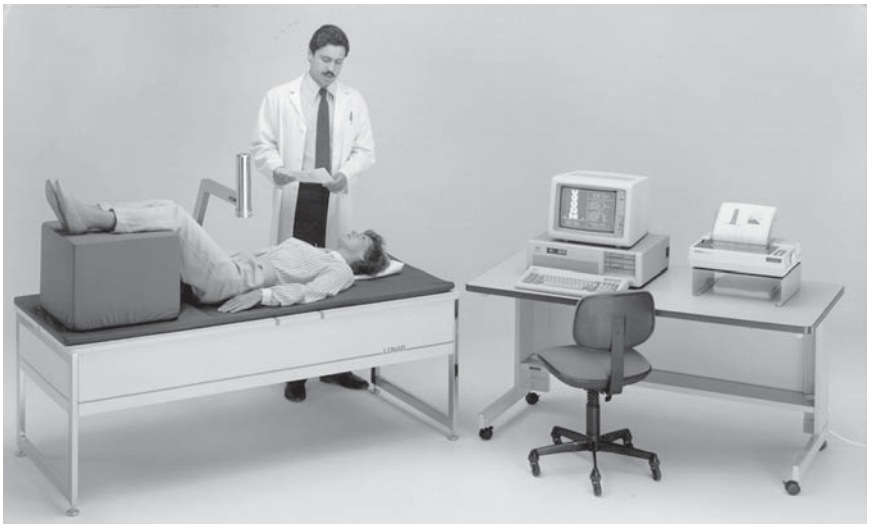

Fig. 1-8. An early Lunar DP3 dual-photon absorptiometer. This device utilized ^{153}Gd to generate photon energy. Photo courtesy of GE Medical Systems, Madison, WI.

DPA studies of the spine required approximately 30 minutes to complete. Studies of the proximal femur took 30 to 45 minutes to perform. Total body bone density studies with DPA required 1 hour. Skin radiation dose was low during spine or proximal femur studies at 15 mrem. Accuracy of DPA measurements of the spine ranged from 3 to 6% and for the proximal femur, 3 to 4% *(48)*. Precision for measurements of spine bone density was 2–4% and around 4% for the femoral neck.

DPA was considered a major advance from SPA because it allowed the quantification of bone density in the spine and proximal femur. DPA did have several limitations, however. Machine maintenance was expensive. The ^{153}Gd source had to be replaced yearly at a cost of $5000 or more. It had also been noted that as the radioactive source decayed, values obtained with DPA increased by as much as 0.6% per month *(49)*. With replacement of the source, values could fall by as much as 6.2%. Although mathematical formulas were developed to compensate for the effect of source decay, it remained a cause for concern, potentially affecting both accuracy and precision. The precision of 2–4% for DPA measurements of the spine and proximal femur limited its application in detecting changes in bone density. With a precision of 2%, a change of at least 5.5% from the baseline value had to be seen before one could be certain at the 95% confidence level that any change had occurred at all *(50)*. With a precision of 4%, this figure increased to 11.1%. At a lower 80% confidence level, the required changed for precision values of 2 and 4% were 3.6 and 7.2%, respectively. As a practical matter, this meant that DPA bone density studies would not show significant changes for up to 5 years. This was too long a period to wait to be clinically useful.

In DPA spine bone density studies in which the photon beam passed in a PA direction, the highly trabecular vertebral body could not be separated from its more cortical posterior elements. In addition, the cortical shell of the vertebral body could not be separated from its trabecular interior. Calcifications in the overlying soft tissue or abdominal aorta will attenuate such a beam, falsely elevating the bone density values. Arthritic changes in the posterior elements of the spine also affect the measurement *(51)*. These effects are discussed in greater detail in Chapters 2 and 9. PA DXA studies of the spine are not immune to these effects either but lateral DXA spine studies can be performed to overcome these limitations. Studies of the spine in the lateral projection were never available with DPA.

The ability to make site-specific predictions of fracture risk of the spine and proximal femur or global fracture risk predictions with DPA was established in prospective trials *(19,39)*. Like SPA, DPA is rarely performed in the United States now, because of the availability of DXA with its technological improvements.

Dual-Energy X-Ray Absorptiometry

The underlying principles of DXA are the same as those of DPA. With DXA, however, the radioactive isotope source of photon energy has been replaced by an X-ray tube. There are several advantages of X-ray sources over radioactive isotopes. There is no source decay that would otherwise require costly replacement of the radioactive source. Similarly, there is no concern of a drift in patient values due to source decay. The greater source intensity or "photon flux" produced by the X-ray tube and the smaller focal spot allows for better beam collimation resulting in less dose overlap between scan lines and greater image resolution. Scan times are faster and precision is improved.

Because X-ray tubes produce a beam that spans a wide range of photon energies, the beam must be narrowed in some fashion in order to produce the two distinct photoelectric peaks necessary to separate bone from soft tissue. The major manufacturers of central DXA systems in the United States have chosen to do this in one of two ways. GE Medical Systems of Madison, WI and Norland, a CooperSurgical Company of Fort Atkinson, WI, use rare earth K-edge filters to produce two distinct photoelectric peaks. Hologic Inc. of Bedford, MA uses a pulsed power source to the X-ray tube to create the same effect.

K-edge filters produce an X-ray beam with a high number of photons in a specific range. The energy range that is desired is the energy range that is just above the K-absorption edge of the tissue in question. The K-edge is the binding energy of the K-shell electron. This energy level varies from tissue to tissue. The importance of the K-edge is that at photon energies just above this level, the transmission of photons through the tissue in question drops dramatically. That is, the photons are maximally attenuated at this energy level *(52)*. Therefore, to separate bone from soft tissue in a quantifiable fashion, the energy of the photon beam should be just above the K-edge of bone or soft tissue for maximum attenuation. GE Medical Systems uses a cerium filter in its central[8] devices that has a K-shell absorption edge at 40 keV. A cerium-filtered X-ray spectrum at 80 kV will contain two photoelectric peaks at about 40 and 70 keV. The samarium K-edge filter employed by Norland in its central devices has a K-shell absorption edge of 46.8 keV. The samarium-filtered X-ray beam at 100 kV produces a low-energy peak at 46.8 keV. In the Norland system, the high-energy peak is variable because the system employs selectable levels of filtration but the photons are limited to less than 100 keV by the 100 kV employed. The K-edge of both cerium and samarium results in a low-energy peak that approximates the 44 keV low-energy peak of gadolinium-153 used in old dual-photon systems.

Hologic central DXA devices utilize a different system to produce the two photoelectric peaks necessary to separate bone from soft tissue. Instead of employing K-edge filtering of the X-ray beam, Hologic employs alternating pulses to the X-ray source at 70 kV and 140 kV.

Most regions of the skeleton are accessible with DXA. Studies can be made of the spine in both an posterior–anterior (PA)[9] and lateral projection. Lumbar spine studies acquired in the lateral projection have the ability to eliminate the confounding effects of dystrophic calcification on densities measured in the PA direction *(53)*. Lateral scans also eliminate the highly cortical posterior elements that contribute as much as 47% of the mineral content measured in the PA direction *(54)*. The utility of lateral DXA lumbar spine studies can be limited by rib overlap of L1 and L2 and pelvic overlap of L4, more so when performed in the left lateral decubitus position than the supine position *(53,55)*. Bone density in the proximal femur, forearm, calcaneus, and total body can also be measured with DXA.

Scan times are dramatically shorter with DXA compared to DPA. Early DXA units required approximately 4 minutes for studies of the PA lumbar spine or proximal femur. Total body studies required 20 minutes in the medium scan mode and only 10 minutes in the fast scan mode. Newer DXA units scan even faster, with studies of the PA spine or proximal femur requiring less than 1 minute to perform.

The values obtained with DXA studies of the skeleton are highly correlated with values from earlier studies performed with DPA. Consequently, the accuracy of DXA is consid-

[8] A central device is a bone densitometer that can be used to quantify bone density in the spine and proximal femur. The distinction between central and peripheral devices is discussed in Chapter 2.

[9] Although spine bone density studies with DXA are often referred to as PA spine studies, the beam actually passes in a posterior to anterior direction. Such studies are correctly characterized as PA spine studies, but accepted convention is to refer to them as PA spine bone density studies. The Lunar Expert, a fan-array DXA scanner, does acquire spine bone density studies in the PA projection.

ered comparable to that of DPA *(56-59)*. DXA spine values and Hologic and Norland DXA proximal femur values are consistently lower than values obtained previously with DPA. There are also differences in the values obtained with DXA equipment from the three major manufacturers.[10] Values obtained with either a Hologic or Norland DXA unit are consistently lower than those obtained with a Lunar DXA unit, although all are highly correlated with each other *(60–62)*. Comparison studies using all three manufacturers' central DXA devices have resulted in the development of formulas that make it possible to convert values for the lumbar spine and femoral neck obtained on one manufacturer's device to the expected value on another manufacturer's device (*see* Appendix II) *(63)*. The margin of error in such conversions is still too great to use such values in following a patient over time, however. Such values should only be viewed as "ball park" figures. Another set of formulas makes possible the conversion of any manufacturer's BMD value at the lumbar spine or total hip to a second value called the "standardized bone mineral density" (sBMD *see* Appendix II) *(63,64)*. The sBMD is always reported in mg/cm^2 to distinguish it from the manufacturer's BMD, which is reported in g/cm^2.

Perhaps the most significant advance seen with DXA compared to DPA is the marked improvement in precision. Expressed as a coefficient of variation, short-term precision in normal subjects has been reported as low as 0.9% for the PA lumbar spine and 1.4% for the femoral neck *(56)*. Precision studies over the course of 1 year have reported values of 1% for the PA lumbar spine and 1.7 to 2.3% for the femoral neck *(59)*.

Radiation exposure is extremely low for all types of DXA scans. Expressed as skin dose, radiation exposure during a PA lumbar spine or proximal femur study is only 2 to 5 mrem.[11] The biologically important effective dose or whole-body equivalent dose is only 0.1 mrem *(65)*.

DXA has been used in prospective studies to predict fracture risk. In one of the largest studies of its kind, DXA studies of the proximal femur were demonstrated to have the greatest short-term predictive ability for hip fracture compared to measurements at other sites with SPA or DPA *(19)*.

DXA central devices are called "pencil-beam" or "fan-array" scanners. Examples of pencil-beam scanners are the Lunar DPX® Plus, DPX®-L, DPX-IQ™, DPX®-SF, DPX®-A, DPX-MD™, DPX-MD+™ and DPX-NT™, the Hologic QDR® 1000 and QDR® 2000 and the Norland XR-36™, XR-46™, Excell™ and Excell™plus.[12] Examples of fan-array DXA scanners are the Lunar Expert® and Prodigy™ and the Hologic QDR® 4500 A, QDR® 4500 C, QDR® 4500 W, QDR® 4500 SL, Delphi™, and Discovery™. The difference between the pencil-beam and fan-array scanners is illustrated in Figs. 1-9 and 1-10. Pencil-beam scanners employ a collimated or narrowed X-ray beam (narrow like a pencil) that moves in tandem in a rectilinear pattern with the detector(s). Fan-array scanners utilize a much broader or fan-shaped beam and an array of detectors, so that an entire scan line can be instantly quantified. Scan times are reduced to as short as 10 seconds for a PA study of the lumbar spine. Image resolution is also enhanced with the fan-array scanners as shown in the extraordinary images in Fig. 1-11. This has created a new application for bone densitometry scanning called

[10] *See* Chapter 5 for a detailed discussion of the difference in values obtained using central devices from different manufacturers, conversions equations, and the development of the sBMD.

[11] *See* Chapter 13 for a listing of radiation dose according to device and scan type.

[12] Specific descriptions and photographs of these scanners can be found in Chapter 13.

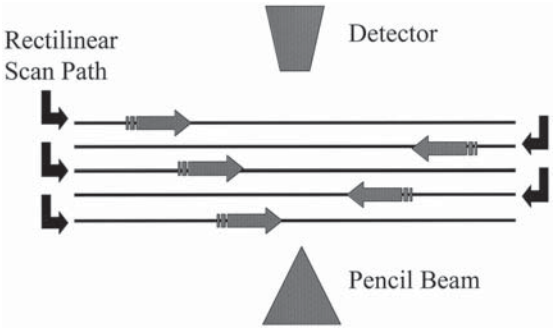

Fig. 1-9. Pencil-beam DXA densitometers. The single detector or sequential detectors move in tandem with the narrowed X-ray beam in a rectilinear scan path.

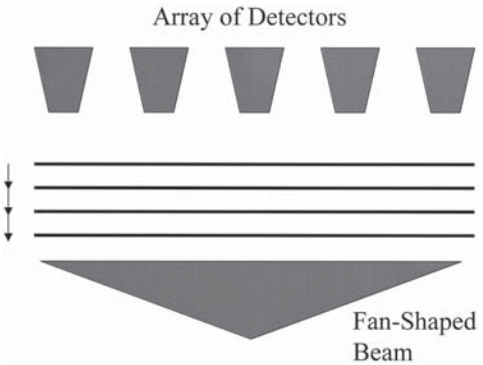

Fig. 1-10. Fan-array DXA densitometers. An array of detectors and fan-shaped beam make possible the simultaneous acquisition of data across an entire scan line.

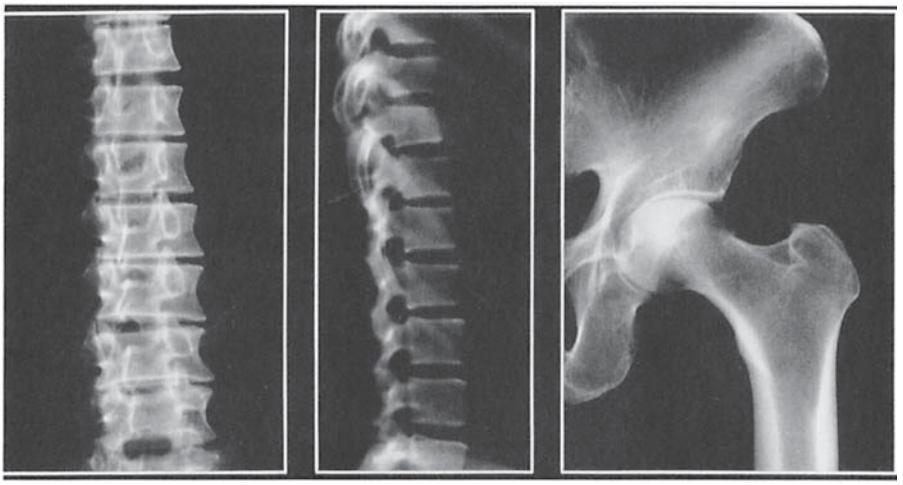

Fig. 1-11. Images from the fan-array imaging densitometer, the Lunar EXPERT-XL. Images courtesy of GE Medical Systems, Madison, WI.

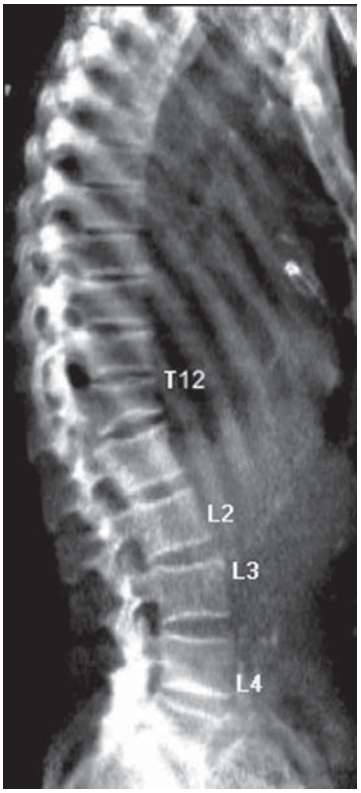

Fig. 1-12. LVA™ image acquired on the Lunar Prodigy™. A fracture is apparent at T12. A safety pin is also seen over the anterior chest. Case courtesy of GE Medical Systems, Madison, WI.

morphometric X-ray absorptiometry (MXA). With MXA, images of the spine obtained in the lateral projection can be used for computer analysis of the vertebral dimensions and diagnosis of vertebral fracture. Fan-array scanners have also been developed to image the lateral spine in its entirety to allow a visual assessment of vertebral size and shape. Examples of scanners with this capability are the Hologic Delphi™, Discovery™, and the Lunar Prodigy™. Figures 1-12 and 1-13 are lateral spine images from the Lunar Prodigy™. In the LVA™ (Lateral Vertebral Assessment)[13] image in Fig. 1-12 a fracture is suggested at T12. In Fig. 1-13, the dimensions of the suspect vertebra are measured with morphometry. Figs. 1-14 and 1-15 are IVA™ (Instant Vertebral Assessment) images from the Hologic Delphi™. No fractures are apparent in Fig. 1-14. Note the multiple thoracic deformities in Fig. 1-15.

DXA has effectively replaced DPA in both research and clinical practice. The shortened scan times, improved image resolution, lower radiation dose, improved precision, application to more skeletal sites, and lower cost of operation with DXA have relegated DPA to an honored place in densitometry history.

[13] This application on newer GE Medical Systems devices is now called DVA (Dual-energy Vertebral Assessment). An image of the spine in the PA projection can be obtained in addition to the lateral view with DVA.

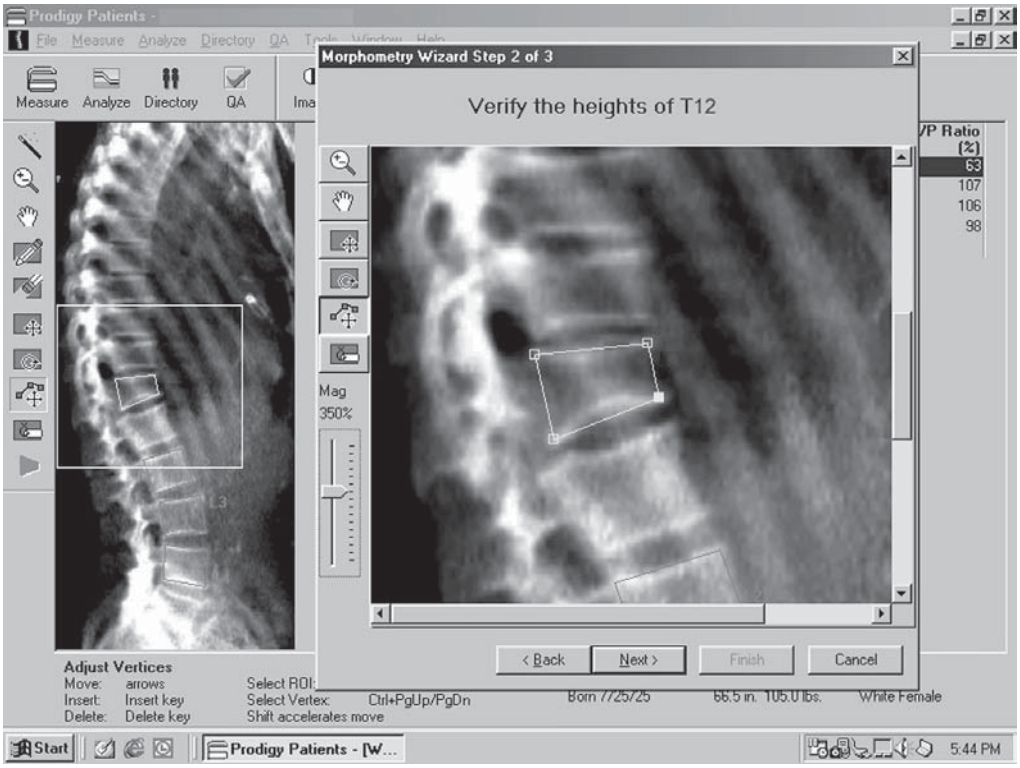

Fig. 1-13. LVA™ image acquired on the Lunar Prodigy™. Morphometric software allows the user to define the vertebral edges and measure the vertebral heights to quantitatively diagnose fracture. Case courtesy of GE Medical Systems, Madison, WI.

Peripheral DXA

DXA technology is also employed in portable devices dedicated to the measurement of one or two appendicular sites. As such, these devices are characterized as "peripheral" (pDXA) devices. Because these devices employ dual-energy X ray, they do not require a water bath or tissue-equivalent gel surrounding the region of the skeleton being studied. As a consequence, they are somewhat easier to maintain and use than SXA devices. Examples of pDXA units are the Lunar PIXI®, the Norland pDEXA® and the Norland Apollo™, the Schick accuDEXA™, and the Osteometer DexaCare® DTX-200 and G4. These devices are discussed in detail in Chapter 13.

Single-Energy X-Ray Absorptiometry

SXA is the X-ray based counterpart of SPA, much as DXA is the X-ray-based counterpart of DPA. SXA units were used to measure BMD in the distal radius and ulna and calcaneus. Like their DXA counterparts, SXA units did not utilize radioactive isotopes but did require a water bath or tissue-equivalent gel surrounding the region of the skeleton being measured. The accuracy and precision of SXA were comparable to SPA *(66)*. With the development of portable DXA devices for the measurement of forearm and heel bone density that do not require a water bath or tissue-equivalent gel, SXA is largely obsolete, just like its predecessor SPA.

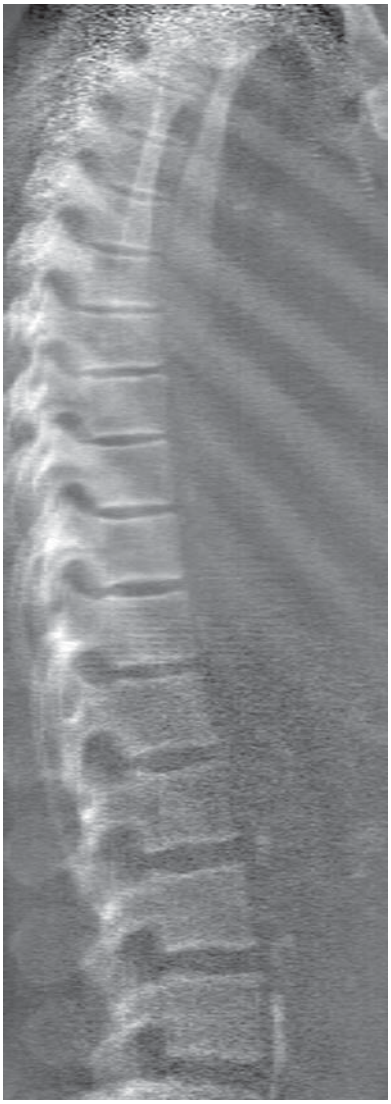

Fig. 1-14. IVA™ image acquired on the Hologic Delphi™. No fractures are apparent in the thoracic and lumbar spine although aortic calcification is seen anterior to the lumbar spine. Case courtesy of Hologic Inc., Bedford, MA.

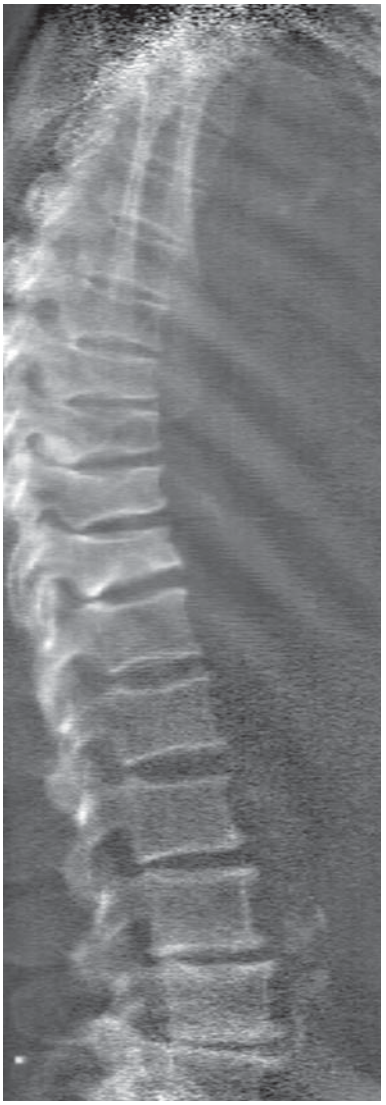

Fig. 1-15. IVA™ image acquired on the Hologic Delphi™. There are multiple deformities in the thoracic spine as well as osteophytes in the lower lumbar spine. Aortic calcification is also seen anterior to the lumbar spine. Case courtesy of Hologic Inc., Bedford, MA.

Quantitative Computed Tomography

Although QCT is a photon absorptiometric technique like SPA, SXA, DPA, and DXA, it is unique in that it provides a three-dimensional or volumetric measurement of bone density and a spatial separation of trabecular from cortical bone. In 1976, Ruegsegger et al. *(67)* developed a dedicated peripheral QCT scanner using ^{125}I for measurements of the radius. Cann and Genant *(68,69)* are credited with adapting commercially available CT scanners for the quantitative assessment of spinal bone density.

It is this approach that has received the most widespread use in the United States, although dedicated CT units for the measurement of the peripheral skeleton, or pQCT units, are in use in clinical centers. QCT studies of the spine utilize a reference standard or phantom that is scanned simultaneously with the patient. The phantom contains varying concentrations of K_2HPO_4 and is placed underneath the patient during the study. A scout view (*see* Fig. 1-16) is required for localization and then an 8- to 10-mm thick slice is measured through the center of two or more vertebral bodies that are generally selected from T12 to L3 *(70)*. A region of interest within the anterior portion of the vertebral body is analyzed for bone density and is reported as mg/cm^3 K_2HPO_4 equivalents (*see* Fig. 1-17). This region of interest is carefully placed to avoid the cortical shell of the vertebral body. The result is a three-dimensional trabecular density unlike the two-dimensional areal mixed cortical and trabecular densities reported with PA studies of the spine utilizing DPA or DXA.

A study of the spine with QCT requires about 30 minutes *(35)*. The skin radiation dose is generally 100 to 300 mrem. This overestimates the biologically important effective dose because only a small portion of marrow is irradiated during a QCT study of the spine *(65)*. The effective dose or whole-body equivalent dose is generally in the range of only 3 mrem (30 μSv). The localizer scan that precedes the actual QCT study will add an additional 3 mrem to the effective dose. These values are quite acceptable in the context of natural background radiation of approximately 20 mrem per month. Older CT units, that by their design are unable to utilize low kVp settings for QCT studies, may deliver doses 3 to 10 times higher.

The accuracy of QCT for measurements of spine BMD can be affected by the presence of marrow fat *(70–72)*. Marrow fat increases with age, resulting in an increasingly large error in the accuracy of spine QCT measurements in older patients. The accuracy of QCT is reported to range from 5 to 15%, depending on the age of the patient and percentage of marrow fat. The presence of marrow fat results in an underestimation of bone density in the young of about 20 mg/cm^3 and as much as 30 mg/cm^3 in the elderly *(70)*. The error introduced by marrow fat can be partially corrected by applying data on vertebral marrow fat with aging originally developed by Dunnill et al. *(73)*. In an attempt to eliminate the error introduced by marrow fat, dual-energy QCT (DEQCT) was developed by Genant and Boyd *(74)*. DEQCT clearly reduced the error introduced by the presence of marrow fat to as low as 1.4% in cadaveric studies *(71,72)*. In vivo, the accuracy with DEQCT is 3 to 6% *(35,70)*. Radiation dose with DEQCT is increased approximately 10-fold compared to regular or single-energy QCT (SEQCT) and precision is not as good. The precision of SEQCT for vertebral measurements in expert hands is 1 to 3% and for DEQCT, 3 to 5% *(70,75)*.

The measurement of bone density in the proximal femur with QCT is not readily available. Using both dedicated QCT and standard CT units, investigators have attempted to utilize QCT for measurements of the proximal femur but this capability remains restricted to a few research centers *(76,77)*.

QCT of the spine has been used in studies of prevalent osteoporotic fractures and it is clear that such measurements can distinguish osteoporotic individuals from normal individuals as well or even better than DPA *(78–81)*. Fractures are rare with values above 110 mg/cm^3 and extremely common below 60 mg/cm^3 *(82)*. Because QCT can isolate and measure trabecular bone, which is more metabolically active than cortical bone, rates of change in disease states observed with QCT spine measurements tend to

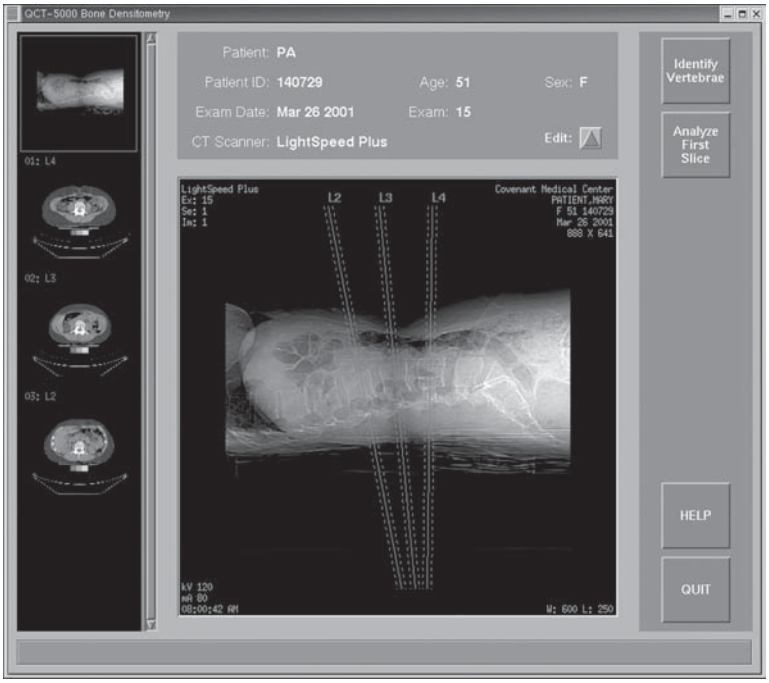

Fig. 1-16. QCT-5000™ scout image. Reproduced courtesy of Image Analysis Inc., Columbia, KY.

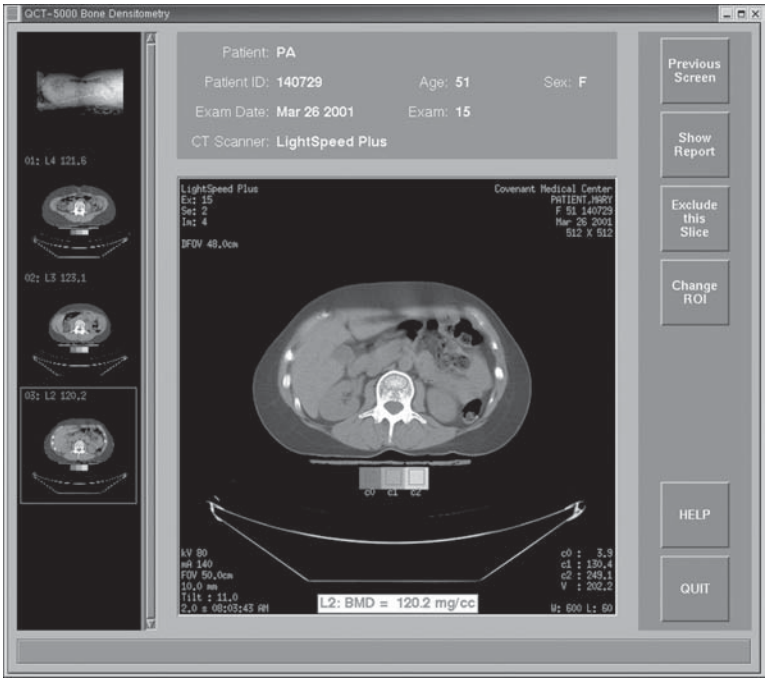

Fig. 1-17. QCT-5000™ axial spine image. This is a three-dimensional volumetric measurement, reported in mg/cm^3 or mg/cc. The L2 BMD shown here is 120.2 mg/cc. This measurement is 100% trabecular. Reproduced courtesy of Image Analysis Inc., Columbia, KY.

be greater than those observed with PA spine studies performed with DPA or DXA *(68,83)*. This greater magnitude of change partially offsets the effects of the poorer precision seen with QCT compared to DXA.[14] The correlations between spine bone density measurements with QCT and skeletal sites measured with other techniques are statistically significant but too weak to allow accurate prediction of bone density at another site from measurement of the spine with QCT *(26,80,81)*. This is no different however, from attempting to use BMD at the spine obtained with DXA to predict BMD at other skeletal sites.

Peripheral QCT

pQCT is becoming more widely available. pQCT devices are utilized primarily for the measurement of bone density in the forearm. Like QCT scans of the spine, pQCT makes possible true three-dimensional or volumetric measurements of bone density in the forearm, which may be particularly useful when the size of the bone is changing, as in pediatric populations. Information on a commercially available pQCT device, the Stratec XCT 2000™, can be found in Chapter 13.

QUANTITATIVE ULTRASOUND BONE DENSITOMETRY

Research in quantitative ultrasound (QUS) bone densitometry has been ongoing for more than 40 years. Only in the last few years, however, has QUS begun to play a role in the clinical evaluation of the patient. Ultrasound technologies in clinical medicine have traditionally been imaging technologies used, for example, to image the gall bladder or the ovaries. Like photon absorptiometric technologies, however, the application of ultrasound in bone densitometry is not primarily directed at producing an image of the bone. Instead, a quantitative assessment of bone density is desired with the image being secondary in importance.

In theory, the speed with which sound passes through bone is related not only to the density of the bone, but to the quality of the bone as well. Both bone density and bone quality determine a bone's resistance to fracture. Therefore, the speed of sound through bone can be related to the risk of fracture. These relationships can be illustrated mathematically. For example, the bone's ability to resist fracture (R) can be described as the amount the bone deforms when it is subjected to a force (F) that is moderated by the bone's ability to resist that force, the elastic modulus (E) as shown in Equation 1.

$$R = \frac{F}{E} \tag{1}$$

Studies have shown that the elastic modulus, E, is determined by both bone density and bone quality. Mathematically this is represented in Equation 2, where K is a constant representing bone quality and ρ represents bone density.

$$E = K\rho^2 \tag{2}$$

From such an equation, it becomes clear that the bone's ability to resist a force and not fracture is determined by changes in bone density and bone quality. When ultrasound

[14] *See* Chapter 11 for a detailed discussion on the interaction between precision and rate of change in determining the time interval required between measurements to demonstrate significant change.

passes through a material, the velocity of the sound wave is also related to the elastic modulus *(84,85)* and density of the material as shown in Equation 3.

$$V = \sqrt{\frac{E}{\rho}} \tag{3}$$

When Equations 2 and 3 are combined, it becomes clear that the velocity of ultrasound through bone is directly related to the square root of the product of bone density and bone quality.

$$V = \sqrt{\frac{K\rho^2}{\rho}} \tag{4}$$

$$V = \sqrt{K\rho} \tag{5}$$

The velocity with which ultrasound passes through normal bone is quite fast and varies depending on whether the bone is cortical or trabecular. Speeds of 3000 to 3600 m/s are typical in cortical bone with speeds of 1650 to 2300 m/s typical of trabecular bone.

In order to calculate velocity, ultrasound densitometers must measure the distance between two points and the time required for the sound wave to travel between these two points. The velocity is reported as the speed of sound (SOS). Higher values of SOS indicate greater values of bone density.

A second ultrasound parameter is broadband ultrasound attenuation (BUA). This parameter is reported in decibels per megahertz (dB/MHz). BUA is perhaps best understood using the analogy of a child's slinky toy. When the toy is stretched out and then suddenly released, the energy imparted to the rings by stretching them causes the rings to oscillate for a period of time, with the oscillations becoming progressively less and then finally stopping as the energy is lost. The same thing happens to the sound wave as it passes through bone. Some of the energy is lost from the sound wave and the oscillations of the sound wave are diminished. How much energy is lost is again related to the density of the bone and to architectural qualities such as porosity and trabecular connectivity *(84,85)*. Like SOS, higher BUA values indicate greater bone density.

Most devices report both SOS and BUA. However, one manufacturer has mathematically combined SOS and BUA into a proprietary index called the Stiffness Index. Another manufacturer reports a proprietary index called the Quantitative Ultrasound Index (QUI) and an estimated BMD that is derived from the measurements of SOS and BUA. QUS devices are considered peripheral devices and are generally quite portable. They employ no ionizing radiation, unlike their SXA or DXA peripheral counterparts. The calcaneus is the most common skeletal site assessed with QUS, but devices exist that can be applied to the radius, finger, and tibia. In heel QUS measurements, heel width apparently has little if any effect on BUA but may have a slight effect on SOS *(86)*. Most ultrasound devices require some type of coupling medium between the transducers and the bone. This is often accomplished with water when the heel is placed directly into a water bath. Ultrasound gel may be used in place of direct contact with water for heel measurements and measurements at other skeletal sites. Systems that utilize water baths into which the foot is placed are called "wet" systems. Systems that do not require water submersion but utilize gel instead, are called "dry" systems. There is one system for the heel in which neither water submersion or gel are required, making it truly dry. The Lunar Achilles+™, the Lunar Achilles Express™, the Lunar Insight™,

the Sunlight Omnisense™ 7000S, the Quidel QUS-2™, the McCue C.U.B.A. Clinical™, the Hologic Sahara™ Clinical Bone Sonometer, and the Osteometer Ultrasure DTU-1 are all examples of QUS densitometers currently available for clinical use. These devices are discussed in more detail in Chapter 13.

The technical differences between QUS devices from various manufacturers are even greater than those seen with DXA devices. Different frequency ranges and transducer sizes may be employed from device to device. Within the same skeletal site, slightly different regions of interest may be measured. As a consequence, values obtained on one QUS device are not necessarily comparable to values obtained on another QUS device.

The physics of ultrasound suggest that it should provide information about the bone that goes beyond a simple measurement of mass or density. Clinical research has tended to confirm this assumption, although perhaps not to the extent that was originally hoped. In a very large study of 5662 older women, both SOS and BUA predicted the risk of hip fracture as well or better than did measurements of BMD at the femoral neck using DXA *(87)*. Similar findings were reported in the Study of Osteoporotic Fractures by Bauer et al. *(88)*.

The precision of QUS measurements is generally excellent. In addition, because of the speed with which measurements can be made and the lack of any ionizing radiation, measurements can be made in duplicate or triplicate at any one examination. The average value of such replicate studies can be used, which dramatically improves precision. In a study from Njeh et al. *(89)* in which the precision of six different calcaneal QUS devices was determined, the short-term precision for SOS, expressed as the root-mean-square percent coefficient of variation (RMS-%CV) ranged from 0.11 to 0.42. For BUA, the RMS-%CV ranged from 1.39 to 6.30. Typically, better precision values are seen for SOS than for BUA.

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2 Skeletal Anatomy in Densitometry

CONTENTS

Densitometry is primarily a quantitative measurement technique rather than a skeletal imaging technique. Nevertheless, there are unique aspects of skeletal anatomy in densitometry that must be appreciated to properly utilize the technology and interpret the quantitative results as well as the skeletal images.

CHARACTERIZING THE SKELETON IN DENSITOMETRY

The bones of the skeleton can be described by four characteristics, one of which is unique to densitometry. The characterizations are important, as this often determines which skeletal site is the most desirable to measure in a given clinical situation. A skeletal site may be described as axial or appendicular, weight-bearing or nonweight-bearing, central or peripheral, and predominantly cortical or trabecular.

The Axial and Appendicular Skeleton

The axial skeleton includes the skull, ribs, sternum, and spine *(1)*, as shown in Fig. 2-1. In densitometry, the phrase "axial skeleton" or "axial bone density study" has traditionally referred to the lumbar spine and PA lumbar spine bone density studies. This limited use is no longer appropriate because the lumbar spine can also be studied in the lateral projection and the thoracic spine can be measured as well. The skull and the ribs are quantified only as part of a total body bone density study and as a consequence, the phrase "axial bone density study" has never implied a study of those bones, although they are part of the axial skeleton. The appendicular skeleton includes the extremities and the limb girdles as shown in Fig. 2-1. The scapulae and the pelvis are therefore part of the appendicular skeleton. The proximal femur is also obviously part of the appendicular skeleton, although it is often mistakenly described as being part of the axial skeleton. Contributing to this confusion is the current practice of including dual energy X-ray bone density studies of the proximal femur and pelvis under the same Current Procedural

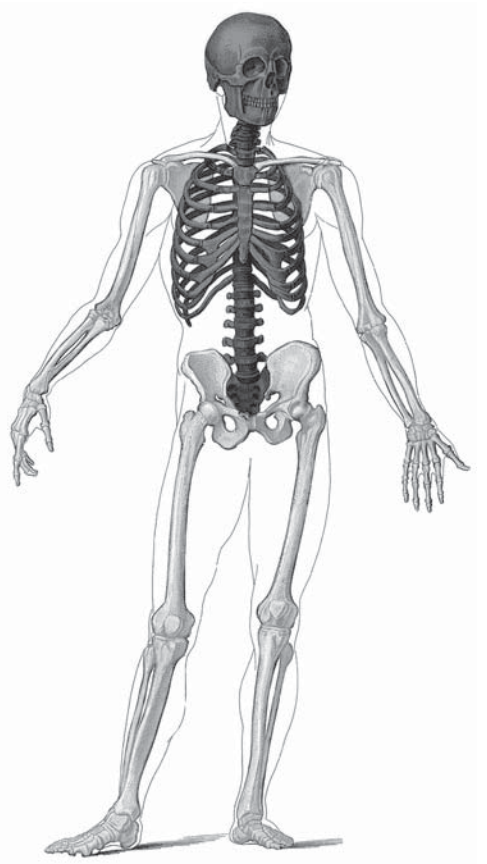

Fig. 2-1. The axial and appendicular skeleton. The darker shaded bones comprise the axial skeleton. The lighter shaded bones comprise the appendicular skeleton. Image adapted from EclectiCollections™.

Technology (CPT) code[1] of 76075 used for DXA spine bone density studies in which the studies are described as studies of the axial skeleton *(2)*.

The Weight-Bearing and Nonweight-Bearing Skeleton

Regions of the skeleton are also characterized as weight bearing or nonweight-bearing. This division is obvious but not without clinical significance. The cervical, thoracic, and lumbar spine and lower extremities are weight-bearing regions of the skeleton. Portions of the pelvis are weight-bearing. The small calcaneus is also part of the weight-bearing skeleton and is perhaps the most sensitive of all the bones to the effects of weight-bearing forces. The remainder of the skeleton is nonweight-bearing.

The Central and Peripheral Skeleton

Skeletal sites may also be characterized as central or peripheral. This classification is unique to densitometry. The spine, in either the PA or lateral projection, is considered a

[1] *See* Appendix VII for a list of CPT codes used in bone densitometry.

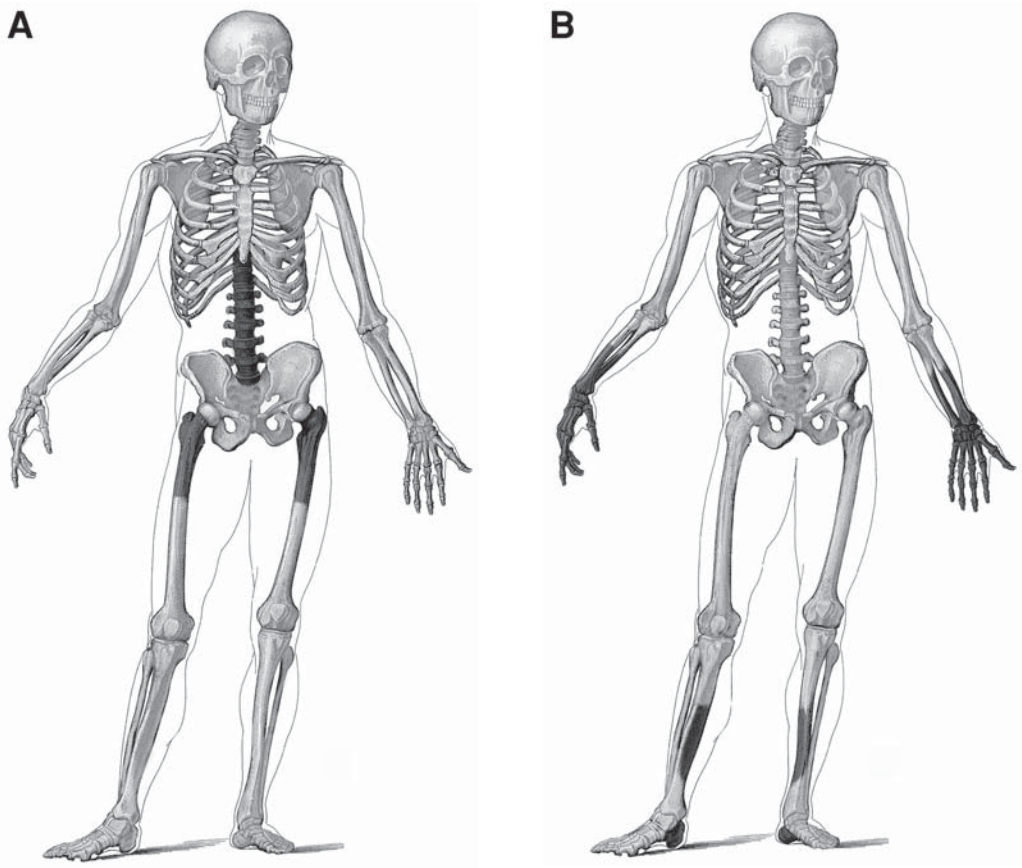

Fig. 2-2. (A,B) The central and peripheral skeleton. The darker shaded bones in **(A)** comprise the central skeleton. The darker shaded bones in **(B)** comprise the peripheral skeleton. Images adapted from EclectiCollections™.

central site. The proximal femur is also a central site even though it is not part of the axial skeleton like the spine. The calcaneus and the various forearm sites are all peripheral sites although the calcaneus is a weight-bearing site, whereas the forearm sites are not. As an extension of this terminology, bone densitometers that are used to measure bone density in the spine, hip, or both are called "central" machines even though the machines may also have software that allows them to be used to measure a peripheral site like the forearm. The description of a bone densitometer as a central machine is generally reserved for DXA and older DPA devices. Although QCT is used clinically to measure bone density in the spine, as a matter of convention, QCT is rarely described as a central technique, although it would be appropriate to do so. Densitometers that can only be used to measure the distal appendicular skeleton like the forearm or calcaneus are called "peripheral" machines. Because there is no current application of QUS for the central skeleton, it is understood that QUS devices are peripheral devices. As a consequence, it is not necessary to distinguish between central and peripheral QUS devices so the term *peripheral* is not used in conjunction with QUS devices. Figure 2-2 illustrates the central and peripheral skeleton.

The Trabecular/Cortical Composition of the Skeleton

The skeleton is composed of two types of bone: cortical bone and trabecular bone. Cortical bone is also called compact bone or haversian bone. It is typically found in the shafts of long bones and the vertebral endplates. Trabecular bone is also called cancellous bone or spongious bone and is primarily found in the vertebral bodies, pelvis, and distal ends of long bones. Trabecular bone contains hematopoietic or fatty marrow. Eighty percent of the skeleton is cortical bone. The remaining 20% is trabecular bone. Trabecular bone consists of plates, arches, and struts with marrow occupying the spaces between these structures. Cortical bone is a more solid structure forming the outer casing of the bones *(1)*.

Skeletal metabolism as a whole is roughly equally distributed between the two types of bone even though the skeleton is 80% cortical bone. This is because trabecular bone has a higher metabolic rate per unit of volume than cortical bone *(3)*. In any one bone however, rates of change in bone density may be greater at sites that are predominantly trabecular in composition compared to sites that are predominantly cortical. Rates of change are also greater in axial trabecular bone than in appendicular trabecular bone. If a patient is being followed over time to look for changes in the BMD from a disease process or therapeutic intervention, the greatest magnitude of change will generally be seen at a site that is predominantly trabecular bone. There are certain disease processes, however, that seem to have a predilection for sites that are predominantly cortical in composition. Hyperparathyroidism, for example, may cause demineralization at predominantly cortical sites, like the femoral neck or 33% radial site. Conversely, Cushing's disease may preferentially destroy the trabecular bone of the axial skeleton. In a disease like acromegaly, hypogonadism may cause a profound decrease in the trabecular bone of the spine, while excessive growth hormone causes an increase in the density of the cortical bone of the appendicular skeleton.[2]

Forearm Composition

The exact percentage of trabecular and cortical bone of many of the sites used in densitometry remains controversial. In a classic study, Schlenker and VonSeggen *(4)* quantified the average percentage of cortical and trabecular bone along the length of the radius and ulna in four cadaveric female forearms. The forearms were taken from women aged 21, 43, 63, and 85 years. The distribution and percentage of trabecular bone in the radius and ulna were similar. The maximum percentage of trabecular bone was seen in the first two centimeters proximal to the radial and ulnar styloids. The percentage of trabecular bone then dropped precipitously in both bones in a transitional region that lay between 2 and 3 cm proximal to either styloid and remained very small throughout the remainder of the proximal radius and ulna. The percentage of trabecular bone in the four subjects in the most distal 10% of the radius ranged from 50 to 67%, whereas in the region that represented 30 to 40% of the total length measured from the styloid tip, the percentage of trabecular bone ranged from only 0.6% to 6.8%.

Vertebral Composition

The composition of whole vertebra or the isolated vertebral body remains in dispute. The traditional view is that 55 to 75% of the calcium content of the whole vertebra is in trabecular bone. These figures are largely derived from early anatomic studies in which

[2] *See* Chapter 6 for a discussion of the effects of diseases on bone density.

the methods used to arrive as such conclusions were poorly described *(5,6)*. The traditional view was challenged in 1987 by Nottestad et al. *(7)* who performed anatomic dissections of 24 vertebrae taken from 14 normal individuals, 10 of whom were women with an average age of 72 years and 4 of whom were men with an average age of 63 years. The vertebrae were ashed and the calcium content was assayed using atomic absorption spectrophotometry. Nottestad et al. found that trabecular bone accounted for only 24.4% of the calcium content of whole female vertebrae. Trabecular calcium accounted for 41.8% of the calcium content in the vertebral body. The percentages were less in men, averaging 18.8 and 33.5%, respectively. Eastell et al. *(8)* refuted this finding based on anatomic dissections of L2 from 13 individuals, 6 men whose average age was 38.5 years and 7 women whose average age was 40.9. In this study, cortical and trabecular contributions to calcium content were determined by microdensitometry and by dissection and ashing. They reported that the whole vertebra was 72% trabecular bone in women and 80% trabecular bone in men. Adjusting these figures to compensate for the expected difference between the two-dimensional measurements that were actually performed and the three-dimensional structure of whole vertebrae, the percentages of trabecular bone in whole vertebrae dropped slightly to 69% in women and 77% in men.

Femoral Composition

The composition of the commonly measured sites in the proximal femur was briefly studied by Baumel *(9)* using anatomic dissection of the upper end of the femur in six cadavers (age at death 49 to 79 years). In this small study, the percentage of trabecular bone in the femoral neck was 36.45% (±3.85%) and in the trochanter, 39.06% (±3.79%).

All Sites

Despite these controversies, clinically useful characterizations of the composition of densitometry sites can be made. Table 2-1 lists the most commonly assessed skeletal sites and their relative proportions of trabecular and cortical bone *(10)*. Note that the spine, when measured with QCT, is described as 100% trabecular bone. This is because the three-dimensional, volumetric measure that is obtained with QCT allows the center of the vertebral body to be isolated from its cortical shell and the highly cortical posterior elements. The two-dimensional areal measurement employed in DPA and DXA measurements of the spine cannot do this. Although the posterior elements are eliminated from the scan path on a lateral spine study performed with DXA, elements of the cortical shell remain. Therefore, although the measurement of the spine in the lateral projection with DXA is a highly trabecular measurement of bone density, the measurement is not a measure of 100% trabecular bone.

THE SPINE IN DENSITOMETRY

Studies of the lumbar spine performed with DPA or DXA are generally acquired by the passage of photon energy from the posterior to anterior direction. They are properly characterized as PA spine studies. Nevertheless, these studies are often called AP spine studies, probably because plain films of the lumbar spine are acquired in the AP projection. The Lunar Expert, a fan-array scanner, actually does acquire lumbar spine bone density images in the AP direction. Compared to plain radiography, however, the beam direction in a DXA study of the spine has less influence on the appearance of the image and little if any influence on the measured BMC or BMD. Studies of the lumbar spine may

Table 2-1
Percentage of Trabecular Bone at Central and Peripheral Sites

PA Spine[a]	66%
Lateral Spine[b]	?
Femoral Neck	25%
Trochanter	50%
Ward's[b]	?
Total Body	20%
Calcaneus	95%
33% Radius or Ulna[c]	1%
10% Radius or Ulna[d]	20%
8-mm Radius or Ulna[e]	25%
5-mm Radius or Ulna[e]	40%
4–5% Radius or Ulna[f]	66%
Phalanges	40%

[a] These percentages are for DXA PA spine studies only. A volumetric measurement of 100% trabecular bone could be obtained with QCT.

[b] These sites are considered to be highly trabecular but the exact percentage of trabecular bone is not known.

[c] This site is often called the "proximal" site.

[d] This site is often called the "distal" site.

[e] Distance in mm indicates the separation distance between the radius and ulna at the site in question.

[f] This site is often called the ultradistal site, but may be called simply "distal" as well.

also be acquired in the lateral projection using DXA. Such studies may be performed with the patient in the supine or left lateral decubitus position, depending on the type of DXA unit employed.

Vertebral Anatomy

The whole vertebra can be divided into two major components: the body and the posterior elements. The posterior elements consist of the pedicles, the lamina, the spinous process, the transverse processes, and the inferior and superior articulating surfaces. The appearance of the image of the spine on an AP or PA spine study is predominantly determined by the relative density of the various elements that make up the entire vertebra. Figure 2-3A is a photograph of a posterior view of the lumbar spine with the intervertebral discs removed. Figures 2-3B and 2-3C demonstrate the appearance of the spine as first the transverse processes and then the vertebral bodies are removed from the photograph. What remains in Fig. 2-3C is characteristic of the appearance of the lumbar spine on a PA DXA lumbar spine study and consists largely of the posterior elements. The posterior elements form the basis of the DXA lumbar spine image seen in Fig. 2-4.

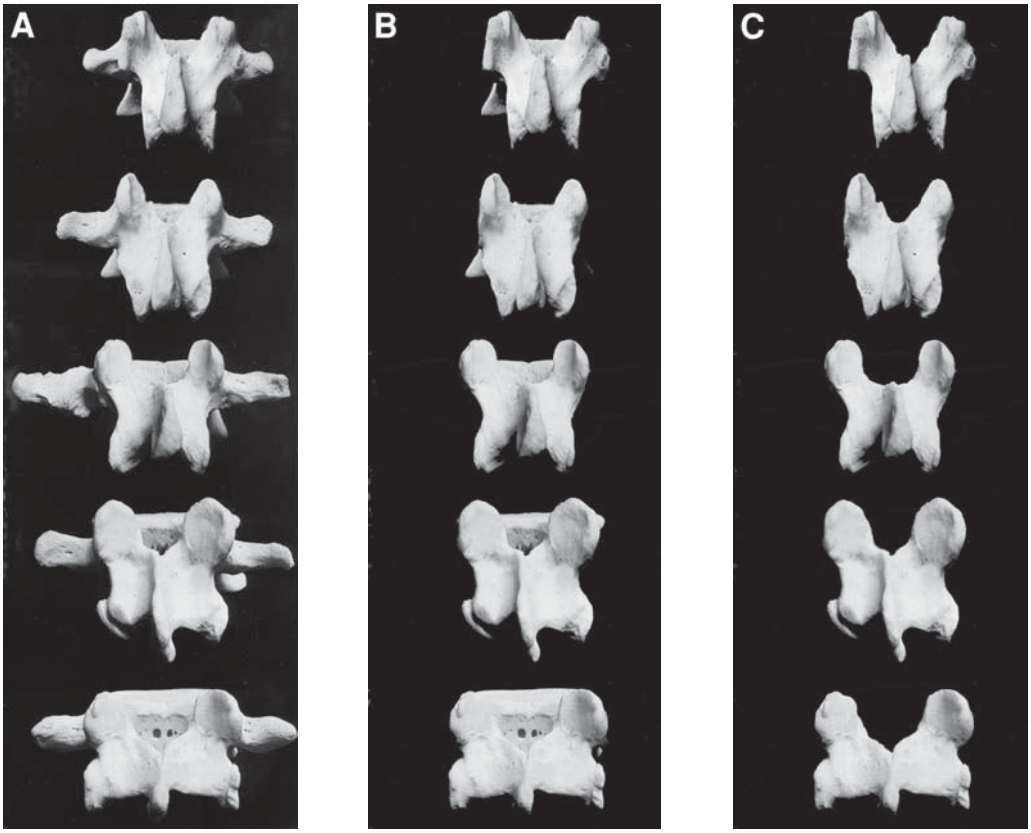

Fig. 2-3. The lumbar spine in the posterior view. **(A)** Intact vertebrae. **(B)** The transverse processes have been removed. **(C)** The vertebral bodies have been removed, leaving only the posterior elements. (Adapted from McMinn RMH, Hutchings RT, Pegington J, and Abrahams PH. [1993] *Colour Atlas of Human Anatomy*, 3rd edition, p. 83. By permission of the publisher Mosby.)

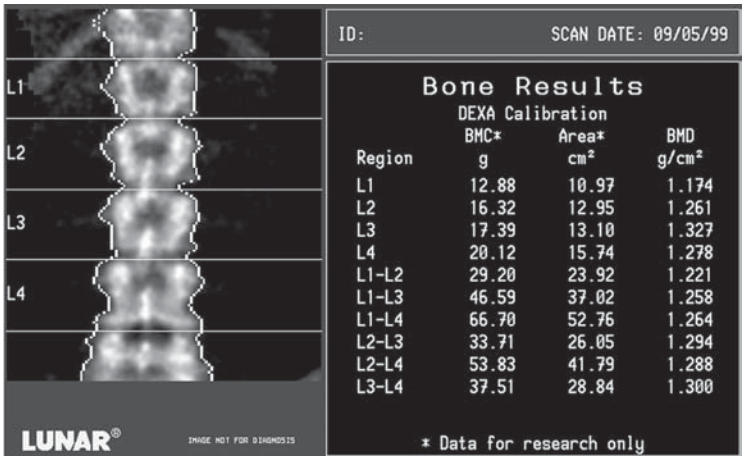

Fig. 2-4. A DXA PA spine study acquired on the Lunar DPX. The shapes of the vertebrae in this image are primarily created by the posterior elements. The shapes in this study are classic. The expected increase in BMC and area is also seen from L1 to L4. The increase in BMD from L1 to L3, with a decline from L3 to L4, is also typical.

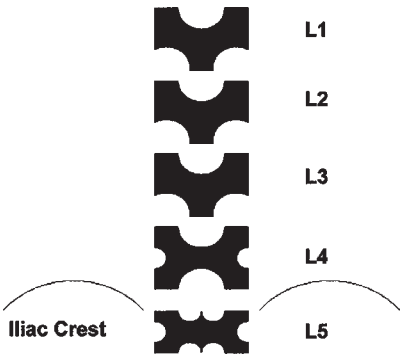

Fig. 2-5. A graphic illustration of the characteristic shapes of the lumbar vertebrae as seen on a DXA PA spine study.

The transverse processes are eliminated from the scan field and the vertebral bodies are not well seen because they are both behind and equally or less dense than the posterior elements. In a study of 34 lumbar vertebrae taken from 10 individuals, aged 61 to 88, the average mineral content of the posterior elements was 47% of the mineral content of the entire vertebra *(11)*.

The unique shapes of the posterior elements of the various lumbar vertebrae can be used as an aid in identifying the lumbar vertebrae. The posterior elements of L1, L2, and L3 have a U- or Y-shaped appearance. L4 can be described as looking like a block H or X. L5 has the appearance of a block I on its side. Figure 2-5 is a graphic illustration of these shapes. Compare these shapes to the actual posterior elements seen in Fig. 2-3C and the DXA lumbar spine study shown in Fig. 2-4. Although the transverse processes are generally not seen on a spine bone density study, the processes at L3 will sometimes be partially visible because this vertebra tends to have the largest transverse processes. This fact can also be helpful in lumbar vertebral identification. Figures 2-6A and 2-6B are the spine image only from the study shown in Fig. 2-4. In Fig. 2-6B, the shapes of the posterior elements have been outlined for emphasis.

On PA or AP DXA lumbar spine studies, L1 through L4 are quantified. Although L5 can be seen, it is not usually quantified because of potential interference from the pelvis. In fact, even if labeled on the scan, some software programs will not analyze L5 unless it is deliberately mislabeled L4. L1 frequently has the lowest BMC and BMD of the first four lumbar vertebrae. In a study of 148 normal women aged 50 to 60, Peel et al. *(12)* found that the BMC increased between L1–L2, L2–3, and L3–4 although the increase between L3–4 was roughly half that seen at the other levels as shown in Table 2-2. BMD increased between L1–2 and L2–3 but showed no significant change between L3–4. The average change between L3–4 was actually a decline of 0.004 g/cm^2. The largest increase in BMD occurred between L1–2. The apparent discrepancies in the magnitude of the change in BMC and BMD between the vertebrae are the result of the progressive increase in area of the vertebrae from L1 to L4. The DXA PA lumbar spine study shown in Fig. 2-4 illustrates the progressive increase in BMC and area from L1 to L4 and the expected pattern of change in BMD between the vertebral levels.

Studies from both Peel et al. *(12)* and Bornstein and Peterson *(13)* suggest that the majority of individuals have five lumbar vertebrae with the lowest set of ribs on T12.

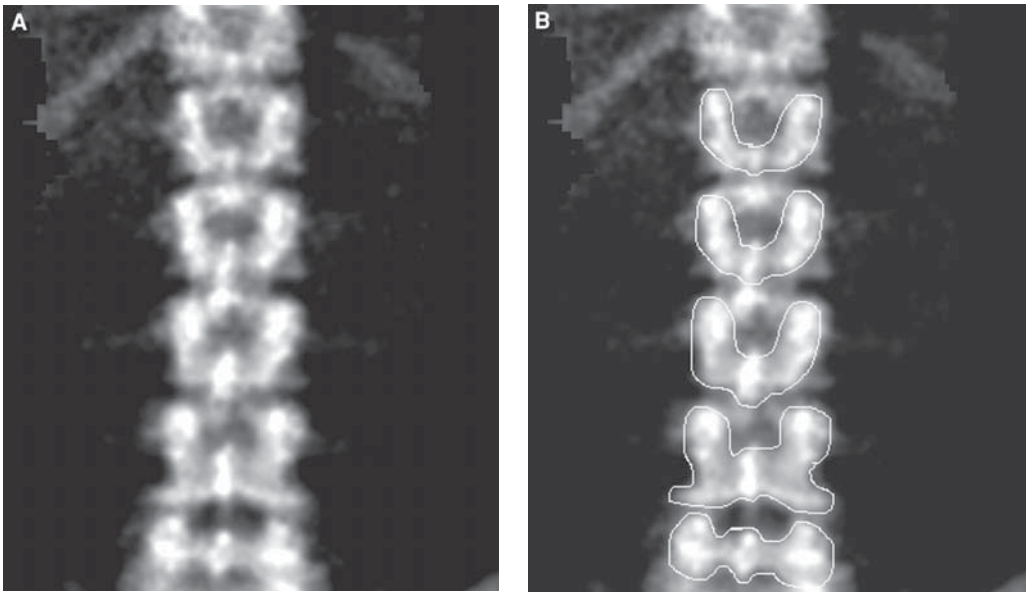

Fig. 2-6. (A) A DXA PA spine image acquired on the Lunar DPX. This is the spine image from the study shown in Fig. 2-4, with the intervertebral disk markers and bone-edge markers removed for clarity. **(B)** The shapes have been outlined for emphasis.

Table 2-2
Incremental Change in BMC and BMD Between Adjacent Vertebrae in 148 Normal Women Ages 50–60 as Measured by DXA

Vertebrae	*Increase in BMC (g)*	*% Increase in BMC*	*Increase in BMD (g/cm²)*	*% Increase in BMD*
L1–2	2.07	13.7	0.090	7.9
L2–3	2.43	14.8	0.050	4.3
L3–4	1.13	5.0	–0.004[a]	–0.8[a]

[a] Not statistically significant

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Bornstein and Peterson *(13)* found that only 17% of 1239 skeletons demonstrated a pattern of vertebral segmentation and rib placement other than five lumbar vertebrae with the lowest ribs on T12. Similarly, Peel et al. *(12)* found something other than the expected pattern of five lumbar vertebrae with the lowest ribs on T12 in only 16.5% of 375 women. An additional 7.2% had five lumbar vertebrae but had the lowest level of ribs on T11. Therefore, 90.7% of the women in this study had five lumbar vertebrae. Only 1.9% or 7 women out of 375 had six lumbar vertebrae. In 3 of these women, ribs were seen on L1. This was the only circumstance in which ribs were seen on L1. Of the entire group, 7.5% had only four lumbar vertebrae. In the majority of cases here, the lowest ribs were seen on T11. Table 2-3 summarizes these findings.

Table 2-3
Percentage of Women with Various Combinations of Numbers of Lumbar Vertebrae and Position of Lowest Ribs

No. of Lumbar Vertebrae	*Position of Lowest Ribs*	*% of Women*
5	T12	83.5%
5	T11	7.2%
4	T12	2.1%
4	T11	5.3%
6	T12	1.1%
6	L1	0.8%

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Table 2-4
The Effect of Mislabeling T12 as L1 on BMC and BMD in AP-DXA Spine Measurements

Measurement		*Difference*	*Mean %*
BMC	L1	1.61 g	11.5
	L2–4	3.47 g	8.4
	L1–4	4.8 g	8.4
BMD	L2–4	0.035 g/cm^2	3.6
	L1–4	0.039 g/cm^2	3.5

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Knowledge of the frequency of anomalous vertebral segmentation, the characteristic shapes created by the posterior lumbar elements on a PA lumbar spine study and the expected incremental change in BMC and BMD can be used to label the vertebrae correctly. If the vertebrae are mislabeled, comparisons to the normative databases will be misleading. The expected effect of mislabeling T12 as L1 is a lowering of the BMC or BMD at L1, which would then compare less favorably to the reference values for L1. The BMC and BMD averages for L1–4 or L2–4 would also be lowered. The degree to which BMC is lowered by mislabeling is substantially greater than BMD as shown in Table 2-4 *(12)*. The assumption that the lowest set of ribs is found at the level of T12 is often used as the basis for labeling the lumbar vertebrae. As can be seen in Table 2-3, this assumption would result in the vertebrae being labeled incorrectly in 13.3% of the population. As a consequence, all of the criteria noted here should be employed in determining the correct labeling of the lumbar vertebrae. This should obviate the need for plain films for the sole purpose of labeling the vertebrae in the vast majority of instances. Figure 2-7 is a PA spine study in which the labeling of the lumbar vertebra was not straightforward. The characteristic shapes of the vertebrae are easily seen, but no ribs appear to be projecting from what should be T12. Note the block H shape of the vertebra labeled L4 and the visible transverse processes on the vertebra labeled L3. Statistically, it is likely that there are five lumbar vertebrae here with the lowest set of ribs on T11. The appearance of L3 and L4 would also support this labeling. Plains films, acquired for the purpose of diagnosing spine fracture, confirmed that the labeling shown in Fig. 2-7 is correct.

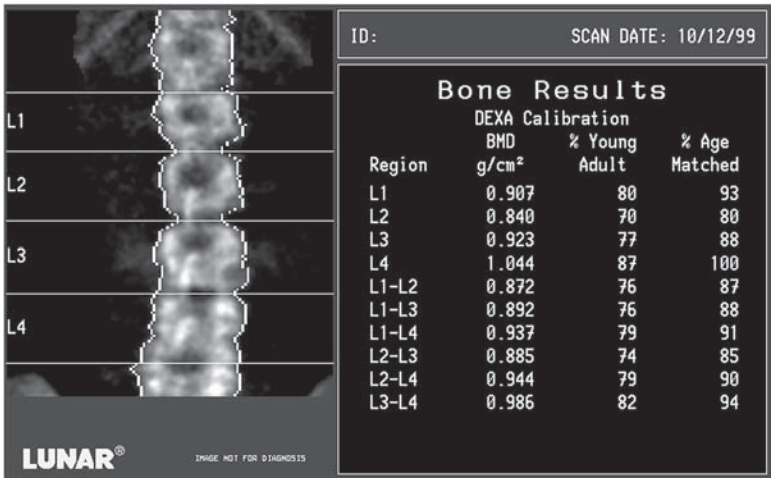


Fig. 2-7. A DXA PA spine study acquired on the Lunar DPX. The vertebra labeled L4 has a classic block H or X shape. No ribs are seen however, protruding from the vertebra that should be T12. It is far more likely that this represents five lumbar vertebrae with the lowest ribs on T11 than six lumbar vertebrae with the lowest ribs on T12. Also note that the BMD at L1 is higher than at L2, which is unusual. A lateral lumbar spine X ray of this patient, shown in Fig. 2-9, confirmed a fracture at L1.

PA and AP lumbar spine bone density measurements are extremely useful in predicting fracture risk and following the effects of a variety of disease processes and therapeutic interventions. Unfortunately, the lumbar spine is also the site most commonly affected by structural changes or artifacts that may affect either the accuracy or precision of the measurement or both.

Artifacts in PA or AP Spine Densitometry

The PA lumbar spine has been, and continues to be, used extensively in densitometry for diagnosis, fracture prediction, and monitoring. Unfortunately, it is also the skeletal site most often affected by structural changes and artifacts that may limit its utility.

Vertebral Fractures

The BMD of a fractured vertebra will be increased because of the fracture itself. This increase in density could erroneously lead the physician to conclude that the bone strength is better and the risk for fracture, lower, than is the case. Vertebral fractures in osteoporosis frequently occur in the T7–T9 region and in the T12–L2 region *(14,15)*. Because DXA measurements of the lumbar spine are often employed in patients with osteoporosis, osteoporotic fractures in the lumbar spine, particularly at L1 and L2, are a common problem, rendering the measurement of BMD inaccurate if the fractured vertebrae are included. An increased precision error would also be expected if the fractured vertebrae were included in BMD measurements performed as part of a serial evaluation of BMD. Although a fractured lumbar vertebra can be excluded from consideration in the analysis of the data, this reduces the maximum number of contiguous vertebrae in the lumbar spine available for analysis. For reasons of statistical accuracy and precision, the BMD for three or four contiguous vertebrae is preferred over two-vertebrae averages or the BMD of a

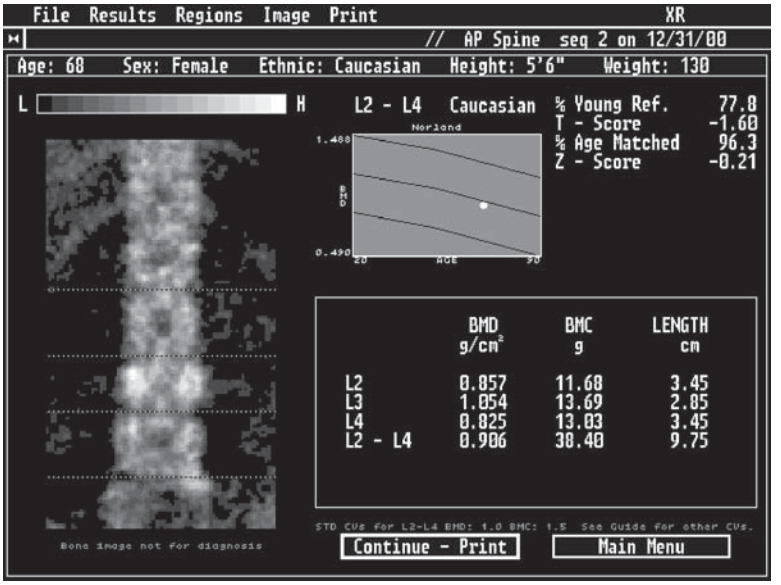


Fig. 2-8. A DXA PA spine study acquired on the Norland XR-36. The image suggests a loss of vertebral height and increased sclerosis at L3. Although the BMD at L3 is expected to be higher than at L2, the BMD at L3 here is markedly higher. These findings suggest a fracture at this level but this must be confirmed. In any case, the L2–L4 BMD will be increased by this structural change. Case courtesy of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

single vertebra. Figure 2-8 illustrates a PA lumbar spine study in which a fracture was apparent at L3. Although the BMD at L3 is expected to be higher than either L2 or L4, it is disproportionately higher. The L2–4 BMD will be increased because of the effect of the fracture on the BMD at L3. In the DXA PA lumbar spine study shown in Fig. 2-7, the image does not as readily suggest a fracture. The BMD at L1 however is higher than the BMD at L2, which is unusual. A plain lateral film of the lumbar spine of this patient, shown in Fig. 2-9, confirmed a fracture at L1.

Degenerative Changes and Dystrophic Calcification

Other structural changes within the spine can affect BMD measurements. Osteophytes and facet sclerosis can increase the BMD when measured in the AP or PA projection. Aortic calcification will also potentially affect the BMD when measured in the AP or PA spine because the X-ray beam will detect the calcium in the aorta as it passes through the body on an anterior to posterior or posterior to anterior path. It is therefore useful to note how often these types of changes are expected in the general population and the potential magnitude of the effect these changes may have on the measured BMD in the lumbar spine.

Effect of Osteophytes on BMD. In 1982, Krolner et al. *(16)* observed that osteophytes caused a statistically significant increase in the BMD in the AP spine when compared to controls without osteophytes. More recently, Rand et al. *(17)* evaluated a population of 144 postmenopausal women, aged 40 to 84 years, with an average age of 63.3 years, for the presence of osteophytes, scoliosis, and aortic calcification. These women were generally healthy women referred for the evaluation of BMD because of suspected postmenopausal osteoporosis. Table 2-5 lists the percentages of these women

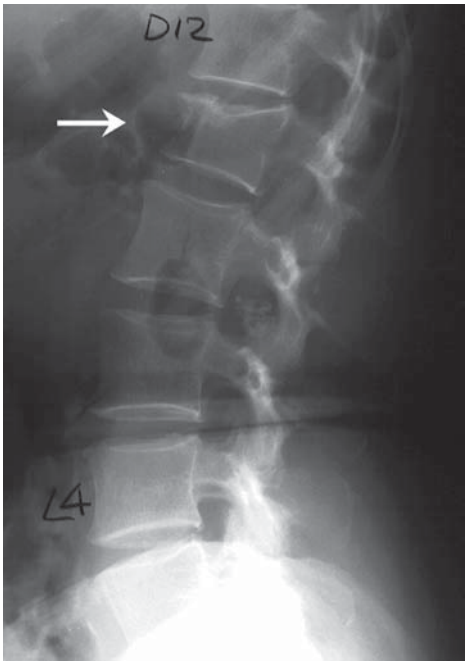


Fig. 2-9. The lateral lumbar spine X ray of the patient whose DXA study is shown in Fig. 2-7. A fracture at L1 is indicated by the arrow.

Table 2-5
Frequency of Specific Types of Degenerative Changes in the Spines of 144 Women Aged 40–84

Type of Degenerative Change	*% with Change (n)*
Osteophytes	45.8 (66)
Osteochondrosis	21.5 (31)
Vascular Calcification	24.3 (35)
Scoliosis	22.2 (32)
Any type	59.0 (72)

Adapted with permission of the publisher from ref. *17*.

found to have these types of degenerative changes. Based on these findings, Rand et al. estimated the likelihood of degenerative changes in the spine as being less than 10% in women under the age of 50. In 55-year-old women, however, the likelihood jumped to 40% and in 70-year-old-women, to 85%. Of these types of degenerative changes, however, only the presence of osteophytes significantly increased the BMD. The magnitude of the increase caused by the osteophytes ranged from 9.5% at L4 to 13.9% at L1. Cann et al. *(18)* also estimated the increase in BMD from osteophytes in the spine at 11%. In 1997, Liu et al. *(19)* studied 120 men and 314 women, aged 60 to 99 years.

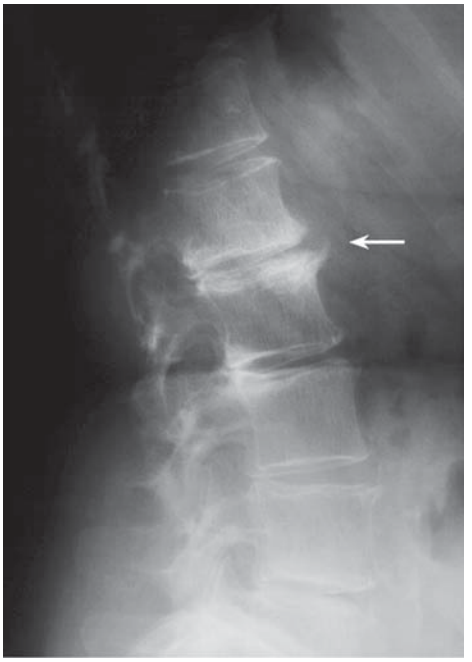
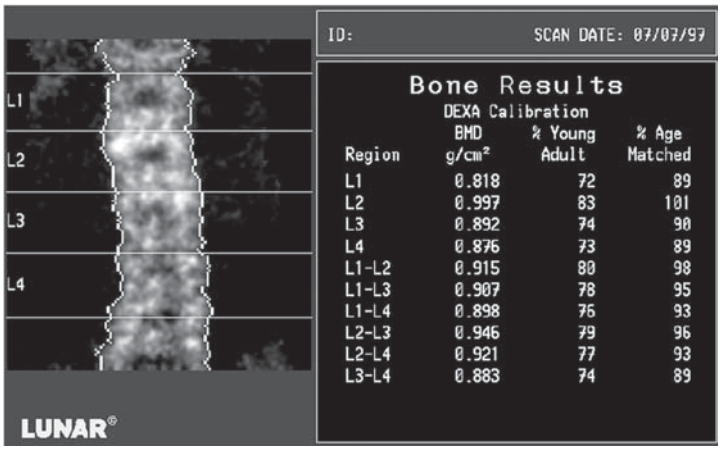


Fig. 2-10. A lateral lumbar spine X ray of the patient whose DXA study is shown in Fig. 2-11. The arrow indicates a region of endplate sclerosis and osteophyte formation.



Bone Results
DEXA Calibration

Region	BMD g/cm²	% Young Adult	% Age Matched
L1	0.818	72	89
L2	0.997	83	101
L3	0.892	74	90
L4	0.876	73	89
L1-L2	0.915	80	98
L1-L3	0.907	78	95
L1-L4	0.898	76	93
L2-L3	0.946	79	96
L2-L4	0.921	77	93
L3-L4	0.883	74	89

Fig. 2-11. A DXA PA spine study acquired on the Lunar DPX. A sclerotic process is suggested at L2 by the image. The BMD is also increased more than expected in comparison to L1 and is higher than L3, which is unusual. These findings are compatible with the endplate sclerosis and osteophytes seen in Fig. 2-10.

Lumbar spine osteophytes were found in 75% of the men and 61.1% of the women. The effect of osteophytes on the BMD was sufficiently great to cause 50% of the men and 25% of the women with osteopenia to be misdiagnosed. About 20% of the men and 10% of the women with osteoporosis were misdiagnosed because of the effect of osteophytes on the BMD. In Fig. 2-10, osteophytes are clearly visible at L2 on the lateral lumbar

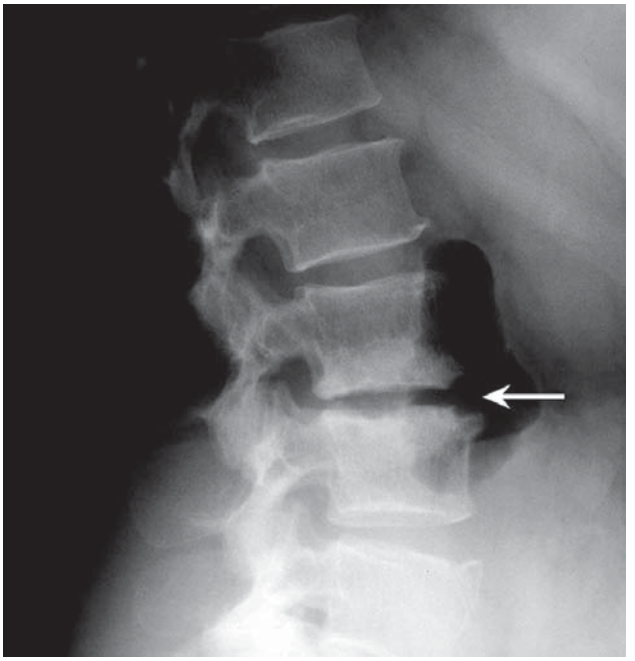
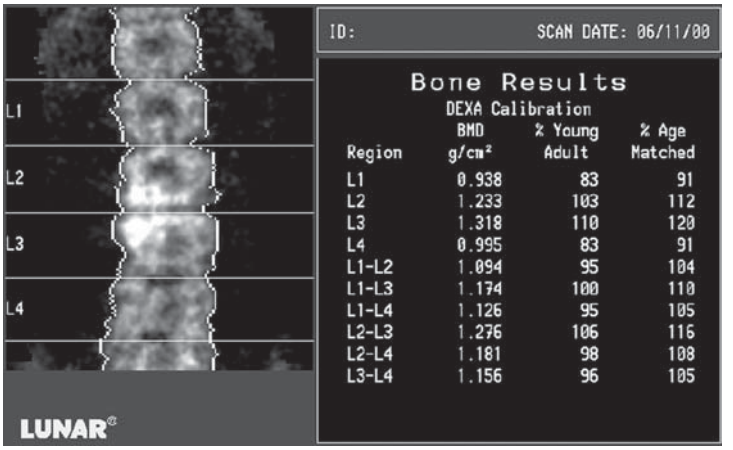


Fig. 2-12. A lateral lumbar spine X ray of the patient whose DXA study is shown in Fig. 2-13. The arrow indicates a region of marked endplate sclerosis.



Region	BMD g/cm²	% Young Adult	% Age Matched
L1	0.938	83	91
L2	1.233	103	112
L3	1.318	110	120
L4	0.995	83	91
L1-L2	1.094	95	104
L1-L3	1.174	100	110
L1-L4	1.126	95	105
L2-L3	1.276	106	116
L2-L4	1.181	98	108
L3-L4	1.156	96	105

Fig. 2-13. A DXA PA spine study acquired on the Lunar DPX. The image dramatically suggests the sclerotic process seen on the X ray in Fig. 2-12. There is a marked increase in the BMD at L2 and L3 compared to L1 and L4.

radiograph. The appearance of this region on the DXA PA lumbar spine study in Fig. 2-11 suggests a sclerotic process at this level. Osteophytes and end-plate sclerosis are also seen on the plain film in Fig. 2-12. The effect on the DXA image of the lumbar spine, shown in Figure 2-13 is dramatic. There is also a disproportionate increase in the BMD at L2 and L3 compared to L1 and L4.

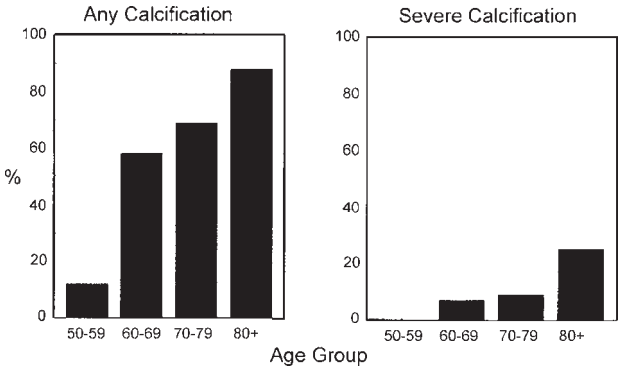


Fig. 2-14. The prevalence of aortic calcification in women aged 50 and over. (Reprinted from ref. *20* with kind permission from Elsevier Science Ireland Ltd., Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.)

Effect of Aortic Calcification on BMD. Although it did not significantly increase BMD, vascular calcification was seen in 24.3% of the 144 postmenopausal women studied by Rand et al. *(17)*. In a study of aortic calcification in 200 women, aged 50 or older by Frye et al. *(20)*, the percentage of women with aortic calcification and the effect on BMD measured in the PA lumbar spine was noted. A grading system for both linear calcifications and calcified plaques was applied to lateral spine films with a grade of 0 indicating neither type of calcification and a grade of 2 indicating the most severe degree. The percentage of women with any degree of aortic calcification and severe calcification is shown in Fig. 2-14. The percentage with any degree of aortic calcification was extremely low under age 60 but increased dramatically in women aged 60 and older. The percentage of women with severe aortic calcification however remained low throughout the 50s, 60s and 70s. Even in women aged 80 and older, the percentage did not exceed 30%. Table 2-6 summarizes the effect on BMD in women of any degree of aortic calcification and severe aortic calcification. Neither effect was statistically significant. These findings are similar to those of Frohn et al. *(21)*, Orwoll et al. *(22)*, Reid et al. *(23)*, Banks et al. *(24)*, and Drinka et al. *(25)*, in which no significant effect of aortic calcification was seen on the BMD measured in the PA spine. The studies from Orwoll et al. *(22)* and Drinka et al. *(25)* were performed in men. A recent ex vivo study from Cherney et al. *(26)* quantified the effect of removal of the aorta on PA lumbar spine bone density. After choosing eight cadavers at random, PA lumbar spine DXA bone density studies were performed before and after the removal of the aorta. The age at death ranged from 67 to 87 years, with an average age of 79 years. Removal of the aorta resulted in an average decrease in PA lumbar spine BMD of 4.64%. The authors do not describe the severity of any observed aortic calcification. Nevertheless, their results are in keeping with those from Frye et al. *(20)* in which a small effect on lumbar spine bone density was observed with severe aortic calcification.

Aortic calcification is not easily seen on most DXA PA lumbar spine studies. In Fig. 2-15A, however, the faint outline of the calcified aorta is visible. The aorta is easily seen on the lateral DXA image in Fig. 2-15B. Figure 2-16 shows both studies. In this case, the effects of the calcified aorta on the BMD measurement can be eliminated on the DXA lateral spine study.

Table 2-6
The Effect of Aortic Calcification on BMD in the Spine

	BMD			
Site	*Observed*	*Expected*	*Difference*	*% of Expected*
BMD spine				
Any Grade 1 or 2	0.93	0.92	0.01	101.4
Any Grade 2	0.94	0.89	0.05	106.7

Adapted from ref. *20* with kind permission from Elsevier Science Ireland Ltd., Bay 15K, Shannon Industrial Estate, Co. Clare, Ireland.

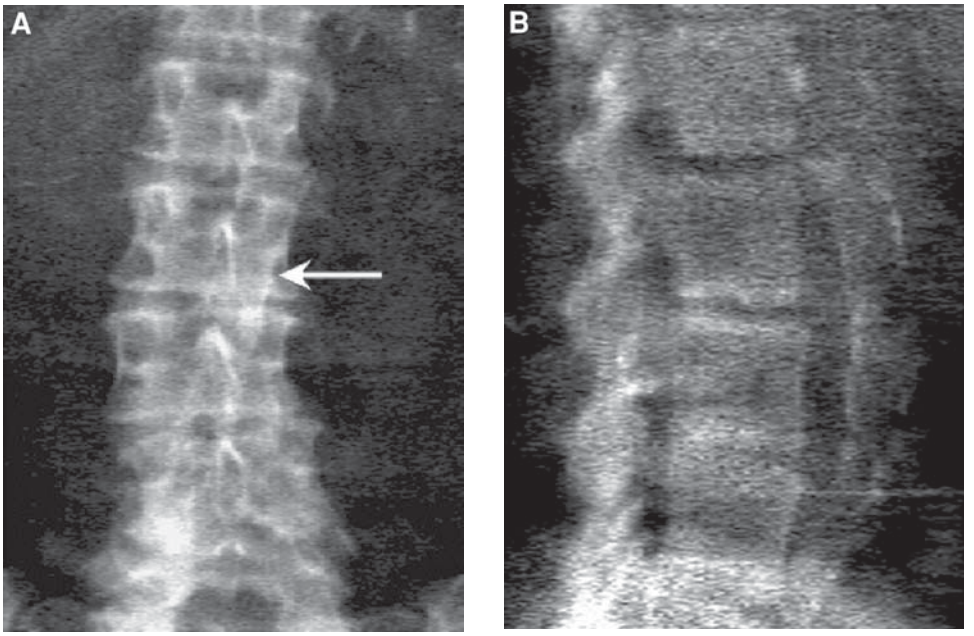


Fig. 2-15. PA and lateral DXA lumbar spine images acquired on the Hologic QDR-4500. The arrow seen in **(A)** indicates the faint outline of the calcified aorta that is easily seen on the lateral study in **(B)**. Case courtesy of Hologic Inc., Bedford, MA.

Effect of Facet Sclerosis on BMD. Unlike aortic calcification, facet sclerosis can have a profound effect on the measured BMD in the AP or PA projection. In the study by Drinka et al. *(25)* noted earlier, 113 elderly men were evaluated with standard AP and lateral lumbar spine films and DPA of the lumbar spine. A grading system for facet sclerosis was developed with a grade of 0 indicating no sclerosis and a grade of 3 indicating marked sclerosis. As shown in Table 2-7, grade 1 sclerosis had no significant effect on the BMD. Grades 2 and 3, however, markedly increased the BMD at the vertebral levels at which the facet sclerosis was found. Figure 2-17 is a PA spine BMD study in which facet sclerosis is suggested at L3 by the appearance of the image. The BMD values at L3 and L4 are also markedly higher than expected based on the values at L1 and L2. The plain film of this patient shown in Fig. 2-18 confirms facet sclerosis at the lower lumbar levels.

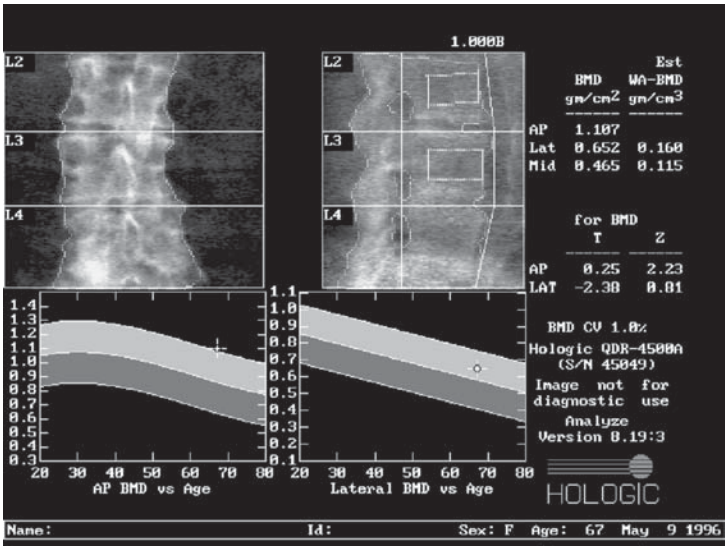


Fig. 2-16. A DXA PA and lateral lumbar spine study acquired on the Hologic QDR-4500. These are the analyzed studies for the images shown in Fig. 2-15. Case courtesy of Hologic Inc., Bedford, MA.

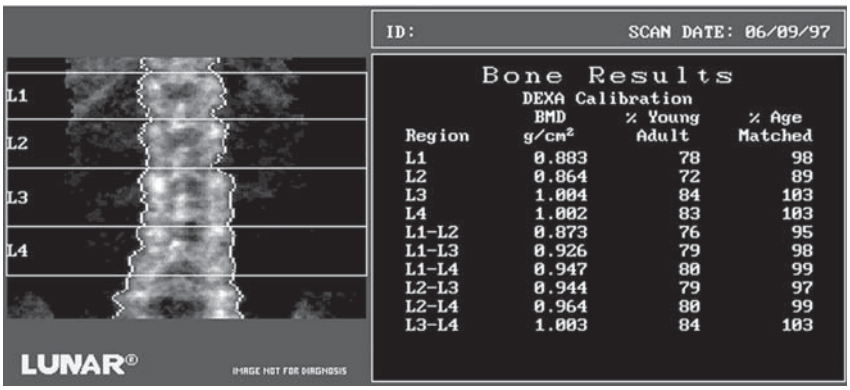


Fig. 2-17. A DXA PA lumbar spine study acquired on the GE Lunar DPX. There is a marked increase in the BMD between L2 and L3, which is maintained at L4. The image faintly suggests sclerosis in the region of the facet joints at L3 and L4. This is more dramatically seen in the plain film of this patient shown in Fig. 2-18.

The Vertebral Rotation and PA Lumbar Spine Bone Density

Rotation of the vertebral bodies is often a component of idiopathic scoliosis, although it is not frequently seen in adult-onset degenerative scoliosis. To study the effect of vertebral body rotation on bone density measured in the lumbar spine with DXA, Girardi and colleagues *(27)* utilized a cadaveric spine with intact soft tissue. The spine, which spanned the ninth thoracic vertebra to the sacrum, was mounted at both ends in the neutral midline position. Calibration markings on the mounts allowed for the spine to be rotated in 10° increments to a maximum of 60° in either direction. The bone density of L1 through L4 was measured with DXA in duplicate in the neutral position and at each 10° increment in both directions.

Table 2-7
The Increase in BMD from Facet Sclerosis

	Grade 2	*Grade 3*
L1	0.275	0.465
L2	0.312	0.472
L3	0.184	0.343
L4	0.034	0.247
Average	0.201	0.382

Values are in g/cm^2.

Adapted with permission of the publisher from ref. *25*.

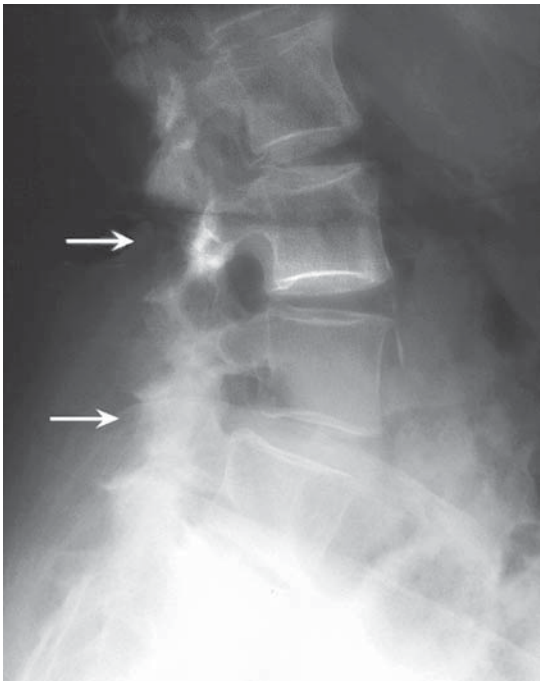


Fig. 2-18. A lateral lumbar spine X ray of the patient whose bone density study is shown in Fig. 2-17. The arrows indicate sclerotic regions in the posterior elements.

The vertebral segment area increased with increasing rotation up to 50° in either direction from midline and then decreased between 50° and 60°. The BMC remained relatively constant throughout rotation except at the extreme of 60° on either side of the midline, at which point it decreased. Because BMD is determined by dividing the BMC by area, the increasing area with rotation resulted in BMD decreasing with rotation to either side of the midline. From neutral to 60°, the decrease in BMD was almost 20%. In clinical practice then, rotation of the spine for any reason, should be expected to cause an apparent decrease in bone density when measured with DXA.

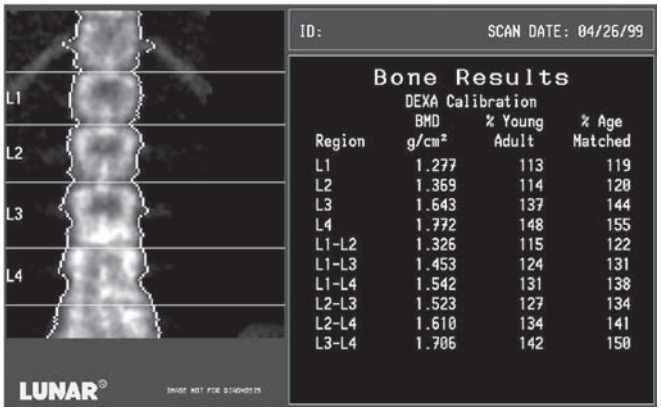


Fig. 2-19. A DXA PA lumbar spine study acquired on the Lunar DPX. The image suggests increased density at L3 and L4, but there is also a linear vertical lucency over L4. The BMD values are markedly increased at L3 and L4. This patient had previously undergone an L3–L4, L4–L5 interbody fusion and laminectomy at L4. Although the laminectomy alone would decrease the BMD at L4, the fusion mass has increased the BMD at L3 and L4 dramatically.

Other Causes of Artifacts in PA and AP Lumbar Spine Studies

Potential causes of apparent increases in the BMD in the AP or PA lumbar spine have been identified by Stutzman et al. *(28)*. These include pancreatic calcifications, renal stones, gall stones, contrast agents, and ingested calcium tablets in addition to osteophytes, aortic calcification, and fractures. Figures 2-19, 2-20, and 2-21 illustrate other structural changes in the spine that will affect the BMD measured in the PA projection.

The Spine in the Lateral Projection

The effect on BMD measured in the AP or PA projection from aortic calcification, facet sclerosis, osteophytes, and other degenerative changes in the spine can be nullified by quantifying the bone density of the spine in the lateral projection as shown in Fig. 2-15B. In addition, the highly cortical posterior elements and a portion of the cortical shell of the vertebral body can be eliminated from the measurement, resulting in a more trabecular measure of bone density in the spine. The measurement is not a 100% trabecular measure as portions of the cortical vertebral body shell will still be included in the measurement. In addition to the elimination of artifact or confounding degenerative changes, the lateral spine BMD measurement is desirable in those circumstances in which a trabecular measure of bone density is indicated and particularly in circumstances in which changes in trabecular bone are being followed over time. The higher metabolic rate of trabecular bone compared to cortical bone should result in a much larger magnitude of change in this more trabecular measure of bone density compared to the mixed cortical–trabecular measure of bone density in the PA spine.

Vertebral identification in the lateral projection can be difficult. The lumbar vertebrae are generally identified by the relative position of the overlapping pelvis and the position of the lowest set of ribs. The position of the pelvis tends to differ however, when the study is performed in the left lateral decubitus position compared to the supine position. Rupich et al. *(29)* found that the pelvis overlapped L4 in only 15% of individuals when studied in the supine position. Jergas et al. *(30)* reported a figure of 19.7% for

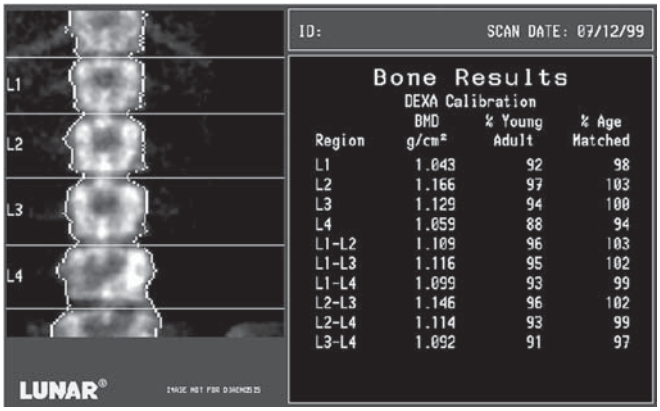


Fig. 2-20. A DXA PA spine study acquired on the Lunar DPX. The image is unusual at L4, with what appears to be an absence of part of the posterior elements. This was confirmed with plain films. This should decrease the BMD at L4.

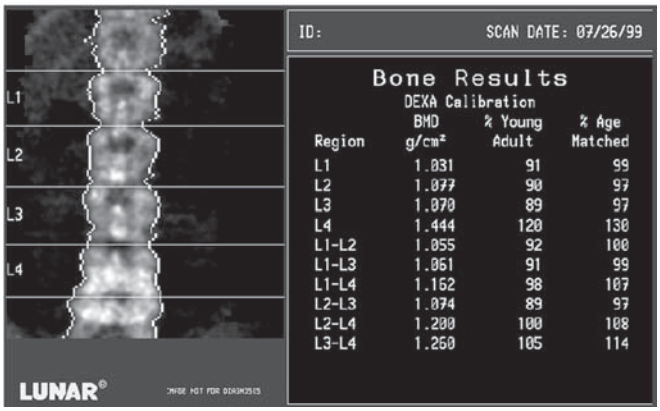


Fig. 2-21. A DXA PA spine study acquired on the Lunar DPX. The image suggests a marked sclerotic reaction at L4 and L5. There is also a marked increase in the BMD at L4, compared to L3. This sclerotic process was thought to be the result of an episode of childhood discitis. The patient was asymptomatic.

L4 overlap for individuals studied in the supine position. In DXA studies performed in the left lateral decubitus position, pelvic overlap of L4 occurred in 88% of individuals in the study by Peel et al. *(12)*. In the other 12%, the pelvis overlapped L5 in 5% and the L3–4 disc space or L3 itself in 7%. As a consequence, although the position of the pelvis tends to identify L4 in most individuals scanned in the left lateral decubitus position, it also eliminates the ability to accurately measure the BMD at L4 in those individuals. The ribs are less useful than the pelvis in identifying the lumbar vertebrae. Rib overlap of L1 can be expected in the majority of individuals whether they are studied in the supine or left lateral decubitus position *(12)*. This may not be seen, however, in the 12.5% of individuals whose lowest set of ribs in on T11.

Although the location of the pelvis and the presence of rib overlap aid in identification of the vertebrae, they also limit the available vertebrae for analysis. When a lateral spine DXA study is performed in the left lateral decubitus position, L4 cannot be analyzed in

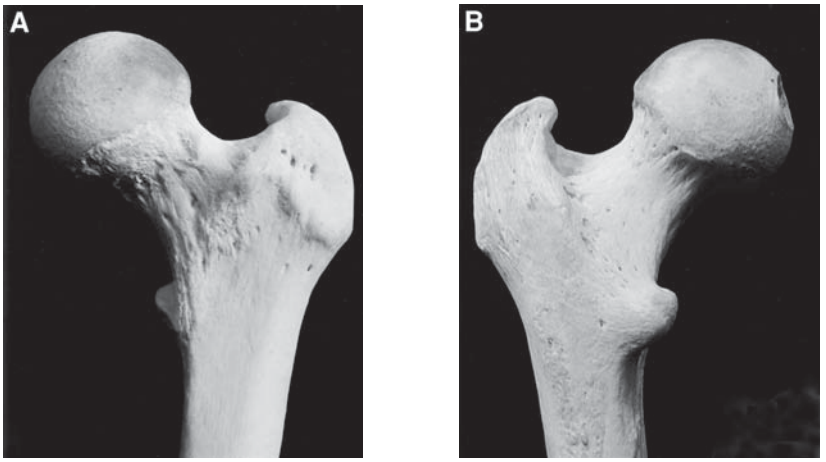


Fig. 2-22. (A) The proximal femur as viewed from the front. The lesser trochanter is behind the shaft of the femur. **(B)** The proximal femur as viewed from behind. The lesser trochanter is clearly seen to be a posterior structure. (Adapted from McMinn RMH, Hutchings RT, Pegington J, and Abrahams PH. [1993] *Colour Atlas of Human Anatomy*, 3rd edition, p. 267–268. By permission of the publisher Mosby.)

the majority of individuals because of pelvic overlap. L1 is generally not analyzed because of rib overlap, regardless of whether the study is performed supine or in the left lateral decubitus position. Rupich et al. *(29)* also found that rib overlay L2 in 90% of individuals studied in the supine position. It was estimated that rib BMC added 10.4% to the L2 BMC. As a consequence, when lateral DXA studies are performed in the left lateral decubitus position, L3 may be the only vertebra that is not affected by either pelvic or rib overlap. In the supine position, L3 and L4 are generally unaffected. This means that depending on the positioning required by the technique, the value from a single vertebra or from only a two-vertebrae average may have to be used. This is undesirable, although sometimes unavoidable, from the standpoint of statistical accuracy and precision.

If the vertebrae are misidentified in the lateral projection, the effect on BMD can be significant. In the study by Peel et al. *(12)*, misidentification of the vertebral levels would have occurred in 12% of individuals in which the pelvis did not overlap L4 in the left lateral decubitus position. If L2 was misidentified as L3, the BMD of L3 was underestimated by an average of 5.7%. When L4 was misidentified as L3, the BMD at L3 was overestimated by an average of 3.1%. Although spine X-rays are rarely justified for the sole purpose of vertebral identification on a DXA study performed in the PA or AP projection, this may occasionally be required for DXA lumbar spine studies performed in the lateral projection. Analysis may be restricted to only one or two vertebrae because of rib and pelvic overlap. This reduces the statistical accuracy and precision of the measurement. Because of this reduction in accuracy, consideration should be given to combining lateral DXA spine studies with bone density assessments of other sites for diagnostic purposes.

THE PROXIMAL FEMUR IN DENSITOMETRY

Proximal Femur Anatomy

The gross anatomy of the proximal femur is shown in Fig. 2-22A and 2-22B. In densitometry, the proximal femur has been divided into specific regions of interest.

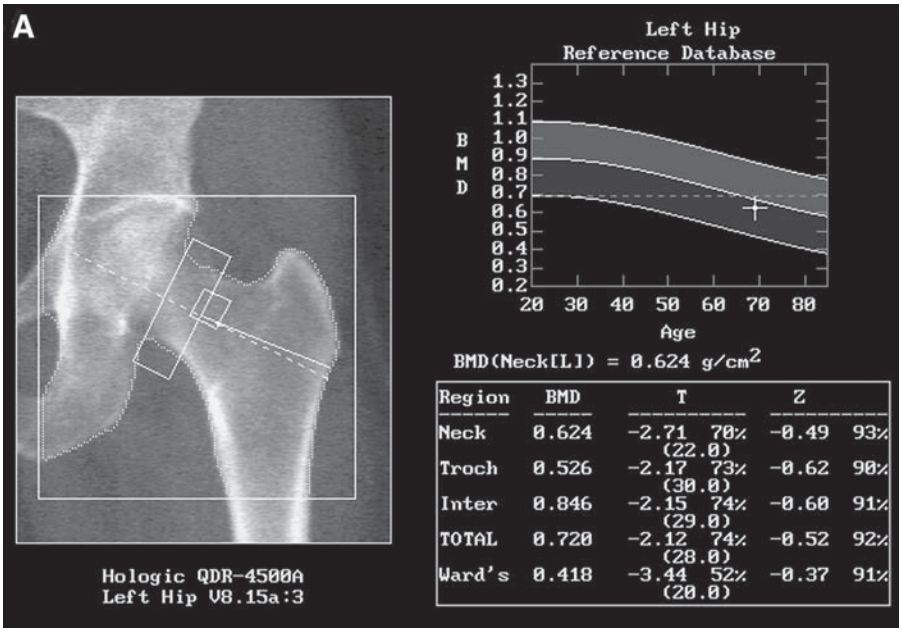


Fig. 2-23. DXA proximal femur studies. Five regions of interest are defined. **(A)** Hologic QDR 4500 DXA study. Case courtesy of Hologic Inc., Bedford, MA. **(B)** Lunar Prodigy. Four regions of interest are labeled for emphasis on this study. The total region of interest, which is not outlined, includes the neck, trochanter, and shaft.

The proximal femur studies shown in Fig.s 2-23A and B illustrate these regions, which are based on the anatomy shown in Figs. 2-22A and B. Ward's area is a region with which most physicians and technologists are not familiar. Ward's triangle, as it was originally called, is an anatomic region in the neck of the femur that is formed by the intersection of three trabecular bundles as shown in Fig. 2-24. In densitometry, Ward's

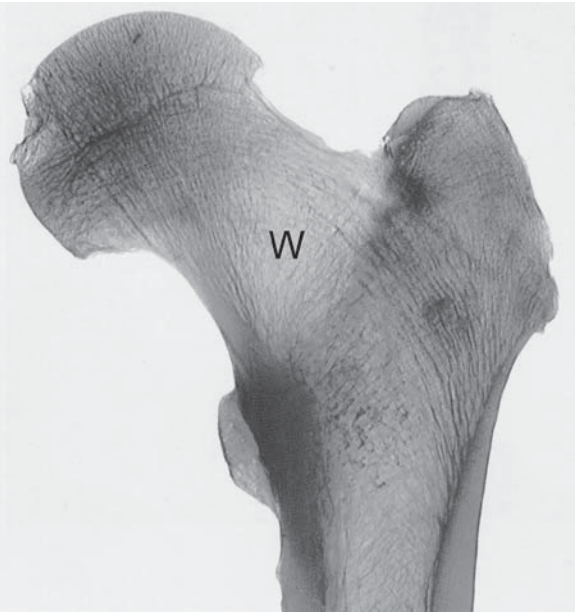


Fig. 2-24. Ward's triangle, indicated by the letter W, is formed by the intersection of bundles of trabeculae in the femoral neck. (Adapted from McMinn RMH, Hutchings RT, Pegington J, and Abrahams PH. [1993] *Colour Atlas of Human Anatomy*, 3rd edition, p. 271. By permission of the publisher Mosby.)

triangle is a calculated region of low density in the femoral neck rather than a specific anatomic region. Because the region in densitometry is identified as a square, the region is generally now called Ward's area, instead of Ward's triangle. The total femur region of interest encompasses all of the individual regions: the femoral neck, Ward's area, the trochanteric region and the shaft. Each of these regions within this one bone contains a different percentage of trabecular and cortical bone as noted in Table 2-1.

Effect of Rotation on BMD in the Proximal Femur

The lesser trochanter is an important anatomic structure from the perspective of recognizing the degree to which the femur has been rotated during positioning for a proximal femoral bone density study. Precision in proximal femur bone density testing is highly dependent on reproduction of the degree of rotation of the proximal femur from study to study. In positioning the patient for a proximal femur study, internally rotating the femur 15 to 20° will bring the femoral neck parallel to the plane of the scan table. This rotation is accomplished with the aid of positioning devices provided by the manufacturers. In this position, BMD values in the femoral neck are the lowest. If the femoral neck rotation is increased or decreased from this position, the femoral neck BMD value will increase. Table 2-8 illustrates the magnitude of the increase in BMD in a cadaver study from Goh et al. *(31)*. The apparent length of the neck of the femur will decrease as rotation is increased or decreased from the basic position. When the neck of the femur is parallel to the plane of the scan table, the X-ray beam passes through the neck at a 90° angle to the neck. With changes in rotation, the neck is no longer parallel to the scan table and the beam enters the neck at angle that is greater or lesser than 90°. The result is an apparent

Table 2-8
The Effect of Increasing Internal or External Rotation from the Neutral Position on the Femoral Neck BMD (g/cm^2) of Cadaveric Femurs

	Neutral	*External Rotation from Neutral of*			*Internal Rotation from Neutral of*		
Cadaver No.	*0°*	*15°*	*30°*	*45°*	*15°*	*30°*	*45°*
1	0.490	0.524	0.549	0.628	0.510	0.714	0.845
2	0.574	0.567	0.632	0.711	0.581	0.619	0.753
3	0.835	0.872	0.902	1.071	0.874	1.037	1.222
4	0.946	0.977	1.005	1.036	1.102	1.283	1.492

Reproduced with permission of the publisher from ref. *31*.

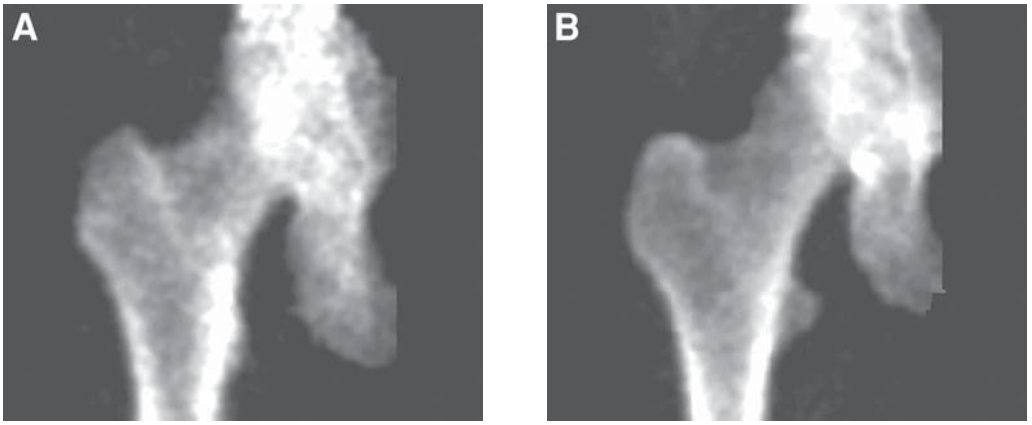


Fig. 2-25. Images of the proximal femur acquired during a DXA study. In **(A)** the lesser trochanter is clearly seen but is small and rounded, indicating proper internal rotation of the proximal femur during positioning. Compare this lesser trochanter to the lesser trochanter seen in **(B)**. This is the same patient seen in **(A)** but here the proximal femur was not rotated internally sufficiently causing the lesser trochanter to appear large and pointed.

shortening of the length of the neck and an increase in the BMC in the path of the beam. The combination results in an apparent increase in BMD. The only visual clue to consistent rotation is the reproduction of the size and shape of the lesser trochanter. Because the trochanter is a posterior structure, leg positioning in which the femur has not been rotated sufficiently internally tends to produce a very large and pointed lesser trochanter. Excessive internal rotation of the proximal femur will result in a total disappearance of the lesser trochanter. The size of the lesser trochanter in the DXA proximal femur image in Fig. 2-25A indicates correct internal rotation. This can be compared to the size of the lesser trochanter seen in the DXA proximal femur study in Fig. 2-25B. The lesser trochanter is very large and pointed, indicating insufficient internal rotation. Although this would be undesirable in a baseline study of the proximal femur, follow-up studies using the proximal femur in this patient should be done with this same degree of rotation. Any change in rotation from the baseline study would be expected to affect the magnitude of change in the BMD, decreasing the precision of the study.

Effect of Leg Dominance on BMD in the Proximal Femur

In general, there does not seem to be a significant difference in the BMD in the regions of the proximal femur between the right and left legs of normal individuals *(32–35)*. Leg dominance, unlike arm dominance, does not appear to exert a significant effect on the bone densities in the proximal femur and is not used to determine which femur should be studied. When proximal femur bone density studies first became available, the default or automatic positioning mode for the proximal femur was the right side. This was subsequently changed to the left side. The reason for the change, however, only reflected the orientation of the machine and the technologist's ease of access to the left leg.

Effect of Scoliosis, Osteoarthritis, Osteophytes, Surgery, and Fracture on BMD in the Proximal Femur

Structural changes and artifacts that interfere with DXA proximal femoral BMD measurements occur less often than at the spine. Osteoarthritic change in the hip joint may cause thickening of the medial cortex and hypertrophy of the trabeculae in the femoral neck, which may increase the BMD in the femoral neck and Ward's area *(36)*. The trochanteric region is not apparently affected by such change and has been recommended as the preferred site to evaluate in patients with osteoarthritis of the hip *(37)*. Osteophytes in the proximal femur are apparently much less common than osteophytes in the lumbar spine *(19)*. They also appear to have little effect on the bone densities measured in the proximal femur. In patients with scoliosis, however, lower bone densities have been reported on the side of the convexity *(38)*. If a "worst-case" measurement is desired, the bone density in the proximal femur should be measured in the femur on the side of the convexity. Proximal femur fracture and surgically implanted prostheses will render measurements of bone density in the proximal femur inaccurate.

If osteoarthritis or some other process restricts the ability of the patient to rotate the femur properly, the study should not be done. An attempt should be made to scan the opposite proximal femur if possible. Similarly, if pain restricts the patient's range of motion such that the femur cannot be properly positioned, the study should not be done as the results will be not be valid.

THE FOREARM IN DENSITOMETRY

Nomenclature

The nomenclature used to describe the various sites in the forearm that are assessed with densitometry is confusing. Commonly measured sites are the 33% or 1/3rd site[3], the 50%, and 10% sites, the 5-mm and 8-mm sites, and the ultradistal site. The sites designated by a percentage are named based on the location of the site in relation to the overall length of the ulna. This is true for the site regardless of whether the site is on the ulna or the radius. In other words, the 50% site on the radius is located at a site on the radius that is directly across from the site on the ulna that marks 50% of the overall ulnar length, not 50% of the overall radial length. The 5-mm and 8-mm sites are located on either bone at the point where the separation distance between the radius and ulna is 5- or 8-mm,

[3] Although a mathematical conversion of 1/3 to a percentage would result in a value of 33.3%, the site when named as a percentage is called the 33% site and is located on the radius or forearm at a location that represents 33%, not 33.3%, of the length of the ulna.

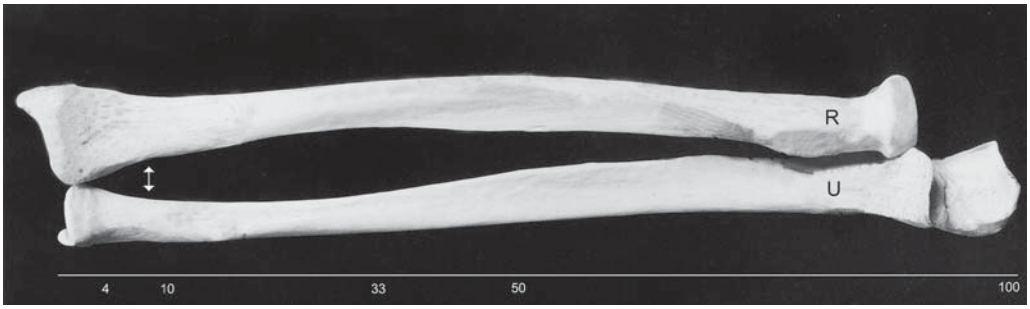


Fig. 2-26. The forearm. The scale at the bottom of the figure indicates ulnar length. The numbers reflect the percentage of ulnar length at which commonly measured sites are centered on either bone. The arrow between the two bones indicates the 8-mm separation point. R identifies the radius. U identifies the ulna. (Adapted from McMinn RMH, Hutchings RT, Pegington J, and Abrahams PH. [1993] *Colour Atlas of Human Anatomy*, 3rd edition, p. 110. By permission of the publisher Mosby.)

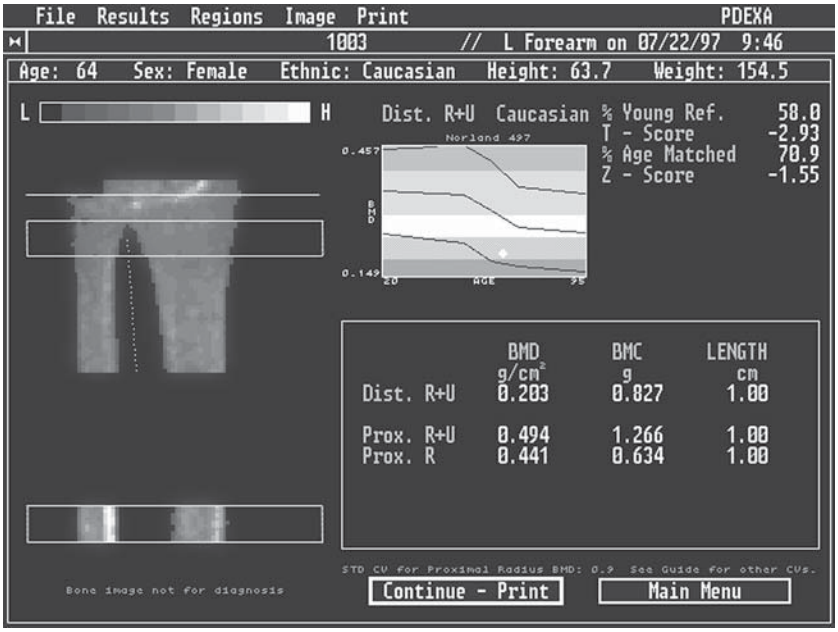


Fig. 2-27. A DXA study of the forearm acquired on the Norland pDEXA. Note the location of the regions of interest called the distal (dist.) and proximal (prox.) regions of interest. BMD values are given for the radius and ulna combined at both regions and for the radius alone at the proximal region of interest.

respectively. In Fig. 2-26, the approximate location of these sites is indicated. The 33% and 50% sites are both characterized as proximal sites, whereas the 10% site is considered a distal site. The ultradistal site is variously centered at a distance of either 4% or 5% of the ulnar length. There is nothing inherent in the definition of distal, ultradistal and proximal however, that specifies the exact location of sites bearing these names. In Figs. 2-27, 2-28, 2-29, and 2-30, the location of variously named regions of interest from several different DXA forearm devices can be compared.

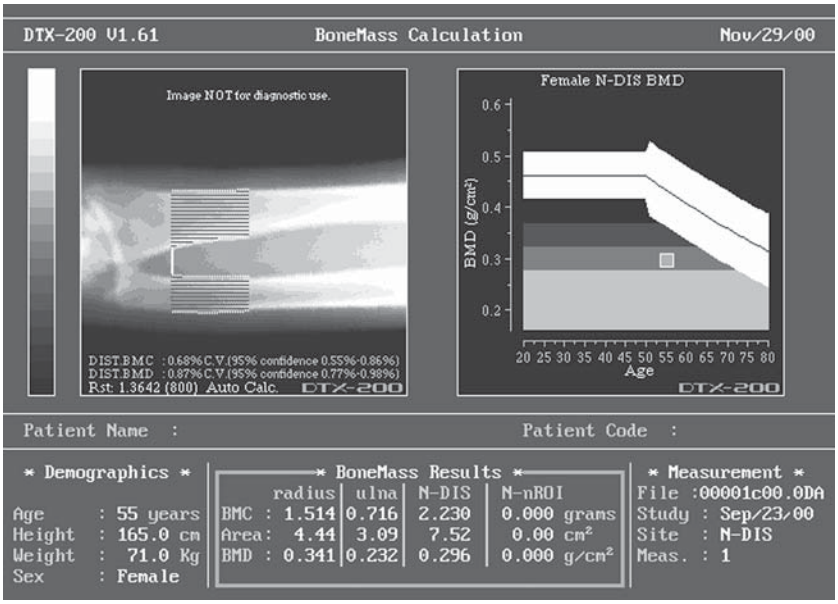


Fig. 2-28. A DXA study of the forearm acquired on the Osteometer DexaCare DTX-200. The region of interest is called the distal (DIS) region and begins at the 8-mm separation point. Values are given for each bone and for both bones combined. This distal region of interest is not the same as the distal region of interest shown in Fig. 2-27.

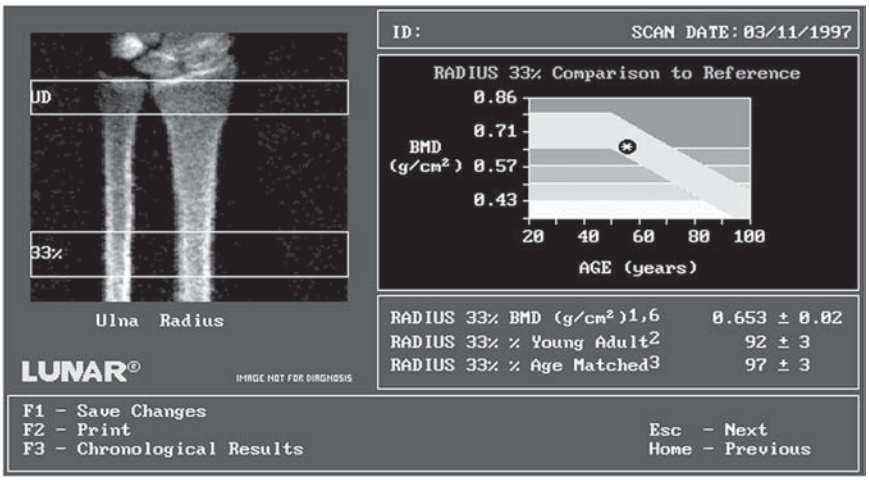


Fig. 2-29. A DXA study of the forearm acquired on the Lunar DPX. The two primary regions of interest are the ultradistal (UD) and 33% regions. These are similar but not identical in location to the distal and proximal regions seen in the study in Fig. 2-27.

The clinically important difference between these sites is the relative percentages of cortical and trabecular bone found at the site. Table 2-1 summarizes the percentages of cortical and trabecular bone at the various sites on the radius. These values are transferable to sites at the same location on the ulna.

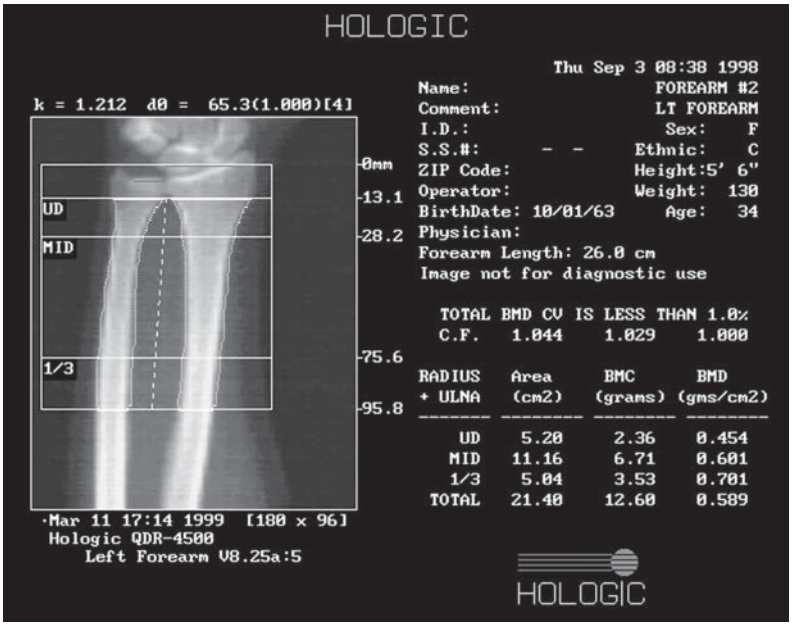


Fig. 2-30. A DXA study of the forearm acquired on the Hologic QDR-4500. Three regions of interest are shown here. An ultradistal (UD), mid, and 1/3 region of interest are indicated. The 1/3 region of interest is located similarly to the 33% region of interest shown in Fig. 2-29. Note that the mid-region here is clearly not located at a point that would correspond to 50% of ulnar length. It is between the ultradistal and 1/3 sites.

Effect of Arm Dominance on Forearm BMD

Unlike the proximal femur, arm dominance has a pronounced effect on the bone density in the forearm. In healthy individuals, the BMC at the 33% radial site differs by 6 to 9% between the dominant and nondominant arms *(39)*. A difference of 3% has been reported at the 8-mm site *(40)*. If the individual is involved in any type of repetitive unilateral arm activity, the difference between the dominant and nondominant arm densities will be magnified to an even greater extent. Two studies of tennis players, an activity in which the dominant arm is subjected to repeated loading and impact, illustrated the effect of unilateral activity. In a study by Huddleston et al. *(41)*, the BMC in the dominant forearm at the 50% radial site measured by SPA was 13% greater than in the nondominant arm. In a more recent study from Kannus et al. *(42)* using DXA, the side-to-side difference in BMD in tennis players averaged 10.8% at the distal radius and 9.9% at the midradius. The corresponding values in the non-tennis playing controls were only 3.4% and 2.5%, respectively. Because of these recognized differences, the nondominant arm has traditionally been studied when the bone content or density is quantified for the purposes of diagnosis or fracture risk assessment. Most reference databases for the machines in current use have been created using the nondominant arm. Comparisons of the dominant arm to these reference databases would not be valid. Some manufacturers supply databases for the dominant arm that can be used for comparisons if the dominant arm is to be studied. The operator's manual for the densitometry device should be consulted to determine which arm was used to create the database(s) provided by the manufacturer.

Effect of Artifacts on BMD in the Forearm

The forearm sites are relatively free from the confounding effects of most of the types of artifacts that are often seen in the lumbar spine. The presence of a prior fracture in the forearm will affect the BMC or BMD measurements in the forearm close to the prior fracture site. A study from Akesson et al. *(43)*, suggested that in women with a prior fracture of the distal radius, the BMC was increased by 20% at the distal radius of the fractured arm in comparison to the nonfractured arm, irrespective of arm dominance. It is obviously important for the technologist to ask if the patient has experienced a prior wrist or forearm fracture. Unfortunately, this same study from Akesson et al. noted that in a group of older women who were known to have previously had a distal radial fracture, many of the women did not recall the fracture or incorrectly recalled which arm was fractured. It was noted however, that the forearm most often fractured was the dominant forearm.

The effect of movement during a forearm scan was quantified by Berntsen et al. *(44)* using SXA forearm studies performed as part of the Tromsø Study.[4] More than 7900 forearm studies were evaluated for the presence of movement artifacts, which were graded I to III depending on the severity. Movement artifacts were found in 14.2% of the studies. Berntsen et al. found that movement was more likely in older individuals with the prevalence of movement artifact increasing to 20% of the scans in the oldest age group. Movement artifact appeared to slightly decrease the measured BMD. The effect on precision was studied in a subset of 111 patients. The authors found a doubling of precision[5] when movement was present, which was independent of the severity of the movement artifact. Although this study was performed utilizing only one type of forearm densitometer, the authors noted that these results should be applicable to any forearm scan for which data acquisition requires 3 to 5 minutes.

THE METACARPALS, PHALANGES, AND CALCANEUS

Other skeletal sites can be studied using the techniques available today. The metacarpals, phalanges, and calcaneus were among the very first sites studied with the older techniques of radiographic photodensitometry and radiogrammetry. These sites are increasingly utilized today with the advent of computerized radiographic absorptiometry, computerized radiogrammetry, and DXA and ultrasound units. Figure 2-31 illustrates the anatomy of the hand and the location of the metacarpals and phalanges. The middle phalanges of the index, long, and ring fingers are the phalangeal regions most often quantified. Figure 3-32 illustrates the appearance of the phalanges on a computerized radiographic absorptiometry study, whereas Fig. 3-33 illustrates the appearance of the metacarpals on a computer-assisted radiogrammetry study. The anatomy of the calcaneus[6] is illustrated in Fig. 3-34. The calcaneus contains an extremely high percentage of trabecular bone and is exquisitely sensitive to weight-bearing activities. Both the phalanges and the calcaneus have been shown to be useful sites for the prediction of hip fracture risk *(45–47)*. The relative percentages of trabecular and cortical bone for the phalanges and calcaneus are found in Table 2-1.

[4] The Tromsø Study is a population-based study, conducted in Tromsø, Norway, that focuses on lifestyle-related diseases such as osteoporosis.

[5] *See* Chapter 11 for a discussion of precision. Because precision is a measure of variability, an increase in precision is undesirable.

[6] The calcaneus is also known as the os calcis or heel.

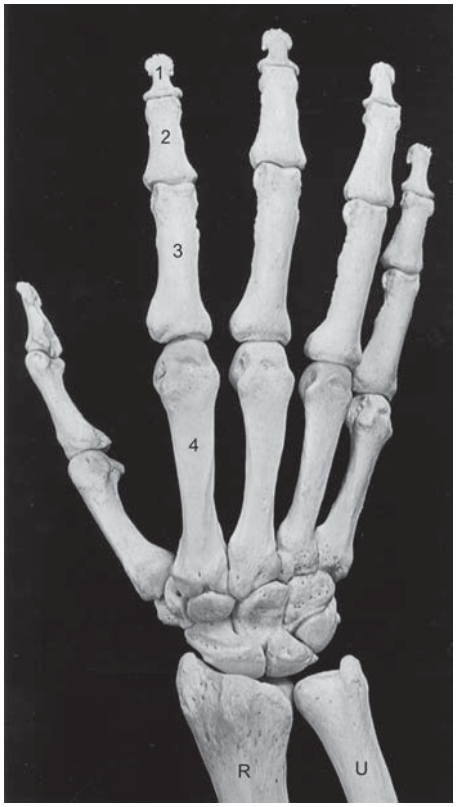


Fig. 2-31. The dorsal surface of the hand. The numbering on the index finger would apply to the long, ring, and small fingers as well. 1, 2 and 3 are the distal, mid- and proximal phalanges, 4 indicates the metacarpal. R and U indicate the radius and ulna, respectively. (Adapted from McMinn RMH, Hutchings RT, Pegington J, and Abrahams PH. [1993] *Colour Atlas of Human Anatomy*, 3rd edition, p. 112. By permission of the publisher Mosby.)

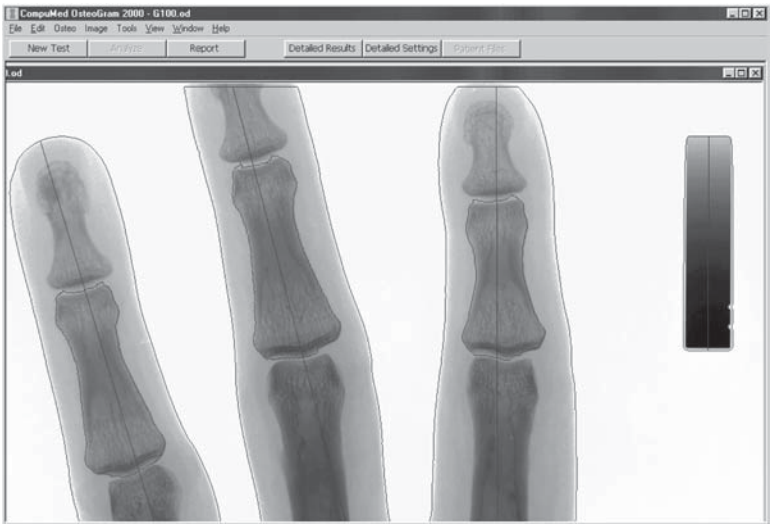


Fig. 2-32. A radiographic absorptiometry analysis of the mid-phalanges of the index, long, and ringer fingers. Case provided courtesy of CompuMed Inc., Los Angeles, CA.

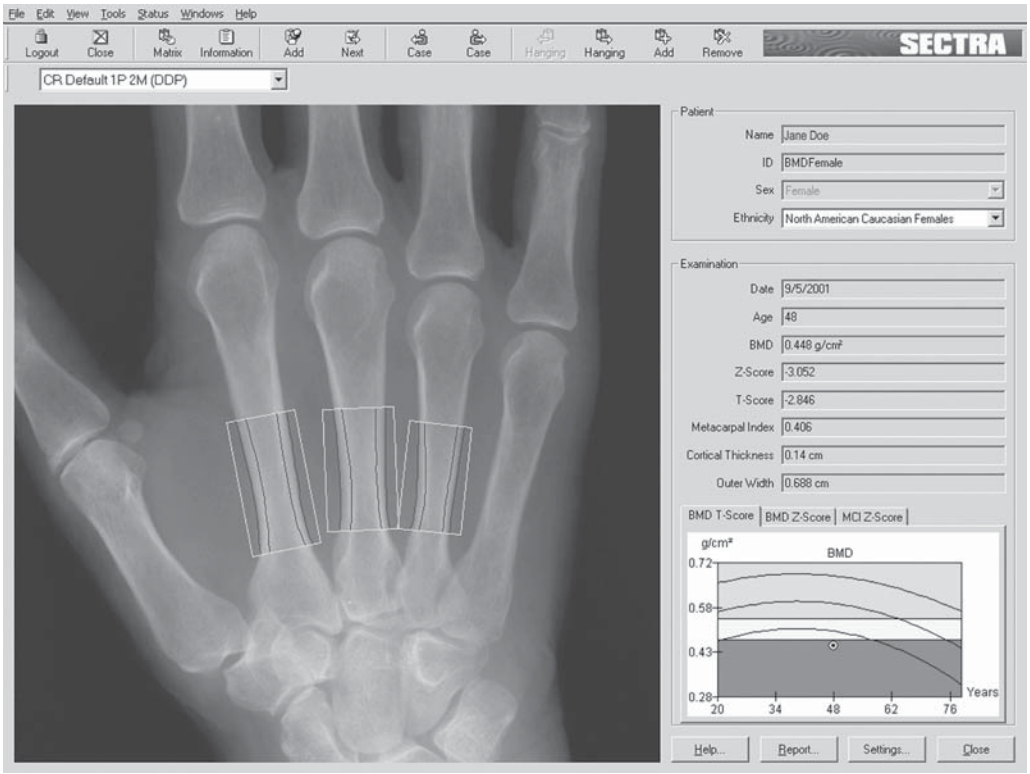


Fig. 2-33. An X-ray image from computer-assisted radiogrammetry of the metacarpals of the index, long, and ring finger. Case provided courtesy of Sectra Pronosco, Denmark.

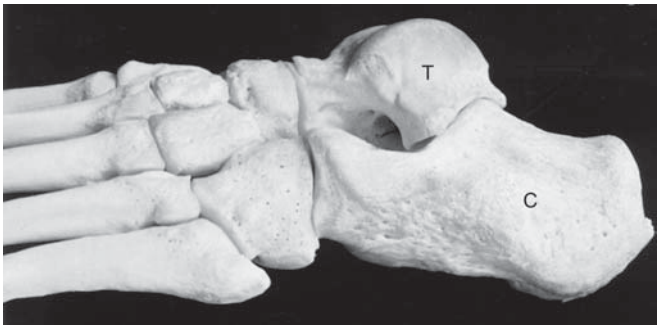


Fig. 2-34. A lateral view of the bones of the left foot. The T indicates the talus. The C indicates the calcaneus. (Adapted from McMinn RMH, Hutchings RT, Pegington J, and Abrahams PH. [1993] *Colour Atlas of Human Anatomy*, 3rd edition, p. 284. By permission of the publisher Mosby.)

BONE PHYSIOLOGY

Although the relevance of bone physiology to clinical densitometry may not be immediately apparent, the density of bone as measured in clinical practice is the outcome of the physiology and pathophysiology of bone. The densitometrist is generally not concerned with the development of bone or changes in bone that occur at the microscopic level. Nevertheless, the bone density at any given time and the changes in bone density

that the densitometrist observes and interprets are the direct outcomes of bone physiology and pathophysiology. A brief review of these processes is appropriate when considering skeletal anatomy in densitometry.

Bone is composed of both organic and inorganic materials. Approximately 70% of the weight of a bone is from its inorganic material *(48)*. An additional 5 to 8% is from water and the rest is from its organic material. Of the inorganic material, approximately 95% is a calcium phosphate crystalline hydroxyapatite and the remaining 5% are various impurities such as carbonate, chloride, or fluoride.[7] The organic material found in bone is primarily type I collagen. It also contains a variety of noncollagenous proteins and cells.

As noted previously, the bones in the skeleton belong to either the axial or appendicular skeleton. The long bones in the appendicular skeleton can be divided into four sections: epiphysis, physis or growth cartilage, metaphysis, and diaphysis. The epiphysis is found at both ends of the long bone and develops from an ossification center that is separate from the rest of the bone. The growth cartilage separates the epiphysis from the metaphysis. After longitudinal growth has ceased in the adult, the growth cartilage disappears leaving only a remnant called the epiphyseal line to mark the boundary between the epiphysis and metaphysis. The metaphysis is a cone-shaped region that tapers to blend with the middle portion of the shaft of the long bone, called the diaphysis. The cavity of a long bone is called the medullary canal and is bounded by a cortex–marrow junction.

Within each bone are different surfaces such as the periosteal surface, cortical–endosteal surface, and trabecular–endosteal surface *(49)*. These surfaces are also called envelopes because they create and bound specific spaces within the bone. The periosteum is the outermost bone surface. As an envelope, it encloses the hard and soft tissues within a bone. Both types of endosteal surfaces are the bone surfaces adjacent to marrow. The endosteal envelope encloses the majority of the soft tissues of the bone. The endosteal surfaces may thus be considered the innermost bone surfaces. Consequently, bone tissue itself is inside the periosteal envelope and outside the endosteal envelope. The response of bone cells to various stimuli can vary widely among the cells found in the periosteal and cortical–endosteal and trabecular–endosteal envelopes. The periosteal envelope increases throughout life, being predominantly a region in which net bone gain takes place. The cortical–endosteal envelope also expands throughout life, usually outpacing the increase in the periosteal envelope. As a consequence, the cortex of the bone tends to thin with advancing age. The trabecular–endosteal envelope is a bone surface with a high rate of metabolic activity in comparison to the other surfaces.

Bone Growth, Modeling, and Remodeling

The densitometrist works with bone at the macroscopic or gross level. From this perspective, bone appears to be a hard, inert substance. In fact, bone is extremely active at the microscopic level undergoing growth, modeling, or remodeling, depending on the stage of life. Longitudinal growth occurs in the skeleton of the child and adolescent from proliferation of cartilage at the growth plates, which subsequently undergo calcification. Modeling refers to a change in the shape or axis of a bone in response to mechanical or physiologic stresses. Remodeling is the process by which old bone is removed and new bone is synthesized *(50)*. This is a lifelong process by which the body renews the bone.

[7] These impurities can replace the phosphate in the hydroxyapatite and may alter its physical properties.

Both modeling and remodeling are relevant to the work of a densitometrist although a densitometrist does not need to be expert in either. A basic understanding of the physiology and pathophysiology of the remodeling process in particular, is adequate.

Bone Modeling

Bone modeling, or the change in shape or orientation of the bone in response to physiologic or mechanical force, is governed by Wolff's Law *(51)*, which states:

> *Every change in the form and function of bones, or of their function alone, is followed by certain definite changes in their internal architecture and equally definite secondary alteration in their external conformation, in accordance with mathematical laws.*

In brief, Wolff's Law states "form follows function." The brilliance of bone modeling is meeting the needs of mechanical usage in the most efficient manner with the smallest amount of bone tissue necessary. This prevents the skeleton from being so heavy that mobility is impossible or so fragile that mobility results in fracture.

The emphasis in modeling is the change in shape or alignment of the bone. There is also a net gain of bone tissue that occurs during this process. This results in new periosteal bone with little gain in endosteal bone. Modeling, unlike remodeling, is largely absent after age 20.

Bone Remodeling

Parfitt posed the question of why bone, which survives for thousands of years after death, needs to remodel itself during life *(52)*. At the microscopic level, the answer to this question would explain the events that trigger the bone remodeling process. A potential explanation lies in the basic functions of the skeleton.

The primary function of the skeleton is mechanical. According to Parfitt *(49)*, the skeleton maintains the shape of the body and provides protection for the internal organs. It also provides a framework for the bone marrow and for the transmission of muscular contractions that result in movement and ambulation. A second function of the skeleton is the regulation of extracellular fluid (ECF) composition, in particular calcium homeostasis, through exchanges of the bone mineral with the ECF. Remodeling is postulated to be necessary for the skeleton to sustain both of these functions.

The mechanical competence of the skeleton is maintained by stochastic[8] and targeted remodeling. In theory, the purpose of stochastic remodeling is to *prevent* fatigue damage by removing bone before it reaches some critical age. That age may be different depending on the bone. Targeted remodeling would *repair* bone that has already undergone fatigue damage. It appears that a bone turnover rate of 2 to 5% per year is sufficient to maintain the skeleton's mechanical competence.

In the axial skeleton, adjacent to red marrow, the rate of bone turnover is 15 to 35% per year. This rate of bone turnover greatly exceeds the 2 to 5% per year needed to sustain mechanical competence. The comparatively excessive remodeling appears to sustain the ECF regulatory functions of the skeleton. This dichotomy in remodeling rates also suggests that ECF regulatory functions are primarily limited to the trabecular bone of the axial skeleton, with the primary function of the trabecular bone of the appendicular skeleton being mechanical.

[8] Stochastic is an adjective that means random or subject to probabilities.

The Basic Multicellular Unit in Bone Remodeling

Bone remodeling is accomplished by the basic multicellular unit (BMU).[9] The BMU is a group of cells whose actions result in the resorption of bone and subsequent new bone formation to replace the resorbed bone. The end result of the activity of the bone BMU is the creation of a discrete packet of bone called the bone structural unit (BSU) *(50)*. There can be many BSUs, made at different times, within any one bone. These are held together by a collagen-free connective tissue that histomorphometrists call a cement line.

Within the BMU are two major cell types: the osteoclast and the osteoblast. The BMU also contains blood vessels, nerves, and connective tissue. The osteoclast is a large, multinucleated cell of hematopoietic origin derived from macrophages *(53)*. The osteoclast is the cell responsible for bone resorption. The lifespan of the osteoclast is not definitely known but is postulated to be only days. The cell does clearly undergo a preprogrammed death or apoptosis.

The osteoblast is the cell responsible for bone formation. It is presumed to originate from a pluripotent mesenchymal stem cell, although its origins and various stages of development are not well understood *(54)*. It is believed to pass through an osteoprogenitor stage on its way to becoming a preosteoblast and, finally, a mature osteoblast. An osteoblast that has become encased in its own mineralized matrix further matures into an osteocyte. An osteoblast lying on a quiescent bone surface will develop into a flattened cell called a lining cell.

In cortical bone a tunnel is created by osteoclastic bone resorption. This resorption or erosion period lasts approximately 30 days *(50)*. Preosteoblasts are drawn to the tunnel and mature into osteoblasts. Bone matrix is synthesized by the osteoblasts and after a period of time known as the mineralization lag time, is mineralized. The formation period lasts about 90 days, during which time the erosion tunnel is refilled with new bone that has a central or haversian canal. The new bone is laid down in layers of alternating direction, called lamellar bone. The lamellar bone surrounding the Haversian canal is the newly formed BSU.

In trabecular bone, osteoclastic bone resorption occurs on the surface of the bone, rather than by tunneling. Over a period of about 40 days, a resorption cavity is created. Preosteoblasts migrate into the resorption cavity and mature into osteoblasts. Matrix is synthesized and subsequently mineralized over a period of approximately 150 days. The resorption cavity is filled with this new, lamellar bone, becoming a trabecular BSU.

Under normal circumstances in the mature skeleton, bone resorption and bone formation are coupled. At any given remodeling site, bone formation predictably follows bone resorption such that resorbed bone is replaced with an equal amount of new bone. This predictable sequence of events in both cortical and trabecular bone remodeling is called ARF, an acronym for activation, resorption, and formation *(50)*. In disease states like osteoporosis, even though the ARF sequence remains, resorption and formation may be uncoupled, leading to an imbalance in resorption and formation and a net bone loss. The rate at which BMUs are activated, initiating bone resorption, is called the activation frequency. In some disease states, the activation frequency may increase or decrease producing changes in bone mass.

[9] The term *basic multicellular unit* is considered synonymous with bone remodeling unit (BRU).

Ninety to ninety-five percent of the newly secreted bone matrix is type I collagen. Before the collagen fibrils are formed, procollagen molecules undergo cleavage of their extension peptides. These amino- and carboxy terminal peptides[10] from the procollagen molecule are quantifiable as measures of bone formation. During bone formation, osteoblasts secrete osteocalcin,[11] which is a protein containing 49 amino acids. Bone-specific alkaline phosphatase (BAP or BSAP) is found on the surface of osteoblasts. During bone formation, BSAP is released into the circulation. Both osteocalcin and BSAP can be quantified as measures of bone formation as well.

Once the triple helix type I collagen fibrils are formed, the mechanical strength of the collagen is enhanced by cross-linking the fibrils with modified forms of the amino acid lysine. These collagen cross-links are called pyridinium cross-links. During bone resorption, free forms of pyridinoline and deoxypyridinoline are released and can be measured in the urine as markers of bone resorption. The C-terminal and N-terminal telopeptides associated with the cross-linking sites on the collagen fibrils are also cleaved from the collagen fibrils during resorption and can be measured as markers of bone resorption as well.

The markers of bone resorption and bone formation are collectively called biochemical markers of bone remodeling or bone turnover. Assays for some of these markers are available for clinical use. In disease states characterized by high rates of bone remodeling, levels of markers of both bone formation and resorption may be increased, whereas the converse is true in states of reduced bone remodeling. In clinical practice, it is not uncommon to measure two markers at any one time to assess the status of bone remodeling. One marker will be a formation marker such as BSAP and the second will be a marker of bone resorption, such as N-telopeptide. Measurable changes in the levels of these markers occur more quickly than changes in bone density, making them attractive as a means of assessing therapeutic efficacy of bone active interventions. Many of the antiresorptive bone-active agents used in clinical medicine cause a reduction in the levels of biochemical markers as a result of their efficacy in reducing bone turnover. An anabolic agent like 1-34 rhPTH appears to stimulate bone formation and as a consequence, the levels of markers of bone formation are increased in response to therapy. In clinical practice however, the precision[12] of biochemical markers is poor compared to DXA for assessing therapeutic efficacy.

High levels of bone turnover have been associated with increased risk of fracture, independent of the level of bone density *(55–57)*. Both the number and the depth of the resorption cavities in trabecular bone have been proposed as a mechanism by which vertebral fractures may occur that is partially independent of bone density *(58,59)*. As a corollary, reductions in bone turnover that occur more quickly than changes in bone density in response to antiresorptive therapies may be responsible for some of the initial rapid reduction in vertebral fracture risk seen with such therapies *(60)*. Markers of bone remodeling are appearing in clinical practice as part of the assessment of patients with metabolic bone disorders and often in conjunction with the assessment of bone density. Although the densitometrist may not be directly involved with the interpretation of biochemical markers, an understanding of the origin and implications of these markers should prove increasingly useful.

[10] The full name of these peptides is procollagen I carboxy-terminal (PICP) or nitrogen-terminal (PINP) extension peptide.

[11] Osteocalcin is also known as bone GLA protein.

[12] *See* Chapter 11 for a discussion of the important of precision.

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3 Statistics in Densitometry

CONTENTS

Many physicians in clinical practice have not had formal training in statistics. A basic knowledge of certain aspects of statistics is essential for the physician densitometrist. Quality control procedures for the various machines require some statistical analyses. The computer-generated reports of bone density data include statistical devices such as *T*- and *z*-scores and confidence intervals. To interpret serial studies, the physician must understand the concept of precision and be able to calculate the precision of repeat measurements in his or her facility. These concepts and others are discussed in this chapter.

THE MEAN, VARIANCE, AND STANDARD DEVIATION

Most statistical textbooks begin with a discussion of the mean, variance, and standard deviation. This is appropriate here as well because many of the statistical devices used in densitometry begin with a calculation of the mean and standard deviation for a set of bone density measurements.

The Mean

The mean is the average value for a set of measurements. As an example, consider Mrs. B. who underwent three spine bone density studies on the same day. Between each study, she stood up and then resumed her position on the scan table. The results of her three studies are shown in Table 3-1. The average of the three spine bone density studies is simply the sum of the three studies divided by the number of studies, in this case, 3.

Table 3-1
Individual and Mean Spine BMD Values for Patient, Mrs. B.

Patient	*Scan 1*	*Scan 2*	*Scan 3*	*Mean or $\bar{X}$*
Mrs. B.	1.011	1.030	1.022	1.021

Values are in g/cm^2.

In statistical terminology, the average is called the mean. Statistical shorthand for the formula for calculating the average or mean is shown in Equation 1.

$$\bar{X} = \frac{\Sigma X}{n} \tag{1}$$

The mean or $\bar{X}$ (pronounced X-bar) is equal to the sum, Σ, of all X measurements divided by the number of measurements, n. In this case, the mean of Mrs. B.'s three spine bone density measurements is 1.021 g/cm^2.

The Variance and Standard Deviation

Although the average or mean value for the set of three measurements on Mrs. B. is 1.021 g/cm^2, it is reasonable to ask how much the individual measurements vary from the average measurement. This question can be answered by calculating the variance and standard deviation for this set of data.

The variance, abbreviated s^2, is the average of the squares of the differences between each individual measurement and the mean. The formula is as follows:

$$s^2 = \frac{\Sigma (X - \bar{X})^2}{n - 1} \tag{2}$$

In Equation 2, each measurement, X, is substrated from the mean, $\bar{X}$, in order to find the difference between the measurement and the mean. Because some of the differences will be negative, the differences are squared to remove the negative sign. Each of the three squared differences is added and then the sum is divided by n–1, or the number of measurements minus 1, to find the average squared difference between the individual measurements and the mean. The rationale behind the use of n–1 instead of n to find the variance is discussed in Chapter 11.

Remember that the variance is the average of the squared differences between the individual values and the mean. The square root of the variance is called the standard deviation, written as s in statistical formulas and often abbreviated as SD in medical literature. It should be apparent now why the variance is abbreviated as s^2. Both the standard deviation and the variance are measures of variability in a set of data.

To calculate the variance for Mrs. B., the following calculations are made. First, the difference between each of the three measurements and the mean is calculated as shown in Equations 3 through 5:

$$1.011 - 1.021 = -0.010 \tag{3}$$

$$1.030 - 1.021 = -0.009 \tag{4}$$

$$1.022 - 1.021 = 0.001 \tag{5}$$

Then, each of the three differences is squared as shown in Equations 6 through 8:

$$(-0.010)^2 = 0.001 \tag{6}$$

$$(0.009)^2 = 0.000081 \tag{7}$$

$$(0.001)^2 = 0.000001 \tag{8}$$

The three squared differences from equations 6 though 8 are then added.

$$0.00001 + 0.000081 + 0.000001 = 0.000182 \tag{9}$$

Finally, this sum is divided by the number of measurements minus 1 as shown in equation 10. This number is the variance.

$$s^2 = \frac{0.000182}{2} = 0.000091 \tag{10}$$

The square root of the variance is the SD. Therefore,

$$s = SD = \sqrt{0.000091} = 0.010 \tag{11}$$

The mean or average BMD based on the three spine bone density measurements on Mrs. B. is 1.021 g/cm^2. The variance and SD from this set of data on Mrs. B. are 0.000091 g/cm^2 and 0.010 g/cm^2 (with rounding), respectively. Because the SD represents a measure of variability of the individual measurements about the mean, it is now reasonable to ask, what proportion or percentage the SD is of the mean? This brings us to a discussion of the coefficient of variation.

COEFFICIENT OF VARIATION

The coefficient of variation (CV) is an important concept in bone densitometry because it is frequently used to describe the accuracy and precision of the various technologies. The CV is calculated by dividing the SD by the mean, $\bar{X}$, for a set of data. The formula is as follows:

$$CV = \frac{SD}{\bar{X}} \tag{12}$$

The CV is expressed as a percentage by multiplying by 100. This is called the percent coefficient of variation (%CV).

To calculate the CV for the three measurements on Mrs. B. the SD of 0.01 g/cm^2 is divided by the mean of 1.021 g/cm^2. This value is 0.010. To express this as a percentage, 0.010 is multiplied by 100 yielding 1.0%. The %CV is therefore 1.0%. The CV and %CV are measures of variability about the mean, just as are the variance and SD. The CV and %CV, however, are measures of proportional variability.

STANDARD SCORES

Standard scores allow you to compare values created from different scales to a common scale that is based on standard deviation units *(1)*. Standard scores such as the *T*-score and *z*-score are used extensively, but not exclusively, in bone densitometry.

For example, imagine that a group of physicians, group A, was tested on their knowledge of bone densitometry. Arbitrarily, the highest score that could be made on the test was 75 and the lowest score that could be made was 25. A second group of physicians,

group B, was also tested on their knowledge of bone densitometry. On this test, however, the highest score that could be made was 100 and the lowest score that could be made was 50. Sometime later, a physician from group A confided to a physician from group B that his score on the test was 70 and that he thought this score was generally above average for the test. The physician from group B, whose score was 75, was initially relieved to learn that he had outperformed his colleague on the test. Unfortunately, the physician from group B failed to recognize that two very different scales were used to grade the tests making it impossible to directly compare the raw scores of 70 and 75. The only way to compare how well the two physicians actually did, is to convert their test scores to a third, common scale. This can be done using any one of several standard score scales. Figure 3-1 illustrates the relationships among several standard score scales, including the *T*-score, *z*-score, and Army General Classification Test (AGCT) scale. Each of these scales assigns an arbitrary value on the scale to the raw average value. For each SD change from the raw average value, the standard score increases or decreases by a predetermined amount.

Z-Scores

In the *z*-score scale, the mean or average value for a set of raw data is arbitrarily assigned a *z*-score of 0. For each SD increase above or below the mean, the *z*-score increases by a value of 1. If the value lies above the mean, the *z*-score value is preceded by a + sign. If it lies below the mean, a – sign precedes it. If neither a + or – sign precedes the *z*-score, a + sign is assumed. In essence the *z*-score tells you how many SDs above or below the mean the value in question lies. For example, if the *z*-score is –3.2, the value in question lies 3.2 SD below the mean value. If the *z*-score is +1.5, the value in question lies 1.5 SD above the mean. *Z*-scores are not unique to bone densitometry. Any type of numerical data can be converted to a *z*-score as long as the mean and standard deviation are known. Psychologists have used this type of scale extensively in psychological and IQ testing.

In order to compare the test scores of the two physicians from group A and group B, it becomes clear that it is necessary to calculate the mean and SD for the test scores for group A and also for group B. When this is done, it is found that the average score for group A was a raw score of 60 with an SD of 5. The average for group B was 80 with an SD of 5. Because the physician from group A had a raw score of 70, his score is 10 points above the average. Because the SD for this group was 5, the group A physician's raw score is 2 SDs above the mean. His *z*-score, therefore, is +2. Although the raw score of the physician from group B appears to be higher, because the average from group B was 80 and the SD was 5, the *z*-score for the physician from group B is actually –1. The physician from group A has the better score in comparison to his peers than does the physician from group B.

T-Scores

On the *T*-score scale, the mean value is arbitrarily assigned a *T*-score value of 50. For each SD change, the *T*-score increases or decreases by a value of 10 depending on whether the value is above or below the mean. For example, if the value in question is 3 SDs above the mean, the corresponding *T*-score would be 80. If the value were 1.5 SDs below the mean, the *T*-score would be 35. For the two physicians from group A and group B discussed previously, their *T*-scores would be 70 and 40, respectively.

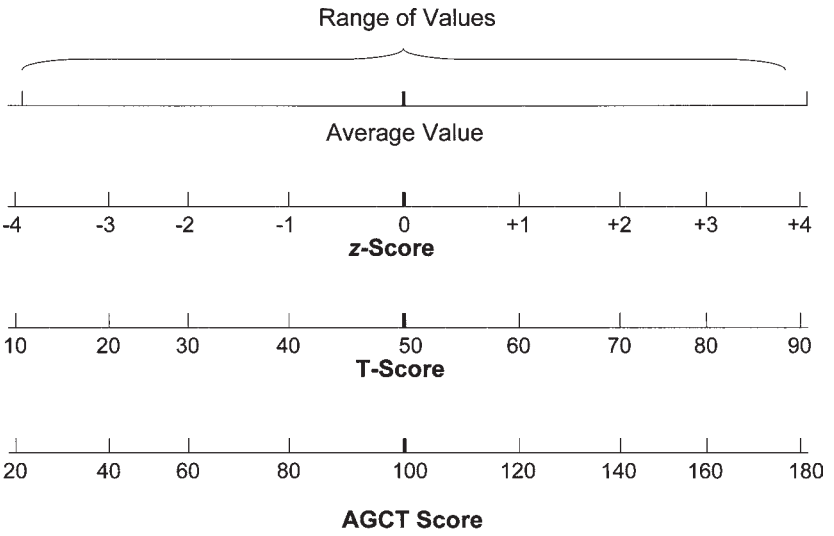

Fig. 3-1. Standard score scales. These scales are based on the standard deviation. Note that a true *T*-score has very different units than the *z*-score.

A *z*-score or *T*-score can be calculated for any set of numerical data for which one can calculate the mean and SD. There is nothing inherent in the definition of these standard scores that limits their application to only a single kind of data. In bone densitometry, however, the *T*-score has undergone some modification and both the *T*-score and *z*-score have acquired specific characteristics that are quite distinct from their use in general statistics.

Standard Scores on Bone Density Reports

T-scores and *z*-scores are found on the computer-generated bone densitometry printouts from virtually every manufacturer of bone density equipment. Figure 3-2 is the printout from a spine bone density study performed on an older Lunar DPX device. The individual BMD values for each vertebra are listed as well as the BMD values for each possible combination of contiguous vertebrae. The two columns adjacent to the BMD values reflect *z*-scores. One column is entitled "young-adult *z*" and the other, "age-matched *z*." Based on an understanding of the *z*-score, it is clear that these *z*-scores indicate how many standard deviations above or below the mean value, the patient's BMD value lies. But what mean value and SD were used to calculate these *z*-scores? The young-adult *z*-score was calculated using the average peak bone density and SD for the young adult. The column entitled age-matched *z* reflects the use of the average bone density that would have been predicted on the basis of the patient's age. In this case, the L2–4 BMD average of 1.288 g/cm^2 has a young-adult *z*-score of 0.73 and an age-matched *z*-score of 0.92. This means that the L2–4 BMD is 0.73 standard deviations *above* the average peak bone density of the young adult and 0.92 standard deviations *above* the BMD that would have been predicted on the basis of the patient's age.

Figure 3-3 is a bone density printout from a spine study performed on a Hologic QDR-4500. The BMD values for each individual vertebra and the average BMD value for L1–4 are evident. Adjacent to these values, two of the four columns are now entitled

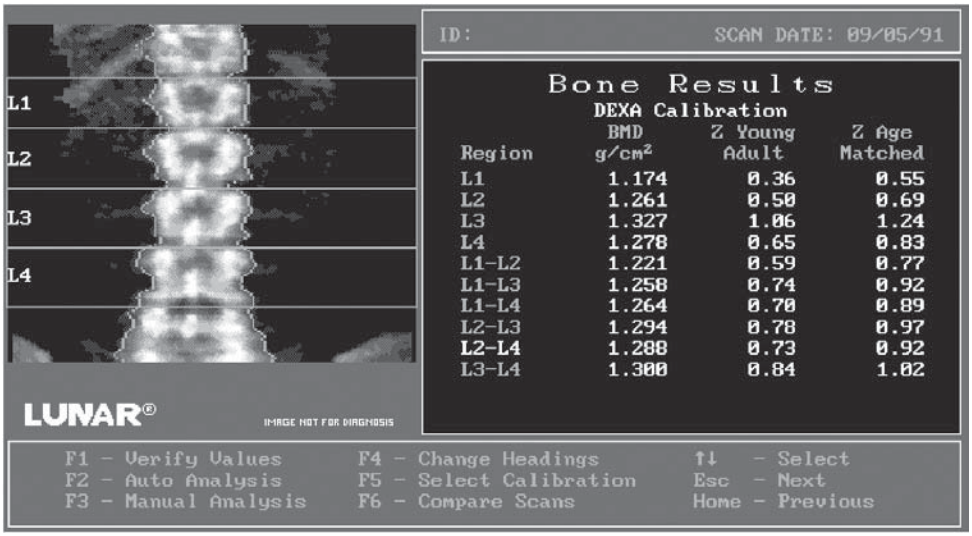

Fig. 3-2. A Lunar DPX PA spine study in which the standard scores are presented as young-adult *z*-scores and age-matched *z*-scores, reflecting the older, albeit, correct terminology for the standard score comparisons. The standard scores and BMD are listed for each vertebra and every possible combination of contiguous vertebrae.

simply "*T*-score" and "*z*-score." There is nothing in the title of these columns to definitely indicate which average value is being used to calculate these standard scores. The "30.0" in parentheses next to the "*T*" however, indicates that the comparison is to the average bone density of a 30-year-old. Figure 3-4 is a Norland DXA PA spine study. A *T*-score of –0.5 and *z*-score of 0.72 are noted for the L2–L4 average BMD. When the formats used in these Hologic and Norland DXA studies are employed, the average value used to calculate the *T*-score is *always* the average peak BMD of the young adult. The average value used to calculate the *z*-score is *always* the average age-matched BMD. It is obvious, however, that the values in the *T*-score column do not look like true *T*-scores. *T*-scores, after all, should be scores like 30 or 75. The use of either a + or – sign to indicate the position relative to the mean value is not required with the traditional *T*-score. These values in the *T*-score column actually look more like *z*-scores. And in fact, that is exactly what they are. These are *z*-scores that, *in bone densitometry only*, are renamed *T*-scores. This allows one to understand without so stating that the reference average in use here is the young-adult peak BMD and that the reference average in use for the calculation of the *z*-score is the age-matched BMD. Therefore, the *T*-score of -3.33 for the L1–L4 average BMD seen on the Hologic QDR 4500 study means that the L1–L4 average BMD is 3.33 standard deviations below the average peak BMD of the young adult. This convention of renaming the young-adult *z*-score the *T*-score has been increasingly adopted by all manufacturers of bone density equipment and has also found its way into the bone density literature. In Fig. 3-5, a Lunar Prodigy PA spine study reflects the use of the *T*- and *z*-score terminology, although the abbreviations YA and AM for young adult and age-matched still remain. It is important to remember that the young-adult *z*-score is identical to the *T*-score in this context. The age-matched *z*-score is identical to what is now simply called the *z*-score.

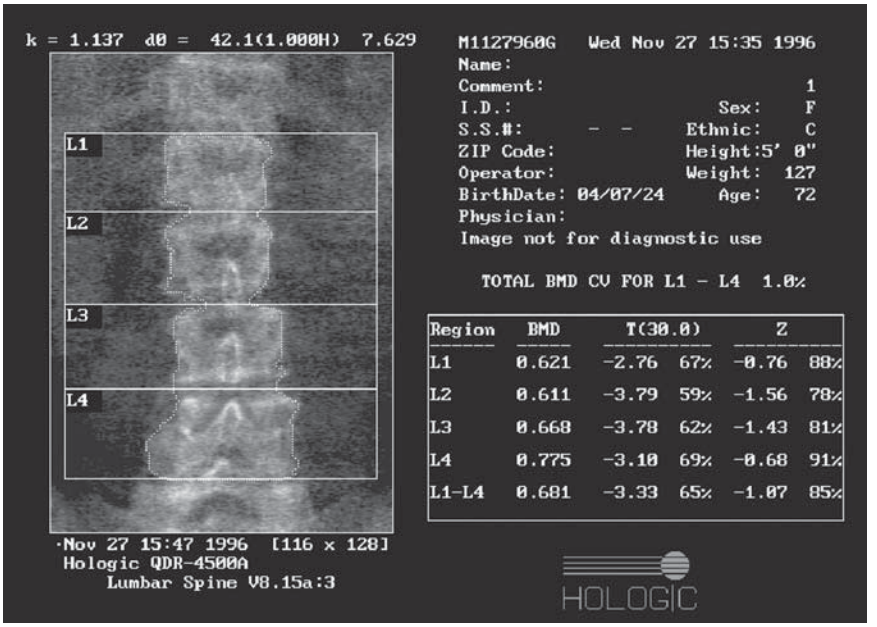

Fig. 3-3. A Hologic QDR 4500 PA spine study in which the standard scores are presented using the terminology of *T*-score and *z*-score, rather than young-adult *z*-score and age-matched *z*-score. This terminology has become the accepted format for standard score comparisons. These values, in addition to the BMD, are given for each vertebra and for the contiguous vertebrae of L1–L4. Study provided courtesy of Dr. Paul Miller, Colorado Center for Bone Research, Lakewood, CO.

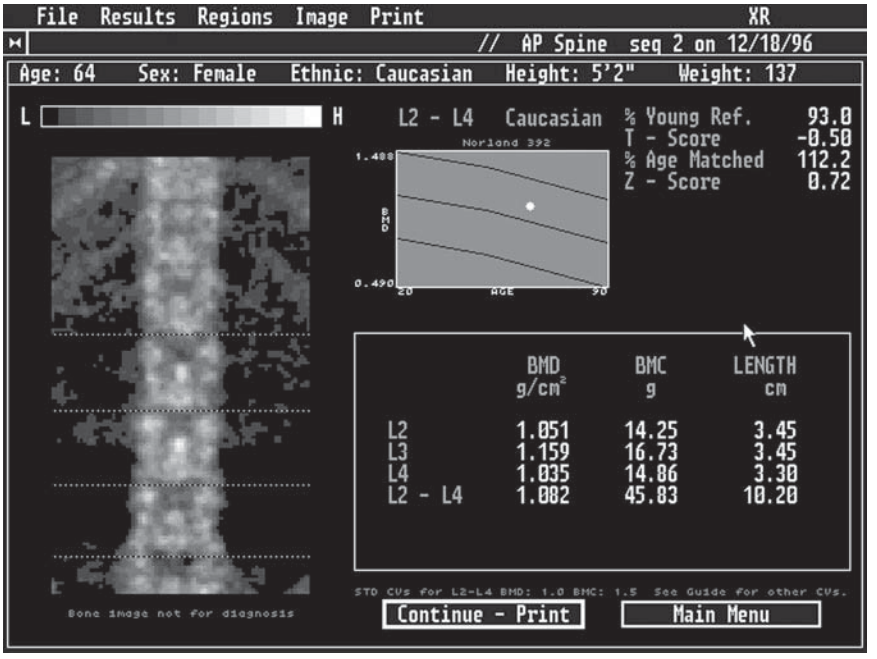

Fig. 3-4. A Norland XR-36 DXA PA spine study. The *T*-score and *z*-score are given for the L2–L4 BMD. Study courtesy of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

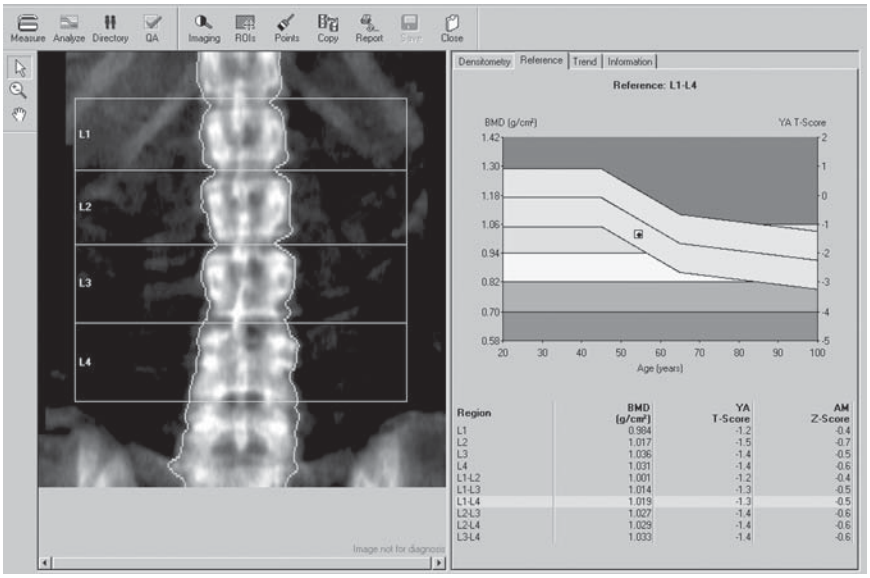

Fig. 3-5. A Lunar Prodigy DXA PA spine study. The older terminology of young-adult *z*-score and age-matched *z*-score has been replaced with young-adult (YA) *T*-score and age-matched (AM) *z*-score.

MEASURES OF RISK

One of the many applications of densitometry is the assessment of risk for fragility fracture. There are several different measures of risk that are commonly used in bone densitometry: prevalence, incidence rate, incidence or absolute risk, relative risk, attributable risk, and odds ratios.

Prevalence and Incidence

Both prevalence and incidence rate can be considered as measures of a disease experience within a population. They differ principally in that prevalence is derived from observations of a population made at a single point in time, whereas the incidence rate is derived from observations that are made only after observing a population over a period of time.

Prevalence

There are two ways of expressing prevalence: point prevalence and period prevalence. In this context, it is not terribly important to distinguish between the two, but the information is presented here for the sake of completeness.

Point prevalence is the number of persons with a disease at the time of the observation divided by the total number of individuals in the population at risk for the disease. This is often expressed as a percentage. If the point prevalence is very small, it may be expressed as the number of cases per 1000 individuals in the population at risk in order to utilize whole numbers instead of fractions.

The period prevalence is the ratio of the number of individuals with a particular disease at a specific point in time *within a specified time interval* divided by the number of individuals in the population at risk for the disease *at the midpoint of that time* interval.

Both these measures of prevalence are considered rates. The point prevalence is the more commonly used measure of the two. If the term *prevalence* is used without a modifier, it is reasonable to assume that point prevalence is being discussed. For example, Melton et al. *(2)* reported that the prevalence of a bone density more than 2 SD below the young-adult mean in the spine in Caucasian women aged 50 and over was 31.8%. This figure is based on a one-time measurement of BMD at the spine in a group of women from Rochester, Minnesota with extrapolation of the figures to the entire population of Caucasian women over age 50 in the United States in 1990. This is a point prevalence rate.

Incidence

Like prevalence, there are two types of measures of incidence. One is a rate. The other is a risk. Incidence risk however, is also called absolute risk. To clarify matters, incidence risk will be discussed under the heading of absolute risk in the next section.

The incidence rate, or simply incidence, is the number of new cases of any disease that have occurred within a specified period of time divided by the average number of individuals at risk for the disease multiplied by the length of the time interval. This value may be multiplied by 1000 and expressed as the incidence per 1000 person-years at risk. Other multipliers may be used as well. For example, Cooper et al. *(3)* reported that the vertebral fracture incidence rate in women in Rochester, Minnesota was 145 per 100,000 person-years. The number of individuals at risk for the disease in the population is not the same as the number of individuals in the population at the beginning of the time interval because, once having developed the disease, the individual is no longer considered at risk. This is important in distinguishing the incidence rate from absolute risk.

Absolute, Relative, and Attributable Risk

Absolute Risk

As noted previously, incidence risk is also known as absolute risk. The term *absolute risk* will be used here. This is the number of individuals developing a disease within a specified period of time divided by the number of individuals at risk for the disease *at the beginning* of the time interval. In the context of this discussion, a certain level of bone density determines risk. The disease is fracture. For example, assume that 1000 women with the same level of bone density in the femoral neck are followed over a period of time. During the observation period, 160 of these women develop a hip fracture. The absolute risk for hip fracture in women with this level of bone density in the femoral neck is 0.16 (160 women with fractures ÷ 1000 women at risk at the beginning of the observation period). Expressed as a percentage, the absolute risk becomes 16%. These values used in the calculation of absolute risk were not taken from the literature. The numbers are for the purpose of illustration only.

Relative Risk

Relative risk is the ratio of two absolute risks. In Fig. 3-6, the relationship between absolute risk and relative risk is illustrated. The values for absolute risk in Fig. 3-6 were not taken from the literature. They are used only for purposes of this exercise. For example, what is the relative risk for fracture for individuals who have a BMD that is equal to the mean or a SD score of 0 compared to the group with a BMD that is 1 SD below the mean or an SD score of –1?

This simply asks the question of what is the second group's risk (the group with the SD score of –1) compared to the first group's (the group with the SD score of 0). Another

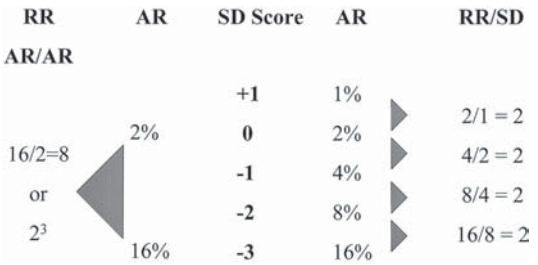

Fig. 3-6. The relationship between absolute risk, relative risk, and the standard deviation score. Relative risk is the ratio of two absolute risks.

way of putting this would be to say what is the second group's risk *relative* to the first group's risk?

As shown in Fig. 3-6, the group with the SD score of –1 has an absolute risk for fracture of 4%. The group with the SD score of 0 has an absolute risk for fracture of 2%. The relative risk is therefore 4% ÷ 2% or 2. An appropriate interpretation of this finding would be that there is a doubling of risk or a twofold increase in risk conferred by the decline in BMD of 1 SD.

In the medical literature, data from the majority of the prospective fracture trials evaluating the ability of bone mass measurements to predict fracture risk are presented as the increase in relative risk per SD decline in bone density. For example, based on the prospective fracture trial from Melton et al. *(4)*, the increase in relative risk for spine fracture when measured at the spine was 1.9 for each SD decline in bone density. In other words, when the absolute risk for fracture for any group was divided by the absolute risk for the group whose BMD was 1 SD higher, the ratio or relative risk was 1.9.

Using this data from Melton et al. *(4)*, how could the relative risk for spine fracture for an individual whose bone density is 3 SD below the mean at the spine be calculated? The relative risk for such an individual would be equal to 1.9^3 or 6.86. It would *not* be 1.9×3. Figure 3-6 illustrates this exponential relationship.

One of the limitations of relative risk is that the relative risk value alone does not convey information about the absolute risk for any particular group. After all, it would not matter if the absolute risks for two groups used to calculate the relative risk were 2% ÷1%, 4% ÷ 2% or 50% ÷ 25%. The relative risk would be 2 in each case. Nevertheless, relative risk is the strongest indicator of the strength of the relationship between a risk factor, such as low bone mass, and the disease outcome, such as fracture.

Attributable Risk

Attributable risk does not appear frequently in bone density or osteoporosis literature but it is a useful concept to understand. Attributable risk is the difference between two absolute risks. It is the strongest indicator of the benefits of preventing the risk factor in reducing the occurrence of disease. For example, if the absolute risk for fracture was 10% in a group with a low BMD at the spine and 2% in a group with a higher BMD at the spine, the attributable risk would be 10% –2% or 8%. In other words, 8% of the risk of fracture in the group with the lower BMD can be *attributed* to the difference in BMD between the two groups. If we could eliminate the difference in BMD between the two groups by increasing the BMD in the group with the lower BMD, we could theoretically eliminate 8% of the fracture risk.

Odds Ratios

Odds ratios are similar to relative risk. The calculation of relative risk however, requires knowledge of the absolute risk for the groups being compared. This requires data from a prospective study. When groups are evaluated retrospectively another measure of risk must be employed. In this circumstance, odds ratios are calculated. This is done by calculating the odds of disease for each of the two groups and then dividing to obtain the odds ratio.

For example, 1000 individuals are selected based on the individuals having a low spine bone density. The observation is made that 100 of these individuals have a spine fracture. In another group of 1000 individuals who are picked on the basis of having good spine bone densities, only 5 are observed to have a fracture. What are the odds of having a fracture for an individual in either group and what is the odds ratio of the low BMD group compared to the high BMD group?

The odds for fracture in either group are found by dividing the number of individuals with fracture in the group by the number in that group which has not experienced a fracture. Therefore, for the low BMD group the odds are:

$$\frac{100}{1000 - 100} = \frac{100}{900} = 0.111 \tag{13}$$

The odds for the high BMD group are:

$$\frac{5}{1000 - 5} = \frac{5}{995} = 0.005 \tag{14}$$

The odds ratio for the low BMD group compared to the high BMD group then is:

$$\frac{0.111}{0.005} = 22.2 \tag{15}$$

The interpretation of this odds ratio is that fracture is 22.2 times more likely in the low BMD group compared to the high BMD group. These values were not taken from the medical literature and are used for the purposes of illustration only.

For uncommon diseases, the relative risk and odds ratio will be very similar. For common diseases however, the odds ratio will be greater than the relative risk.

CONFIDENCE INTERVALS

Remember Mrs. B. who had the three spine bone density tests for which the mean, SD, and the CV were previously calculated? What if three more measurements were performed on Mrs. B. the next day? After each measurement, Mrs. B. was asked to get up from the scan table and then resume her position just as she did for the first set of three measurements the day before. The values for the second set of measurements on Mrs. B. are shown in Table 3-2.

Although these values in Table 3-2 are very similar to the values seen in Table 3-1, they are not identical. The fact that the three scans do not produce identical results is not surprising. The ability of the machine to reproduce the results is not perfect. There is a small amount of error that is inherent in the testing regardless of how well the technician performs the test. This is true for any type of quantitative measurement used in clinical medicine today. The average value for the set of three measurements on the first and second day is different because the three measurements used to calculate each average are slightly different. The same thing would be true if three measurements were performed on Mrs. B. on a third or fourth day. The average BMD value for each set of three

Table 3-2
Individual and Mean Spine BMD Values
for Patient, Mrs. B. on Day 2

Patient	*Scan 1*	*Scan 2*	*Scan 3*	*Mean or $\bar{X}$*
Mrs. B.	1.024	1.015	1.018	1.019

Values are in g/cm^2.

measurements may be different because the individual measurements used to calculate the average may be slightly different. It is useful, therefore, to know what the range of average values would be if repeated sets of three measurements each were performed on Mrs. B. an infinite number of times. This range is called the confidence interval and is calculated by finding the standard error of the sample mean. The standard error is different from, but related to, the standard deviation. The formula for the standard error (SE), is as follows:

$$SE = \frac{SD}{\sqrt{n}} \tag{16}$$

where *SD* is the standard deviation and *n* is the number of measurements. The SD for the first set of three measurements on Mrs. B. was previously calculated as being 0.01 g/cm^2. The SE, therefore, for that first set of three measurements is:

$$SE = \frac{0.01}{\sqrt{3}} = 0.006 \tag{17}$$

The value of 0.006 g/cm^2 is the SE of the sample mean. The sample refers to the set of three measurements. The mean (or average) for this sample has already been calculated and found to be 1.021 g/cm^2. The SE and sample mean are used to calculate the 95% confidence interval (CI) for the sample. The 95% CI is bounded by the mean plus or minus two times the SE.[1] The formula is written as follows:

$$95\%\ CI = \bar{X} \pm 2 \times SE \tag{18}$$

The 95% confidence interval based on the first set of three measurements on Mrs. B. is:

$$95\%\ CI = 1.021 \pm 2 \times 0.006 \tag{19}$$

$$95\%\ CI = 1.009 \text{ to } 1.033 \tag{20}$$

The interpretation of the 95% CI is that 95% of the means that would be obtained from an infinite number of series of three scans each will fall within the range of 1.009 g/cm^2 to 1.033 g/cm^2.

There are two characteristics of the SE that become apparent on reviewing the formula for its calculation. First, the SE will always be smaller than the SD. Second, the greater the number of measurements, or *n*, which make up the sample, the smaller the SE will be.

[1] The actual value by which the SE is multiplied depends on the sample size. For samples with an *n* of greater than 20, the value is very close to 2. For smaller samples, the value will be slightly larger. The formula shown here is a practical characterization of the calculation of the 95% CI.

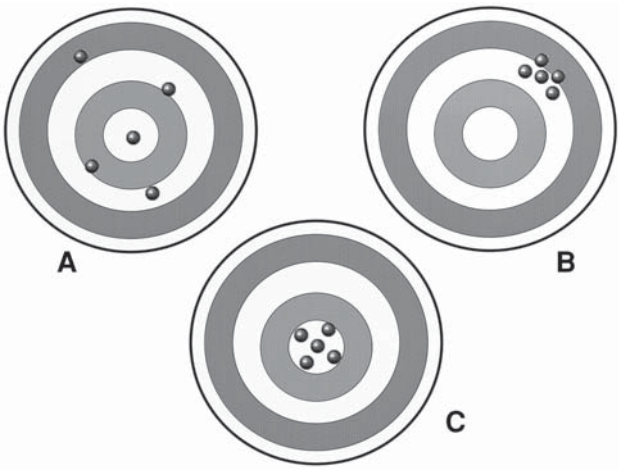

Fig. 3-7. Accuracy and precision. Target A illustrates accuracy without precision. Target B illustrates precision without accuracy. In target C, a high degree of both accuracy and precision is illustrated.

The smaller the SE, the more narrow the CI. The more narrow the CI, the greater the likelihood that the average value from the limited sample of scans is representative of the average that would be obtained if Mrs. B. was tested an infinite number of times.

Another example of a CI comes from Cummings et al. *(5)* who estimated a woman's lifetime risk of having a hip fracture. Using population-based data, it was calculated that the lifetime risk of hip fracture for a 50-year-old white woman was 15.6%. The 95% CI for this risk was 14.8% to 16.4%. This very narrow CI gives increasing credibility to the risk estimate of 15.6%.

CIs and statistical significance are closely related but CIs tend to provide more useful clinical information. Many medical journals now require that confidence intervals be presented in addition to assessments of statistical significance for reported data. In densitometry an understanding of CIs is imperative in interpreting the significance of changes in the BMD over time. This is discussed in the following section on precision and in greater detail in Chapter 11.

ACCURACY AND PRECISION

Quantitative measurement techniques should be both accurate and precise. In Fig. 3-7, the concepts of *accuracy* and *precision* are presented using the analogy of an archer's target. Five arrows have hit the target A. One arrow is in the bull's eye and the other four are close. But of these four arrows, one is off to the right, one is off to the left, and one is below the bull's eye and one is above it. The archer has, at least, hit the target and could be described as being reasonably accurate as he has placed one arrow in the bull's eye and the other four around it. But he certainly did not reproduce his shot each time. He is not, therefore, precise. Target B illustrates the abilities of an archer who is precise, but not very accurate. This archer has grouped all five arrows tightly in the upper right quadrant of the target. He has reproduced his shot each time, even though none of the shots was accurate. The skill of an archer who is both accurate and precise is illustrated in Fig. 3-7 by the five arrows grouped tightly around the bull's eye on target C.

Accuracy

In bone densitometry, accuracy describes the degree to which the measurement of bone density reflects the true bone density. In other words, if the bone in question was removed from the body, measured, and then ashed and assayed, the true bone density could be determined. How close does a bone density measurement by any technique come to reproducing this *true* or *real* BMD? Accuracy can be described quantitatively by the SD or %CV, although the latter is used more often. Remember that the %CV describes the proportion by which the individual measurements vary from the mean value as a percentage. In the context of a discussion of accuracy, the mean value is synonymous with the true BMD. The SD used to calculate the CV or %CV represents the variability of the actual individual BMD measurements about this true BMD value. Therefore, if the accuracy of a DXA PA spine bone density measurement is said to have a %CV of 3 to 6%, this means that the measurements of BMD tend to vary about the true value by 3 to 6% of the true value or real BMD. Even though such a statement describing the accuracy of DXA may at first glance seem to be critical of the technology, remember that the %CV is describing the variability of the measurement about the true value. Therefore, the smaller the %CV, the better.

Precision

Precision is the ability to reproduce the measurement when it is performed under identical conditions when there has been no real biologic change in the patient. The three spine bone density measurements on Mrs. B. on the same day, in fact, within a few minutes of each other, did not produce exactly the same result. This was true because there was a certain amount of error introduced by repositioning the patient on the table in between measurements. There may also have been a small amount of error introduced during the analysis of the data by the technician. And finally, the technique itself is not perfect even when the technician exactly reproduces the positioning of the patient and the procedures used to analyze the data.

Like accuracy, precision is often characterized by the SD or %CV. The CV for the first set of three measurements on Mrs. B. was calculated in the discussion of the CV earlier in this chapter and was found to be 0.010. Expressed as a percentage, the CV becomes 1%. In the context of precision, this means that the individual measurements tend to vary from the average of the measurements by 1% of the average BMD. Again, the smaller the %CV, the better the precision of the technique.

When a bone density measurement is being performed for the purposes of diagnosing osteoporosis based on bone density criteria, the assessment of fracture risk or to document the effects of any disease process on the bone density, accuracy is a vitally important attribute. Clearly, it is desirable for the measured bone density to be as close to the true or real bone density as possible. When the bone density measurement is one of a series of measurements being done to detect changes in the bone density over time, accuracy is far less important that precision. This is because it is the magnitude of the difference between measurements that is of interest. It becomes relatively unimportant whether the first measurement was accurate or not. In order to interpret serial changes in BMD, the densitometrist must have some quantitative idea of the precision of the testing being employed. If this is not known, there is no way to know if the changes being observed are real or simply due to the error inherent in the test. The calculation of precision for bone density measurements and the determination of significant change in BMD are discussed in detail in Chapter 11.

TYPES OF DATA

The particular type of data that is collected generally determines the type of statistical analysis that is appropriate to use. Although the classification of some types of data is intuitive, some classifications are less intuitive or even arbitrary.

Quantitative Data

Quantitative data is basically numerical data. Within this broad category, numerical data may be continuous or discrete. Bone density data, for example, is continuous quantitative data, whereas the number of bone density measurements that a patient may have had is discrete quantitative data. Continuous data is numerical data that can be any fractional value on an interval scale. Height, weight, and blood pressure, as well as bone density, are all types of continuous quantitative data. Any of these variables may be any one of many values on the scale on which they are measured, including fractional values. The potential values are not limited to whole numbers. In contrast, discrete quantitative data are data that can only be whole numbers, such as the number of children in a family or, as noted above, the number of bone density scans that a patient may have.

Qualitative or Categorical Data

If data are classified as belonging to categories, the data are considered qualitative data. Such data are discrete and generally consist of counts or the number of individuals belonging to each category. This type of data is also called categorical data. Categorical data can be ordinal or nominal, depending on whether there is a logical order to the categories. For example, individuals might be placed into height categories of tall, medium or short (remember that the actual measurement of height is a continuous quantitative variable, which is different from the current example). This is clearly qualitative or categorical data. There also is a logical order to these categories, with medium in between tall and short. This is an example of ordinal data. Nominal data has no obvious order. Hair color, for example, cannot be ordered. Qualitative count data of the number of individuals with brown, blond, or black hair can be obtained, but the categories of brown, blond, or black hair have no apparent order. The word *apparent* is key here. It may be a matter of opinion in some cases as to whether there is a natural order to some types of qualitative data. For example, normal, osteopenia, and osteoporosis are categories into which individuals could be placed based on their bone density values. The number of individuals in each category is discrete, count, qualitative data. This data could also be considered ordinal because osteopenia could be viewed as being in between normal and osteoporotic, giving an obvious order to the categories. The classification of qualitative data as ordinal or nominal can be influenced by the statistician's interpretation of the meaning of the categories.

Data and Variables

In a strict sense, physicians and researchers acquire data. Statisticians analyze variables. Variables are simply data that are put into a form that makes them amenable to statistical analysis. Continuous quantitative data and ordinal categorical data are appropriate in their original form for statistical analysis and do not have to undergo any type of transformation to be analyzed statistically. The same is not always true for nominal categorical data however. Nominal categorical data must often be transformed into dichotomous categories such as yes–no or present–absent. With only two possible out-

comes, such data is also called binary data. For example, a group of women could be studied to determine which women have a spine fracture and which do not. The number of individuals in the categories of "fractured" and "not fractured" are count, categorical data. These are also nominal data because there is no obvious order to the categories of "fractured" and "not fractured." These categories represent a dichotomous situation. The categories could be renamed to simply "present" or "absent" in reference to the finding of fracture. They could also be considered as "yes" or "no" in response to the question, "Is a fracture present?" Although this example seems relatively straightforward, the transformation is necessary for the statistician. When the statistician incorporates this type of binary data into a statistical analysis, it can be consolidated into only one variable. For example, for the purpose of statistical analysis, the statistician may employ the single variable representing the presence of a fracture.

CORRELATION

Correlation is a measure of the strength and direction of the association between two variables. It is generally expressed as a dimensionless number known as the correlation coefficient. The most commonly used correlation coefficient is called Pearson's correlation coefficient. The correlation coefficient for a sample is denoted by the letter "*r*." Values for *r* can range from –1 to +1. The greater the numerical value of *r*, the stronger is the association between two variables. Therefore, the strongest associations would be indicated by an *r* value of either +1 or –1. If the relationship between the two variables is a direct one, the sign in front of the *r* value will be positive. If the relationship is an inverse one, the sign will be negative. For example, in a study reported by Takada et al. *(6)*, an *r* value of 0.56 was reported for bone density in the phalanges as measured by RA and bone density in the spine as measured by DXA. The correlation coefficient describes a direct relationship; that is, the BMD as measured by RA increased as the BMD measured by DXA increased. The association between the two variables was not a perfect one. Therefore, the bone density in the phalanges as measured by RA could not be perfectly predicted from the spine bone density measurement performed with DXA. Nevertheless, there was a direct association or relationship between the BMDs measured at both sites. In another study from Hansen *(7)*, the strength of the association between body weight and BMD at a variety of skeletal sites was reported. The BMDs at the spine, forearm, femoral neck, and trochanter were all noted to be positively related to weight. That is, the BMD increased as weight increased. This association, therefore, will be expressed as a positive *r* value. The *r* values ranged from 0.20 to 0.35 between weight and the BMDs at the various skeletal sites. Although these *r* values were low and would tend to suggest that the strength of the association between weight and BMD was far from perfect, all of the *r* values were statistically significant. One could conclude that the association between weight and BMD was positive or direct, but weak. Nevertheless, the *r* values were statistically significant, implying that the association was unlikely to be due to chance. An example of an inverse correlation is the finding from Mazess et al. *(8)* of an *r* value of –0.16 for the association between age and femoral neck BMD in a cross-sectional study of 218 women, ages 20 to 39. This means that as age increased, the BMD in the femoral neck decreased. Although this value of *r* is again very small, it was statistically significant. Note that correlation does not prove cause and effect. It only quantifies the strength of a relationship or association.

STATISTICAL SIGNIFICANCE AND THE *P* VALUE

Statistical significance is virtually always discussed in the context of the likelihood of coming to an incorrect conclusion based on the acquired data. There are many ways to test for statistical significance. The choice of technique is determined by the nature of the study being performed. The various techniques for significance testing are not relevant to the discussion here. However, the results of significance testing are usually presented in the form of a "*P*" value. Traditionally, two levels of the *P* value have become synonymous with significant and very significant. Values of *P* that are less than or equal to 0.05 are considered significant. Values of *P* that are less than or equal to 0.01 are considered very significant. In the previous discussion of correlation, it was noted that Hansen *(7)* found a direct association between body weight and BMD at a variety of skeletal sites. These associations were expressed as correlation values of *r*, which ranged from 0.20 to 0.36. It was noted above that these correlations were weak but statistically significant. In fact, the correlations were very significant with a *P* value of less than 0.001. This value is interpreted as meaning that there is less than 1 chance in 1000 of obtaining results such as those seen by Hansen if there is really no association at all between weight and BMD. Statistical significance, of course, does not necessarily imply medical or practical significance. That is for the clinician to decide.

REGRESSION ANALYSIS

Regression analysis is the development of a mathematical model based on real-world observations or measurements. The model is intended to describe mathematically the relationship between an independent variable or variables and a dependent variable. There are different types of regression analyses and a variety of reasons to employ them. No matter what the circumstance, an important caveat to remember about such mathematical models is, "All models are wrong. Some are useful" *(9)*. The model is, after all, only a mathematical analogy for real-world events.

Linear regression is common in the medical literature. The simplest mathematical model or equation in linear regression usually takes the form:

$$y = \alpha + \beta x \tag{21}$$

in which y is the dependent variable we would like to predict from our knowledge of x, the independent variable. The dependent variable y is a quantity that can be measured. It is important to note that there is only one x variable. The slope of the regression line is β and α represents the y-intercept, the value of y when x is zero. A third term, ε, is usually added, representing random variability, but conceptually, it is not needed here. In multiple linear regression, there are two or more x variables. As the name suggests, a plot of a linear or multiple linear regression equation results in a straight line. In nonlinear regression, there is again only one x variable, but a graph of x versus y results in a curve.

Two other common forms of regression analyses are logistic regression and proportional hazards regression. In logistic regression, there may be any number of x variables. The dependent variable, y, however, is a qualitative, binary variable. In other words, y represents a quality such as diseased or not diseased, normal or osteoporotic and there can be only two choices. In proportional-hazards regression, there can again be any number of x variables and y is survival time. Other types of regression analyses are Poisson regression and ordinal regression. In these types of regression analyses, the dependent

variable *y* is count data or ordinal data, respectively. The number of independent variables and the nature of the dependent variable basically determine the type of regression analysis that is appropriate for any given circumstance.

One of the more common uses of regression analysis is to determine if predictable relationships exist between variables. For example, does bone density decline predictably with age? Regression analysis can be performed using age as the independent variable *x* and bone density as the dependent variable *y* that we wish to predict. Regression analysis can also be performed to evaluate the relationship between one independent variable *x* and the dependent variable *y*, after adjusting for other independent variables. For example, we might wish to know if the risk for hip fracture increased with declining bone density after adjusting for the effects of age and sedative use. Bone density, age and sedative use are independent *x* variables and fracture risk is the dependent *y* variable we wish to predict. Multiple regression analysis can be used in this circumstance. Regression analyses can also be used to predict outcomes on the basis of independent variables. In other words, regression can be used to predict the risk of fracture based on knowledge of an individuals bone density, age, and sedative use.

STATISTICAL EVALUATIONS OF DIAGNOSTIC TESTS

In evaluating the clinical utility of any diagnostic test, including test instruments designed to select individuals for bone densitometry, several statistical measures are often used. The various measures are intended to indicate the probability of having or not having a particular disease based on the outcome of the test. Because bone density values are continuous data or variables, cut points must be selected that define the states of "diseased" and "nondiseased." Categories such as diseased and nondiseased are nominal data, as described earlier. Nominal data are necessary to determine probabilities. Cut points in bone densitometry are readily available by utilizing various *T*-scores or *z*-scores. The nominal data categories can then be described as at or above a certain standard score or, conversely, at or below a certain standard score. Once a cut point has been picked, a diagnostic test's utility in identifying diseased or nondiseased individuals can be characterized by its sensitivity, specificity, predictive value, and likelihood ratio. A receiver operating characteristic (ROC) curve can also be created to "test the test."

Sensitivity and Specificity

Sensitivity and specificity are easily illustrated by considering a population of 1000 women in whom the spine bone density has been measured. A cut point can be chosen, most simply by picking a *T*-score such as –2.5 to determine the exact percentages of women with spine *T*-scores of –2.5 or poorer and spine *T*-scores better than –2.5. The women with *T*-scores of –2.5 or poorer are considered diseased. Based on World Health Organization (WHO) criteria,[2] they have osteoporosis. The women with *T*-scores better than –2.5 are considered nondiseased in this example. They do not have osteoporosis, although many of them may be osteopenic. By using the *T*-score to pick a cut point that defines the categories of diseased and nondiseased, quantitative continuous bone density data has been converted into two qualitative nominal data categories.

In this example, illustrated in Table 3-3, there are 500 women in the diseased group and 500 women in the nondiseased group. All of the women are asked to complete a

[2] *See* Chapter 9 for a discussion of the WHO criteria for the diagnosis of osteoporosis.

Table 3-3
The Results of a Diagnostic Test in 1000 Individuals with a Disease Prevalence of 50%

	+ Test	*–Test*	*Total*
Diseased	400	100	500
Nondiseased	200	300	500
Total	600	400	1000

questionnaire that elicits a history of various risk factors for low bone density, after which the questionnaire is scored. It is hoped that a score at or above a certain value will indicate a high probability of having a bone density *T*-score of –2.5 or poorer or of "being diseased." Those women with such a score would be considered as having a positive test.

Sensitivity is the ratio of the number of individuals with the disease who test positive to the total number of individuals with the disease. These individuals can be considered "true positives." Specificity is the ratio of the number of individuals without the disease who test negative to the total number of individuals without the disease. These individuals are considered "true negatives." Both values can be expressed as a percentage by multiplying by 100. In Table 3-3, of the 500 women with the "disease," 400 tested positive. The sensitivity is calculated as follows:

$$\text{Sensitivity} = \frac{\text{Number of diseased individuals who test positive}}{\text{Total number of diseased individuals}} \tag{22}$$

$$\text{Sensitivity} = \frac{400}{500} = 0.80 \text{ or } 80\% \tag{23}$$

Specificity is calculated in a similar manner, using the 300 women without the disease who indeed tested negative and the total of 500 nondiseased women.

$$\text{Specificity} = \frac{\text{Number of non–diseased individuals who test negative}}{\text{Total number of non–diseased individuals}} \tag{24}$$

$$\text{Specificity} = \frac{300}{500} = 0.60 \text{ or } 60\% \tag{25}$$

Therefore, this particular questionnaire has a sensitivity of 80% and a specificity of 60% for identifying women with a bone density *T*-score of –2.5 or poorer at the lumbar spine.

Although this questionnaire correctly identified 80% of the women who were considered diseased, it failed to identify 20% of the diseased women. These women are said to have a false-negative test. Mathematically, the false-negatives are equal to 1-sensitivity. Similarly, although the questionnaire correctly identified 60% of the women who were not diseased, 40% of the nondiseased women had a positive test and were incorrectly labeled as diseased. These women are considered false-positives. Mathematically, the false-positives are equal to 1-specificity.

In the examples described above, the bone density or the disease status of the individual is known. In clinical practice, however, an individual completing such a questionnaire would not have previously had her bone density measured. The question the physician must answer is, "What is the probability that an individual with a positive test

has the disease in question?" Or, the question may be, "How likely is it that an individual with a negative test does not have the disease?" The answer to these questions lies in the positive and negative predictive values for the test.

The positive predictive value (PPV or PV+) of a test is expressed as follows:

$$\text{PPV} = \frac{\text{Total number of individuals with the disease who test positive}}{\text{Total number of individuals who test positive}} \quad (26)$$

In the example in Table 3-3, 600 women tested positive but only 400 were actually diseased. Therefore:

$$\text{PPV} = \frac{400}{600} \text{ or } 0.66 \text{ or } 66\% \quad (27)$$

The negative predictive value (NPV or PV–) is calculated in an analogous fashion. In the same example, there were 400 women who had a negative test, but only 300 women who had a negative test and were not diseased. Therefore:

$$\text{NPV} = \frac{\text{Number of individuals who are not diseased and test negative}}{\text{Total number of individuals who test negative}} \quad (28)$$

$$\text{NPV} = \frac{300}{400} \text{ or } 0.75 \text{ or } 75\% \quad (29)$$

In this example, then, if an individual has a positive test, there is a 66% chance that a diseased state or bone density *T*-score of –2.5 or less will be found. On the other hand, if the individual has a negative test, there is a 75% chance that a nondiseased state or bone density *T*-score better than –2.5 will be found.

Positive and negative predictive values of a test are highly dependent on the prevalence of the particular disease in the population *(10)*. The positive and negative predictive values that were calculated from the data in Table 3-3 are appropriate for that population only, in which the prevalence of disease, defined as a *T*-score of –2.5 or poorer, is 50%. It is necessary to know the prevalence of the disease in the population being tested in order to correctly calculate the positive and negative predictive values of a test using its sensitivity and specificity. Additionally, for PPVs and NPVs derived from a sample population to be useful in a given patient population, the prevalence of disease must be the same in the two populations. To avoid this dependence on prevalence, likelihood ratios (LR) can be utilized to characterize the clinical utility of a test.

Likelihood Ratios

LRs are also calculated using the sensitivity and specificity of a diagnostic test. The positive LR (LR+) is the ratio of the probability of a positive test in diseased patients to the probability of a positive test in patients who are not diseased. Mathematically, this is expressed as follows:

$$\text{LR+} = \frac{\text{Sensitivity}}{1 - \text{Specificity}} \quad (30)$$

The negative LR (LR–) is the ratio of the probability of a negative test in patients with the disease to the probability of a negative test in patients who are not diseased. Mathematically, the LR– is expressed as follows:

$$\text{LR–} = \frac{1 - \text{Sensitivity}}{\text{Specificity}} \quad (31)$$

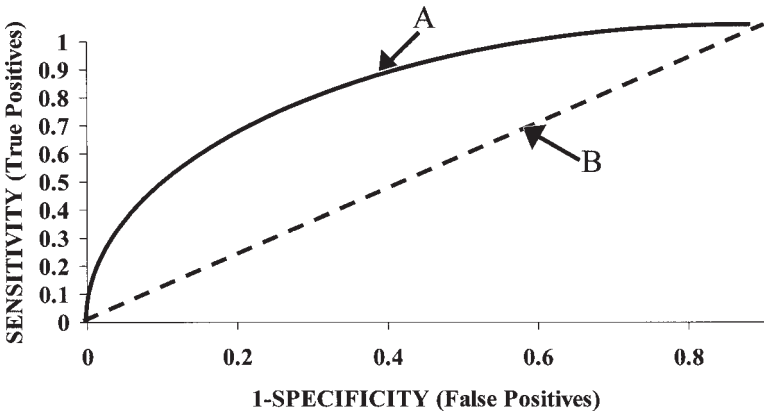

Fig. 3-8. A stylized ROC curve. Sensitivity is plotted on the *y*-axis and 1-specificity is plotted on the x-axis. The points on curve A should be above the dashed 45° line B for the test to have diagnostic utility as shown here.

LRs are less dependent on prevalence than predictive values. As an assessment of the utility of a diagnostic test, the greater either LR is from 1, the better is the ability of the test to discriminate between patients with and without the disease. The LR+ should be greater than 1. This suggests that it is more likely to find a positive test in a patient with the disease than in a patient without the disease. The LR– should be less than 1, which suggests that a negative test is less likely to be found in a patient with the disease than in a patient without the disease.

Receiver Operating Characteristic Curves

The sensitivity and specificity of a diagnostic test are dependent on the cut point chosen to identify the diseased population from the nondiseased population. If changing a cut point results in an increase in sensitivity, the specificity will decrease. Similarly, if the specificity is increased, the sensitivity will decrease. This relationship between sensitivity and specificity can be examined using a ROC curve. Sensitivity is plotted on the *y*-axis and 1-specificity is plotted on the *x*-axis. By examining the ROC curve, the cut point that gives the optimum combination of sensitivity and specificity can be determined. The ROC curve also provides graphic evidence of the utility of the test. A stylized ROC curve is shown in Fig. 3-8. The points along the ROC curve should be above and not touch the dashed 45° line that has been added to the graphic. This 45° line represents equal values of sensitivity and 1-specificity or equal values for true positives and false-positives. A test with such values would provide no useful information about the probability of a patient having the disease in question.

The area under the ROC curve (AUC or AUROC) measures the probability that, in randomly paired diseased and nondiseased patients, the predicted probability of disease is greater for patients with the disease. Values for the AUC of 0.70 or less are unacceptable for a diagnostic test *(11,12)*. A value of greater than 0.90 suggests superb predictive accuracy. For example, the development cohort ROC curve of the Simple Calculated Osteoporosis Risk Estimation (SCORE) questionnaire for identifying women with a bone density *T*-score of –2 or poorer is shown in Fig. 3-9. Here, the AUC is an acceptable 0.811 *(13)*. SCORE is discussed in more detail in Chapter 8.

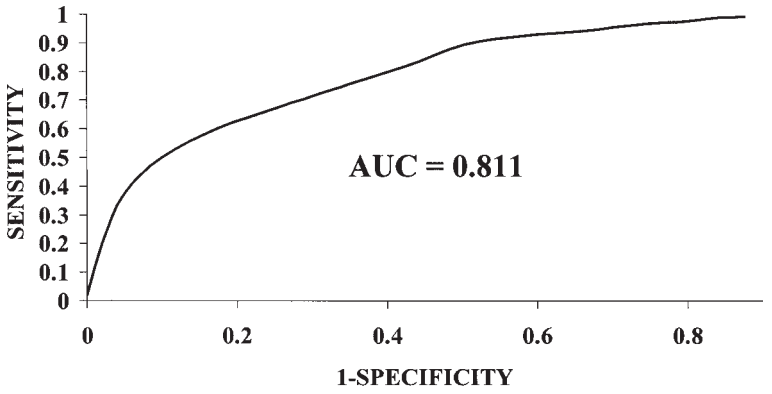

Fig. 3-9. The ROC curve from the development cohort of SCORE. The AUC is 0.811. Note that all the points on the curve are above an imaginary 45° line. From ref. *13* with permission of the publisher, permission conveyed by the Copyright Clearance Center.

REGRESSION TO THE MEAN

Regression to the mean (RTM) is a statistical phenomenon that was first observed by Sir Francis Galton[3] in 1886. Galton was investigating the hereditary nature of height. In a study of a group of parents and their children, Galton *(14)* observed that the average or mean height of the children of the taller parents was closer to the mean height of all the children than was the mean height of their parents to the mean height of all the parents. The opposite was also true. The mean height of the parents of the taller children was closer to the mean height of all the parents than was the mean height of their children to the mean of all the children. This phenomenon was originally called regression toward mediocrity. Today it is called regression to the mean (RTM).

RTM is not a biological phenomenon. It is a statistical phenomenon that is created when certain conditions are met during data analysis. The three conditions *(15)* are 1) a variable is measured on two separate occasions, 2) the value of the variable can change because of biologic or measurement variability or both, and 3) a subgroup is defined based on a high or low value of the first measurement. In these circumstances, the average value of the second measurement for the subgroup will be closer to the mean of the first measurement for the entire group than was the average value of the first measurement of the subgroup. In other words, the mean of the subgroup at the time of the second measurement has regressed back toward the mean of the first measurement of the entire group. It should be clear that not only is this a statistical phenomenon, it is a group phenomenon. Although RTM is an extremely important concept that affects the design of clinical trials and clinical trial data analysis, it has no relevance in the interpretation of serial measurements made in individuals *(16)*. This is an important distinction, because RTM has been inappropriately suggested as invalidating serial bone density measurement in individuals in clinical practice, as discussed in Chapter 11 *(17)*.

[3] Sir Francis Galton (1822–1911) was a physician as well as a statistician, geographer, meteorologist, and explorer. He is a considered a pioneer in statistical correlation and regression as well as in the science of fingerprint identification.

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4 Quality Control

CONTENTS

Although much has been written about quality control procedures in densitometry, much of this literature has been concerned with data collection in clinical research rather than patient data collected as part of medical care. Quality control, although absolutely necessary in clinical research, is no less necessary in clinical practice. The original indications for bone mass measurements from the National Osteoporosis Foundation published in 1988 and the guidelines for the clinical applications of bone densitometry from the International Society for Clinical Densitometry published in 1996 called for strict quality control procedures at clinical sites performing densitometry *(1,2)*. The Canadian Panel[1] of the International Society for Clinical Densitometry published specific guidelines for quality control procedures in 2002 *(3)*. Such procedures are crucial to the generation of accurate and precise bone density data. When quality control is poor or absent, the bone density data may be incorrect. The interpretation made by the physician based on that incorrect information would be in error. The medical management of the patient may be adversely affected. The patient will also have been exposed to a small amount of radiation inappropriately and wasted time and money. In clinical trials, the results from hundreds or thousands of individuals are usually averaged and conclusions based on the average values. Small errors in machine performance are made insignificant by the averaging of so many results. In clinical practice, this luxury does not exist. Decisions are made based on one measurement from one patient, which means that strict quality control in clinical practice is even more important than in clinical trials. Despite inherently superb accuracy and precision in today's densitometers, alterations in the functioning of the machines can and will occur. Quality control procedures to detect these alterations in machine function should be utilized by every clinical site performing densitometry regardless of the frequency with which measurements are performed.

Quality control procedures used in densitometry were derived from procedures originally developed for quality control in analytical chemistry and industry *(4)*. The adapta-

[1] The Canadian Panel of the International Society for Clinical Densitometry represents the International Society for Clinical Densitometry in Canada and oversees the society's programs in Canada.

tion of these procedures for use in bone densitometry is generally credited to Drs. Orwoll and Oviatt *(5)*. The most commonly used methods are control tables, visual inspection of a Shewhart chart, Shewhart rules and the cumulative sum chart (CUSUM). All of these methods require that a phantom be scanned to establish a baseline value and then regularly, to establish longitudinal values.

PHANTOMS

Manufacturers of X-ray-based bone densitometers routinely provide phantoms for use with their machines. Some phantoms, like the anthropomorphic Hologic spine phantom, are used with densitometers from other manufacturers. Other phantoms, such as the European Spine Phantom (ESP) or the Bona Fide phantom were developed independently of any one manufacturer and intended for use on multiple machines. The manufacturer-supplied phantom is often designed with the specific attributes of the manufacturer's machine in mind, making it the preferred phantom to use with that machine. The perfect phantom that could be used on all machines to test all things does not as yet exist.

Some, but not all, manufacturers provide two phantoms to be used for different purposes. One phantom may be used for daily quality assurance functions during which the mechanical operation and calibration of the machine are tested. The second phantom may be designed to mimic a region of the skeleton and used for quality control to detect a shift or drift in BMD values.

Phantoms that attempt to replicate a particular region of the skeleton are called anthropomorphic phantoms. These phantoms are made of hydroxyapatite or aluminum. Although hydroxyapatite is preferred by the Food and Drug Administration for such a phantom, aluminum is appropriate as well since aluminum behaves very much like bone when X-rayed. The phantom may be encased in an epoxy-resin or plastic block or placed within some other type of material to simulate human soft tissue. Water or uncooked rice can be used for this purpose. The perfect anthropomorphic phantom would replicate the size and shape of the bone or bones in question, have varying densities within a single bone or region, contain a range of densities likely to be encountered clinically and be surrounded by a material that adequately mimics human soft tissue. Replicating the size and shape of the particular bone or bones and having a nonuniform density throughout the bone tests the edge-detection methodology of the particular system. In other words, it tests the machines ability to distinguish bone from soft tissue. If the phantom bears no resemblance in size or shape to the particular bone or has very sharp, smooth edges, or if the density of the material is uniform within the bone, the edge-detection program of the machine will not be adequately tested. If the material surrounding the phantom does not adequately replicate human soft tissue, once again the ability of the machine to tell bone from soft tissue will not be not maximally tested. In order to test a system's abilities at various levels of bone density, it is desirable to have a range of densities contained within the phantom. At the same time, this range should reflect values that are likely to be encountered in clinical practice for the test to be truly useful. Most of the manufacturer-supplied phantoms in use today have some of these attributes but not all. Which attributes are emphasized by a manufacturer generally depends on those attributes that the manufacturer wishes to test as a part of the routine quality control program for their machine.

The European Spine Phantom

The development of the European Spine Phantom (ESP) resulted from efforts to develop a more perfect spine phantom that could be used on all central devices. It was developed independently of any manufacturer under the direction of the Committee d'Actions Concertés-Biomedical Engineering (COMAC-BME) *(6)*. The ESP is a semi-anthropomorphic phantom. Its three vertebrae are made of hydroxyapatite and vary in density, with standardized BMDs of 500, 1000, and 1500 mg/cm^2 *(7)*. The vertebrae are encased in a plastic and epoxy-resin material equivalent to about 10% fat that is molded into an oval shape with flattened sides measuring 28 cm by 18 cm. The use of the ESP has generally been restricted to clinical research trials, primarily because of its expense. It was originally hoped that the ESP could be used to standardize BMD on any central bone densitometer. Unfortunately, this has not proven to be the case. It is an excellent phantom for cross-calibration of central DXA densitometers however.

The Bona Fide Spine Phantom

The Bona Fide phantom is hydroxyapatite encased within an acrylic block. The acrylic provides a soft tissue equivalent of 26% fat while the phantom spans a range of densities from 0.7 to 1.5 g/cm^2 *(8)*. The block may remain in its cloth carrying case during scanning, increasing ease of use. Like the ESP phantom, the Bona Fide phantom is not manufacturer-specific and may be used for cross-calibration of central DXA devices.

The Hologic Spine and Hip Phantoms

The Hologic anthropomorphic spine phantom, although intended for use with Hologic DXA devices, is often used with DXA devices from other manufacturers. The phantom itself consists of four anatomically correct vertebrae made of calcium hydroxyapatite. The vertebrae are encased in an epoxy resin to simulate soft tissue. The four vertebrae have similar densities and areas and the soft tissue simulation of the epoxy-resin approaches 60% fat. Each Hologic spine phantom will have a factory-specified L1–L4 BMD. Consistent daily calibration can be obtained with the Hologic anthropomorphic spine phantom, although the lack of a range of BMD values make it less suitable for cross-calibration of central DXA devices. The Hologic anthropomorphic hip phantom has found less of a role in clinical medicine. It does not offer any quality control testing capabilities to the clinician that cannot be obtained with the anthropomorphic spine phantom other than proximal femur edge detection, which is under the control of the machine software, rather than the hardware *(8)*.

The Lunar Spine Phantom

The Lunar spine phantom is a rectangular aluminum bar which is intended to replicate the lower half of T12, all of L1, L2, L3, and L4, and the upper half of L5. Each vertebra has a different density that is achieved by varying the thickness of the aluminum. The area of each vertebra is different as well. The densities of L1 to L4 are 0.92, 1.076, 1.239, and 1.403 g/cm^2, respectively. The L2–L4 BMD is 1.256 g/cm^2. To simulate soft tissue, the aluminum phantom is submerged in a water bath with a depth of approximately 15 cm. The aluminum phantom is also available encased in an epoxy-resin block, avoiding the necessity of a water bath and improving ease of use.

Table 4-1
A Control Table

Date	*Phantom Value*	*Within Control Limits*
10/09/2000	1.179	Yes
10/10/2000	1.187	Yes
10/11/2000	1.162	No
10/11/2000	1.170	Yes
10/12/2000	1.184	Yes

Control limits of ±1.5% or 1.164 to 1.200 g/cm^2 were established based on a 10-phantom average BMD of 1.182 g/cm^2.

USING THE PHANTOM TO CREATE CONTROL TABLES AND CHARTS

Most daily quality assurance procedures to detect mechanical failures on today's densitometers are automated. The program will indicate a passing or failing condition. Before outright mechanical failure occurs, however, regular scanning of the quality control phantom and the application of Shewhart charts and rules or CUSUM charts can detect drifts or shifts in machine values that require correction in order to ensure continued accuracy and precision. Abrupt shifts in values are generally easy to detect. Drifts can be more subtle and therefore, more insidious. The confirmed occurrence of either indicates that the machine is "out of control" (OOC).

Manufacturers generally recommend scanning the phantom 10 times on the same day without repositioning the phantom in between studies. This is also the procedure often used as part of quality control procedures in longitudinal clinical research trials. Subsequent phantom scans are then performed at least three times a week and on every day that a patient is scanned.

The average value of the 10 phantom scans should be calculated. The range that represents the average value ±1.5% should also be calculated. The average value +1.5% and the average value –1.5% become the upper and lower limits of BMD within which all subsequent measurements of the phantom should fall. These upper and lower limits are called control limits. A control table, as shown in Table 4-1, can then be created. The first column lists the date of the phantom scan. The second column gives the actual BMD value. In the third column, a yes or no entry indicates whether the phantom BMD value fell within the established control limits.

A control graph offers some advantages over the control table. A control graph is created using the same average value from 10 consecutive phantom scans and control limits based on ±1.5% of the average value. The vertical or *y*-axis of the graph reflects the BMD values in g/cm^2. The horizontal or *x*-axis reflects time in days. The BMD that corresponds to the 10-phantom average should be indicated by drawing a solid horizontal line across the graph. The upper and lower control limits values are similarly indicated by drawing a dashed line across the graph. Subsequent phantom values are easily tracked by plotting the results on the control graph. Such a graph is called a Shewhart chart.

Table 4-2
Ten Hologic Spine Phantom Scans Performed on a Lunar DPX on the Same Day to Establish a Baseline Phantom BMD Value for Quality Control

Phantom Scan	*Date*	*BMD L1-L4 g/cm²*
Scan 1	4/22/00	1.181
Scan 2	4/22/00	1.173
Scan 3	4/22/00	1.176
Scan 4	4/22/00	1.180
Scan 5	4/22/00	1.190
Scan 6	4/22/00	1.174
Scan 7	4/22/00	1.189
Scan 8	4/22/00	1.192
Scan 9	4/22/00	1.177
Scan 10	4/22/00	1.187

The average value for the 10 phantom scans is 1.182 g/cm². The SD is 0.007 g/cm² and 1.5% of the average value is 0.018 g/cm².

The results of 10 scans of the anthropomorphic Hologic spine phantom that were performed on a Lunar DPX are shown in Table 4-2. The average value for the 10 scans was calculated as 1.182 g/cm². To find the upper and lower control limits, the average value was multiplied by 1.5%. This was determined to be 0.018 g/cm² (1.182 g/cm² × 0.015). Therefore, the range of values within which all subsequent phantom scan values should fall is 1.182 g/cm² ± 0.018 gm/cm² or from 1.164 g/cm² to 1.200 g/cm². Figure 4-1 is the Shewhart chart that was created for this set of 10 phantom scans onto which subsequent phantom scan values have been plotted. The phantom BMD values obtained over time from a scanner that is operating perfectly should randomly fall on either side of the 10-phantom BMD average value but remain within the control limit boundaries of ±1.5%. If a value falls outside the boundaries, the phantom scan should immediately be repeated. If it falls outside the boundaries again, or "fails," the manufacturer should be contacted for additional instructions.

A visual inspection of the Shewhart chart can also provide more subtle clues to machine malfunction or a machine going OOC. The pattern of the values should be reviewed to ensure that the values appear to be randomly falling on either side of the average value in addition to being within the control limits. If this randomness appears to be lost, the machine may be drifting. If an imaginary straight line drawn through the center of the phantom values is above or below the average value, a shift may have occurred. In either of these cases, the manufacturer should again be contacted for instructions. An inspection of the Shewhart chart in Fig. 4-1 suggests a possible drift in values. Arrow 1 on the graph in Fig. 4-1 indicates a point at which it appears that the phantom values are no longer randomly scattered on either side of the average but instead are concentrated below the average. This suggests that the scan values may be starting to drift downward. These situations can and do occur even though the absolute BMD values obtained from the daily phantom scans remain within the established range and other daily quality assurance procedures continue to give "PASS" indications.

Table 4-3
Twenty-Five Hologic Spine Phantom Scans Performed on a Lunar DPX on 25 Consecutive Days to Establish a Baseline Phantom Value for Quality Control

Phantom Scan	*Date*	*BMD L1-L4 g/cm²*	*Phantom Scan*	*Date*	*BMD L1-L4 g/cm²*
Scan 1	4/22/00	1.181	Scan 14	5/14/00	1.189
Scan 2	4/23/00	1.172	Scan 15	5/15/00	1.174
Scan 3	4/24/00	1.176	Scan 16	5/16/00	1.186
Scan 4	4/25/00	1.172	Scan 17	5/20/00	1.181
Scan 5	4/29/00	1.180	Scan 18	5/21/00	1.170
Scan 6	4/30/00	1.185	Scan 19	5/22/00	1.179
Scan 7	5/01/00	1.179	Scan 20	5/23/00	1.178
Scan 8	5/02/00	1.176	Scan 21	5/28/00	1.180
Scan 9	5/06/00	1.177	Scan 22	5/29/00	1.181
Scan 10	5/07/00	1.169	Scan 23	5/30/00	1.168
Scan 11	5/08/00	1.180	Scan 24	6/03/00	1.182
Scan 12	5/09/00	1.167	Scan 25	6/04/00	1.172
Scan 13	5/13/00	1.179			

The average value for the 25 phantom scans is 1.177 g/cm^2. The SD is 0.006 g/cm^2 and 1.5% of the average value is 0.018 g/cm^2. Compare these average and SD values to those calculated for the 10 scans in Table 4-2.

The control table described earlier is simpler to create and maintain than the Shewhart chart but the ability to visually inspect the data for drifts or shifts is lost. The creation of a Shewhart control table or chart constitutes the minimum quality control program that should be in use in every facility performing densitometry.

The creation of an average baseline phantom value by scanning the phantom 10 times on the same day without repositioning may not reflect the day-to-day variability in machine values and the effects of repositioning that would be expected as the phantom is scanned over time. Several groups have consequently recommended that the baseline phantom value be established by scanning the phantom once a day for 15 to 25 consecutive days and then averaging these 15 to 25 scans. It is thought that this will more accurately reflect the day-to-day variability in machine values and result in fewer "false alarm failures." For example, the average BMD of the same Hologic spine phantom when scanned on 25 consecutive days as shown in Table 4-3 was 1.177 g/cm^2 resulting in a range for the average ± 1.5% of 1.159 g/cm^2 to 1.195 g/cm^2. In both cases, 1.5% of the mean value was 0.018 g/cm^2 but the range of acceptable values was different from that seen when the phantom was scanned 10 times on the same day without repositioning. Figure 4-2 is the graph of subsequent scans now plotted against the baseline phantom value obtained after scanning the phantom once on each of 25 consecutive days.

Notice in Fig. 4-2, when the mean was calculated using 25 scans performed on consecutive days, the same phantom values do not give any indication of a loss of random scatter. More sophisticated evaluations of this type of data can be done to determine if, in fact, there has been a shift in values. Nevertheless, this type of chart is the foundation of a good quality control program.

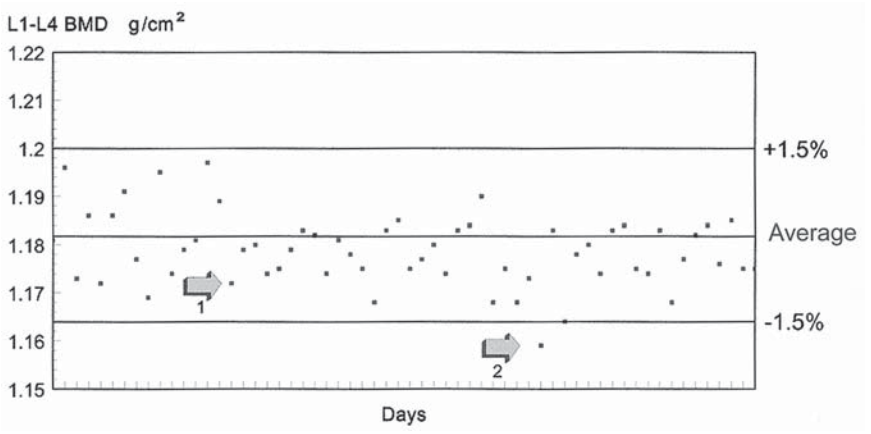

Fig. 4-1. A quality control chart with control limits of ±1.5%. The average BMD of the phantom was established by scanning the phantom 10 times on the same day. Arrow 1 indicates a point at which values appear to be drifting downward. Arrow 2 indicates a violation of the 1.5% rule.

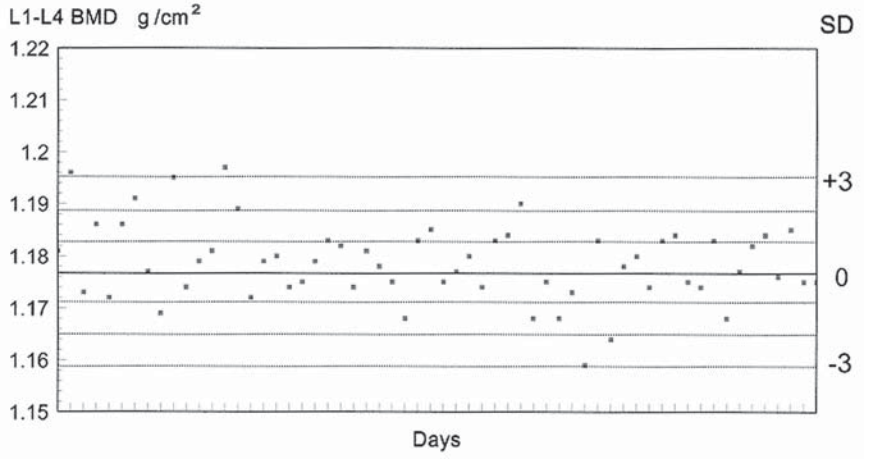

Fig. 4-2. A Shewhart chart for quality control. The average BMD of the phantom was established by scanning the phantom once on 25 consecutive days.

SHEWHART RULES AND CUSUM CHARTS

The field of analytical chemistry recognized the need for strict quality control many years ago. Like bone densitometry, analytical chemistry involves the use of machines for quantitative measurements. Techniques had to be developed to determine that the machines continued to function properly over long periods of time in order to ensure consistency in the results *(4)*. The methods common to analytical chemistry have been adapted for use in bone densitometry *(5)*. These methods utilize the BMD values from the phantom scans as described earlier: the average phantom value and the values from phantom scans performed over time. The two most commonly used methods for tracking machine performance are Shewhart rules and the CUSUM chart.

Shewhart Rules

Shewhart[2] rules have been used in analytical chemistry since the 1950s. In order to utilize Shewhart rules, it is necessary to establish a baseline value and control limits for the phantom measurement and create a Shewhart chart as described earlier. Establishing the baseline phantom value by scanning the phantom on each of 15 to 25 consecutive days, rather than multiple times on the same day is recommended. If, for some reason, this is impractical, a 10-phantom average created by scanning the phantom 10 times on the same day can certainly be used. Once the average value of the phantom scans is determined, the SD for the set of scans should be calculated. A Shewhart chart can then be created onto which the BMD data from subsequent phantom measurements is plotted as was done in Fig. 4-2. The *y*-axis of the graph should reflect both the actual BMD values and SD units as shown in Fig. 4-2. To utilize SD units, the average BMD is assigned a value of 0 on the *y*-axis of the graph and the SD tics are labeled +1 or –1, +2 or –2, and so on. In other words, the *y*-axis reflects both the measured BMD and the *z*-score[3] of the daily phantom BMD measurements. The average phantom value used to construct the Shewhart chart in Fig. 4-2 was previously found to be 1.177 g/cm^2. The SD was also previously found to be 0.006 g/cm^2 for this set of measurements. It is not necessary to calculate the *z*-score for each of the phantom measurements. When the measured BMD is plotted on the graph, it becomes visually apparent how many SDs from the average the value actually lies because of the SD or *z*-score scale on the *y*-axis. Remember that with a perfectly functioning machine, the values plotted on the graph are expected to be randomly scattered on either side (i.e., above and below) of the average BMD or *z*-score of 0.

As these values are being plotted, "rules" are applied to detect trends or "failures" that may indicate a change in machine performance. These are called Shewhart rules or sensitizing rules *(9)*. Different combinations of rules have been tested in densitometry in order to minimize false alarms and increase the ability of the Shewhart rules to detect true alterations in machine performance *(5,10,11)*.

Shewhart rules are usually "set" at a certain level. In other words, a triggering or warning level is selected. When this level is exceeded, the Shewhart rules are applied. For example, Shewhart rules may be set at a warning level of the average ± 2 SD *(4)*. If the phantom BMD value is more than 2 SD above or below the average BMD, the Shewhart rules are applied to detect potential machine failures. A machine failure is then deemed to have occurred if any one or more of the following Shewhart rules have been violated:

- A phantom BMD value exceeding the average ± 3 SD.
- Two consecutive phantom BMD values on the same side of the average exceeding the average by ± 2 SD.
- Two consecutive phantom BMD values differing by more than 4 SD.
- Four consecutive phantom BMD values on the same side of the average exceeding the average by ± 1 SD.
- Ten consecutive phantom BMD values falling on the same side of the average regardless of their distance from the average.

[2] Dr. William Andrew Shewhart (1891–1967), as a scientist with Western Electric, devised the basis for the application of statistical methods to quality control. In 1931, his book, *Economic Control of Quality of Manufactured Product*, was published. In it, he presented his methods for statistical sampling.

[3] In this context, *z*-score has nothing to do with reference population BMD data. It is simply the number of SDs above or below the average value. *See* Chapter 3 for a discussion of the *z*-score scale.

Not all violations of the rules will be found to be machine failures that require correction and as such, are considered false alarms. In order to reduce the false alarms, a "filter" is sometimes applied to the "sensitizing rules." One such filter is to calculate the average BMD for 10 consecutive phantom measurements after a violation of one of the Shewhart rules has occurred. If this 10-scan average differs by more than 1 SD from the baseline average value, the violation is confirmed. Another method is to "set" the triggering of the rules at a higher level, such as the 3 SD level. When this approach is employed, the occurrence of a single value outside the 3 SD limits then triggers the application of the other rules.

Without such "filters" or "triggers," Shewhart rules, although easy to use, produce a high false alarm rate. Even if a machine is in perfect working order, a violation of the Shewhart rules is expected to occur once every 39 scans *(11)*. When the filter is added, the false alarm rate drops to once every 631 scans. Unfortunately, although the addition of the filter to Shewhart rules reduces the number of false alarms, it may also have the undesirable effect of delaying detection of true shifts in machine performance.

Shewhart rules may also be utilized by calculating the average ± a percentage of the average as was done in the quality control chart in Fig. 4-1 *(12)*. For most of the central DXA scanners in clinical use today, repeat phantom measurements will generally result in a SD for the baseline set of phantom measurements that is roughly 0.5% of the average value. Consequently, 1.5% of the average value for the phantom BMD will approximately equal 3 SDs. For example, when the statistics were calculated for the 10 phantom measurements performed on the same day shown in Table 4-2, the average was 1.182 g/cm^2 with a SD of 0.007 g/cm^2. One-and-a-half percent of the average was 0.018 g/cm^2. In this case, 1.5% of the average is equal to 2.6 SDs. In the case of the 25 phantom scans shown in Table 4-3 with an SD of 0.006, the 1.5% value of 0.018 g/cm^2 is equal to 3 SDs. The percent values can be used to invoke the Shewhart rules. Using a value of 0.5% of the average as equaling 1SD, the Shewhart rules would be applied if a phantom value exceeded the baseline average value ± 1% (instead of the average ± 2 SD). A violation would be deemed to have occurred in any of the following circumstances:

- A phantom BMD value exceeds the average by ± 1.5%.
- Two consecutive phantom BMD values on the same side of the average exceed the average by ± 1%.
- Two consecutive phantom BMD values differ by more than 2%.
- Four consecutive phantom BMD values on the same side of the average exceed the average by ± 0.5%.
- Ten consecutive phantom BMD values fall on the same side of the average regardless of their distance from the average.

The 10-scan average filter described here would confirm a failure if the 10-scan average differed from the baseline average by more than 0.5% (instead of one SD).

In quality control "jargon," each of these rules has its own name. In the order listed above, the rules are known as the:

- 3 SD or 1.5% rule
- 2 SD twice or 1% twice rule
- Range of 4 SD or range of 2% rule
- Four ± 1 SD or four ± 0.5% rule
- Mean × 10 rule

When any of the Shewhart rules are confirmed, the machine is OOC and the manufacturer should be consulted to determine the cause and corrective action. Once corrective action has been taken, a new phantom baseline BMD must be established by scanning the phantom as described earlier. A new Shewhart chart can then be constructed to monitor machine performance.

CUSUM Charts

CUSUM charts are not as easy to use as Shewhart charts and rules, but these are the types of charts employed by many professional densitometry quality control centers. This technique was originally developed for use in industry *(13)* and was subsequently adapted for use in bone densitometry *(11,14,15)*. The principle underlying CUSUM charts is the expected random variation in the phantom measurement. Remember that even in a perfectly functioning machine, daily phantom BMD values are expected to randomly fall above or below the average phantom value. It other words, the daily phantom BMD value is expected to "vary about the average value." The magnitude of the variation, however, even though some measurements will be above (or greater) than the average value and some will be below (or less) than the average value, should remain relatively constant.

In order to utilize the CUSUM chart, a baseline spine phantom value must again be established by scanning the phantom 10 times consecutively or once on each of 15 to 25 consecutive days as was done previously for the application of Shewhart rules. For all subsequent scans, the difference between the average value and the subsequent value is calculated. The differences are progressively summed and plotted on the CUSUM chart. Mathematically, this is expressed in Equation 1 as:

$$CS_n = \sum_{p=1}^{n} \left(BMD_p - BMD_{Mean} \right) \tag{1}$$

where *CS* is the cumulative sum, *n* is the total number of measurements, BMD_{Mean} is the average phantom value and BMD_p is the phantom value for each of the *n* measurements. Each sequential value of *CS* is plotted on the graph. The vertical axis of the graph is marked in SD units of the average value. For a properly functioning machine, the values plotted on the CUSUM chart should be scattered in a horizontal pattern around 0 (0 is equal to the average phantom value). If the pattern is rising or falling, the machine is not functioning properly.

The construction of a CUSUM chart begins again with the data in Table 4-3. The phantom was scanned once each day for 25 consecutive days. The average value of the phantom was found to be 1.177 g/cm^2 and the SD was calculated to be 0.006 g/cm^2. Table 4-4 illustrates the calculations of the cumulative sum for the next 10 phantom measurements. Figure 4-3 illustrates the CUSUM plot for these 10 measurements and 30 additional measurements that followed. In Fig. 4-3, instead of BMD on the vertical axis, SD units or *z*-scores are utilized. The CUSUM plot for these 40 phantom scans clearly appears to be rising rather than being horizontal.

Although the CUSUM chart is inspected visually to determine machine malfunction indicated by the nonhorizontal plot, two methods have been developed to determine mathematically when control limits have been exceeded. One method involves the superimposition of a V-mask in which the slope of the arms on the mask is determined mathematically *(14)*. The slope is normally some multiple of the SE of the average phantom value. The stringency of the mask can be changed by increasing or decreasing the slope

Table 4-4
Calculation of the Cumulative Sum for Sequential Phantom Scans[a]

Date	*Phantom BMD g/cm²*	*Difference from Phantom Value g/cm²*	*Cumulative Sum of the Differences g/cm²*	*Cumulative Sum of the Differences Expressed in SD units (z-score)*
6/05/96	1.181	0.004	0.004	0.67 (0.004 ÷ 0.006)
6/06/96	1.196	0.019	0.023 (0.004 + 0.019)	4.33 (0.023 ÷ 0.006)
6/10/96	1.173	–0.004	0.019 (0.019 – 0.004)	3.17 (0.019 ÷ 0.006)
6/11/96	1.186	0.009	0.028 (0.019 + 0.009)	4.67 (0.028 ÷ 0.006)
6/12/96	1.172	–0.005	0.023 (0.028 – 0.005)	3.83 (0.023 ÷ 0.006)
6/13/96	1.186	0.009	0.032 (0.023 + 0.009)	5.33 (0.032 ÷ 0.006)
6/17/96	1.191	0.014	0.046 (0.032 + 0.014)	7.66 (0.046 ÷ 0.006)
6/21/96	1.169	–0.008	0.038 (0.046 – 0.008)	6.33 (0.038 ÷ 0.006)
6/24/96	1.195	0.018	0.056 (0.038 – 0.003)	9.33 (0.056 ÷ 0.006)
6/25/96	1.174	–0.003	0.053 (0.056 – 0.003)	8.83 (0.053 ÷ 0.006)

[a] The *z*-score of the cumulative sum is plotted on the CUSUM chart.
The average phantom value is 1.177 g/cm² and the SD is 0.006 g/cm².

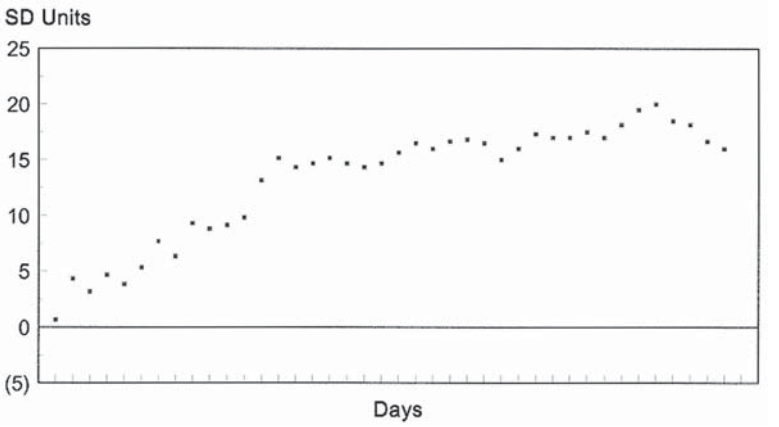

Fig. 4-3. A CUSUM chart. The values are clearly rising rather than being horizontal.

of the V-mask. The other method, called tabular CUSUM, involves the mathematical calculation of upper and lower control limits *(11)*. In either case, when values fall outside the control limits or the arms of the mask, an alarm is triggered indicating that the machine is OOC and that the manufacturer should be contacted.

The calculation of the control limits for tabular CUSUM is more tedious than complex although the equations used for these calculations appear somewhat intimidating at first. The upper control limit is calculated using Equation 2:

$$CS_{H_{max^{(i)}}} = \frac{X_i - \mu_0}{\sigma} - k + CS_{H_{max^{(i-1)}}} \quad (2)$$

Table 4-5
Tabular CUSUM Limits for the 10 Phantom Scans Shown in Table 4-4

Date	*Phantom BMD g/cm²*	$CS_{H_{max}}$	$CS_{L_{max}}$
6/05/00	1.181	0.167	0
6/06/00	1.196	2.834	0
6/10/00	1.173	1.667	0.167
6/11/00	1.186	2.667	0
6/12/00	1.172	1.334	0.333
6/13/00	1.186	2.334	0
6/17/00	1.191	4.167	0
6/21/00	1.169	2.334	0.833
6/24/00	1.195	4.834	0
6/25/00	1.174	3.834	0

The $CS_{H_{max}}$ approached but did not exceed 5. The $CS_{L_{max}}$ was reset to 0 on 7 occasions because the value fell below 0. The mean and SD for the baseline phantom values used in these calculations are 1.177 g/cm² and 0.006 g/cm², respectively.

In other words, to calculate the upper limit of the maximum cumulative sum for scan i ($CS_{H_{max}}$), subtract the average phantom value(μ_0) from the phantom value for scan i (X_i) and then divide this difference by the SD (σ) from the baseline phantom data. Now subtract the value of k which is 0.5 (this has the effect of subtracting half a standard deviation). The resulting value is then added to the value of $CS_{H_{max}}$ that had been calculated for the previous phantom scan (scan i–1). The lower limit of the maximum cumulative sum is calculated in an analogous fashion using Equation 3:

$$CS_{L_{max^{(i)}}} = \frac{\mu_0 - X_i}{\sigma} - k + CS_{L_{max^{(i-1)}}} \quad (3)$$

The process is identical except that in this case the value for phantom scan i is subtracted from the average phantom value, which is the opposite of what was done in order to calculate the upper control limit. When either of the two control limits falls below 0, the *CS* for that limit is set back to 0, the value that is then used for subsequent calculations for that *CS*. When either of the *CS* limits exceeds a value of 5, a possible machine failure is deemed to have occurred. Table 4-5 illustrates the calculation of the upper and lower CS control limits for 10 scans that were performed after the initial establishment of the baseline phantom mean value and SD previously shown in Table 4-3.

CUSUM charts or tabular CUSUM are most easily performed with the help of sophisticated statistical software programs. There is no reason however that clinical densitometry centers cannot employ CUSUM methodology although it is certainly less intuitive to use than Shewhart charts and rules.

AUTOMATED QUALITY CONTROL PROCEDURES

In recent years, densitometry manufacturers have increasingly automated quality control procedures. Calibration standards may be contained within the devices and checked routinely at the touch of a button. Quality control graphs may be generated by the system software, on which phantom values over time are plotted. Shewhart rules may be automatically applied to the results, prompting messages of Pass, Fail, or notification

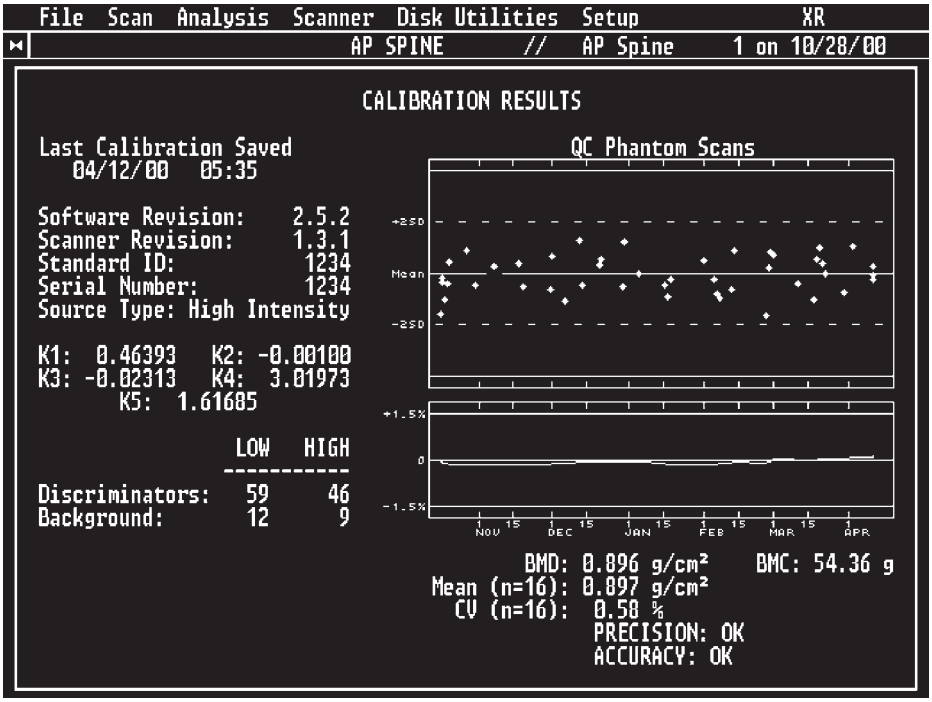

Fig. 4-4. The Norland XR-36 quality control screen. The upper Shewhart chart tracks the precision of the machine while the lower Shewhart chart tracks accuracy. Courtesy of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

of specific rule failures. Such innovations are indeed welcome but they are useless unless they are performed on a regular basis. It is also imperative that the densitometrist knows what to look for and understands the information presented.

A quality control graph from a Norland XR-Series densitometer is shown in Fig. 4-4. The upper graph reflects the precision of the system *(16)*. In the upper graph, the solid horizontal line reflects the average value for the 16 most recent scans. The dashed horizontal lines indicate ± 2 SD about the average. The value of the SD used to establish this range is a value for the phantom that is entered into the computer during the setup of the system. The BMD values of the individual scans are plotted on the graph. Approximately 1 out of every 20 scans is expected to fall outside the range defined by the average ± 2 SD simply because, statistically, this range will contain only 95% of the values. The computer will also calculate the SD for each set of 16 scans. This value is not plotted, but is used by the computer. Clearly, the average and SD will change as new phantom scans are performed and added to the set of the 16 most recent scans. This type of calculation is called a "moving average." The results are monitored for changes in the BMD as well as increases in the SD. Shewhart rules are applied to detect unacceptable changes in the BMD. The acceptable limits for an increase in the SD are calculated mathematically. If the system passes all tests, the notation of "OK" is seen after "PRECISION" at the bottom of the graph. Other messages may be seen however, which should prompt a call to the manufacturer. For example, an "OUT OF RANGE" notation indicates that the SD from the most recent 16 scans has increased beyond acceptable limits. A "WARNING 1" notation indicates that

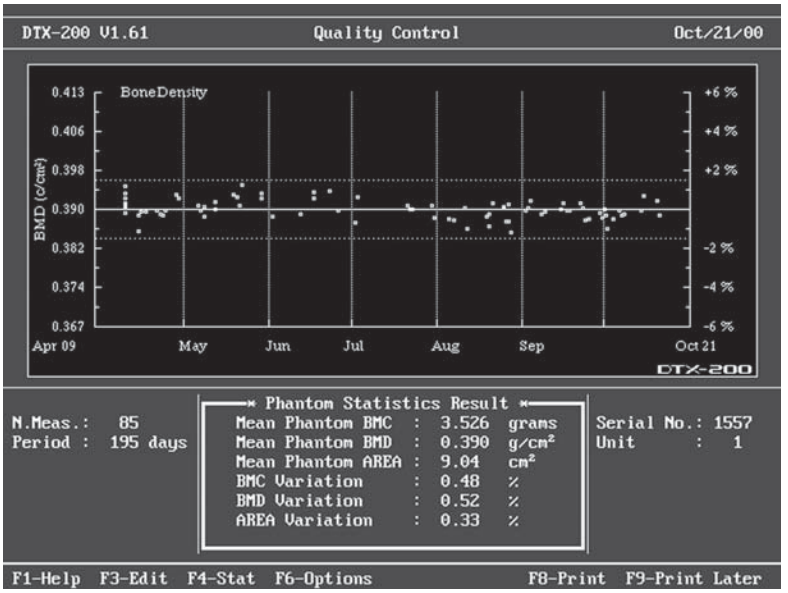

Fig. 4-5. The DTX-200 quality control screen. This is a Shewhart chart with control limits of ±1.5%.

a single phantom BMD value is more than three SDs from the average. This is a violation of the Shewhart three SD rule. "WARNING 2" is a violation of either the Shewhart two SD twice or range of four SD rule and "WARNING 3" is a violation of the Shewhart four ±1 SD rule.

The lower graph reflects the accuracy of the system *(16)*. The solid horizontal line represents the phantom BMD value that was entered into the computer during the setup of the system. The dashed horizontal lines indicate a range of ±1.5% about this value. The values plotted on this graph are the average BMD values for the last 16 phantom scans. If the average value for the 16 most recent phantom scans falls within ±1.5% of the true phantom value, "OK" will be seen next to the word "ACCURACY" at the bottom of the graph. An "OUT OF RANGE" message will appear if the value falls outside those limits. If eight consecutive values fall on the same side of the true phantom value, a "TREND WARNING" message will appear.

The quality control graphs and calculations for the Norland pDEXA® are very similar to those of the XR-Series. The control limits for the accuracy of the pDEXA® system are ±2.5% instead of 1.5% *(17)*.

Hologic scanners also provide automated quality control graphing procedures *(18)*. The BMD of a phantom is established during the initial calibration procedures for the scanner. The control limits of ±1.5% of the phantom BMD value are defined on a graph onto which subsequent spine phantom BMD data is plotted. Underneath the graph, two tables are displayed. The table titled "Reference Values" lists the average or mean value and SD for the spine phantom established during machine calibration. The table titled "Plot Statistics" lists the number of phantom scans plotted (*n*), the mean, SD, and %CV for those scans. There are no sensitizing rules built into the quality control program in the computer. With this automated plot, however, Shewhart rules are easy to apply.

Other manufacturers have automated charting of phantom values. Figure 4-5 is such a chart from the Osteometer DTX-200 DexaCare®, a dedicated DXA forearm scanner.

Table 4-6
Recommendations from the Canadian Panel of the International Society for Clinical Densitometry for Documentation of a Quality Control Program

1. Current operating manual from equipment manufacturer
2. Appropriate positioning devices
3. Appropriate calibration standard
4. Calibration history for specific densitometer
5. Precision data and estimates of site-specific precision errors
6. Maintenance and upgrade records
7. Software version/upgrade records
8. Cross-calibration records in the event of an equipment change
9. Data and database archiving procedures
10. Local, provincial, and federal licensures of equipment as required
11. Medical physicist inspection reports as required

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The dashed horizontal lines on the graph represent control limits of ±1.5%. None of the 85 phantom values has fallen outside the control limits and the values appear to be randomly scattered about the average value. If such charts are not available, they are easily created using the information in this chapter.

All densitometry centers should implement quality control procedures that minimally consist of control tables or charts with defined control limits of ±1.5% for the average of 10 phantom scans performed on 1 day or 25 scans performed on consecutive days. Shewhart rules with a filter can then be implemented, using rules defined on the basis of percent or SD, to further strengthen the quality control program. The application of CUSUM charts and calculations as performed at professional quality control centers is more labor intensive and not necessarily of greater benefit to the clinical densitometry center. The recommendations *(3)* from the Canadian Panel of the International Society for Densitometry for a complete quality control program include not only the creation of a control chart with limits of 1.5% but the maintenance of logs and manuals for each densitometer that include the items listed in Table 4-6. These recommendations are certainly appropriate for densitometry facilities in the United States as well as Canada.

REPLACING A DENSITOMETER

Densitometers are extremely durable and rarely subject to such widespread component failure that replacement of the equipment becomes necessary. Periodic software updates and upgrades to a device purchased years ago can keep that device's applications as current as most new models. Periodically, however, a densitometer must be replaced or a replacement simply becomes desirable. This creates a dilemma for the densitometrist who has been or who anticipates following serial BMD measurements in patients originally measured with the device being replaced.

Under ideal circumstances, provisions should be made to keep the old machine in use after the installation of the new machine until all patients who are currently being followed can be recalled and measured on both devices. This completes the follow-up on the old machine and creates a baseline on the new device. Alternatively, an in vivo or in vitro cross-calibration study can be performed. For an in vivo cross-calibration

study, between 60 and 100 patients will be needed whose bone densities span peak to osteoporotic values. Linear regression methods[4] can be used to develop cross-calibration equations with a standard error of the estimate[5] of around 3% *(19)*. Once the cross-calibration equation is created, it can be used to predict the value on the old machine from the value that is obtained on the new machine. With the help of a statistician or statistical software program, the 95% CI for a predicted value for an individual can be calculated.[6] If an in vivo cross-calibration study is not feasible, an in vitro study may be done using a phantom. The phantom should be scanned on both devices, 60 to 100 times over a similar period of days. Linear regression is again used to create the predictive equation. It is important to remember that linear regression equations are useful for prediction only within the range of values that were used to create the equation in the first place. In vivo and in vitro cross-calibration studies and the predictive equations that come from such studies are extremely useful but not as desirable as scanning patients being followed on both devices, as difficult as that may be.

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[4] *See* Chapter 3 for a discussion of linear regression. Many statistical calculators or software programs can be used to calculate the regression equation.

[5] The standard error of the estimate (SEE) is also known as the SD from the regression line. It is an estimate of the variability about the line of means predicted by the regression equation.

[6] The actual formula for calculation of the 95% CI for a predicted individual y value for a given x is:

$$[\bar{y} + b\,(x - \bar{x})] \pm t_{n-2,0.05} \sqrt{s^2_{y \cdot x}\left[1 + \frac{1}{n} + \frac{(x - \bar{x})^2}{\sum (x - \bar{x})}\right]}$$

The explanation of this formula is beyond the scope of this book. The help of a statistician or statistical software program is recommended.

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5 Bone Density Data

From DPA to DXA and Manufacturer to Manufacturer

CONTENTS

The extraordinary advances in bone density technology since the 1970s have enhanced the physician's ability to detect and manage metabolic bone disease. At the same time, these advances have created a dilemma as physicians have attempted to compare results obtained on early DPA devices with today's DXA devices. As DXA technology has advanced, data from pencil-beam systems is being compared with data from fan-array systems. Data from one manufacturer's pencil-beam DXA device may need to be compared to data from another manufacturer's pencil-beam device. This situation is not dissimilar to circumstances created during the evolution of other types of quantitative measurement techniques used in clinical medicine. For example, the measurement of some parameter in blood may have initially been performed using one type of assay, only to be later replaced by a different assay. There may be different ranges of normal, depending on the assay and even depending on the laboratory. Although it would be ideal for a patient being followed with a quantitative measurement technique for any reason to return year after year to the same laboratory to be tested using the same assay, this is not a reasonable expectation. In the context of bone densitometry, it is useful to have some ability to compare measurements originally made with DPA, to measurements being made with DXA. Additionally, the differences between the values obtained on different manufacturer's DXA devices with their respective reference ranges must be appreciated.

FROM DPA TO DXA

When DXA was approved for clinical use in 1988, it was immediately apparent that these systems offered substantial advantages over ^{153}gadolinium-based DPA systems. It was just as clear, however, that although the results obtained on any one patient with DXA were highly correlated with results from DPA, the BMD values were not identical. DPA

is rarely used today having been replaced by DXA. Nevertheless, a DPA study may be part of a patient's medical record and circumstances may arise in which a physician would like to compare the older DPA results with those from today's modern DXA devices. Several studies have looked at the relationship between DPA and DXA values. Based on the findings from these studies, predictive equations were developed to allow the user to convert one device's values to the other. There is a margin of error in these predictions, which negates drawing quantitative conclusions about the magnitude of any change in BMD that may have occurred in the interval between the two studies. The comparisons do illustrate what a clinician might expect to see in such circumstances however.

Hologic DXA and Lunar DPA

Kelly et al. *(1)* evaluated the relationship between BMD values in the spine in 85 individuals ranging in age from 21 to 78 years using the Lunar DP4, a ^{153}Gd DPA device, and the Hologic QDR-1000, a pencil-beam DXA device. The correlation for the measurement of spine BMD between the two devices was extremely good with $r = 0.98$. Not surprisingly, however, the two instruments did not give exactly the same results. Values obtained on the QDR-1000 were consistently lower than those obtained on the DP4. The equation that was derived to predict the DXA QDR-1000 values from the DPA DP4 values was:

$$QDR_{BMD} = (0.84 \times DPA_{BMD}) - 0.033$$

Pacifici et al. *(2)* evaluated lumbar spine BMD in 52 women using the Hologic QDR-1000 and the Lunar DP4. Again, the results were correlated with a statistically significant *r* value of 0.94. The values in the spine obtained with the QDR-1000 were approximately 6.8% lower than those obtained with the DP4. The equation for predicting the DP4 spine value from the measurement of spine BMD with the QDR-1000 was:

$$DPA_{BMD} = 0.0242 + (1.0727 \times QDR_{BMD})$$

A larger comparison trial was performed by Holbrook et al. *(3)* in which 176 individuals had lumbar spine bone density studies and 217 individuals had proximal femur bone density studies on both the Hologic QDR-1000 and the Lunar DP3 (an early DPA device). Once again, the values obtained with the DXA device were consistently lower than those obtained with the DPA device for both the spine and proximal femur. The average difference in this study was 16%. Nevertheless, the BMDs measured with the two devices were statistically correlated. In this study, equations were developed to allow the conversion of values obtained with the Hologic QDR-1000 to Lunar DP3 values. Equations for the BMDs in the spine were given for individual vertebrae rather than an average. The equations were:

$$L1\ DP3_{BMD} = 0.300 + (0.878 \times L1\ QDR_{BMD})$$
$$L2\ DP3_{BMD} = 0.239 + (0.944 \times L2\ QDR_{BMD})$$
$$L3\ DP3_{BMD} = 0.205 + (0.970 \times L3\ QDR_{BMD})$$
$$L4\ DP3_{BMD} = 0.152 + (1.005 \times L4\ QDR_{BMD})$$
$$Neck\ DP3_{BMD} = 0.133 + (0.977 \times Neck\ QDR_{BMD})$$
$$Ward's\ DP3_{BMD} = 0.146 + (0.983 \times Ward's\ QDR_{BMD})$$
$$Trochanter\ DP3_{BMD} = 0.012 + (1.104 \times Trochanter\ QDR_{BMD})$$

Table 5-1
The Ratio of BMD Values Obtained on the Lunar DP4, Lunar DPX and Hologic QDR-1000

Site	*DPX/DP4*	*QDR/DP4*	*QDR/DPX*
AP lumbar spine	0.90	0.78	0.87
Femoral neck	1.02	0.83	0.82
Ward's area	1.01	0.73	0.72
Trochanter	0.99	0.83	0.85

Calculated from data from ref. *6*.

Lunar DXA and Lunar DPA

BMD values in the spine obtained with the Lunar DPX, the first clinically available DXA device from what is now GE Medical Systems, were originally reported as being approximately 3% lower than those that would be obtained with a Lunar DP3. This finding was based on an initial study of 41 subjects by Mazess et al. *(4)*.

Lees and Stevenson *(5)* studied 70 subjects (2 men and 68 women) who underwent PA spine and proximal femur bone density studies using the Lunar DPX and Lunar DP3. The results between the two instruments were statistically significantly correlated. The *r* value ranged from 0.96 at Ward's area in the proximal femur to 0.98 for the L2–4 BMD. The BMD values in the lumbar spine were again lower on the DXA than on the DPA device. The equation for predicting the L2–4 BMD for the DPX from a measurement of L2–4 on the DP3 was:

$$\text{L2–4 DPX}_{\text{BMD}} = -0.110 + (1.052 \times \text{L2–4 DP3}_{\text{BMD}})$$

There was less difference between the BMD values in the femoral neck, Ward's area and the trochanter obtained on the DPX and DP3 than in the lumbar spine. Unlike the spine, the DPX values at these sites in the proximal femur were slightly *higher* than the DP3 values for the same sites. The equations for predicting the values that would be anticipated on the DPX from measurements of the proximal femur sites on the DP3 were:

$$\text{Neck DPX}_{\text{BMD}} = 0.028 + (1.002 \times \text{Neck DP3}_{\text{BMD}})$$

$$\text{Ward's DPX}_{\text{BMD}} = 0.004 + (1.031 \times \text{Ward's DP3}_{\text{BMD}})$$

$$\text{Trochanter DPX}_{\text{BMD}} = 0.043 + (0.955 \times \text{Trochanter DP3}_{\text{BMD}})$$

Hologic DXA, Lunar DXA, and Lunar DPA

The general relationship between Lunar DP4 values, Hologic QDR-1000, and Lunar DPX values is summarized in a study from McClung and Roberts *(6)*. Ninety-three subjects underwent bone density measurement on all three machines at the PA spine and proximal femur. The ratio of mean values obtained for each combination of machines is shown in Table 5-1. Note that the PA spine values obtained with either DXA device are lower than those obtained with the DP4. The three regions in the proximal femur are lower when obtained with the QDR-1000 compared to the DP4 but are slightly higher than the DP4 in the femoral neck and Ward's area when obtained with the DPX. The Hologic QDR-1000 values are consistently lower than the Lunar DPX values at all sites.

Although these equations can be used to predict DXA values from earlier DPA measurements and vice-versa, the margin of error in these equations limits their utility to *exactly* predict BMD. They can be used to *approximate* the BMD, however. This is often reassuring to the patient who has previously had a DPA study and is now undergoing a DXA study. Even if there has been no change in the BMD over time, the spine BMD on the DXA study is expected to be lower. If the DXA device is a Hologic or Norland DXA device, the BMDs in the proximal femur are also expected to be lower. If the DXA device is a Lunar device, the BMDs in the proximal femur may be slightly higher.

DXA: FROM LUNAR TO HOLOGIC TO NORLAND

The central DXA devices from all the major manufacturers have inherently superb accuracy and precision in quantifying the bone density at virtually any skeletal site. The BMD obtained on any one machine, however, will not be identical to the BMD obtained on a device from a different manufacturer. Comparison studies using combinations of machines provide conversion equations for the measurement of bone density on one device to the anticipated value on another device.

The Hologic QDR-1000, the Lunar DPX and the Norland XR-26 were compared in an in vitro study by Arai et al. *(7)*. Solutions of various concentrations of potassium phosphate enclosed in an acrylic resin and submerged in water were used to simulate bone and soft tissue. The various concentrations of potassium phosphate were measusred on each of the three machines to determine both the accuracy of the machines and the correlation between the BMDs measured by each of the machines. Each machine accurately measured the BMD. The correlation between each pair of machines was highly statistically significant with an *r* value of 0.9999. The measured values were not identical however. Values obtained with the Lunar DPX were 8.08% higher than those obtained with the Norland XR-26 and 4.96% higher than those obtained with the Hologic QDR-1000. The QDR-1000 values were 2.96% higher than those obtained with the XR-26. An anthropomorphic Hologic spine phantom was also used in this study to compare the three DXA devices. The spine phantom was scanned 10 times on each manufacturer's machine. The BMD values obtained on the Lunar DPX were 16% higher than those obtained on the XR-26, whereas the values obtained on the QDR-1000 were 1.5% lower than the XR-26.

Hologic DXA and Norland DXA

In vivo comparisons of spine measurements made using the Norland XR-26 and the Hologic QDR-1000 were conducted by Lai et al. *(8)* in 65 subjects. The correlation for BMD at the spine was 0.990 and was highly significant. BMDs obtained on the Norland XR-26 tended to be lower than those obtained on the QDR-1000. The equation for predicting the Hologic BMD from the measurement of BMD on the Norland XR-26 was:

$$\text{Hologic QDR 1000 Spine}_{BMD} = -0.1 + (1.09 \times \text{Norland XR-26 Spine}_{BMD})$$

Lunar DXA and Hologic DXA

The Lunar DPX and the Hologic QDR-1000 were compared in a study of 46 women by Pocock et al. *(9)*. These women underwent lumbar spine and proximal femur studies on both machines on the same day. The correlations were extremely good with *r* values of 0.98, 0.94, 0.96, and 0.96 for the lumbar spine, femoral neck, Ward's area, and the trochanter, respectively. The absolute BMD values were 16% lower on the QDR-1000

Table 5-2
Conversion Formulas for BMDs of the AP Spine Between DXA Devices

Hologic QDR-2000 $Spine_{BMD}$	=	$(0.906 \times$ Lunar DPX-L $Spine_{BMD}) - 0.025$
Hologic QDR-2000 $Spine_{BMD}$	=	$(0.912 \times$ Norland XR 26 $Spine_{BMD}) + 0.088$
Lunar DPX-L $Spine_{BMD}$	=	$(1.074 \times$ Hologic QDR 2000 $Spine_{BMD}) + 0.054$
Lunar DPX-L $Spine_{BMD}$	=	$(0.995 \times$ Norland XR 26 $Spine_{BMD}) + 0.135$
Norland XR-26 $Spine_{BMD}$	=	$(0.983 \times$ Lunar DPX-L $Spine_{BMD}) - 0.112$
Norland XR-26 $Spine_{BMD}$	=	$(1.068 \times$ Hologic QDR 2000 $Spine_{BMD}) - 0.070$

Adapted from ref. *10* with permission from the American Society for Bone and Mineral Research.

in the spine when compared to the DPX and 17% lower in the femoral neck. The equation for predicting the QDR BMD in the femoral neck based on a measurement of BMD in the femoral neck on the Lunar DPX was:

$$\text{QDR Femoral Neck}_{BMD} = 0.007 + (0.76 \times \text{DPX Femoral Neck}_{BMD})$$

This is in keeping with the study from McClung and Roberts *(6)*, in which the ratios of Hologic QDR values to Lunar DPX values at these sites as seen in Table 5-1 suggested similar findings.

STANDARDIZATION OF ABSOLUTE BMD RESULTS

It is clear from the extremely good correlations between DXA measurements of BMD at the spine and proximal femur using the central devices from the major manufacturers in the United States that these devices are indeed measuring the same thing. The measured BMD values obtained on the various machines may differ markedly because of differences in calibration and bone edge detection algorithms among the machines. Because of this, there has been a great deal of interest in developing a standardized BMD to which all DXA results could be converted, regardless of which manufacturer's machine was used.

Standardization of Central DXA Absolute BMD Values

In November 1990, the major manufacturers of DXA equipment agreed to work together in the area of standards as part of an international committee, known as the International Committee for Standards in Bone Measurement. Under the auspices of this committee, a study of 100 healthy women *(10)* was performed in which each of the women underwent PA spine and proximal femur studies on the Hologic QDR-2000, the Norland XR-26 Mark II, and the Lunar DPX-L. The women ranged in age from 20 to 80, with an average age of 52.6 years. The difference in PA lumbar spine BMD was greatest between the Norland XR-26 and the Lunar DPX-L, averaging 0.118 g/cm^2 or 12.2%. The average difference between the Lunar DPX-L and the Hologic QDR-2000 was 0.113 g/cm^2 or 11.7%. The average difference in BMD at the PA lumbar spine between the Norland XR-26 and the Hologic QDR-2000 was the smallest at only 0.012 g/cm^2 or 1.3%.

Based on this data, equations were derived for the conversion of PA lumbar spine BMD obtained on any one of these manufacturer's machines to the BMD that would be expected to be obtained on each of the other two. The equations for each of the three pairs of scanners are shown in Table 5-2.

Table 5-3
Formulas for the Conversion of Manufacturer-Specific PA Spine BMDs to the Standardized BMD (sBMD)

$sBMD_{SPINE} = 1000\ (1.0761 \times \text{Norland XR-26 } BMD_{SPINE})$
$sBMD_{SPINE} = 1000\ (0.9522 \times \text{Lunar DPX-L } BMD_{SPINE})$
$sBMD_{SPINE} = 1000\ (1.0755 \times \text{Hologic QDR-2000 } BMD_{SPINE})$

Adapted from ref. *9* with permission from the American Society for Bone and Mineral Research.

Table 5-4
Conversion Formulas for BMDs in the Femoral Neck Between DXA Devices

Hologic QDR-2000 $Neck_{BMD}$	=	$(0.836 \times \text{Lunar DPX-L } Neck_{BMD}) - 0.008$
Hologic QDR-2000 $Neck_{BMD}$	=	$(0.836 \times \text{Norland XR 26 } Neck_{BMD}) + 0.051$
Lunar DPX-L $Neck_{BMD}$	=	$(1.013 \times \text{Hologic QDR 2000 } Neck_{BMD}) + 0.142$
Lunar DPX-L $Neck_{BMD}$	=	$(0.945 \times \text{Norland XR 26 } Neck_{BMD}) + 0.115$
Norland XR-26 $Neck_{BMD}$	=	$(0.961 \times \text{Lunar DPX-L } Neck_{BMD}) - 0.037$
Norland XR-26 $Neck_{BMD}$	=	$(1.030 \times \text{Hologic QDR 2000 } Neck_{BMD}) + 0.058$

Adapted from ref. *10* with permission from the American Society for Bone and Mineral Research.

In order derive an equation to convert each manufacturer's reported BMD to a standardized BMD (sBMD), the ESP[1] was scanned on each of the three devices. Equations were developed based on the BMD value for the central vertebra of the ESP averaging 1000 mg/cm^2 when scanned on each of the devices. These formulas are shown in Table 5-3. In November 1994, the Committee for Standards in DXA approved these formulas for the standardization of PA spine BMD values *(11)*. Using these formulas, a PA spine sBMD obtained by scanning a patient on a Norland, Hologic, or Lunar DXA device should be within 2 to 5% of the sBMD that would be obtained when the patient was scanned on either of the other two devices.

The value for the sBMD is multiplied by 1000 to convert it to *mg/cm^2* rather than reporting it as g/cm^2. This serves to readily distinguish the sBMD from the nonstandardized value. In other words, if the BMD obtained in the spine on a Lunar DPX-L is 0.985 g/cm^2, this value becomes 938 mg/cm^2 when reported as the sBMD (0.985 × 0.9522 = 0.9379 g/cm^2 × 1000 = 938 mg/cm^2). Using these formulas to convert the average spine BMD in the study population to the sBMD, the differences in BMD between the three machines were greatly reduced. Instead of an average difference of 12.2% between the Norland and Lunar values, the difference in the sBMD was only 2.8%. The difference between Hologic and Lunar was reduced to 2.2% and the difference between Hologic and Norland was 2.7%.

Conversion formulas were also developed by Genant et al. *(10)* for the femoral neck for each pair of scanners. These formulas are shown in Table 5-4.

In December 1996, the International Committee for Standards in Bone Measurement[2] approved formulas for the sBMD for the total femur region of interest *(12)*. The total

[1] *See* Chapter 4 for a discussion of the ESP.
[2] Formerly the Committee for Standards in DXA.

Table 5-5
Formulas for the Conversion of Manufacturer-Specific Total Femur BMD to the Standardized BMD (sBMD)

$sBMD_{TOTAL\ FEMUR}$	=	$1000\ [(1.008 \times \text{Hologic } BMD_{TOTAL\ FEMUR}) + 0.006]$
$sBMD_{TOTAL\ FEMUR}$	=	$1000\ [(0.979 \times \text{Lunar } BMD_{TOTAL\ FEMUR}) - 0.031]$
$sBMD_{TOTAL\ FEMUR}$	=	$1000\ [(1.012 \times \text{Norland } BMD_{TOTAL\ FEMUR}) + 0.026]$

From ref. *12*.

femur region of interest includes the femoral neck, Ward's area, the trochanter, and the shaft of the proximal femur. This region appears to have equal diagnostic utility but better precision than the femoral neck. The formulas for the sBMD for the total femur, shown in Table 5-5 were based on the work by Genant et al. *(10)* from which the formulas for sBMD of the spine were also derived. The sBMD from any one of the three central DXA devices should fall within 3 to 6% of the sBMD on any of the other two.

Standardization of DXA BMD Results for the Femoral Neck, Trochanter, and Ward's Area

In 2001, Lu et al. *(13)* developed equations for an sBMD for the femoral neck, trochanter, and Ward's area based on information obtained from studies of the same 100 women whose data was previously used to create formulas for the sBMD of the spine and total femur *(10,12)*. The authors developed site-specific standardization formulas for the hip subregions. They compared the utility of the subregion formulas in reducing the disparity in BMD results among the three manufacturers' devices to that of the total femur standardization formulas developed previously when both sets of formulas were applied to the hip subregions. The authors applied the formulas to bone density data from a multicenter clinical trial involving 3139 postmenopausal women. Bone density data was acquired on 51 Hologic, 17 Lunar, and 2 Norland DXA scanners. Table 5-6 shows the difference between scanners for each subregion depending on whether no calibration, the total femur, or subregion calibration was used. The site-specific subregion formulas were clearly superior in reducing the disparity between the machine specific subregion values compared to the total femur standardization formulas. As shown in Table 5-6, the overall variation in values at the femoral neck that appeared to be the result of using different manufacturer's scanners was 42%. Use of the total hip sBMD formula reduced this variation to 20%, whereas use of the specific femoral neck sBMD formula reduced the variation to 0.2%. The basic formula for calculating the sBMD for the various regions in the proximal femur from the manufacturer's data is as follows:

$$sBMD = 1000\ [a + (b \times BMD)]$$

In this formula, a and b are regression parameters and are shown in Table 5-7 for each scanner type and subregion. Multiplying by 1000 as shown in the formula converts the original units of g/cm^2 to mg/cm^2 as was done for the sBMD of the PA spine and total femur.[3] The actual standardization formulas for the three subregions in the proximal femur are shown in Table 5-8.

[3] The terms total hip and total femur are used interchangeably. Neither is exactly correct but total femur is preferred.

Table 5-6
Comparison of Baseline Mean BMD Among Manufacturers With and Without Standardization by Different Formulas

		Mean BMD Differences Between Scanner Types (mg/cm²)				
ROI	*BMD*	*Hologic-Lunar*	*Hologic-Norland*	*Lunar-Norland*	*R^2 (%)[a]*	*p Value[b]*
FN	No Calibration	–130[c]	–64[c]	66[c]	42	<0.001
	Total Hip Calibration	–73[c]	–53[c]	–20[c]	20	<0.001
	FN Calibration	6	5	0	0.2	0.0795
TR	No Calibration	–96[c]	–31[c]	65[c]	21	<0.001
	Total Hip Calibration	–41[c]	–20[c]	21[c]	5	<0.001
	TR Calibration	16[c]	4	12	0.6	<0.001
W	No Calibration	–165[c]	–69[c]	95[c]	43	<0.001
	Total Hip Calibration	–112[c]	–59[c]	53[c]	24	<0.001
	W Calibration	29[c]	7	–22[c]	2.6	<0.001

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[a]R^2 is the percentage of BMD variation explained by scanner types with a lower value meaning less variation among manufacturers in the measured value.

[b]*p* value is based on *F*-test for the effect of manufacturers.

[c]$p < 0.001$.

ROI, region of interest; BMD, bone mineral density; FN, femoral neck; TR, trochanter; W, Ward's area.

Table 5-7
Standardization Formulas for Hip Subregions and Total Hip

Manufacturer	*Parameter*	*FN*	*TR*	*W*	*Total Hip*
Hologic	a	0.019	–0.017	0.101	0.006
	b	1.087	1.105	0.940	1.008
Lunar	a	–0.023	–0.042	–0.106	–0.031
	b	0.939	0.949	0.980	0.979
Norland	a	0.006	0.057	0.001	0.026
	b	0.985	0.961	1.091	1.012

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FN, femoral neck; TR, trochanter; W, Ward's area

Table 5-8
Standardization Formulas for Proximal Femur Subregions

$$sBMD_{FEMORAL\ NECK} = 1000\ [(1.087 \times Hologic\ BMD_{FEMORAL\ NECK}) + 0.019]$$
$$sBMD_{FEMORAL\ NECK} = 1000\ [(0.939 \times Lunar\ BMD_{FEMORAL\ NECK}) - 0.023]$$
$$sBMD_{FEMORAL\ NECK} = 1000\ [(0.985 \times Norland\ BMD_{FEMORAL\ NECK}) + 0.006]$$
$$sBMD_{TROCHANTER} = 1000\ [(1.105 \times Hologic\ BMD_{TROCHANTER}) - 0.017]$$
$$sBMD_{TROCHANTER} = 1000\ [(0.949 \times Lunar\ BMD_{TROCHANTER}) - 0.042]$$
$$sBMD_{TROCHANTER} = 1000\ [(0.961 \times Norland\ BMD_{TROCHANTER}) + 0.057]$$
$$sBMD_{WARD'S} = 1000\ [(0.940 \times Hologic\ BMD_{WARD'S}) + 0.101]$$
$$sBMD_{WARD'S} = 1000\ [(0.980 \times Lunar\ BMD_{WARD'S}) - 0.106]$$
$$sBMD_{WARD'S} = 1000\ [(1.091 \times Norland\ BMD_{WARD'S}) + 0.001]$$

Derived from Lu et al. Ospeoporos Int 2001;12:438–444.

sBMD, standardized bone mineral density; BMD, bone mineral density.

Table 5-9
Standardization Equations for the Ultradistal, Mid, and Proximal Forearm for Four DXA Devices

suBMD	=	(0.945 × PIXI BMD) + 0.015
suBMD	=	(1.158 × Hologic Radius + Ulna Ultradistal BMD) – 0.019
suBMD	=	(0.802 × Osteometer BMD) + 0.071
suBMD	=	(1.027 × Norland Distal BMD) + 0.084
smBMD	=	(1.011 × PIXI BMD) + 0.033
smBMD	=	(0.894 × Hologic Radius + Ulna Mid BMD) – 0.030
smBMD	=	(0.856 × Osteometer BMD) + 0.094
smBMD	=	(1.106 × Norland Distal BMD) + 0.105
spBMD	=	(1.091 × PIXI BMD) + 0.119
spBMD	=	(0.861 × Hologic Radius + Ulna 1/3BMD) + 0.020
spBMD	=	(0.917 × Osteometer BMD) + 0.188
spBMD	=	(0.596 × Norland Proximal BMD) + 0.114

suBMD, standardized BMD for the ultradistal region; smBMD, standardized BMD for the midregion; spBMD, standardized BMD for the proximal region.

From ref. *14* with permission of the American Society for Bone and Mineral Research.

Standardization of Forearm DXA Results

The difficulty in creating an sBMD for forearm bone density is compounded by the multitude of potential sites in the forearm and the different definitions of those sites among the various manufacturers of forearm measurement devices. Shepherd and colleagues *(14)* have developed standardization equations for the ultradistal, mid, and proximal forearm for six devices, five of which employ DXA. The sixth device utilized radiogrammetry. The study was commissioned by the International Committee for Standards in Bone Measurement. The DXA devices used in the study were the Hologic QDR-4500A, the Osteometer DTX-200, the Aloka DCS-600EX,[4] the Lunar PIXI and the Norland pDEXA. The Pronosco X-posure System,[5] which utilizes computer-assisted radiogrammetry, was the sixth device used.

One hundred and one women, aged 20 to 80 years, with 13 to 19 subjects per decade were studied on each of the six devices. Women were excluded if they were pregnant, had a history of distal radial fracture, or had any bone diseases other than osteoporosis. Seventy-four percent of the women were white.

The regions of interest on the forearm with the six devices in question varied considerably.[6] The PIXI and the DTX-200 measured only one region of interest (ROI) on the forearm and although similar, the two regions were not identical in location or size. Similarly, the pDEXA measures a distal and proximal ROI, whereas the QDR-4500A measures three regions of interest, two of which are similar, but not identical to the distal and proximal regions found on the pDEXA. There was no attempt to alter the manufacturers' ROIs in this study. In order to develop equations for all six devices for the ultradistal, mid, and proximal forearm, the single ROI from the PIXI and DTX-200 was used for all three sites. The distal ROI on the pDEXA was used in the standardized BMD equation for the midregion as well as the distal region. The standardized BMD equations for the four DXA devices available in the United States are shown in Table 5-9. The

[4] This device is not available in the United States.

[5] The device used in this study is no longer sold in the United States but is FDA-approved for clinical use.

[6] *See* Chapter 2 for a discussion of the various regions of interest in the forearm.

authors noted that these equations are specific for the devices in this study. Unlike the sBMD for the spine and proximal femur, the sBMD values for the forearm sites are reported in the original units of the measurement for the particular device.

The Utility of the sBMD

The sBMD is attractive as a means of comparing a BMD value obtained on one manufacturer's device with a BMD value obtained on another. This is useful in large population studies and clinical trials in which devices from several manufacturers must be used. The root-mean-square (RMS) error in the calculation of the sBMD is estimated to be 4% for the PA spine and total femur and even larger for the proximal femur subregion *(13)*. This error is simply too large to base important clinical decisions on the comparison of sBMD values obtained on different devices for an individual.

FROM DXA MACHINE TO DXA MACHINE WITHIN MANUFACTURERS

It is not uncommon for patients to have had a DXA study at another facility that must be compared to a DXA study at a second facility. Even if the studies have been performed on DXA machines from the same manufacturer, the results may vary slightly. If the machines have been properly calibrated and maintained using good quality control measures, the differences should be minimal. In a study performed at three different locations, three men and two women underwent duplicate total body and lumbar spine bone density studies at each location *(15)*. The studies were performed on a Lunar DPX-L at one site and on a Lunar DPX at the other two locations. The differences in total body BMD among the three locations were less than 1.2% and the differences in lumbar spine BMD were less than 1.7%. When this is expressed as the %CV[7] between testing locations, the %CV for total body BMD between sites was 0.7% and for the lumbar spine, 1.4%. Two similar studies using the Hologic QDR-1000 also demonstrated good agreement between BMD studies performed at different locations using Hologic DXA devices. The %CV between 13 locations in one study was 1.4% for the spine and 2.1% for the hip *(16)*. In a second study, the %CV at the spine between eight locations for in vitro phantom measurements was 0.92%. For in vivo measurements on two subjects, the %CV at the spine was 3.68% and 1.85% at the femoral neck *(17)*. Kolta et al. *(18)* studied the accuracy and precision of 62 DXA densitometers (51 Hologic, 11 Lunar) using the ESP.[8] The phantom was scanned five times without repositioning on each densitometer. In general, the results among devices from the same manufacturer were highly comparable, with 95% confidence limits of agreement of ±0.026 g/cm^2 for Hologic devices and ±0.025 g/cm^2 for Lunar devices for in vitro BMD. Large differences were observed, however. Extreme differences between devices from the same manufacturer were as much as 5.4% for Hologic and 3.6% for Lunar. Although some of the intersite variation seen in in vivo studies may be due to differences in positioning or analysis, differences in machine calibration may explain the variation seen in in vitro studies. Kolta et al. *(18)* noted that only 36% of the devices in their study were calibrated within ±0.5% and only 60% were calibrated within ±1%. In contrast, Gaither et al. *(19)* found that 73% of 128 DXA devices (61 Hologic, 67 Lunar) were

[7] *See* Chapter 3 for a discussion of the %CV.
[8] *See* Chapter 4 for a description of the ESP.

calibrated within ±0.5% and 91% were within ±1.0%. These authors also noted a worst-case difference of 5% between devices from the same manufacturer.

These types of differences between machines from the same manufacturer are generally not large enough to cause any problems in the diagnosis of low bone mass or the prediction of fracture risk, but they do present additional problems in the serial assessment of changes in BMD. Clearly, intersite variation between machines from the same manufacturers can be much larger than that indicated here if strict quality control and consistently correct positioning and analysis procedures are not observed at the densitometry facility.

FROM PENCIL-BEAM TO FAN-ARRAY DXA DATA

The latest generation of central DXA scanners are fan-array scanners that were first introduced with the Hologic QDR-2000 *(20)*. The terminology reflects a change in design in these scanners in which a fan-shaped beam is projected through an entire scan line and captured by an array of detectors. This is markedly different from the earlier pencil-beam devices in which a very narrow X-ray beam was projected in a plane that was perpendicular to the region of interest. This narrowed beam moved in tandem with a single detector in a rectilinear path across the region of interest. Fan-array technology such as that found on the Hologic QDR-4500 and the Lunar Prodigy produces extraordinary skeletal image resolution and faster scan speeds. The extraordinary images such as those seen in Figs. 1-12 to 1-15 are utilized for skeletal morphometry. Dual-energy Vertebral Assessment™ (DVA™) and Instant Vertebral Assessment™ (IVA™) images of the spine are approved by the Food and Drug Administration for structural diagnosis, such as fracture. The physical dimensions of the proximal femur can be accurately and precisely measured with today's sophisticated computers as well. Some of these dimensions have been shown to be independent predictors of hip fracture risk as discussed in Chapter 10.

The difference in design between pencil-beam systems and fan-array systems introduced an additional issue in comparing data generated on any manufacturer's pencil-beam device to data generated on the same manufacturer's fan-array device. Because the imaging geometry is different with fan-array densitometers, there can be some magnification of the image that is dependent on the distance of the region of interest from the beam and detectors and the angle of the beam. Theoretically, the BMC and area measurement should be altered to a similar degree causing a minimal effect on BMD (because BMD is calculated by dividing BMC by area). The effect has been estimated as approximately 3%/cm for BMC and area but under 0.5%/cm for BMD *(21–23)*.

Using the Hologic spine phantom, Eiken et al. *(24)* compared the measurement of area, BMC, and BMD on the Hologic QDR-1000/W, a pencil-beam device, with that obtained on the Hologic QDR-2000, a fan-array device. As predicted, the BMC and area increased to a similar degree leaving the BMD unchanged when measurements were obtained on the QDR-2000 compared to the QDR-1000/W. Blake et al. *(22)* confirmed these findings using both spine phantom and spine and hip measurements on 20 subjects.

In a larger study, Faulkner et al. *(25)* evaluated the differences in BMD in the spine and proximal femur using the Hologic QDR-1000/W and the Hologic QDR-2000. Sixty-nine women underwent PA spine and proximal femur studies on both devices. At the spine, there were no statistically significant differences observed in the BMC, area, or BMD between the pencil-beam and fan-array device, although the BMD obtained with the fan-array device was slightly higher. In the proximal femur, BMD values obtained with the

fan-array device were again all slightly higher than those obtained with the pencil-beam device. Although the differences in BMD for all regions in the proximal femur except the femoral neck were *statistically* significant between the two devices, the *actual* differences were *extremely small*. Similarly, BMC and area measurements were all slightly increased when obtained on the fan-array device for all regions in the proximal femur with the exception of the femoral neck.

Mazess and Barden *(26)* compared results obtained in 111 individuals on the Prodigy, a fan-beam device and the DPX-IQ, a pencil-beam device. The average values from duplicate scans on the Prodigy were compared to single scans on the DPX-IQ. The mean difference in PA spine BMD between the two densitometers was 0.002 g/cm^2. The mean difference in both femoral neck and total body BMD was 0.006 g/cm^2. These values were less than 1% of the mean BMDs in the various regions.

The differences in BMD between pencil-beam and fan-array devices are not large enough to be clinically significant in terms of the accuracy of the measurement or comparisons to the reference databases developed using pencil-beam devices. The differences can introduce an additional source of error into serial measurements, however. This potential change in BMD, which is the sole result of changing from a pencil-beam to a fan-array system, must be kept in mind if the physician attempts to compare scans obtained on a patient over a period of time that were acquired using first one device and then the other.

REFERENCE DATABASES

Two of the most common applications of bone densitometry are the diagnosis of osteoporosis and the assessment of fracture risk. These applications depend on comparisons of the BMD to the reference database that is supplied by the manufacturer of the bone densitometry equipment. The diagnosis of osteopenia or osteoporosis using WHO criteria depend on comparing the patient's BMD to the average peak BMD of the young adult and noting how many SDs below this value the patient's value lies. In other words, the diagnosis depends on the *T*-score.[9] Most fracture risk data in the medical literature is presented as the increase in relative risk per SD decline in bone density from the age-adjusted mean bone density for the population that was studied.[10] Relative fracture risk for an individual patient is often calculated using this published data and the *T*-score or the *z*-score, although neither is technically correct. Lifetime or 10-year fracture risk probabilities are determined using a patient's *T*-score. Qualitative assessments of fracture risk typically utilize *T*-score cut points that coincide with the WHO criteria for the diagnosis of osteopenia and osteoporosis. Diagnosis and fracture risk predictions depend not solely on the measurement of bone density but also on the standard scores that are determined from comparisons to the reference databases.

It is logistically impossible to have every member of the population in a given country undergo bone density measurements to create a reference database. Therefore, a sample of the population is studied to create a "reference" population. From this sample population, the average BMD value for the young adult and for each age group is calculated. Depending on the make-up of the individuals in the sample, a slightly different average or mean BMD will be obtained with each sample of the population that is studied. As seen in Chapter 3, the SD (upon which the *T*-score or young-adult *z*-score are based) that is

[9] *See* Chapter 3 for a discussion of the derivation of the *T*-score.
[10] *See* Chapter 10 for a discussion of predicting fracture risk with bone densitometry.

calculated for the values from any given sample, is dependent on the average value of the sample and the number of individuals that make up that sample. Thus, the SD will also vary from sample to sample. Once the data are collected, different statistical methods can be employed to create the reference curves for the population. In the creation of reference databases, each manufacturer has necessarily utilized a different sample of the population and then applied the statistical methods that seemed most appropriate for that sample.

These statistical and design issues confound the recognized systematic differences in the measurement of bone mass and density between the different manufacturers' devices. The BMD values from one machine can be converted using the calibration equations noted previously to another manufacturer's machine. The BMD values can also be converted to an sBMD. This has no effect on the *T*-score or *z*-score however because the average BMD and SDs obtained from the different samples within a population used to create the various reference databases will be different.

Pocock et al. *(9)* observed the effect of differences in the reference databases between the Hologic QDR-1000 and the Lunar DPX on the percent young-adult and percent age-matched comparisons for the spine and femoral neck after studying 46 women. The percent comparisons for the spine tended to be very similar on the two devices. At the femoral neck however, the percent young-adult comparisons were 6.2% lower on the QDR-1000. The percent age-matched comparisons were 3.3% lower on the QDR-1000.

Other authors confirmed these observations. Laskey et al. *(27)* noted the effect of the differences in databases used for the Lunar DPX and the Hologic QDR-1000 for spine and proximal femur bone density. Fifty-three subjects underwent spine and proximal femur bone density measurements on the same day on both devices. Laskey, like Pocock, found that the comparisons of the measured BMD to the reference database for the young-adult or age-matched adult in the spine were similar. In the regions in the proximal femur, however, the differences were substantial. The magnitude of the difference approximated 1 SD. This difference was sufficient to potentially have clinical ramifications. For example, when applying the WHO BMD criteria for the diagnosis of normalcy, osteopenia or osteoporosis, a 1 SD difference could result in a different diagnosis depending on which manufacturer's machine was used.

This problem was also studied by Faulkner et al. *(28)*. *T*-scores and young-adult *z* scores[11] at the spine were compared for 83 women and in the proximal femur for 120 women who underwent bone density studies on a Lunar DPX and Hologic QDR-1000/W. The difference between the *T*-scores on the QDR-1000/W and the young-adult *z*-scores on the Lunar DPX at the spine was not statistically or clinically significant as it was less than 0.1 SD. At the femoral neck however, there was a systematic difference of 0.9 SD.

Faulkner et al. observed that these differences in the reference databases could be due to a combination of factors: different inclusion criteria, relatively small numbers of individuals used to calculate the average and SD young-adult values, and different statistical methods employed in the calculation of the reference curves. Faulkner suggested correcting the proximal femur data from both manufacturers by employing proximal femur data that was obtained during the NHANES III study of the US population.

[11] The *T*-score and young-adult *z*-score are conceptually identical. At the time of this study, the standard score comparison to the average peak BMD was called the "young-adult *z*-score" on Lunar devices. The same comparison on Hologic devices was called the *T*-score. Lunar devices today utilize the *T*-score terminology.

The initial publication of NHANES III bone density data in 1995 *(29)* reported data collected between 1988 and 1991 using the Hologic QDR-1000. In this data set there were 194 non-Hispanic white women aged 20 to 29 whose bone density was used to calculate the young-adult average BMD value and SD in five regions in the proximal femur. The average BMD in the femoral neck for these young adults from NHANES III was 0.849 g/cm^2 with a SD of 0.11 g/cm^2. Faulkner substituted these values for the femoral neck young adult average and SD values used in the QDR-1000 reference database of 0.895 g/cm^2 and 0.10 g/cm^2, respectively. The equivalent Lunar DPX BMD young-adult BMD was then calculated using the cross-calibration equation from Genant et al. *(10)*. This resulted in a Lunar value of 1.000 g/cm^2 for the average young-adult BMD in the femoral neck compared to the value of 0.980 g/cm^2 used in the manufacturer-supplied database prior to October 1997. The SD for the young-adult of 0.11 g/cm^2 from NHANES III was substituted for the Lunar reported SD of 0.12 g/cm^2. When the *T*-scores and young-adult *z*-scores were recalculated for each machine using the values based on the NHANES III data, the differences between the two manufacturers' databases largely disappeared.

NHANES III was conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention. The first phase of bone density data collection occurred from 1988 to 1991. A second data collection phase took place from 1991 to 1994. There were no specific inclusion or exclusion criteria used to select individuals for bone density measurements in this study other than the presence of prior hip fracture or current pregnancy, which were grounds for exclusion. The individuals who received bone density measurements were otherwise part of a random sample of the population of the United States. During the first phase, proximal femur bone density data was collected on 7116 men and women aged 20 and older *(29)*. There were 3217 non-Hispanic whites, 1831 non-Hispanic blacks, and 1840 Mexican-Americans in this study population. The addition of bone density data from the second phase increased the total sample to 14,646 men and women age 20 and older, 6181 of whom were non-Hispanic whites, 4021 who were non-Hispanic blacks, and 3858 who were Mexican-Americans *(30)*. In this much larger sample, the non-Hispanic white female young-adult average values and SDs are based on 409 women rather than the 194 women used for this calculation from the phase 1 data only. The updated average BMD at the femoral neck for 20- to 29-year-old non-Hispanic white women from the complete NHANES III database was 0.858 g/cm^2 with an SD of 0.120 g/cm^2. At the total femur, the peak BMD was 0.942 g/cm^2 with an SD of 0.122 g/cm^2. The complete NHANES III non-Hispanic white database is found in Appendix IX.

All three major manufacturers of central DXA devices provide extensive reference databases for their machines. Methodological descriptions of the acquisition of these databases can be found in the operator's manuals for the devices and elsewhere. More detailed descriptions of the databases currently in use in the United States are found in Appendices X–XII.

With the development of the cross-calibration equations between manufacturers and the sBMD for the total femur, it became possible for the proximal femur data from NHANES III to be adopted as a common femur database for manufacturers even though the data was obtained solely on Hologic DXA devices. Based on the equations for sBMD, the total femur mean sBMD for US white women aged 20 to 29 using the NHANES III reference data is 955 mg/cm^2 with an SD of 123 mg/cm^2 *(30)*. Age-specific reference data using the sBMD for the total femur from NHANES III are shown in Appendix IX.

Standardized NHANES III proximal femur data are offered as part of the reference databases by manufacturers, either in conjunction with the manufacturer-derived databases or as a replacement for the manufacturer-derived proximal femur data after September 1997.

These database methodologic issues and their potential clinical ramifications remain for the spine and peripheral skeletal sites. NHANES III for the proximal femur is the only common reference database in use. Studies of other skeletal sites have suggested that a common reference database would reduce or eliminate diagnostic disagreement between different manufacturers' devices at those sites as well *(31,32)*. At present, however, there is no common database among the various devices for the PA or lateral spine, forearm sites, heel, or phalanges as measured by any technique.

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6 The Effects of Age, Disease, Procedures, and Drugs on Bone Density

CONTENTS

A bone density measurement is a quantitative assessment made at a single point in time. Although the measurement is accurate, the test itself cannot provide any insight into why the density is what it is at that moment. To interpret quantitative bone density results and place them in their proper context, a clinician must be knowledgeable about the effects of age, disease, and drugs on bone density. When an abnormally high or low bone density is found, a densitometrist is expected to provide a differential diagnosis for potential causes of the abnormality. Knowledge of the diseases that can affect bone density at various skeletal sites is imperative. If a clinician wishes to determine if a disease process is affecting bone density, the sites that are potentially affected by that disease process must be known in order to choose the appropriate skeletal region to measure. Similarly, if the effect of a disease process on bone density is to be followed over time, the expected magnitude of the change must be known in order to choose the appropriate interval between measurements.[1] The skeletal sites affected by certain drugs and the magnitude of changes over time from those drugs must also be appreciated for similar reasons. All of this must be interpreted against the background of the expected age-related changes in bone density. Brief summaries of the effects of age, disease, procedures, and drugs on the skeleton follow. The reader is referred to the cited references for more detailed descriptions of the actual studies.

AGE-RELATED CHANGES IN BONE DENSITY

There is general agreement that bone density peaks relatively early in life and then tends to decline from a process that is called "age-related" bone loss. The exact age of attainment of peak bone density at the various skeletal sites remains controversial, as does

[1] *See* Chapter 11 for a discussion of the interval between measurements as determined by the precision of testing and the expected magnitude of change.

the age at which age-related bone loss begins at each site. Most studies that have evaluated these issues have been, of necessity, cross-sectional rather than prospective in design. In addition, there is no single study that has attempted to span childhood to old age or to evaluate every skeletal site within a defined age range. As a consequence, many studies must be reviewed to obtain an overview of changes in bone density with age at the various skeletal sites being measured today.

Bone Density in Children

In a cross-sectional study of 110 boys and 124 girls ranging in age from 8 to 17 years, BMD in the proximal femur, PA lumbar spine, and total body was measured using DXA (Hologic QDR-2000, Bedford, MA) *(1)*. For both the boys and girls, BMC and BMD increased at the spine, proximal femur, and total body between the ages of 8 and 17. The BMD values of the 17-year-old girls were also compared to BMD values from a separate group of healthy 21-year-old women. No significant difference was seen in BMD at any site between the 17-year-old girls and the 21-year-old women, suggesting that peak bone density had been reached by the age of 17 in the girls.

In a cross-sectional study of 266 subjects (136 boys, 130 girls) ages 4 to 27 years, BMD was measured in the total body, PA spine, and femoral neck using DXA (Lunar DPX. Madison, WI) *(2)*. The average age of the subjects was 13 years. BMD increased at all sites in boys until the age of 17.5 years. In girls, BMD increased at the total body and spine until the age of 15.8 years and in the proximal femur, until the age of 14.1 years.

In a very large, cross-sectional study of 778 Caucasian children (433 girls and 345 boys), ages 2 to 20, BMD was measured in the total body, PA and lateral spine, radius, and proximal femur with DXA (Norland XR-26, Ft. Atkinson, WI) *(3)*. BMD increased significantly at the PA lumbar spine and proximal femur until age 14 in girls. In boys, BMD in the proximal femur increased until age 16. BMD in the PA lumbar spine increased throughout the age range in boys. Total body BMC and BMD increased until age 16 in girls and continued to increase in boys throughout the age range in this study. Radial bone density increased until age 16 in girls and throughout the age range in boys.

BMD was measured in the PA and lateral spine using DXA (ODX-240, Oris, Gif-sur-Yvette, France) in 574 girls and young women ages 10 to 24 years and in the PA spine only in 333 women aged 27 to 47 years *(4)*. PA spine and lateral spine BMD increased markedly between ages 10 and 14 or until the first year after menarche. There were additional increases in BMD and BMC at the PA spine between the ages of 14 and 17 but not in the lateral spine. After age 17 or 4 years after menarche, BMD did not increase significantly and did not differ from the BMD seen in the older group of women. The authors estimated that 86% of peak adult bone density in the spine is achieved by age 14 or the second year after menarche.

The BMD in the spine and distal radius was measured with DXA in 121 normal children (69 boys, 52 girls) ages 3 to 18 years *(5)*. BMD increased at both sites throughout this age range. The correlation between the BMD at the spine and distal radius was significant at $r = 0.83$.

A study of 247 girls ages 11 to 32 was performed using DXA (Lunar DPX-L) to measure BMD in the total body *(6)*. The investigators found that 99% of total body BMD was achieved by age 22.1 ± 2.5 years and that 99% of peak BMC is attained by age 26.2 ± 3.7 years.

Bone Density in Premenopausal Women

Mazess and Barden studied 300 young women between the ages of 20 and 40 *(7)*. BMD was measured in the PA spine and proximal femur using DPA and at the ultradistal and 33% radial sites using SPA. BMD did not change significantly with age at any site. BMD tended to decrease with age at the femoral neck and Ward's area, but the change was not statistically significant. Additional BMD measurements were obtained at the spine and midradius after 2 years *(8)*. In this longitudinal extension of the original study, there was no evidence of age-related bone loss at either the spine or 33% radial site.

Hansen *(9)* evaluated 249 healthy premenopausal women whose average age was 39 years, measuring BMD at the distal forearm using SPA and at the PA spine and proximal femur using DXA (Hologic QDR-1000). In this study, no decline in BMD was seen at any site after age 30 and peak BMD appeared to be reached prior to age 30.

Two other large cross-sectional studies have suggested that BMD in the proximal femur does decline in women prior to menopause. Rodin et al. *(10)* found a significant premenopausal decline in femoral neck BMD in a study of 225 women who ranged in age from 18 to 52. Similarly, Bonnick et al. *(11)* found a decline in proximal femoral BMD after the age of 30 in a study of 237 premenopausal women ages 20 to 45. In this latter study, no increase in BMD in the spine or proximal femur was seen in any age group, suggesting that peak BMD in both regions was achieved prior to the age of 20. There was no significant change in spine BMD, again suggesting that spine BMD does not change.

Hui et al. *(12)* measured bone density in 130 healthy premenopausal women at the PA lumbar spine and proximal femur with DXA (Hologic QDR 1000W) on three occasions each over a 1- to 9-year period. The average age of the women at the start of the study was 40.4 years and the average follow-up was 3.9 years. In the PA lumbar spine, BMC, bone area, and BMD all increased during the study. The L2–L4 BMD increased at a rate of 0.00209 g/cm^2 per year. In contrast, total hip BMC, bone area, and BMD did not change significantly during the study. At the femoral neck, however, a significant decline in BMD was noted, which was the result of a decline in BMC and an increase in area. The rate of decline in BMD at the femoral neck was –0.00357 g/cm^2 per year. The authors found that greater losses of BMD at the femoral neck were associated with weight loss and lower levels of estrogen.

Dissimilar BMDs Between Skeletal Sites at Peak and Prior to Menopause

Two hundred thirty-seven premenopausal women between the ages of 20 and 45 were evaluated with DXA (Lunar DPX) measurements of the PA spine and proximal femur to determine if differences exist in *z*-scores for the spine and proximal femur *(11)*. The reference population for the calculation of the mean BMD and the SD were the 20- to 29-year-old women of the study population. Twenty to 24% of the 20 to 29-year-old women had differences in *z*-scores of more than1 between the lumbar spine and any of the three sites in the proximal femur (neck, Ward's, trochanter). In the 30- to 45-year-old women, however, this percentage increased to 32 to 46%. In the younger age group, the percentage of women having higher *z*-scores in the spine or higher *z*-scores in the proximal femur was roughly equally split. In the older age group, however, there was clearly a shift in percentages favoring a higher *z*-score in the spine. This appeared to be due to the earlier onset of bone loss from the proximal femur in this age group. Table 6-1 gives these findings in greater detail.

Table 6-1
Dissimilar Spine and Femoral *Z*-Scores in Premenopausal Women

Site Comparison	*20–29 years (n=122) %*	*30–45 years (n=115) %*
Lumbar vs Femoral Neck		
FN > L (1+)	11.5	6.9
FN > L (0–1)	39.3	15.7
L > FN (0–1)	36.9	38.3
L > FN (1+)	12.3	39.1
Lumbar vs Wards		
W > L (1+)	11.4	5.2
W > L (0–1)	39.3	20.9
L > W (0–1)	39.3	35.8
L > W (1+)	9.8	39.1
Lumbar vs. Trochanter		
T > L (1+)	9.8	6.1
T > L (0–1)	37.7	24.3
L > T (0–1)	42.6	43.4
L > T (1+)	9.8	26.1

Note: FN > L (+1) indicates that the femoral neck *z*-score is greater than the lumbar spine *z*-score by more than 1; (0–1) indicates the *z*-scores differ by 1 or less. Reproduced with permission of the publisher from ref. *11*.

Bone Density in Perimenopausal Women

Changes in spine BMD in pre-, peri- and postmenopausal women were evaluated in a longitudinal study by Pouilles et al. *(13)*. The subjects were 230 Caucasian women ranging in age from 45 to 66 years. Menopausal status was determined by menstrual history and estradiol and LH levels. Based on these determinants, 71 women ages 45–51 were premenopausal throughout the study, 42 women ages 47–57 experienced menopause during the study and were considered perimenopausal, and 117 women were postmenopausal throughout the study. BMD in the PA spine was assessed using DPA. The women were followed for an average of 27 months. Bone loss in the premenopausal women averaged 0.8% per year. In the perimenopausal women, bone loss was 2.3% per year. In the postmenopausal women, bone loss was again 0.5% per year. The authors noted that approximately half the bone loss observed in the first 10 years after menopause was seen in the first 3 years after menopause. There was no difference in the rates of bone loss between the perimenopausal women and the postmenopausal women 3 years past menopause.

Changes in radial BMD in perimenopausal women compared to premenopausal women were studied by Gambacciani et al. *(14)*. BMD was measured in the distal radius using DPA. The measurements were repeated every 6 months for 2 years. At the onset of the study, there was no significant difference in distal radial BMD between the two groups. In the premenopausal women, radial BMD did not change significantly during the two years of the study. BMD was 436.5 ± 19.8 mg/cm^2 at baseline and 434.6 ± 15.8 mg/cm^2 at 24 months. In the perimenopausal group however, there was a significant decline in distal radial BMD. At baseline the BMD was 428.5 ± 10.5 compared to the 24-month value of 410.1 ± 8.2 mg/cm^2. This represented an overall decline from baseline of 4.3% in 2 years in the perimenopausal group.

Dissimilar Spine and Femoral BMDs in Perimenopausal Women

Eighty-five Caucasian women between the ages of 45 to 60 who were within 6 months to 3 years past menopause underwent spine and proximal femur bone density testing using DXA (Lunar DPX) *(15)*. These values were compared with reference values (mean and SD) from a group of 30 healthy women between the ages of 40 to 45. Thirty-nine women had both spine and femoral neck *z*-scores that were better than –1. Seventeen women had both spine and femoral neck *z*-scores that were both poorer than –1. Out of the 85 women, 22 (26%) had dissimilar spine and femoral neck *z*-scores. Eight had spine *z*-scores that were better than –1 but femoral neck *z*-scores that were poorer than –1. Fourteen had femoral neck *z*-scores that were better than –1 but spine *z*-scores that were poorer than –1.

In a similar study, Lai et al. *(16)* evaluated 88 Caucasian women, ages 44 to 59, who were within 5 years past menopause. BMD measurements of the lumbar spine and proximal femur were made using DXA (Hologic QDR-1000). The subjects' BMDs were compared to the manufacturer's young-adult reference data in order to calculate the *T*-scores for the subjects. In this study, 18 women had both spine and femoral neck *T*-scores that were better than –1. Thirty-nine had both spine and femoral neck *T*-scores that were both poorer than –1. Of the 88 women, 31 (35%), had dissimilar spine and femoral neck *T*-scores. Twenty-eight had spine *T*-scores better than 1 but femoral neck *T*-scores poorer than –1. Three women had femoral neck *T*-scores that were better than –1 and spine *T*-scores that were poorer than –1.

Because the dissimilarity in either the *T*-scores or *z*-scores seen in these two studies could lead to an incorrect diagnosis, the authors of both these studies concluded that the choice of the measurement site could clearly affect patient management decisions. Both groups suggested that measurement of either the spine or proximal femur alone in the perimenopausal woman might not be appropriate.

Changes in Bone Density in Postmenopausal Women

BMD of the PA and lateral spine and proximal femur was measured in 353 Caucasian women ranging in age from 20 to 84 using DXA (Lunar DPX-L) *(17)*. Of these women, 154 were age 50 or older. Between 50 and 80 years of age, BMD in the PA spine and femoral neck decreased 18% or 0.6% per year. BMD in the lateral spine decreased 35 to 40% or 1.4% per year, whereas BMD in Ward's area decreased 30% or 1.1% per year.

As in young adults and perimenopausal women, dissimilarities in BMD among skeletal sites have also been reported in elderly women. Davis et al. *(18)* studied 744 women with a mean age of 66.6 years. BMD was measured in the PA spine, calcaneus, distal, and proximal radius. A combination of SPA and DPA was used to obtain these measurements. The women were classified by tertiles of BMD at each of the four skeletal sites. Of these women, 15% demonstrated marked heterogeneity in BMD among the four sites, having one or more sites in both the lowest and highest tertiles. Fourteen percent were in the lowest tertile at all four sites and 14% were in the highest tertile at all four sites. Of all of the women who had one site in the lowest tertile, 85% had at least one other site in the lowest tertile but only 24% were low at all four sites. In women who were classified as being in a middle tertile at any one site, there was marked heterogeneity in classification of the other sites. Slightly more than half had other sites that would be classified in the lowest tertile but more than half of these women were in the lowest tertile at only one site. Women classified in the upper tertile at any one site were infrequently found to have another site that would be classified in the lowest tertile.

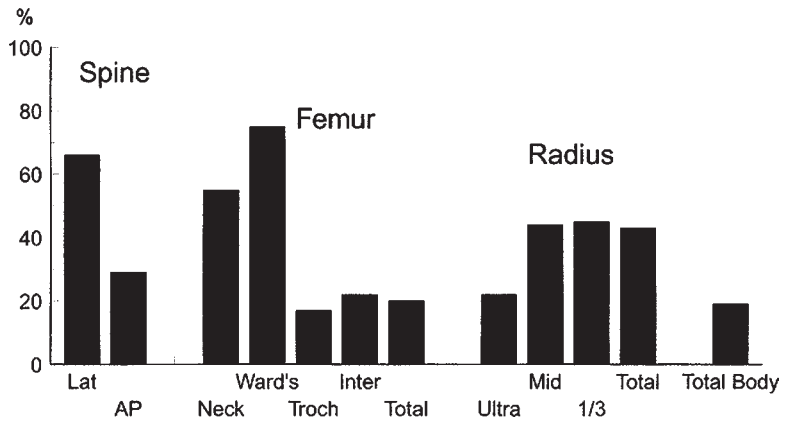

Fig. 6-1. The percentage of women diagnosed with osteoporosis depending on the skeletal site measured. Reproduced with permission of the publisher from ref. *19*.

Not surprisingly then, the diagnosis of osteoporosis may depend on which skeketal site is measured. Greenspan et al. *(19)* studied 120 women 65 years of age and older. BMD was measured in the PA and lateral spine, total body, forearm, and proximal femur using DXA (Hologic QDR-2000). Using the WHO criteria for the diagnosis of osteoporosis, the percentage of individuals who would be classified as osteoporotic at the various skeletal sites was noted. The largest percentage of individuals (66%) was identified as being osteoporotic when the lateral spine BMD was used. The PA spine identified only 29% as osteoporotic. The femoral neck identified 55% as osteoporotic whereas the 1/3 radial site identified 45.4% as osteoporotic. This is graphically represented in Fig. 6-1.

Greenspan et al. *(19)* also determined rates of bone loss in this elderly population. A loss of 1% per year was seen at the lateral spine, whereas the PA spine demonstrated no significant change. Femoral bone loss occurred at a rate of 0.7 to 1% per year, whereas bone loss at the radial sites occurred at a rate of 0.7 to 0.8% per year.

Changes in Bone Density in Men

BMD measurements of the PA spine (n = 315) and proximal femur (n = 282) were made in men ranging in age from 20 to 89 using DPA *(20)*. The rate of loss from the PA spine was extremely small at 0.001 g/cm^2 per year, or approximately 1% per decade. Losses from the trochanteric region were also very small at 0.002 g/cm^2 per year or approximately 2% per decade. In the femoral neck and Ward's area, the rate of loss was greater at 0.005 g/cm^2 and 0.007 g/cm^2 per year, respectively. This would result in a decrease of 21% from the femoral neck and 34% from Ward's area between the ages of 20 and 70 in men.

THE EFFECT OF DISEASES AND PROCEDURES ON BONE DENSITY

Acromegaly

Forty-five subjects (24 women and 21 men) with acromegaly for an average of 11.4 years underwent PA spine, proximal femur, and total body bone density studies with

DXA (Lunar DPX) *(21)*. The subjects ranged in age from 21 to 77 years with a median age of 43 years. Twenty-five individuals were Caucasian and 20 were Black. Twenty percent of the individuals had age-matched *z*-scores in the spine of –1 or poorer, whereas only 8.8% had similar age-matched *z*-scores in the proximal femur. Osteopenia in the spine was correlated with duration of disease and hypogonadism. Total body calcium was increased even in osteopenic patients suggesting that excess growth hormone/insulin-like growth factor-1 (GH/IGF-1) caused a positive bone balance except in the spine. Thirteen percent of subjects in this study had BMD values in the spine that were two or more SDs above the age-matched mean BMD value.

Sixteen patients (10 women, 6 men) with acromegaly were studied by Kotzmann et al. *(22)*. BMD measurements of the PA lumbar spine, femoral neck, and Ward's area were obtained with DXA (Norland XR-26) and compared to BMD measurements in 16 sex and age-matched controls. The average age of the subjects with acromegaly was 49.1 years. BMD in the lumbar spine was not significantly different between the subjects with acromegaly and the controls. BMD in the femoral neck and Ward's area however, was statistically significantly higher in the subjects with acromegaly.

Ankylosing Spondylitis

Low bone density has been frequently observed in ankylosing spondylitis although its etiology remains uncertain. For 2 years Maillefert et al *(23)* followed 54 patients with ankylosing spondylitis to determine the prevalence of osteopenia and osteoporosis and the relationship of any observed bone loss to therapy, physical impairment, or inflammation. There were 35 men and 19 women in the study with an average age of 37.3 years and average disease duration of 12.4 years. In 23 patients, the disease duration was less than 10 years. Bone density was measured at baseline and 2 years with DXA at the PA lumbar spine and proximal femur (Hologic QDR 2000). The mean PA lumbar spine baseline *T*-score and *z*-score for the group was –1.24 and –0.98, respectively. At the proximal femur, the baseline *T*-score and *z*-score was –1.07 and 0.46, respectively. Seventeen percent had *T*-scores at the PA lumbar spine of –2.5 or poorer and 39% had *T*-scores between –1 and –2.5. At the femoral neck, 11% had *T*-scores of –2.5 or poorer and 39% had *T*-scores between –1 and –2.5. At the end of 2 years, there was no significant change in PA lumbar spine bone density for the entire group but there was a significant decline of 1.6% at the femoral neck. Individually, 21% had significant losses at the PA lumbar spine and 20% at the femoral neck. The 24-month percentage changes at the PA lumbar spine and femoral neck were not related to age, gender, disease duration, disease subtype, therapy, or baseline DXA data. At the femoral neck, however, the percent change was related to persistent inflammation as assessed by the erythrocyte sedimentation rate (ESR). The authors noted that a significant percentage of patients with ankylosing spondylitis have low bone density and that proximal femoral bone loss may be due to systemic inflammation.

Alcoholism

The effect of chronic alcoholism on lumbar spine BMD was evaluated in 76 Caucasian men using DPA (Lunar DP3) *(24)*. The average age of the subjects was 47 years. Of the 76 men, 22 had spine BMD measurements more than 2 SD below the young-adult mean BMD for healthy men. As a group, the alcoholic subjects had significantly lower spine BMDs than a group of 62 healthy men who served as controls. Of the alcoholic subjects,

36% were found to have vertebral fractures. Sixty-one percent had a history of nonvertebral fracture with rib fractures occurring in 26%.

Amenorrhea

Hyperandrogenic Amenorrhea

Nine women with androgenic amenorrhea and 30 women with androgenization and either eumenorrhea or oligomenorrhea underwent BMD measurements of the PA lumbar spine with DPA (Scan Detectronic Diagnostic A/S Lab 23) *(25)*. Results were compared to 22 healthy women who served as controls. BMD in the lumbar spine in the nonamenorrheic androgenized women was significantly higher than controls and the amenorrheic androgenized women. BMD was not different between controls and the amenorrheic androgenized women. Serum levels of DHEAS were negatively correlated with BMD in the androgenized women. The authors postulated that the high levels of androgens had a positive effect on bone that was negated in the women with amenorrhea.

Exercise-Induced Amenorrhea

Fourteen amenorrheic athletes whose average age was 24.9 years underwent BMD measurements at the PA lumbar spine with DPA and at the distal radius with SPA (Norland-Cameron Model 178) *(26)*. The results were compared to those obtained in 14 eumenorrheic athletes with an average age of 15.5 years. The average duration of amenorrhea was 41.7 months. BMD was significantly lower in the amenorrheic athletes compared to the eumenorrheic athletes at the lumbar spine. The mean difference was 13.9%. There was no significant difference in BMD at the distal radius between the two groups.

Anorexia Nervosa

Eighteen women with anorexia nervosa underwent radial bone mass measurements at the 33% site with SPA *(27)*. The results were compared to those from 28 healthy women. All of the women with anorexia had been amenorrheic for at least 1 year and had not been taking estrogens, progestins, or corticosteroids. The age of the women with anorexia ranged from 19 to 36 years with an average age of 25 years. The women with anorexia had significantly lower radial bone density than the controls (0.64 ± 0.06 vs 0.72 ± 0.04 g/cm^2, respectively). When the subjects were divided on the basis of the level of physical activity, only the inactive anorectic women continued to have a significantly lower radial bone density than the controls, suggesting that exercise might be protective. Two of the women with anorexia had multiple vertebral compression fractures.

Hay et al. *(28)* evaluated 69 women with anorexia in varying stages of recovery. BMD was measured at the spine by QCT. Results were compared to 31 controls. Bone density was significantly lower in the anorectic subjects compared to the controls (120 mg/cm^3 vs 148 mg/cm^3). These authors did not find any protective effect of exercise on the skeletons of the anorectic women. Bone density in these subjects was significantly associated with the duration of illness and amenorrhea and with weight.

Fifty-one women with anorexia who had been followed for an average of 11.7 years were evaluated with BMD measurements in the lumbar spine with DPA (NOVO Lab 22a, Novo Diagnostic, Bagsvaerd, Denmark) and at the midradius with SPA (Nuclear Data ND 1100A, Nuclear Data Co., Frankfurt, Germany) *(29)*. The subjects were classified into three groups based on their disease outcome. A good outcome meant that the subjects

had regular menses and did not weigh less than 85% of their predicted weight. A poor outcome meant that the subject had not resumed normal menses and weighed less than 85% of predicted. An intermediate outcome indicated that the subject had either not resumed normal menses or weighed less than 85% of predicted. Subjects with a good outcome had significantly higher lumbar and radial bone densities than either of the other two groups. Subjects with an intermediate outcome had higher lumbar bone densities than the subjects with a poor outcome. Subjects with a poor outcome had a lumbar spine *z*-score of –2.18 and a midradial *z*-score of –1.73 compared to a control group of healthy women. Subjects with a good outcome also had negative *z*-scores compared to the control group of –0.26 in the spine and –0.68 at the radius. The authors suggested that recovery of trabecular bone density might be possible with successful treatment of anorexia but that cortical bone recovered more slowly, if at all.

Twenty young women (mean age 23 years) with anorexia *(30)* were compared with 20 healthy age-matched women using measurements of BUA of the calcaneus, pQCT of the distal radius and DXA of the PA lumbar spine and proximal femur. (Sonomed Systems DTU one, Stratec XCT-1400, Hologic QDR 1000). The women with anorexia had significantly lower values than the control group at all measurement sites. Mean values were 35.3 vs 51.03 db/MHz for BUA, 0.73 vs 0.97 g/cm^2 for L1-L4 BMD, 0.71 vs 0.89 g/cm^2 for femoral neck BMD, and 303.2 vs 369.4 g/cm^3 for total radial BMD for anorectics and controls, respectively. The greatest differences between anorectics and controls were seen with BUA of the calcaneus and the PA lumbar spine.

Cirrhosis

Fifty-five cirrhotic patients, 6 with primary biliary cirrhosis, 14 with alcoholic cirrhosis, and 38 with posthepatic cirrhosis who were referred for liver transplantation, underwent bone density testing of the PA spine and proximal femur with DXA (Lunar DPX-L) *(31)*. The subjects were 39 men and 19 women with an average age of 50 ± 7.6 years. Compared to age and sex-matched controls, 15 patients had spine *z*-scores of –2 or poorer, whereas only 5 had *z*-scores in the femoral neck that were –2 or poorer. An additional 13 patients were found to have fractures in the spine that were judged to be atraumatic. The authors observed that the more severe the liver dysfunction, the greater the reduction in femoral bone mass. A significant number of patients were found to have vitamin D deficiency, reduced serum parathyroid hormone levels, and hypogonadism.

Cushing's Syndrome

In a retrospective study, Luisetto et al. *(32)* compared the change in lumbar spine BMD after surgical cure of Cushing's syndrome to the change in BMD seen after successful medical treatment with ketoconazole. Seventeen women and two men with an average age of 41 years underwent DXA bone density studies (Hologic QDR 1000) before and after successful pituitary surgery or treatment with ketoconazole. Nine patients were treated successfully with surgery and 10 patients were treated medically after unsuccessful surgery. In the group treated successfully with surgery, bone density in the lumbar spine increased significantly from 829 mg/cm^2 to 952 mg/cm^2 or 14.8%. In the group treated with ketoconazole after unsuccessful surgery, despite normalization of cortisol levels by ketoconazole, BMD did not change. The authors suggested that ketoconazole might have a detrimental effect on bone density.

Cystic Fibrosis

Fifty-eight men and 49 women with cystic fibrosis underwent PA lumbar spine and proximal femur dual energy X-ray bone density studies using a Lunar DPX-L *(33)*. The patients ranged in age from 18 to 60 with an average age of 28 years. All the patients were Caucasian. Sixty patients were homozygous for the ΔF508 genotype and 16 were compound heterozygotes. Only 15 were not taking pancreatic enzyme replacements. Twenty-seven patients had cystic fibrosis-related diabetes. The manufacturer's reference data was used to calculate *T*- and *z*-scores. The median *T*-score at L1–L4 for the group was –0.78. The median *z*-score at L1–L4 was –0.4. At the femoral neck, the median *T*- and *z*-scores were –0.65 and –0.32, respectively. Using WHO criteria for the diagnosis of osteoporosis based on the measurement of bone density, 42% of the patients had osteopenia and 12% had osteoporosis. The authors found that the percent predicted FEV_1 and daily exercise expenditure were positively correlated to BMD and that the number of intravenous antibiotic treatments was negatively correlated to BMD. The best overall predictor of BMD was the percent predicted FEV_1.

Diabetes

Insulin-Dependent Diabetes Mellitus

Ninety-four subjects (45 men, 49 women) with insulin-dependent diabetes mellitus underwent bone density measurements of the PA spine and proximal femur with DXA (Hologic QDR-1000) *(34)*. The subjects ranged in age from 20 to 56 years with a mean age of 30 years. Disease duration ranged from 1 to 35 years. Diabetic patients had reduced BMD at all sites in comparison to age- and sex-matched controls. *Z*-scores were –0.89 for the spine, –0.99 for the femoral neck, –1.05 for Ward's. Of these subjects, 19.1% met WHO diagnostic criteria for osteoporosis. The presence and severity of diabetic complications was associated with lower BMD.

Noninsulin-Dependent Diabetes Mellitus (NIDDM)

Forty-seven women with NIDDM underwent BMD measurements of the spine and proximal femur with DXA (Hologic QDR-1000) and of the spine with QCT (Toshiba 600 HQ, Toshiba Medical Systems) and were compared to 252 healthy nondiabetic women *(35)*. The average age of the NIDDM patients was 61.3 years. There was no significant difference in BMD at either site by either technique between the women with NIDDM and the controls.

Hyperinsulinemia has been postulated to be an osteogenic factor. In a study of 411 men and 559 women aged 50 to 89 who were not diabetic by history or oral glucose tolerance test, BMD was measured in the lumbar spine and proximal femur using DXA (Hologic QDR-1000) and in the midradius by SPA (Lunar SP2) *(36)*. Fasting insulin levels were positively associated in women only with BMD in the spine and radius. For each 10 μU/mL increase in fasting insulin levels in women, BMD in the spine and radius increased by 0.57 g/cm^2 and 0.33 g/cm^2, respectively.

Ehlers-Danlos Syndrome

Twenty-three women (average age 37.6 years) with type III Ehlers-Danlos syndrome underwent PA lumbar spine and proximal femur DXA measurements (Lunar DPX) *(37)*. The results were compared with those of 23 healthy women (average age 37.2 years) who

were matched for age, menopausal status, and estrogen use. The mean L2–L4 BMD in the Ehlers-Danlos patients was 1.14 ± 0.14 g/cm^2 compared to 1.21 ± 0.15 g/cm^2 in the control group. This difference was not statistically significant. BMD in the femoral neck was 0.91 ± 0.13 g/cm^2 in the Ehlers-Danlos patients and 0.99 ± 0.12 g/cm^2 in the controls. This difference was statistically significant. However, after adjustment for body weight, height, and physical activity, the difference in BMD at the femoral neck was no longer significant.

Estrogen Deficiency (Postmenopausal)

Ninety-three healthy women who had experienced a natural menopause 6 to 60 months earlier were followed prospectively for two consecutive 22-month periods *(38)*. BMD was measured in the spine and proximal femur using DXA (Lunar DPX). The average decline in BMD in the spine was 1.46% per year (+2.6% to –6.9%) in the first period and 1.28% per year (+2.8% to –5.3%) in the second period. In the proximal femur, the average decline in the first period was 1.41% per year (+4.8% to –6.8%) and 1.35% per year (+1.8% to –7.0%) in the second. Individual rates of bone loss were not stable over time. Only 20–30% of women retained their initial classification as fast, intermediate, or slow losers during both observation periods. Of 24 women classified as fast losers during the first observation period, 5 remained fast, 12 became intermediate, and 5 became slow losers during the second period. The mean rate of loss in the fast loser group initially was –3.9%. Women who were originally classified as slow losers at the spine during the initial observation period were reclassified as intermediate or fast losers during the second observation period. Similar patterns were seen at the femoral neck.

BMD measurements were made at the PA spine, lateral spine, and distal forearm using DXA (Hologic QDR-2000) in a cross-sectional study of 363 women who were 6 months to 10 years postmenopausal *(39)*. The most rapid decline in bone density was initially seen in the lateral spine, followed by the PA spine, and then the forearm. Ten years after menopause, however, the overall percent decrease at all three sites was approximately the same at 12% at the PA spine and 13% at the lateral spine and forearm.

Familial Dysautonomia

Patients with familial dysautonomia suffer from a variety of problems related to dysfunction of the autonomic, sensory, and motor nervous systems. They also suffer from skeletal disorders such as kyphoscoliosis, arthropathies, and fractures. The disease is an inherited disorder, most commonly seen in Ashkenazi Jews. The inheritance is autosomal recessive and the gene has been mapped to the 9q31 chromosome. Maayan et al. *(40)* evaluated bone density and fracture prevalence in 79 patients with familial dysautonomia. The patients were 42 males and 37 females with a median age of 12.3 years. Bone density was measured at the PA lumbar spine and proximal femur with DXA (Hologic QDR 4500, Hologic QDR 1000, Lunar DPX, Lunar DPX-IQ). The bone density results were reported as *z*-scores, using the manufacturer's reference databases for calculation of the *z*-scores. At the PA lumbar spine, the mean *z*-score was –2.0. Fifty-three percent of the patients had lumbar spine *z*-scores of –2 or poorer. The mean femoral neck *z*-score was –2.1 with 54% having *z*-scores in this region that were –2 or poorer. The mean total hip *z*-score was –2.2. Fifty percent of the patients had total hip *z*-scores of –2 or poorer. The prevalence of fracture in this group of patients with familial dysautonomia was 53%. The overwhelming majority of these fractures were upper and lower limb fractures. The mean age for the occurrence of fracture was 9.1 years.

Gastrectomy

BMD as measured in the os calcis by DPA was found to be significantly lower in men who had previously undergone partial gastrectomy compared to controls *(41)*. The average of the subjects was 72.1 years and the average time since surgery was 28.5 years. Men who underwent Billroth-II procedures had significantly lower BMDs than men who underwent Billroth-I procedures. Billroth-II operated subjects had BMDs that were 20% lower than controls. Billroth-I operated subjects had BMDs that were 8% lower than controls, a difference that was not statistically significant. Nineteen percent of the men who had undergone partial gastrectomy were found to have vertebral fractures in comparison to only 4.4% of the control group. The relative risk for vertebral fracture in the partial gastrectomy group was calculated to be 4.3.

In a cross-sectional study from Adachi et al. *(42)*, 59 patients (38 men, 21 women) who had undergone gastrectomy at least 5 years earlier underwent DXA studies of the PA lumbar spine (Norland XR-26HS). Their average age was 64 years. Potential causes of bone loss other than gastrectomy were excluded in the study group. The mean L2–L4 BMD in the men was 0.821 and in the women, 0.664 g/cm^2. The mean BMD of the men was 12.5% below the predicted age- and sex-matched BMD. The mean BMD of the women was 16.9% below the predicted age- and sex-matched BMD. Using WHO criteria, 18% of the men and 71% of the women had osteoporosis.

Type 1 Gaucher Disease

Sixty-one adults (32 men, 29 women) with type 1 Gaucher disease were evaluated with DXA (Hologic QDR-1000W) of the lumbar spine, femoral neck, trochanter, and distal radius *(43)*. They ranged in age from 22 to 77 with a mean age of 45.5 years. Mean bone density at each site was significantly below that predicted for age and sex when compared to the manufacturer's reference data. The greatest decrease in BMD was seen in the patients with splenectomy or severe hepatomegaly.

Gluten-Sensitive Enteropathy

Eight subjects with biopsy proven gluten-sensitive enteropathy and magnesium depletion underwent bone density testing of the lumbar spine and proximal femur with DXA (Hologic QDR-1000) *(44)*. Four of eight had lumbar spine *T*-scores –2.5 or less. Five had femoral neck *T*-scores and five had total hip *T*-scores –2.5 or less. All but two had *T*-scores less than 0 at all three sites and only four had *z*-scores greater than 0 at any of the three sites.

Forty-four subjects with celiac disease underwent BMD measurements of the PA lumbar spine, femoral neck, and total body with DXA (Lunar DPX-L) *(45)*. Thirty-four of the subjects were considered as having been successfully treated. The remaining 10 were either newly diagnosed or untreated. Compared to the manufacturer's reference data, subjects with newly diagnosed or untreated celiac disease had BMDs that were significantly lower than age-matched controls at all sites. Subjects with successfully treated celiac disease had BMDs that were not significantly difference from predicted age-matched values.

In a study from Argentina, Gonzalez et al. *(46)* evaluated 127 consecutive postmenopausal women with osteoporosis, who had a mean age of 68. Osteoporosis was defined as at least one nontraumatic fracture and an L2–L4 and/or femoral neck *T*-score below –2.5. Bone density was measured using a Lunar DPX. The Buenos Aires reference population

was used to calculate *T*- and *z*-scores for the study populations. This reference database is reported as similar to the reference database for Caucasian women in the United States. The mean *T*-score for the osteoporotic population was –3.2 and –3.0 for spine and femoral neck, respectively. The prevalence of celiac disease in these osteoporotic women was compared to 747 women, with a mean age of 29, recruited for a population-based study. Screening for celiac disease was done using IgA and IgG antigliadin antibodies (AGA) in all patients. This was followed by antiendomysial antibodies (EmA) and total IgA in the patients testing positive for AGA. Intestinal biopsy was performed in patients with positive EmA and total IgA results. Only 1 of the 127 osteoporotic women was eligible for jejunal biopsy, which did show the characteristic flat mucosa of celiac disease. Celiac disease was diagnosed in 6 of 747 women in the control group. The prevalence of celiac disease was calculated as 7.9 per 1000 in the osteoporotic group and 8 per 1000 in the control group. The background prevalence of celiac disease in Argentina was reported to be 7 per 1000. Celiac disease was twice as common in women than men with most cases occurring before menopause. The authors concluded that celiac disease was not more prevalent in osteoporotics than the general population. As a result, they did not recommend an evaluation for celiac disease in women presenting with osteoporosis and no signs or symptoms of celiac disease.

Human Immunodeficiency Virus Infection

The effect of human immunodeficiency virus (HIV) infection on BMD was studied in 45 men *(47)*. BMD measurements of the total body, PA spine, and proximal femur were obtained with DXA (Lunar DPX). Twenty-one subjects had additional BMD measurements 15 months later. BMD results were compared to sex- and age-matched means supplied by the manufacturer. The average age of the subjects was 36 years and the mean CD4 count was 90. At baseline BMD in the lumbar spine was 3% lower than controls. This value had borderline statistical significance. BMD values in the other regions were not statistically different from controls. In the subjects followed over time, there was a decrease in total body BMD of 1.6% that was statistically significant. The other sites did not demonstrate significant change.

In a study of 50 eugonadal men with HIV and 35 healthy age-matched controls, Fairfield et al. *(48)* found statistically significantly lower PA spine and total hip BMD in the men with HIV. BMD was measured with DXA (Hologic QDR 4500). The average age of the men with HIV was 38.1 years. Baseline PA lumbar spine BMD in the men with HIV was 1.021 g/cm^2 compared to 1.084 g/cm^2 in the control group. At the total hip, the BMD was 0.951 g/cm^2 in the men with HIV and 1.070 g/cm^2 in the control group. There was no difference in the BMD between the two groups at the femoral neck. After adjusting for body mass index, the differences in total hip BMD remained significant between the two groups.

Hypercalciuria

Fifty adults (30 premenopausal women and 20 men under the age of 55) with idiopathic hypercalciuria and nephrolithiasis and 50 age- and sex-matched controls underwent bone densitometry of the lumbar spine using DPA (Norland 2600) *(49)*. BMD in the lumbar spine in the subjects with idiopathic hypercalciuria was significantly lower than in controls. The authors postulated that this difference was due to a negative calcium balance sustained over time.

The BMDs in 62 subjects (42 men, 20 women) with absorptive hypercalciuria, 27 subjects with fasting hypercalciuria and 31 nonhypercalciuric subjects with nephrolithiasis, were evaluated using DXA of the lumbar spine (Lunar DPX and Hologic QDR-1000) and SPA of the 33% radial site (Norland-Cameron) *(50)*. The values were compared to the age- and sex-matched reference values supplied by the manufacturers. Radial bone density did not differ among the three groups and was not different from age- and sex-matched normal values. Compared to sex- and age-matched reference values, lumbar BMD was 9% lower in the subjects with absorptive hypercalciuria and stones and 11% lower in the subjects with fasting hypercalciuria and stones. Lumbar BMD in the subjects with nonhypercalciuric nephrolithiasis was not different from reference values.

Hyperparathyroidism

In a study of patients with mild primary hyperparathyroidism, 22 of 143 patients had lumbar spine BMDs more than 1.5 SD below the sex- and age-matched mean *(51)*. Of these 22 patients, 14 underwent surgery and 8 were followed medically. BMD measurements were performed annually for 4 years using DXA (Hologic QDR-1000) or a combination of DPA and SPA (Lunar DP3 and SP2) at the PA lumbar spine, proximal femur, and distal radius. After surgery, BMD in the lumbar spine rose an average of 15% in the first year, reaching 21% by the fourth year. In the patients not undergoing surgery, BMD did not change significantly over the 4 years.

At baseline in this study, the patients with lumbar spine *z*-scores poorer than –1.5 had an average *z*-score of –2.285. They also had femoral neck and distal radius *z*-scores of –1.695 and –1.522, respectively. The majority of patients with hyperparathyroidism in this study (85%) with lumbar spine *z*-scores better than –1.5 had an average spine *z*-score of –0.061. In this group, BMD was decreased most severely in the distal radius with an average *z*-score poorer than –1. BMD in the femoral neck was also decreased in this group but not as severely as the distal radius when compared to sex- and age-matched controls.

Thirty-three postmenopausal women with mild primary hyperparathyroidism were followed prospectively for 2 years with BMD measurements of the total body, PA lumbar spine, proximal femur, and proximal forearm by DXA (Lunar DPX-L) *(52)*. Seventeen of the women received hormone replacement therapy and 16 received a placebo. In the women receiving placebo with untreated mild hyperparathyroidism, BMD decreased at all sites over the 2 years. Total body BMD decreased 2.3%. BMD in the lumbar spine decreased 1.4%, although this change was not statistically significant. BMD decreased 3.5% in the proximal forearm and 1.4% in the femoral neck.

McDermott et al. evaluated 59 women with mild asymptomatic primary hyperparathyroidism with BMD measurements at the distal and midradius with SPA (Norland) and at the PA lumbar spine and femoral neck with DPA (Norland) *(53)*. Of the 59 women, 43 had never taken estrogen replacement therapy (ERT), whereas 16 were current users of ERT. Results were compared to a control group of 84 healthy women who were not on ERT and 45 healthy women who were current users of ERT. The women with primary hyperparathyroidism who were never users of ERT had lower BMC at the distal and midradius and lower BMD at the lumbar spine and femoral neck compared to controls (20%, 20%, 17%, and 11%, respectively). The women with primary hyperparathyroidism who were current users of ERT had BMCs and BMDs that were not significantly different from controls and that were significantly higher than the hyperparathyroid subjects that had never used ERT. Among the control group, estrogen users had BMCs

in the distal and midradius and BMDs in the spine and femoral neck that were higher than the hyperparathyroid estrogen users (13%, 8%, 11%, and 8%, respectively) although only the difference at the distal radius reached statistical significance.

Hyperprolactinemia

BMD of the lumbar spine was evaluated in 13 women with an average age of 29.2 years with hyperprolactinemia by QCT (GE 8800 CT/T, General Electric Medical Systems, Milwaukee, WI) and compared to sex- and age-matched controls *(54)*. Of the women, seven had idiopathic hyperprolactinemia and six had prolactin-secreting pituitary tumors. The average duration of amenorrhea in the hyperprolactinemic women was 98.9 months. The average BMD of the spine was 10% less in the hyperprolactinemic women compared to controls.

Forearm and vertebral bone mineral density was evaluated by Schlechte et al. in 26 women aged 24–43 years with histologically confirmed prolactin-secreting pituitary tumors, 7 to 10 years after transsphenoidal surgery *(55)*. Ten of the women had persistent amenorrhea and increased prolactin levels, whereas 16 had regular menses and normal prolactin levels. An additional 17 amenorrheic women aged 24 to 42 with untreated hyperprolactinemia were studied. Of these women, 11 were amenorrheic on the basis of a pituitary tumor and in 6, the cause was unknown. Forty healthy women served as controls. BMD in the spine was measured by QCT (Picker International Inc., Highland Heights, OH) and at the 33% radius by SPA (Norland). In women with hyperprolactinemia, the spine bone density was 25% lower than the healthy controls. Women who were considered cured on the basis of normalized serum prolactin levels and resumption of menses also had significantly lower spine BMD than the controls but slightly higher spine BMD than the untreated or noncured women with hyperprolactinemia. BMD at the 33% radius did not differ between the untreated or noncured hyperprolactinemic women and the healthy controls.

Hyperthyroidism

Fifty-two patients (32 women, 20 men) with hyperthyroidism underwent BMD studies of the lumbar spine and proximal femur with DXA (Hologic QDR-1000) *(56)*. Values were compared to a control population. Hyperthyroidism in these patients was due to Graves' disease. The average age of the men with hyperthyroidism was 45.6 years and of the women, 43.8 years. BMD in the lumbar spine was 92.6% of sex- and age-matched reference values in the hyperthyroid subjects. There was no difference in this comparison between the men and women or between the pre- and postmenopausal women with hyperthyroidism. Proximal femur BMD data was not reported.

Fifty-six women with Graves' disease, multinodular toxic goiter, or nodular toxic goiter were evaluated with DXA (Hologic QDR-1000) of the lumbar spine and proximal femur *(57)*. Three hundred fifty healthy women served as controls. In women with active, untreated hyperthyroidism, lumbar spine z-scores averaged –1.50 and femoral neck z-scores averaged –0.67. In women who had been treated in the past for hyperthyroidism but who had been in remission without treatment for an average of 8.5 months, z-scores were significantly lower in the spine and femoral neck in the postmenopausal women only. The z-scores in premenopausal women did not differ from controls. In women being treated with nonsuppressive doses of L-thyroxine, the postmenopausal women again had significantly lower z-scores in the spine and femoral neck when com-

pared to controls (–1.39 and –0.18, respectively). *Z*-scores in the premenopausal women did not differ from controls. The authors noted that postmenopausal women appeared to be at greatest risk for bone loss due to a hyperthyroid state and that trabecular regions of the skeleton were more affected than predominantly cortical regions.

Inflammatory Bowel Disease

Thirty-five patients (17 women and 18 men) with inflammatory bowel disease (IBD) were followed prospectively for 19 months with BMD measurements at the PA lumbar spine and proximal femur with DXA (Hologic QDR-1000) *(58)*. Fourteen patients had Crohn's disease and 21 had ulcerative colitis. They ranged in age from 17 to 60 years with a mean age of 36 years. Crohn's disease patients lost 3.08 ± 4.91% per year in the lumbar spine and 6.91 ± 6.57% per year in the femoral neck. Ulcerative colitis patients without ileoanal anastomosis lost 6.42 ± 7.5% per year in the lumbar spine and 5.59 ± 11.12% per year in the femoral neck. No ulcerative colitis patient with ileoanal anastomosis had a significant bone loss from either site. Patients on steroids had mean bone loss of 6.23 ± 7.04% per year in the spine and 8.97 ± 9.57% per year in the femoral neck. Patients not on steroids had gains of 0.87 ± 0.002 per year in the spine and 0.20 ± 5.78% per year in the femoral neck.

In another study of 79 patients with IBD (34 men, 45 women), bone density was measured with DXA in the PA lumbar spine and proximal femur with DXA (Norland XR-26) *(59)*. Forty-four patients had Crohn's disease and 35 had ulcerative colitis. The mean age of the subjects was 39 years. Of the patients, 19 were taking corticosteroids. A high prevalence of low BMD was found at all sites but the proximal femur sites were affected more often than the spine. At the spine, 54% had *T*-scores poorer than –1 and 18% had *T*-scores that were poorer than –2.5. At the femoral neck, 78% had *T*-scores poorer than –1 and 29% had *T*-scores that were poorer than –2.5. The authors found no significant difference between the *T*-scores for Crohn's disease patients and ulcerative colitis patients.

Sixty patients with Crohn's disease were compared to 60 patients with ulcerative colitis and 60 controls *(60)*. Each of the three groups consisted of 36 women and 24 men, ranging in age from 21 to 75 years. The mean age of the Crohn's disease patients and controls was 36 years and of the ulcerative colitis patients, 38 years. PA lumbar spine, femoral neck, and total body bone density were measured using DXA (Lunar DPX). Patients with Crohn's disease had age-matched *z*-scores that were significantly lower than either the normal subjects or ulcerative colitis patients. The patients with ulcerative colitis had BMDs that were similar to controls.

Intravenous Drug Abuse

A syndrome of diffuse osteosclerosis was first reported with intravenous drug abuse in St. Louis *(61)*. The syndrome is considered rare and its cause is unknown. Patients have presented with aching limbs and a generalized increase in density throughout the skeleton. One such subject, a 38-year-old Caucasian man underwent BMD measurements with DXA (QDR-2000) of the spine and proximal femur and of the spine using QCT (General Electric HiSpeed Advantage) *(62)*. The BMD in all regions was dramatically increased compared to age- and sex-adjusted normal values. Spine values by DXA were 160% of predicted and by QCT, 185% of predicted. Values in the proximal femur ranged

from 188 to 246% of predicted. Bone biopsy in this patient demonstrated dense lamellar bone. Skeletal X rays demonstrated diffuse osteosclerosis that spared only the calvarium and facial bones.

Klinefelter's Syndrome

BMD in the lumbar spine and proximal femur in 32 patients with Klinefelter's syndrome was compared to 24 age-matched male controls *(63)*. The average age of the Klinefelter's syndrome subjects was 25.4 years and the average age of the controls was 25.5 years. BMD was measured with DXA (Hologic QDR-1000). There was no significant difference found in BMD at the PA lumbar spine, femoral neck, Ward's area, or total hip between the two groups.

Marfan's Syndrome

Thirty-two women and 16 children (9 boys, 5 girls) with Marfan's syndrome underwent BMD measurements of the PA lumbar spine and proximal femur with DXA (Hologic QDR-1000W) *(64)*. The women ranged in age from 23 to 58 years and the children ranged in age from 9.9 to 17.5 years. BMD in the spine and proximal femur in both the adults and children was found to be decreased when compared to sex- and age-matched controls. The authors concluded that patients with Marfan's syndrome have decreased BMD in both the axial and peripheral skeleton that may be the result of inadequate development of peak bone density.

Le Parc et al. *(65)* studied 60 adult patients (40 women, 20 men) with Marfan's syndrome. The mean age of the women was 32.6 years and, of the men, 33.4 years. Mean height in the women was 176.3 cm (69.4 in) and, in the men, 188.1 cm (74.1 in). The patients underwent DXA studies of the nondominant forearm and proximal femur (Hologic QDR 1000W). Spine bone density was not measured in this study because of a high incidence of scoliosis and spine surgery. Based on comparisons to the manufacturer's reference database, the Marfan's patients had significantly lower BMDs at all sites in the forearm and proximal femur compared to age- and sex-matched controls. The authors noted that the decrease in BMD was more severe at predominantly cortical sites.

Mastocytosis

Sixteen patients (6 men and 10 women) with mastocytosis underwent bone density measurements of the PA spine, hip, and total body with DXA (Lunar DPX) and of the distal right radius and ulna with SPA (Osteometer DT 100, Roedovre, Denmark) *(66)*. BMD results from the patients with mastocytosis were compared to a reference population of 317 men and 1123 women from the local population. Both low bone density and increased bone density were found in the patients with mastocytosis. Bone density in the proximal femur was increased in both men and women with mastocytosis if there was increased methylimidazoleacetic acid excretion. In patients with moderately increased mast cell mass, low bone density in the proximal femur, and vertebral fractures were seen. Fractures are thought to occur in approximately 16% of patients with mastocytosis *(67)*. In patients with only urticaria pigmentosa, no change in bone density is apparent. In patients with systemic disease however, the changes in bone density range from severe osteoporosis to osteosclerosis.

Multiple Myeloma

A prospective study of BMD in 34 patients (19 women and 15 men) with newly diagnosed multiple myeloma was performed using DXA (Hologic QDR-1000) of the lumbar spine and proximal femur *(68)*. The myeloma patients ranged in age from 43 to 83 years with a median age of 71 years. Controls were 289 healthy volunteers. Lumbar spine BMD was significantly reduced in comparison to age-matched controls, whereas proximal femur BMD was not. The average age-matched *z*-score in the lumbar spine was –0.56. Multiple myeloma patients with vertebral fractures had age-matched *z*-scores poorer than –1 on average. Of the 34 patients, 15 had vertebral fractures at the start of the study (defined as a reduction in height of >20%). There was no correlation between lumbar spine BMD values and the type of paraproteins identified in the myeloma patients. In an another study, however, demineralization was found to be more common in IgA myeloma than in IgG myeloma *(69)*.

Multiple Sclerosis

Low bone density has been reported in multiple sclerosis (MS). Seventy-one women with MS underwent total body BMD measurements with DXA (Norland XR-26) *(70)*. Seventy-one healthy women served as controls. Total body BMC was reduced in the women with MS by approximately 8%. When the women with MS were evaluated based on their ambulatory status, only nonambulatory women with MS were found to have lower total body BMC when compared to controls. The authors concluded that physical disuse is the major contributing factor in reduced bone mass in MS although corticosteroid use also contributes.

Neurofibromatosis

In a small cross-section study of 12 patients with neurofibromatosis-1 and spinal deformities, Illés et al. *(71)* measured PA lumbar spine bone density using DXA. The device used was a Hologic QDR 4500C. There were 6 men and 6 women in the study with an average age of 19.1years (range 7.6 to 52.7 years). Age-based *z*-scores for patients over age 18 and weight-based for patients under age 18 were reported. For the 12 patients, the average *z*-score was –2.5. The *z*-scores were 1 SD or more below the mean in 11 of the 12 patients and 2.5 SD or more below the mean in 8 of the 12 patients. Increasing scoliosis and kyphosis were associated, but not significantly so, with lower bone densities. The authors noted that orthopedic surgeons have reported encountering soft vertebral bone during procedures intended to correct spinal deformities in neurofibromatosis.

Osteoarthritis

Studies of the effects of osteoarthritis on BMD in various regions of the skeleton are challenging. In the presence of osteophytes, joint space narrowing and sclerosis caused by osteoarthritis, accurate measurement of the BMD of the presumably nondiseased bone can be difficult. Nevitt et al. *(72)* reported a study of 4090 women who underwent pelvic radiographs that were assessed for the presence of unilateral or bilateral hip osteoarthritis. A subset of 1225 women also underwent spine radiographs. All of the women underwent PA spine and proximal femur bone density studies with DXA (Hologic QDR-1000) and studies of the os calcis, proximal, and distal radius with SPA (OsteoAnalyzer, Dove Medical Systems, Inc., Newbury Park, CA).

A grading scale was devised for the presence and severity of osteoarthritic changes in the hip joint that ranged from 0 to 4 with 0 indicating that no osteoarthritis was present. An assignment of grade 2 or greater required that the subject have osteophytes or joint space narrowing and at least one other feature such as subchondral sclerosis or cysts or femoral head deformity. Grade 2 was considered as indicative of radiographic osteoarthritis in the hip and grade 3 to 4, indicative of moderate or severe disease.

Women with grade 3 or 4 osteoarthritis in either hip had significantly higher bone densities at all sites, even after adjustment for age compared to women with no evidence of osteoarthritis or only grade 1. The increase in BMD was approximately 8 to 10% at the femoral neck, Ward's area, and lumbar spine and about 3 to 5% at the os calcis, distal radius, and trochanteric region. At the femoral neck, women with grade 3 or 4 hip osteoarthritis had a BMD that was 0.092 ± 0.011 g/cm^2 higher than women without osteoarthritis or only grade 1 findings. Women with grade 2 osteoarthritis also had significant elevations in BMD after adjustment for age at all sites although the increases were smaller in the range of 2 to 4%. The elevation in BMD at the femoral neck in these women averaged 0.037 ± 0.008 g/cm^2. The authors recognized that the inability to adequately rotate the femur internally due to osteoarthritis might artifactually increase the BMD[2] but correcting for this did not alter the finding of significantly increased BMD in the proximal femur in the women with grade 2, grade 3, and grade 4 osteoarthritis. The authors also considered the effects of osteophytes and sclerosis in the spine from osteoarthritis as a potential cause of increased spine BMD. After adjusting the spine BMD for these findings, there was still a strong association between grade 3 or 4 osteoarthritis in the hip and increased spine BMD.

The authors postulated that a possible explanation for increased BMD in the femoral neck of subjects with osteoarthritis of the hip might be bone remodeling with thickening of the medial cortex and trabecular hypertrophy from altered mechanical stress. This would not account for the increased BMD at other sites.

Preidler et al. *(73)* evaluated 68 adults with plain radiography and DXA studies of the proximal femur in order to evaluate the influence of thickening of the medial cortex on bone density in the femoral neck, Ward's area, and trochanter in subjects with osteoarthritis. They found that the BMD in the femoral neck and Ward's area was highly correlated with the cortical thickness, whereas BMD in the trochanter was not. The authors suggested that the trochanteric region of the proximal femur might be the best ROI for evaluation of bone density in subjects with osteoarthritis of the hip.

Paralysis

Hemiplegia

Eighty-seven hemiplegic stroke patients (50 men, 37 women) and 28 age-matched controls underwent radiographic photodensitometry of the hands *(74)*. Bone mass was significantly reduced on the hemiplegic side in the stroke patients. Vitamin D deficiency and disuse were thought by the authors to be the most likely explanations. In another study, this same group observed a significant decrease in bone mass in the hand on the hemiplegic side compared with the contralateral side in 93 hemiplegic stroke patients *(75)*. The authors attributed this difference to a combination of weakness and immobi-

[2]*See* Chapter 2 for a discussion of the effects of femoral rotation on BMD measurements of the proximal femur.

lization. They postulated that this decreased bone mass may explain why hip fractures occur almost exclusively on the hemiplegic side in stroke patients.

One hundred twelve subjects (53 women, 59 men) with hemiplegia from cerebral infarction or hemorrhage underwent BMD measurements of both femurs with DXA (Hologic QDR-1000) *(76)*. The mean age of these subjects was 68.3 years. The mean period after the onset of hemiplegia was 45.7 months. Sixty-three subjects were affected on the right side and 49 subjects were affected on the left. BMD measurements were compared to reference population data supplied by the manufacturer. BMD in the total femur, femoral neck, Ward's, and trochanter was significantly decreased on the paretic side compared to the nonparetic side (8.8%, 6.6%, 10.3%, 10.4%, respectively). BMD in both proximal femurs was significantly decreased in comparison to reference population values. BMDs in the paretic femur were approximately 20–24% below reference values while BMDs in the nonparetic femur were 14–17% below reference values.

Paraplegia

Fifty-three patients (11 women, 42 men) with complete traumatic paraplegia of at least 1 year's duration underwent BMD studies of the PA lumbar spine and proximal femur with DXA (Hologic QDR-1000/W) and at the forearm by SPA (Nuclear Data 1100A) *(77)*. These subjects were wheelchair bound but not bed-ridden. They ranged in age from 21 to 60 with a median age of 35.9 years. Compared to age-matched controls, there was no significant difference in BMD at the lumbar spine. BMD for the total hip was reduced by 33% and was reduced at the femoral shaft by 25%. There was no significant difference in BMD at the cortical forearm site described as being at the junction of the distal and mid-third of the forearm.

Parkinson's Disease

In a study of 52 subjects with Parkinson's disease (PD) (28 men and 24 women), using DXA (Norland XR-26) to measure total body BMC, bone mineral content was found to be significantly decreased when compared to controls *(78)*. The *z*-score for men with PD averaged –0.47 and for women, –0.84. In this same study, metacarpal radiogrammetry did not reveal any significant differences between PD patients and controls.

A brief report in abstract form from Turc et al. *(79)* noted that in 19 men with PD BMD in the PA spine as measured with DXA was significantly reduced in comparison to age-matched controls. BMD averaged 0.965 ± 0.146 g/cm^2 in the PD subjects and 1.063 ± 0.146 g/cm^2 in the controls. Although femoral bone density was also reduced in the PD subjects, the difference from age-matched controls was not significant.

Kao et al. *(80)* also measured PA spine bone density with DPA (M&SE OsteoTech 300, Medical and Scientific Enterprises, Sudbury, MA) in 22 PD subjects (3 women, 19 men) aged 58 to 76. All of the PD subjects had lower PA spine bone densities than healthy age-matched controls. Sixty-eight percent of the PD subjects had spine BMDs that were more than 2 SDs below the age-matched mean BMD.

Pregnancy and Lactation

Controversy exists as to whether a separate entity of pregnancy-induced osteoporosis exists or whether pregnancy is an incidental or precipitating factor in persons who already have osteoporosis. The syndrome is considered rare with about 80 cases documented in the literature. The women who are affected often present with vertebral fractures in the

third trimester or shortly after delivery. Densitometry has demonstrated markedly low bone density in both the spine and proximal femur *(81)*. Five cases of postpregnancy osteoporosis have been reported by Yamamoto et al. *(82)*. These women ranged in age from 24 to 37 years. Of the five women, four were diagnosed after their first pregnancy. The fifth was diagnosed after her second pregnancy. All of the women presented with back pain and vertebral compression fractures, most within 1 month of delivery. BMD measurements were made at the 33% radial site with SPA (Norland-Cameron) and at the spine by either QCT or DXA (Hologic QDR-1000). Measurements were made at various times in the evaluation and management of these patients. BMD at the 33% radial site was not decreased in these women when compared to a reference population. BMD at the spine by either QCT or DXA revealed values lower than expected for the population.

The effect of pregnancy and lactation on bone density was studied by Karlsson et al. *(83)*. DXA measurements of the PA lumbar spine, total body, and proximal femur were performed using a Lunar DPX-L. Seventy-three women who were 5 or fewer days postpartum were compared to 55 age-matched controls. Lumbar spine BMD was 7.6% lower and total body BMD was 3.9% lower in the postpartum women than in the controls. Of the postpartum women, 65 were followed to determine the effects of lactation on BMD. Those women who did not breastfeed showed no changed in bone density. Femoral neck bone density decreased by an average of 2% in the first 5 months after delivery in those women who breastfed for 1 to 6 months with no additional bone loss being seen between months 5 and 12 postdelivery. Women who breastfed for more than 6 months had an 8.5% decline in BMD at Ward's area and a 4.1% decline in BMD at the lumbar spine at 5 months postpartum. No additional loss was seen at 12 months postpartum. Femoral neck BMD decline by 4% in this group at 12 months postpartum. The authors also noted that there appeared to be no difference in BMD between women with two or fewer pregnancies compared to women with four or more pregnancies.

More et al. *(84)* also studied the effects of pregnancy and lactation in 38 healthy Caucasian women with an average age of 26 years. Bone density was measured at the PA lumbar spine, 33% and ultradistal radius with DXA (Lunar DPX-L). Measurements were made within 3 months prior to conception, delivery, and at 6 and 12 months postpartum. Bone density was measured at the radius only at 22 to 24 weeks of gestation. During pregnancy, the average weight gain was 27.6 lb. The women were divided into three groups based on the duration of lactation. The duration of lactation in group 1 was 0 to 1 month. In group 2, the duration was 1 to 6 months and in group 3, 6 to 12 months. For the entire group, PA lumbar spine bone density decreased significantly by 2.1% during pregnancy. Bone density also decreased significantly during pregnancy at the 33% and ultradistal radius by 3.8% at each site. In group 1, there was no difference in PA lumbar spine BMD and 33% radial BMD seen at delivery and at the 6-month and 12-month postpartum visits. Bone density at the ultradistal radial site increased significantly by 5% between delivery and the 12-month postpartum visit in group 1. In group 2, bone density at the PA lumbar spine decreased 4.9% between delivery and the 6-month postpartum visit and then increased 2.3% between the 6-month and 12-month postpartum visits. At 12 months postpartum, the PA lumbar spine bone density was still 2.6% lower than at delivery in group 2. No significant change was noted at the 33% radial site postpartum in group 2 but there was a significant 4.3% decline between delivery and the 6-month postpartum visit at the ultradistal radial site. Between the 6-month and 12-month postpartum visit, the ultradistal radial BMD increased by 3.1%. In group 3, with the longest

duration of lactation, PA lumbar spine bone density decreased by 7.4% in the first 6 months postpartum and continued to decreased during the second 6 months postpartum. Once again, there was no significant change seen at the 33% radial site postpartum in this group, but there was a significant 4.9% loss seen at the ultradistal radius in the first 6 months postpartum that was followed by a 3% gain in the second 6 months postpartum. The authors proposed that during pregnancy fetal skeleton calcium needs were derived from maternal cortical and trabecular sites but primarily trabecular sites met calcium needs during lactation.

Radiotherapy

Bliss et al. *(85)* reported the development of severe pelvic fractures in 5 patients out of 183 who had been treated with radical radiotherapy for carcinoma of the cervix. Two of these patients with fractures had underlying rheumatoid arthritis. In this report, the authors suggested that underlying connective tissue disorders or low bone mass increased the risk for radionecrosis following irradiation.

Tai et al. *(86)* also reported the incidence of pelvic fractures in 336 women treated for endometrial or vaginal cancer with irradiation. Sixteen of the 336 women developed symptomatic pelvic fractures with a median time of onset of 11 months. The 5-year incidence was 2.1%. Of the 16 fractures, 6 were initially misdiagnosed as metastatic lesions.

In a letter to the editor in *Lancet*, Miró and Orecchia *(87)* noted that the reports of pelvic insufficiency fractures in patients treated with irradiation for cancer raised the possibility of an interaction with bone that increases fracture risk. As noted by Bliss et al. *(85)*, underlying low bone mass may increase this risk. If pelvic pain is erroneously assumed to be due to metastatic disease instead of radiation-induced fracture, particularly in the setting of low bone mass, inappropriate treatment could result with a further decline in the patient's quality of life *(86)*.

Regional Migratory Osteoporosis

Regional migratory osteoporosis (RMO) is also known as idiopathic regional osteoporosis, transient osteoporosis, and migratory algodystrophy. It was first described in 1967 *(88)* and its etiology remains unknown. It appears to be closely related to the disorder known as transient osteoporosis of the hip.[3] RMO occurs in middle-aged men. It begins as gradually increasing joint pain in the lower extremities with no prior history of trauma. Pain generally reaches a maximum level after 2 months. Symptoms subside after 3 to 9 months but may recur at the same or another joint. X rays of the affected joint generally reveal preservation of the articular space with periarticular demineralization. The affected joint will be hot on radionuclide scans. Trevisan and Ortolani *(89)* reported bone density findings in three Caucasian men who experienced 13 acute episodes of RMO during the study period. The men were 43, 44, and 54 years of age at presentation. Of the episodes, 46% involved the foot. The knee was involved in 31% of the episodes and the hip was involved in 15.5%. The ankle was involved in only 7.5% of the episodes. Each episode lasted an average of 6.4 months.

Bone density was measured by DXA (Hologic QDR 2000) at the PA lumbar spine, proximal femur, and total body. In all three patients, *T*-scores at the PA lumbar spine and femoral neck were below –2.5. In five episodes, bone loss at the involved joint was

[3] This disorder is discussed later in this chapter.

evaluated by comparing BMC differences between sides or by comparing pre-and postepisode values for the joint. Bone loss ranged from 75.5% to 14.7% and appeared to be related to the severity of the episode. Bone loss in adjacent skeletal regions was evaluated in three episodes in a similar fashion. The process appeared to involve the entire limb with greater loss of BMC seen at trabecular sites than at cortical sites. Recovery of BMC was evaluated in four episodes. BMC recovery was complete in only one episode although in all cases BMC increased. The average increase in BMC was 75.2% and averaged 3.3% per month. The authors noted that systemic osteoporosis has been reported in other cases of RMO.

Renal Failure

Eighty-nine patients with chronic renal failure underwent bone density testing of the spine using QCT *(90)*. Sixty-six were receiving long-term hemodialysis. In the 23 patients not on dialysis, spine BMD was 9% lower than predicted normal values but this difference was not statistically significant. In patients receiving dialysis however, the average *z*-score was –1.3. In 42 patients on dialysis who were followed over 8 months, spinal BMD by QCT decreased an average of 2.9%. Osteosclerosis was found in 11 patients on dialysis.

In a cross-sectional study, 45 patients on continuous ambulatory peritoneal dialysis (CAPD) were evaluated using DXA *(91)*. Total body, spine, and proximal femur bone densities were assessed. BMDs were not significantly different from an age-matched control population. The authors concluded that the prevalence of decreased bone density was not increased in CAPD patients. They also noted that BMD in the lumbar spine, femoral neck, and Ward's area was increased compared to controls in patients with evidence of hyperparathyroid disease. The authors observed that the utility of DXA regional studies to detect osteodystrophy is limited by the confounding effects of hyperparathyroid osteosclerosis.

Rheumatoid Arthritis

BMD of the distal and midradius was measured by DXA (Norland XR-26) in 34 women with rheumatoid arthritis and compared to 40 controls *(92)*. The women with rheumatoid arthritis ranged in age from 40 to 79 years with a mean age of 61 years. The average duration of disease was 12 years. BMD in both the distal and midradius was reduced in the women with rheumatoid arthritis who were in their 50s and 60s compared to controls. Women with rheumatoid arthritis in their 40s and 70s did not have BMDs that were significantly lower than controls. The authors suggested that postmenopausal bone loss may amplify the bone loss seen in rheumatoid arthritis.

Forty-six postmenopausal women with rheumatoid arthritis with a disease duration of 2 to 35 years underwent bone density testing at a variety of skeletal sites *(93)*. The ultradistal radius was evaluated with pQCT (Stratec XCT-960, Birkenfeld, Germany), the os calcis with ultrasound (McCue CUBA, McCue Ultrasonics Ltd., Winchester Hampshire, UK), and the spine and proximal femur with DXA (Norland XR-26 Mark II). Results were compared to 29 healthy postmenopausal women who served as controls. The postmenopausal women with rheumatoid arthritis had significantly lower bone density at all sites when compared to controls except at the lumbar spine and in the cortical measurement at the ultradistal radius. The total ultradistal BMD was 15.6% lower and the trabecular ultradistal BMD was 36.1% lower than controls. Femoral neck BMD was 15.4% lower than controls. Os calcis broadband ultasound attenuation was

31.7% lower and the velocity of sound was 6.6% lower. BMD at the lumbar spine in the women with rheumatoid arthritis was 6.7% lower than controls but this difference was not statistically significant.

BMD measurements of the hand, PA spine, and proximal femur were performed on 202 subjects (61 men, 141 women) with rheumatoid arthritis using DXA (Lunar DPX-L) *(94)*. The average age of the subjects was 58 years and the median disease duration was 1.8 years. BMD measurements of the hand were significantly correlated with BMD at lumbar spine and femoral neck ($r = 0.67$ and $r = 0.63$, respectively). In a separate study of 56 subjects with rheumatoid arthritis, hand BMC was shown to be significantly reduced in subjects with rheumatoid arthritis compared to controls *(95)*. In another 42 subjects with recent onset of rheumatoid arthritis who were followed prospectively with hand BMC, losses of 5.36% in men and 2.14% in women were noted in 1 year *(96)*.

Lane et al. *(97)* evaluated 120 postmenopausal women with rheumatoid arthritis, measuring BMD at the PA lumbar spine and proximal femur with DXA (Hologic QDR-1000) and at the distal radius and os calcis with SPA (OsteoAnalyzer). The women with rheumatoid arthritis were divided into three groups based on corticosteroid use: never users, current users, and past users. Results were compared to 7966 age-matched controls. All of the women were 65 years of age or older. Women with rheumatoid arthritis were found to have significantly lower BMD at all measurement sites when compared to controls. Women with rheumatoid arthritis who were never users had significantly lower BMD at the distal radius, os calcis, and total femur compared to controls. Women with rheumatoid arthritis who were current users had the lowest BMD at the distal radius, os calcis, and total femur. The authors concluded that postmenopausal women with rheumatoid arthritis have lower appendicular and axial bone densities that cannot be attributed to corticosteroid use.

In 1996, Deodhar and Woolf *(98)* reviewed bone densitometry studies in patients with rheumatoid arthritis. They concluded that patients with rheumatoid arthritis have lower bone density in both the appendicular and axial skeletons when compared with controls and that the most rapid bone loss occurred within the first year after the onset of disease. They also noted that the evidence suggested that doses of oral corticosteroids greater than 5 mg per day were associated with significant bone loss in patients with rheumatoid arthritis.

Thalassemia Major

Seventeen patients (9 men, 8 women) with thalassemia major were studied to determine the effects of the disease process on BMC and BMD *(99)*. The average age of the subjects was 24 years. Bone density at the distal radius was measured by Compton scattering and at the distal and midradius by SPA (Norland). Cortical indices of the third metacarpal were also measured. At the distal radius, BMC was found to be 34% lower than controls and at the midradius BMC was 24% lower than controls. The metacarpal cortical indices were 36% lower in the thalassemia subjects than controls. Higher BMC and cortical indices were seen in patients who had received more blood transfusions and longer treatment with desferrioxiamine but this difference was not statistically significant.

Lasco et al. *(100)* studied 40 patients with β-thalassemia major to determine the effects of sex-hormone replacement on bone density. The patients were 20 men and 20 women in their late teens and early 20s. They were divided into two groups, based on serum levels of testosterone in the men and 17 β-estradiol in the women. Men and women in group 1 were hormone replete from exogenous hormone replacement. Men and women in group

2 were hormone deficient and not receiving sex-steroid replacement. A control group consisting of 20 healthy subjects was matched for age, sex, height, and weight. Bone density was measured by DXA (SOPHOS L-XR-A) at the PA lumbar spine and proximal femur. In this cross-sectional study, bone density at the PA lumbar spine was reduced in groups 1 and 2 compared to the control group. The reduction was greater in group 2 than in group 1. Proximal femoral bone density was reduced in group 2 only in comparison to the control group. The authors suggested that the treatment of hypogonadism with sex hormone replacement therapy was beneficial in the prevention and treatment of osteoporosis in thalassemics.

Transient Osteoporosis of the Hip

This disorder was first described in women in the third trimester of pregnancy. It has been reported in both sexes however usually occurring in young to middle-aged patients *(101)*. In men, both hips are affected with equal frequency but in women, the disease is seen almost exclusively in the left hip. The disease presents with progressive pain, loss of range of motion, and a limp without any preceding history of trauma. Localized demineralization is seen in the femoral head, neck, and intertrochanteric region. Radionuclide bone scans demonstrate increased uptake in the regions that are demineralized. The disease is self-limited with spontaneous resolution in 6 to 12 months.

Transplantation

Cardiac Transplantation

Twenty-five patients (21 men, 4 women) were evaluated after orthoptic cardiac transplant with DXA (Lunar DPX-L) of the lumbar spine and total body *(102)*. Bone density testing was performed immediately posttransplant and at 6 and 12 months posttransplant. All patients received immunosuppressive therapy with prednisolone, cyclosporine, azathioprine, and anti-thymocyte globulin. The mean cumulative dose of prednisolone was 9.2 g during the first 6 months and 2.8 g during the second 6 months. Lumbar spine bone loss was rapid with a mean of –6.7% at 6 months and –8.8% at 12 months. Total body calcium fell at 6 months by –2.4% and at 12 months by –2.8%.

Liver Transplantation

Changes in bone density after orthotopic liver transplantation (OLT) in 45 patients with chronic advanced liver disease were reported by Monegal et al. *(103)*. Bone density was measured at the PA lumbar spine and proximal femur with DXA (Lunar DPX-L). Thirty-nine patients were followed for 1 year after transplantation, 34 patients were followed for 2 years, and 20 patients, for 1 year. All patients received triple drug immunosuppression after OLT that consisted of cyclosporin A, azathioprine, and prednisone. Lumbar spine BMD decreased by 5.7% by 3 months after OLT and increased thereafter, reaching baseline levels by the end of the second year. Femoral neck BMD decreased by 4% at 3 months after OLT and had not recovered to baseline levels after 3 years of follow-up. At the trochanter, BMD had decreased by 5.2% at 3 months and had not recovered to baseline levels at the end of 3 years of follow-up. Fifteen patients (33%) developed fractures in the first year. Of the 15 patients, 10 had 30 spine fractures and 1 patient had a hip fracture. There were no differences found in the cumulative dose of prednisone between the fractured and nonfractured patients.

Marrow Transplantation

Twenty-seven women who underwent bone marrow transplant (BMT) underwent bone density testing of the PA lumbar spine with DXA (Hologic QDR-1000) *(104)*. Conditions leading to BMT were acute nonlymphoblastic leukemia *(10)*, chronic myeloid leukemia *(8)*, acute lymphoblastic leukemia *(3)*, non-Hodgkin's lymphoma *(2)*, Hodgkin's disease *(2)*, aplastic anemia *(1)*, and refractory anemia with excess blasts *(1)*. All the subjects had experienced ovarian failure with amenorrhea of an average duration of 35.4 ± 36.1 months. Their average age was 31.3 ± 9.9 years. The average time between BMT and the bone density studies was 33.5 ± 34.5 months. Using WHO criteria,[4] 9 had osteopenia and 5 had osteoporosis. The authors postulated that immunosuppressive therapy and ovarian failure were the principal factors in bone loss after BMT.

In another study of both men and women with allogenic BMT lumbar and femoral neck BMD were reported to be 8 to 13% lower than age-matched controls *(105)*.

Renal Transplantation

BMD measurements of the PA lumbar spine, proximal total femur, and total body were performed on 34 renal transplant recipients (19 men, 15 women) with DXA (Hologic QDR-1000W) *(106)*. Measurements were compared to those made in 34 healthy controls. The average age of the subjects was 45 years. The cause of renal failure was glomerulonephritis in 12, analgesic nephropathy in 6, reflux nephropathy in 3, polycystic kidney disease in 5, nephroangiosclerosis in 2, chronic pyelonephritis in 4, oculorenal syndrome in 1, and Fabry's disease in 1. Immediately after transplant, total body and lumbar spine BMD was decreased in comparison to controls. In women receiving transplants, total femoral BMD was also decreased in comparison to controls. The difference in total femur BMD in men was not statistically different from controls. In the 5 months following transplantation, total body BMD and BMC decreased in both men and women as did BMD in the lumbar spine and total femur. The decrease in total body BMC was 41 g. Lumbar BMD decreased at a rate of 1.6% per month. The authors suggested that the bone loss seen after transplantation may be due to corticosteroid administration to prevent graft rejection.

Weight Loss

Studies in the medical literature have provided conflicting results with regard to the effect of weight loss on bone density, although the majority report small losses in BMC or reduced bone density. Fogelholm et al. *(107)* followed 74 premenopausal women during a 12-month weight reduction program that consisted of 3 months of a very low energy diet and a 9-month walking program followed by 24 months of follow-up. Bone density was measured by DXA (Norland XR-26) at the PA lumbar spine, proximal femur, and distal radius. The average age of these women was 40 years. The mean body mass index (BMI) was 34.0 kg/m^2 and the mean weight was 92 kg (202.8 lb). During the first 3 months, the average weight loss was 13.2 kg (29.1 lb). The subjects lost more fat than fat-free mass and more abdominal than peripheral fat based on body composition studies. During this same time, although femoral neck BMD did not change, PA lumbar spine, trochanter, and distal radial BMD declined a small but statistically significant amount. The declines were 0.02 and 0.01 g/cm^2 at the spine and trochanter, respectively. BMC

[4] *See* Chapter 9 for a discussion of WHO criteria for the diagnosis of osteoporosis.

also declined significantly at the PA lumbar spine, femoral neck, and trochanter by 1.02, 0.47, and 0.72 g, respectively. Bone area decreased in the total body, femoral neck, and trochanter. During the 9-month walking period and 24-month follow-up, the women regained an average of 62% of the prior weight loss. The only significant increase in BMD was seen at the trochanter, which increased 0.01 g/cm^2 during this period. The final BMD at the total body, PA lumbar spine, and femoral neck were lower than before weight reduction. The authors noted that further studies were needed to determine whether the observed changes in BMD, BMC, and area were real or due to technical limitations of DXA. They noted that the changes that they observed were small and likely without clinical significance.

Svendsen et al. *(108)* attempted to determine if soft tissue heterogeneity with weight loss introduced accuracy errors in BMD measurements with DXA. They studied 34 obese subjects, with an average age of 42.1 years and average weight of 102.1 kg (225.1 lb) with abdominal CT and PA lumbar spine DXA both before and after an average 11.3 kg (24.9 lb) weight loss over 1 year. The authors noted that this magnitude of weight loss resulted in changes in the soft tissue heterogeneity that theoretically could cause a false decrease of 1 to 2% in the PA lumbar spine BMD by DXA.

Wilson Disease

Wilson disease is an inborn error of the ATP7B gene on the 13th chromosome, which is involved in the transport of copper. The effects of Wilson disease on bone density were evaluated by Hegedus et al. *(109)* in 21 men and women with an average age of 30.8 years (14–46 years). The diagnosis of Wilson disease was based on laboratory findings, Kayser-Fleischer rings, genetic testing, and in some cases, liver biopsy and 24-hour urinary copper excretion. All patients had low ceruloplasmin levels. Bone density was measured by DXA at the PA lumbar spine and proximal femur (Norland XR-26), distal radius by SPA (Gamma NK-364), and by QUS at the heel (Osteometer DTU-1). The mean *T*-score and *z*-score at the PA lumbar spine was –0.59 and –0.51, respectively. At the femoral neck, the mean *T*- and *z*-score was –0.53 and –0.31. At the distal radius, the mean *T*-score was –0.92 and the mean *z*-score was –0.87. The *T*- and *z*-score for BUA at the heel was –1.84 and –0.92. For SOS at the heel, the mean *T*- and *z*-score was –0.10 and 0.29, respectively. Forty-three percent of the patients with Wilson disease had *z*-scores of –2 or poorer at the PA lumbar spine, femoral neck, and/or distal radius. Thirty-three percent had BUA *z*-scores of –2 or poorer. No patient had an SOS *z*-score of –2 or poorer.

THE EFFECT OF DRUGS ON BONE DENSITY

Alendronate Sodium

The effect of varying doses of alendronate sodium on lumbar spine and proximal femur bone density was evaluated in 994 women with postmenopausal osteoporosis by Liberman et al. *(110)*. The women were followed for 3 years during which time they received either placebo, 5 mg alendronate daily, 10 mg alendronate daily for 3 years, or 20 mg alendronate daily for 1 year followed by 5 mg daily for the remaining 2 years. All of the women received 500 mg of calcium a day. Bone density measurements were obtained at the lumbar spine, proximal femur, mid-forearm, and total body using DXA (Hologic QDR-1000, Lunar DPX-L, Norland XR-26). The placebo group receiving calcium alone lost BMD at all sites. In the alendronate-treated groups, there were

significant gains at the spine, femoral neck, trochanter, and total body. Significant increases from baseline in BMC or BMD at the mid-forearm site were not seen in the alendronate-treated groups. The increase in BMD was most rapid in the first 6 months of treatment. The 10 mg dose of alendronate produced greater gains in BMD than did the 5 mg dose and was as effective as the 20 mg/5 mg regimen. More than 96% of the women receiving 10 mg of alendronate daily had measurable gains in spine BMD. The gain in BMD at the end of 3 years in this group was approximately 8% in the lumbar spine and 5% in the femoral neck. At the end of 1 year, the gain in spine BMD in the 10 mg per day alendronate-treated group was approximately 5%.

The 3-year study by Liberman underwent two extensions for a total follow-up of 7 years. Bone density data after 7 years of continuous use of 10 mg daily of alendronate was reported by Tonino et al. in 2000 in the *Journal of Clinical Endocrinology and Metabolism (111)*. Bone density in the PA lumbar spine increased an average of 11.4% from baseline at the end of 7 years. The authors estimated that after the first 18 months of treatment, each additional year of treatment through 7 years resulted in an additional 0.8% increase in PA lumbar spine bone density.

A second study of 2 years duration of 188 postmenopausal women with low BMD in the spine confirmed a gain of 7.21% in the spine in women taking 10 mg of alendronate per day at the end of 2 years *(112)*. In the total hip, the gain was 5.27% at the end of 2 years. No significant change was seen at any forearm site. BMD measurements were made with DXA (Hologic QDR-1000).

The Fracture Intervention Trial (FIT) was the large phase III trial in which the efficacy of alendronate in reducing fracture risk was evaluated. The FIT trial has two arms that have been dubbed FIT I and FIT II. The results from FIT I *(113)* were published in 1996 and from FIT II *(114)*, in 1998. To be eligible to participate in FIT, a woman had to be at least 2 years postmenopausal and age 55 to 80. A femoral neck bone density of 0.68 g/cm^2 or poorer as measured on a Hologic DXA device was also required for entry into the study. If a woman meeting these criteria had a spine fracture at baseline, she was enrolled in FIT I. If she did not have a spine fracture at baseline, she was enrolled in FIT II. In both arms, calcium supplementation was provided when necessary to achieve a daily intake of 1000 mg of elemental calcium. The women then received either a placebo or 5 mg of alendronate daily. At the end of 2 years, the dose of alendronate was increased to 10 mg daily without breaking the study blind. This change was made because of the publication of trials showing that 10 mg of alendronate daily produced greater gains in bone density than 5 mg of alendronate daily. Changes in bone density from baseline were not reported in the FIT I publication *(113)*. The difference in bone density at the end of 3 years between the alendronate and placebo groups, which is the more important measure to assess efficacy, was reported. At the PA lumbar spine, the alendronate-treated women had a 6.2% higher bone density. At the femoral neck, the difference was 4.1%, at the total hip, 4.7% and at the trochanter, 6.1%. All of these differences were statistically significant. The actual changes from baseline were reported for FIT II *(114)*. At the end of 4 years, the women treated with alendronate had increased their PA lumbar spine bone density an average of 8.3% from baseline. At the femoral neck, the increase from baseline was 3.8% and at the total hip, 3.4%. In FIT I, the reduction in morphometric spine fracture risk was 47% from alendronate therapy. The reduction in clinical spine fracture risk was 55%. Hip fracture risk was also reduced by 51%. In FIT II, the risk of morphometric spine fractures was reduced by 44% with alendronate treatment.

The effect on bone density of 10 mg alendronate daily, 35 mg alendronate twice weekly, and 70 mg of alendronate once weekly was compared by Schnitzer et al. *(115)*. Participating in the 1-year study were 1258 women who were at least 2 years postmenopausal, age 40 to 90 years and with osteoporotic lumbar spine or femoral neck *T*-scores. Bone density was measured at the PA lumbar spine and proximal femur with DXA. At the end of 1 year, PA lumbar spine bone density had increased from baseline 5.4%, 5.2%, and 5.1% in the 10 mg daily, 35 mg once weekly, and 70 mg once weekly alendronate groups, respectively. At the total hip, the increases were 3.1%, 3.4%, and 2.9% for the 10 mg, 35 mg, and 70 mg groups. At the femoral neck, the increases from baseline at the end of 1 year were 2.9%, 2.4%, and 2.3% and at the trochanter, 4.4%, 4.7%, and 3.9%.

Rizzoli et al. *(116)* reported the 2-year results of the 10 mg daily, 35 mg twice weekly, or 70 mg once weekly alendronate trial described above. At the end of 2 years, bone density at the PA lumbar spine had increased from baseline by 7.4%, 7%, and 6.8% in the 10 mg daily, 35 mg twice weekly, and 70 mg once weekly alendronate groups, respectively. At the total hip, bone density had increased from baseline by 4.3%, 4.3%, and 4.1% in the same three groups. Bone density also increased at the femoral neck, trochanter and total body in the three treatment groups. The increases in bone density at all sites in all three groups were statistically significant. There was no statistically significant difference among the three groups at any skeletal site.

The effect on bone density in men with osteoporosis was studied by Orwoll et al. *(117)*. Two hundred forty-one men, with an average age of 63 years participated in the 2-year study. Bone density was measured by DXA. All the men received 500 mg of elemental calcium and 400 to 450 IU of vitamin D throughout the study. In a 3 to 2 ratio, the men were randomly assigned to receive a placebo or 10 mg of alendronate daily. At the end of 2 years, the men receiving alendronate had increases from baseline in bone density of 7.1% at the PA lumbar spine, 2.5% at the femoral neck, 4.3% at the trochanter, and 3.1% at the total hip. These increases were statistically significant compared to both the baseline and placebo values. At the end of 1 year, the increase in PA lumbar spine BMD was approximately 5% and at the femoral neck, approximately 2% in the alendronate-treated men.[5]

Calcitriol

Fifty postmenopausal women with nontraumatic vertebral fractures were followed for 2 years with bone density measurements of the PA spine and total body using DPA *(118)*. All women received 400 IU of vitamin D2 and 1000 mg of calcium a day. Half of the women received 0.25 μg of calcitriol twice a day and half received a placebo. Calcium intake and the dose of calcitriol were adjusted during the study in order to keep serum and urine levels of calcium within specified ranges. At the end of 2 years, women receiving calcitriol had an increase in lumbar spine BMD of 1.94%, whereas the placebo group lost 3.92%. Total body BMD increased in the calcitriol-treated group by 0.21%, whereas the placebo group lost 1.86%.

[5] The changes in BMD at the end of 1 year were not stated in this publication. They have been extrapolated from a visual inspection of the published graph showing the changes in bone density from baseline during the course of the study.

Calcium and Vitamin D

The effects of calcium supplementation and vitamin D3 on bone density were evaluated by Dawson-Hughes et al. *(119)* in a 3-year study of 176 men and 213 women aged 65 and over. BMD was measured by DXA (Lunar DPX-L) in the PA spine, proximal femur, and total body. The subjects received either a double placebo at bedtime or 500 mg of calcium citrate malate and 700 IU of vitamin D3. At the end of 3 years, subjects receiving calcium and vitamin D3 demonstrated an increase in BMD at the femoral neck of 0.50%, at the spine of 2.12%, and of the total body of 0.06%. Subjects receiving the double placebo had an increase in BMD at the spine of 1.22% and a loss in BMD at the femoral neck of –0.70% and a loss in total body BMD of –1.09%. At the end of the first year of the study, the differences in BMD between the placebo group and the calcium-vitamin D3 group were significant at all sites. At the end of the third year, however, only the difference in BMD of the total body was significant. Thirty-seven subjects experienced nonvertebral fractures during the 3-year trial. Of the 37 subjects, 26 were in the placebo group. The relative risk for fracture in the calcium-vitamin D3 group compared to the placebo group was 0.4 (95% CI of 0.2 to 1.0).

Chapuy et al. *(120)* followed 3270 ambulatory women with an average age of 84 years for 18 months. Half the women received 1200 mg of elemental calcium as tricalcium phosphate and 800 IU of vitamin D3 and half received a double placebo. There were 1765 women who completed the study. BMD of the proximal femur was measured by DXA (Hologic QDR-1000) at baseline and after 18 months in 56 women. At the end of 18 months, BMD in the total femur region of interest had increased 2.7% in the calcium-vitamin D3 group and had declined 4.6% in the placebo group. This difference was highly statistically significant. Bone density increased in the femoral neck in the calcium-vitamin D3 group by 2.9% and decreased in the trochanter by 1%. In the double placebo group, the BMD declined by 6.4% in the trochanter and increased by only 1.8% in the femoral neck. During the 18-month study, 151 nonvertebral fractures occurred in the calcium-vitamin D3 group compared to 204 in the placebo group. There were 32% fewer nonvertebral fractures and 43% fewer hip fractures in the calcium-vitamin D3 group compared to the placebo group. Additionally, there was a marked increase in the incidence of hip fracture with time in the placebo group while the incidence remained stable in the calcium-vitamin D3 group.

Corticosteroids

Oral Corticosteroids

The decrease in BMD at the PA lumbar spine and proximal femur was quantified using DXA (Lunar DPX) in 31 asthmatic subjects (18 men, 13 women) receiving glucocorticoid therapy and compared with BMD at those sites in age-matched controls *(121)*. The average dose and duration of corticosteroid therapy in these subjects was 16 mg of prednisone equivalents per day for 10 years. BMD of the lumbar spine was 80% of the sex- and age-matched controls. The BMD of the femoral neck, Ward's area, and trochanter were also reduced in comparison to sex- and age-matched controls at 83%, 78%, and 86%, respectively. The dose and duration of corticosteroid therapy did not correlate significantly with BMD in this study.

Laan et al. *(122)* evaluated the effects of low-dose prednisone on BMD in subjects with rheumatoid arthritis. Forty subjects (28 women, 12 men) with active rheumatoid

arthritis, all of whom were receiving gold salts, were begun on 10 mg of prednisone per day or placebo. The prednisone was gradually discontinued between weeks 12 and 20 of therapy. BMD was measured in the spine by dual-energy QCT (Somatom DR3, Siemens, Erlangen, Germany). There was an 8.2% decline in BMD in the first 20 weeks of therapy in the trabecular region of interest in the spine in the prednisone-treated group, whereas the BMD in the placebo group did not change. No changes were seen in either group in the BMD in the cortical region of interest in the spine in the first 20 weeks of therapy. In the patients who discontinued corticosteroid therapy after 20 weeks, BMD in the trabecular region of interest in the spine increased 5.3% over the next 24 weeks.

BMD in the PA lumbar spine as measured by DPA (Lunar DP3) decreased at a rate of 4.3% per year in the first year and at a rate of 2.3% per year in the second year in subjects who began corticosteroid therapy at the start of the study period *(123)*. These subjects received 1000 mg of calcium during the 2-year follow-up as part of a larger study evaluating the effects of calcitriol and calcitonin on the prevention of corticosteroid-induced bone loss. The mean daily dose of prednisone or prednisolone was 13.5 mg in the first year and 7.5 mg in the second year.

Inhaled Corticosteroids

The effect of inhaled corticosteroids on BMD was evaluated by Marystone et al. *(124)* in a cross-sectional study of 78 Caucasian subjects. The subjects ranged in age from 56 to 91. Thirty-four subjects (27 women, 17 men) had used inhaled corticosteroids and 44 (19 women, 15 men) had used oral corticosteroids. BMD was measured at the ultradistal and mid-radius with SPA (Lunar SP2), and at the lumbar spine and proximal femur with DXA (Hologic QDR-1000). These subjects were drawn from a larger study of 1673 subjects with the non-users of corticosteroids serving as controls. Among the men, BMD did not differ significantly at any site by corticosteroid usage. Among the women, users of oral corticosteroids had BMDs that were 7.2% lower at the midradius, 8.0% lower at the spine and 9.4% lower at the total hip than the nonusers. These differences were statistically significant. Women using inhaled corticosteroids had BMDs at the ultradistal radius, proximal femur, and spine that were intermediate between the oral corticosteroid users and the nonusers. Although the differences were not statistically significant, BMD was 2.3% lower at the total hip and 3.7% lower at the spine in women using inhaled corticosteroids compared to controls.

A comparison of the effects of inhaled budesonide and inhaled beclomethasone on BMD at the spine was performed by Packe et al. *(125)*. Twenty subjects with asthma receiving inhaled budesonide in a median daily dose of 800 μg and 20 subjects receiving inhaled high-dose beclomethasone in a median daily dose of 1000 μg underwent BMD measurements of the spine with QCT. These results were compared to those of 17 asthmatics who had never received any kind of corticosteroid therapy. The average BMD of the budesonide subjects of 139.5 mg/cm^3 was significantly lower than the BMD of 160.6 mg/cm^3 in the asthmatics who had never used steroids. The mean BMD of the beclomethasone subjects of 127.5 mg/cm^3 was not different from the budesonide subjects. The authors noted that the subjects receiving inhaled budesonide or beclomethasone had received previous courses of oral corticosteroids that could account for the decreased BMD.

Estrogen/Hormone Replacement

The effects of cyclic hormone replacement therapy (HRT) with either transdermal estrogen or oral estrogen on BMD in the spine and proximal femur were compared to controls by Hillard et al. *(126)*. Ninety-six Caucasian women between 6 months and 7 years postmenopausal participated in this study. Thirty women served as controls. Sixty-six women received either 0.05 mg transdermal 17-β estradiol continuously and 0.25 mg per day of norethisterone for 14 days of each cycle or oral conjugated equine estrogen 0.625 mg daily and 0.15 mg of dl-norgestrel daily for 12 days of each cycle. BMD measurements of the PA spine and proximal femur were obtained every 6 months for 3 years with DPA (Lunar DP3). In the control group, BMD in the spine declined by 4% and in the femoral neck by 5% at the end of 3 years. BMD increased at both sites in the two groups receiving some form of HRT with no significant difference between the two groups. The average increase in BMD at the spine in the transdermal estrogen-treated group at the end of the first year was 0.033 g/cm^2 and at the end of the third year was 0.046 g/cm^2. In the conjugated estrogen-treated group, the average increase in spine BMD was 0.032 g/cm^2 at the end of the first year and 0.038 g/cm^2 at the end of the third year. At the femoral neck, the average increase in the transdermal estrogen-treated group was 0.015 g/cm^2 at the end of the first year and 0.020 g/cm^2 at the end of the third year. In the conjugated estrogen-treated group, the average gain in femoral neck BMD was 0.003 g/cm^2 at the end of the first year and 0.009 g/cm^2 at the end of the third year. Six of the women receiving HRT had significant losses in BMD from the femoral neck during the 3 years of treatment despite good compliance.

The effects of HRT on BMD in women just beginning therapy were compared to the effects on BMD in women on established HRT by Lees et al. *(127)*. Twenty-nine women who had never taken HRT and 19 women who had been taking HRT were begun on micronized estradiol 2 mg per day orally daily and dydrogesterone 10 mg per day orally for 14 days of each cycle. BMD measurements of the PA lumbar spine and proximal femur were obtained with DXA (Lunar DPX) at yearly intervals for 2 years. In the women just beginning HRT, BMD increased at the spine by 5.3% at the end of 12 months and by 6.4% at the end of 14 months. In the women who had been on HRT, BMD increased to a lesser degree in the spine by 2.1% at the end of 12 months and by 2.3% at the end of 24 months. Femoral neck BMD increased in both groups but there was no difference between the two groups. At the end of 2 years, BMD had increased at the femoral neck in the women beginning HRT by 3.27% and in the women continuing HRT by 2.28%.

The effect of ERT on BMD in women at least 10 years past menopause was evaluated by Kohrt and Birge *(128)*. Twenty-four women ranging in age from 61 to 74 years and who were 10 to 33 years postmenopausal underwent BMD studies with DXA (Hologic QDR-1000/W) of the total body, PA spine, proximal femur, and ultradistal radius + ulna. Measurements were made at baseline and every 3 months for 1 year. Half the women received 0.625 mg of conjugated estrogen daily and 5 mg per day of medroxyprogesterone acetate for 13 consecutive days every 3 months. The other 12 women served as controls. A calcium intake of 1500 mg a day was maintained by all the subjects. In these late postmenopausal women receiving HRT, BMD increased in the total body, lumbar spine, femoral neck, trochanter, and Ward's triangle and declined insignificantly at the ultradistal radius + ulna. Compared to the placebo group, the differences were significant at all sites with the exception of the ultradistal radius + ulna. In the HRT group, BMD at

the total body increased 0.013 g/cm^2 or 1.4%, at the lumbar spine by 0.041 g/cm^2 or 5%, at the femoral neck by 0.019 g/cm^2 or 3.1%, at the trochanter by 0.017 g/cm^2 or 3% and at Ward's triangle by 0.026 g/cm^2 or 5.8%. The decline at the ultradistal radius + ulna was 0.001 g/cm^2 or 0.3%.

Dose-response studies of four estrogen preparations indicate that there are doses of estrogen replacement that are ineffective in preserving skeletal mass. The minimum effective dose of Premarin® (Wyeth-Ayerst, Philadelphia, PA) is considered to be 0.625 mg *(129)*. For Estrace® (Bristol-Myers Squibb, New York, NY), the minimum dose is 0.5 mg *(130)*. The minimum effective dose of Ogen® (Pharmacia & Upjohn, Kalamazoo, MI) is 0.625 mg. and for Estraderm® (Novartis, East Hanover, NJ), 0.05 mg *(131,132)*.

The effects of the withdrawal of ERT on forearm BMC were studied by Christiansen et al. *(133)* in 94 women who were 6 months to 3 years postmenopausal. Women who stopped HRT after 2 years lost BMC from the distal radius as measured by SPA at virtually the same rate as those who did not begin HRT. The loss of BMC was approximately 2.3% per year from the distal radius in the women stopping HRT.

The effects of withdrawal of HRT on the spine and proximal femur were reported by Trémollieres et al. in *Osteoporosis International* in 2001 *(134)*. Fifty healthy postmenopausal women who had been followed with bone densitometry both during HRT and after cessation were included in this study and compared to 81 healthy postmenopausal women who had never received HRT. Bone density was measured at the PA lumbar spine with DXA or DPA followed by DXA (Lunar DPX-L and Lunar DP3). HRT consisted of either 1.5 mg/day of 17-β estradiol given percutaneously or 50 μg/day of 17-β estradiol in a transdermal patch combined with progesterone or a 19-norprogesterone derivative. HRT was utilized for a mean of 5 years. All of the women underwent bone density measurements during the time they received HRT and at least once within the first 18 months after cessation of HRT. Of the 50 women, 30 were followed after cessation of HRT for up to 8 years. The authors found that bone loss from the spine accelerated during the first 2 years after cessation of HRT at a rate that was similar to the rate of bone loss seen in the 81 postmenopausal women who had never received HRT. The rate of loss in the HRT-treated women was –1.64% compared to –1.52% in the never-treated women. After 2 years, the yearly rate of bone loss from the spine decreased. Between years 3 and 5, the rate of bone loss slowed to –0.83% in the previously HRT-treated women compared to –0.70% in the never-treated postmenopausal women. These differences were not statistically significant. The authors concluded that the pattern of bone loss seen in the postmenopausal women stopping HRT was similar to that seen in the immediate postmenopausal years in women who do not use HRT.

The percentage of women who may lose bone despite hormone replacement therapy (HRT) was addressed by Komulainen et al. *(135)*. A subset of 232 women from the Kuopio Osteoporosis Risk Factor and Prevention Study (OSTPRE) were randomized to receive sequential HRT or placebo. BMD was measured at the PA lumbar spine and femoral neck by DXA at baseline, 2.5 years, and 5 years. The women also underwent measurements of FSH, estradiol, and alkaline phosphatase. A woman was identified as a nonresponder to HRT if her 5-year change in BMD was similar to, or worse than, the mean change of the placebo group. In the HRT group, the mean change in PA lumbar spine BMD over 5 years was a significant increase of 1.5%. At the femoral neck, BMD remained stable with an insignificant decrease of 0.4%. In the placebo group, significant losses were seen at both sites, 4.6% at the spine and 4.4% at the femoral neck. Eleven

percent of the women were considered nonresponders to HRT based on changes in lumbar spine BMD. Based on femoral neck BMD 26% of the women receiving HRT were considered nonresponders. Smoking and low body weight were found to be significant predictors of nonresponse to HRT. Additionally, nonresponders had higher FSH levels and smaller increases in estradiol than the responders. The mean changes in FSH and alkaline phosphatase were lower in the nonresponders than in the responders to HRT.

Etidronate

The effects of etidronate alone or etidronate preceded by phosphate were evaluated in a double-blind, placebo-controlled trial of 429 postmenopausal women with one to four vertebral compression fractures and radiographic demineralization *(136)*. The women received either a double placebo, 1 g of phosphate orally twice daily on days 1 through 3 followed by etidronate 400 mg orally daily on days 4 through 17, placebo on days 1 through 3 followed by etidronate on days 4 through 17 or phosphate on days 1 through 3 followed by placebo on days 4 through 17. All women received calcium 500 mg. daily on days 18 through 91. The treatment cycles were repeated eight times. BMD was measured at the lumbar spine and proximal femur with DPA (Lunar DP3, Norland 2600). BMC was measured at the distal and midradius with SPA (Lunar SP2, Nuclear Data 1100, Norland Model 178, OsteoAnalyzer). At the end of 24 months, significant gains in BMD at the spine were seen in the etidronate and etidronate + phosphate-treated groups. The average increase in spine BMD in the etidronate alone group was 4.2% and in the etidronate + phosphate group, 5.2%. The women receiving etidronate alone had a significant gain at the femoral neck at the end of 2 years of approximately 3.5%. No significant change in BMC at the distal or midradius was seen in any treatment group during the 24 months of observation.

GnRH Agonists

Twenty-eight women with endometriosis who ranged in age from 22 to 44 years were treated with 3.6 mg of goserelin acetate depot every 28 days for 6 months *(137)*. BMD measurements of the PA lumbar spine were obtained with DXA (Hologic) at baseline, 6, 12, and 30 months. Results were compared to those in 25 healthy women who served as age-matched controls. There was a significant decrease of 4% in lumbar spine BMD in the treated group after 6 months that persisted for the second 6 months during which no goserelin was administered. Values in the control group did not change during this period. At 30 months, however, BMD values in the treated group had returned to baseline levels.

Eleven women with endometriosis were treated with goserelin 3.6 mg every 28 days for 6 months, whereas 12 women with endometriosis were treated with oral danazol 600 mg for 6 months *(138)*. BMD measurements of the lumbar spine and proximal femur were performed in both groups using DPA (Lunar DP3) at the beginning and end of therapy. During the treatment period, BMD did not change at any site in the danazol-treated group. In the women receiving goserelin, there was a 2.5% decline in spinal BMD and a 1.7% decline in femoral neck BMD at the end of 6 months.

The effects of buserelin on BMC at the 10% and 33% radial sites was evaluated in 18 women who were being treated for 6 months for uterine fibroids *(139)*. BMC measurements at the radius were performed with SPA (Norland Cameron). The women ranged in age from 28 to 49 years. Eighteen healthy women served as controls. Buserelin was administered in a dose of 0.5 mg subcutaneously three times a day for the first 10 days, followed by 200 μg intranasally four times a day for 6 months. No significant changes

in BMC were observed in the treated group in the first 6 months or at the end of a 6-month treatment-free observation period.

Twenty-five women with endometriosis were treated with nafarelin and followed for 12 months with BMD measurements of the PA lumbar spine by DPA and measurements of the distal and midradius by SPA *(140)*. Sixteen of the women received nafarelin in a dose of 200 μg a day, whereas 9 of the women received 400 μg a day. During 6 months of treatment, women receiving the lower dose of nafarelin had no significant change in bone density, whereas women receiving the higher dose experienced losses of 2 to 6%. These values returned to baseline levels 6 months after discontinuation of therapy. An additional study of 17 women with endometriosis was performed by Riis et al. *(141)*. These women were treated with nafarelin 400 μg per day plus 1.2 mg of norethindrone per day for 6 months. BMC was again measured at the distal and midradius with SPA and BMD was measured at the lumbar spine and total body by DPA. There was no significant change in BMC or BMD during the treatment period except in the distal forearm. Six months after treatment, this value had returned to baseline levels.

Heparin

Sixty-one premenopausal women who had been previously treated with subcutaneous or intravenous heparin for at least 1 month were evaluated with bone density measurements of the spine with DPA (Norland 2600) and of the distal third of the radius with SPA (Norland 278A) *(142)*. The average duration of heparin therapy was 26.7 weeks and the average total dose was 4.1×10^6 units. Sixty-one healthy women served as age-matched controls. The mean BMD at the spine and radius did not differ significantly between the two groups. The authors also evaluated the proportion of women in each group whose bone densities fell below either the presumed fracture threshold[6] of 1.000 g/cm^2 or 0.840 g/cm^2 (2 SD below young normals) at the spine and below 0.690 g/cm^2 at the radius (2 SD below young normals). A significantly greater proportion of women who had been treated with heparin fell below these cutoff levels.

Ipriflavone

Ipriflavone is a synthetic flavonoid that is being investigated for its effects on bone density. Passeri et al. studied 28 postmenopausal women over the age of 65 with at least one vertebral fracture and a BMD at the distal radius that was more than 2 SD below the young-adult peak BMD *(143)*. The women received either 200 mg of ipriflavone or placebo three times daily. BMD was measured at the 10% radial site with DPA (Osteoden P, NIM, Verona, Italy) at baseline and after 12 months. Women receiving ipriflavone increased BMD at the 10% radial site by 6% after 12 months, whereas the women receiving placebo had an insignificant loss of 0.3%.

In a larger study of 255 postmenopausal Caucasian women, the effects of ipriflavone on the BMD of the distal radius as measured by DPA (Osteoden P) were reported by Adami et al. *(144)*. These women ranged in age from 50 to 65 years and had a BMD at the distal radius that was at least 1 SD below the age-matched mean BMD. The women received 200 mg of ipriflavone orally or placebo three times daily. All women received 1 g of calcium during the 2 years of the study. At the end of 2 years, women receiving ipriflavone maintained their baseline bone density at the distal radius, whereas women receiving placebo lost slightly more than 3%.

[6]*See* Chapter 10 for a discussion of the fracture threshold.

Medroxyprogesterone Acetate

Thirty women receiving injectable depot medroxyprogesterone acetate for contraception for at least 5 years were evaluated by Cundy et al. *(145)*. BMD was measured at the PA lumbar spine and femoral neck and compared to BMD in 30 premenopausal women and 30 postmenopausal women who served as controls. Compared to the premenopausal women, the women who received depot medroxyprogesterone had BMDs that were 7.5% lower in the lumbar spine and 6.6% lower in the femoral neck. Compared to the postmenopausal women, however, women who received depot medroxyprogesterone acetate had BMDs that were 8.9% higher in the lumbar spine and 4% higher in the femoral neck.

Nandrolone Decanoate

Nandrolone decanoate is an anabolic steroid. Twenty postmenopausal women with osteoporosis were followed with bone mass measurements at the PA lumbar spine and femoral shaft with DPA (Novo Diagnostic) for 12 months *(146)*. Half of the women received 50 mg of nandrolone decanoate intramuscularly every 3 weeks, whereas the remainder received placebo injections. All the women received 1 g of calcium a day. In the lumbar spine, women receiving nandrolone had an increase in BMC of 9.8%, whereas the women receiving placebo lost 3.2%. The increase in spinal BMC from baseline was significant and the difference between groups was also significant. In the femoral shaft, women receiving nandrolone had an increase of 3.5% compared to the placebo group, which lost 3.3%. This difference in the femoral shaft did not reach statistical significance.

Raloxifene

The effects of raloxifene on BMD in 143 postmenopausal women with one or more prevalent spine fractures whose average age was 68.4 years was reported by Lufkin et al. *(147)*. The women were treated with 60 mg per day or 120 mg per day of raloxifene or placebo for 1 year. BMD was measured at the PA lumbar spine, total femur, ultradistal radius, and total body with DXA. All women received 750 mg of calcium per day and 400 IU of vitamin D. At the end of 1 year, there were significant differences in the change in BMD at the total femur between the 60 mg per day group and the placebo group and at the ultradistal radius between both raloxifene groups and the placebo group. At the total femur, the 60 mg per day group increased BMD 0.95%, whereas the placebo group decreased BMD 0.71%. At the ultradistal radius, the 60 mg per day group increased BMD 0.22%, the 120 mg per day group decreased BMD 0.19%, and the placebo group decreased BMD 2.70%. There were no significant differences in BMD at the end of 1 year between the two raloxifene groups and the placebo group at the spine or total body. This was a preliminary report in abstract form presented at the 19th annual meeting of the American Society for Bone and Mineral Research.

In a study of 601 postmenopausal women between the ages of 45 and 60 years, Delmas et al. *(148)* also evaluated the effects of raloxifene on BMD with DXA (Hologic QDR-1000 and QDR-2000). Eligibility for the study was based on age, being 2 to 8 years postmenopausal and having a spine BMD *T*-scores between +2 and –2.5. The women were treated for 2 years with placebo, 30, 60, or 150 mg of raloxifene. All of the women received 400 to 600 mg of elemental calcium daily. At the end of 2 years, all three raloxifene groups demonstrated gains in BMD at the lumbar spine, total hip, and femoral neck that were significantly different from the placebo group. The percent increase from

baseline at the end of 2 years at the lumbar spine, total hip and femoral neck for the 30 mg group was 1.3%, 1% and 0.6%, respectively. For the 60 mg group, it was 1.6%, 1.6%, and 1.2%. For the 150 mg group, the percent change from baseline at 2 years was 2.2%, 1.5%, and 1.5%.

The definitive study of the effects of raloxifene on bone density and vertebral fracture was the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. The results were published in the *Journal of the American Medical Association* in 1999 *(149)*. The MORE trial was a 3-year study in which 7705 women (average age 67 years) who were at least 2 years postmenopausal received a placebo, 60 mg of raloxifene daily, or 120 mg of raloxifene daily. All women received 500 mg of elemental calcium and 400 to 600 IU of vitamin D daily, as well. To be eligible, the women had to have a spine or femoral neck *T*-score of –2.5 or poorer, low bone mass, and one moderate or severe spine fracture or two mild spine fractures, or two moderate spine fractures regardless of the bone density level. PA lumbar spine and proximal femur bone density was measured yearly with DXA. Radiographs of the spine were obtained at baseline, 24 months, and 36 months. In both the 60 mg and 120 mg raloxifene groups, lumbar spine bone density increased during years 1 and 2 and remained constant during the third year. The change in lumbar spine bone density from baseline in the two treatment groups was approximately 2.5% at the end of the first year and 2.75% at the end of the third year.[7] At the end of the third year, there was a statistically significant 2.6% difference in the increase in bone density at the lumbar spine in the group taking 60 mg[8] of raloxifene compared to the placebo group. At the femoral neck, the increases in bone density were smaller as expected in the two raloxifene groups and reached a peak at 24 months. At the end of 36 months, there was a statistically significant 2.1% benefit of treatment at the femoral neck for those women taking 60 mg of raloxifene compared to women taking a placebo. The increase in femoral neck BMD from baseline for the 60 mg raloxifene group was approximately 1.5% at 24 months.[9] At the end of the 3-year study, the women receiving 60 mg of raloxifene a day had a 30% reduction in the risk of new spine fracture.

Risedronate

The efficacy of risedronate in increasing lumbar spine BMD was studied in 648 postmenopausal women for 18 months by McClung et al. *(150)*. The average age of the women was 62 years and all were at least 1 year postmenopausal with an average duration of menopause of 16 years. At entry into the study, the lumbar spine *T*-score was –2 or less. BMD was measured by DXA at the PA lumbar spine, proximal femur, and at the distal and midradius. The women received either 2.5 mg or 5 mg of risedronate daily or placebo. All of the women received 1 g of calcium daily. Risedronate increased BMD at the lumbar spine, femoral neck, and trochanter and at the distal radius in a dose-dependent fashion.

[7] This data was not directly reported in the referenced publication. The changes in lumbar spine bone density from baseline noted above for the treatment groups are based on a visual inspection of the published graph showing the percent changes in bone density from baseline over time in the study.

[8] The 60 mg dose of raloxifene is the amount that is approved by the Food and Drug Administration for the prevention and treatment of postmenopausal osteoporosis.

[9] This data was not directly reported in the publication and is extrapolated from a visual inspection of the published graph showing the percent change from baseline during the study at the femoral neck for the three treatment groups.

At the lumbar spine, both risedronate groups had significant changes in BMD from baseline, whereas the placebo group did not change significantly. The 5 mg risedronate group had a significantly greater increase than the 2.5 mg group. The gains in lumbar spine BMD at the end of 18 months for the 2.5 mg and 5 mg risedronate groups were 2 to 3% and 4 to 5%, respectively. In the femoral neck and trochanter, both risedronate groups again demonstrated significant increases from baseline and significant increases in comparison to the placebo group. The 5 mg risedronate group again demonstrated a significantly greater increase in BMD at both sites than the 2.5 mg group. The average gain in BMD at the femoral neck in the 5 mg group was approximately 3% and at the trochanter, approximately 5%. At the distal radius, only the 5 mg risedronate group had a significant increase in BMD from baseline at 18 months of slightly more than 1%. At the midradius, no group demonstrated a significant change in BMD from baseline values. This data was presented in abstract form at the 19th annual meeting of the American Society for Bone and Mineral Research.

Two major trials of risedronate therapy in postmenopausal osteoporosis were published in 1999 and 2000 *(151,152)*. The trials were almost identical in design and are known as the North American and European Vertebral Efficacy with Risedronate Therapy (VERT) trials. In both trials, the primary endpoint of interest was the reduction in vertebral fracture risk.

In the North American VERT trial *(151)*, 2458 postmenopausal women participated. The women were eligible if they were at least 5 years postmenopausal and not more than 85 years of age. They were required to have at least two spine fractures at study entry or one spine fracture and a PA lumbar spine BMD *T*-score of –2 or less. All the women received 1000 mg of elemental calcium daily. If a serum 25-hydroxyvitamin D level was low at study start, the women also received up to 500 IU of cholecalciferol supplementation daily. The women then received either a placebo, 2.5 mg of risedronate or 5 mg of risedronate daily. DXA was used to measure bone density at the PA lumbar spine and proximal femur at 6-month intervals during the 3-year trial. Approximately 1 year after the trial was started, the 2.5 mg risedronate arm was discontinued. At the end of 3 years, treatment with 5 mg of risedronate daily significantly reduced the cumulative incidence of morphometric vertebral fractures by 41% compared with placebo. At the end of only 1 year, a statistically significant 65% reduction in spine fracture risk was seen in the 5 mg risedronate group. At the end of 3 years at the PA lumbar spine, women receiving 5 mg of risedronate daily increased their bone density by 5.4% from baseline compared to the 1.1% increase in the placebo group. In the proximal femur, the 5 mg risedronate group had increases from baseline of 1.6% at the femoral neck and 3.3% at the trochanter compared to losses of 1.2% and 0.7% in the placebo group. The increases in bone density in the risedronate-treated women were both statistically significant from baseline and significantly different from the changes seen in the placebo group. Bone density was maintained in the risedronate treated women at the midradius at the end of 3 years while the placebo group lost midradial bone density.

In the European VERT trial *(152)* the women had to have at least two spine fractures to be eligible. The trial was otherwise identical in design and involved 1226 postmenopausal women with average lumbar spine *T*-scores in the WHO osteoporotic category. Because the European VERT trial started before the North American VERT trial, the 2.5 mg risedronate group was discontinued after 2 years of this 3-year trial. Morphometric spine fracture risk was significantly reduced in the 5 mg risedronate group by 47%

compared to the placebo group at the end of the trial. At the end of 1 year, the reduction in morphometric spine fracture risk in the 5 mg risedronate group was 61%. Much as was seen in the North American VERT trial, bone density increased significantly from baseline in the 5 mg risedronate treated women at the PA lumbar spine, femoral neck, and trochanter and was maintained at the midradius at the end of 3 years. These changes in bone density in the 5 mg risedronate-treated women were also significantly different from the placebo group.

The effect of risedronate therapy on hip fracture as the primary endpoint of interest was studied in 9331 postmenopausal women age 70 and older by McClung et al. *(153)*. In this study, only women age 70 to 79 were enrolled entirely on the basis of a very low femoral neck bone density *T*-score of –4 or –3 and at least one clinical risk factor for hip fracture. Women age 80 and older could be enrolled on the basis of clinical risk factors for hip fracture alone. As in the VERT trials, all the women received 1000 mg of elemental calcium a day and up to 500 IU of vitamin D a day if the serum 25-hydroxyvitamin D level was low at baseline. The women were then divided into three groups, receiving a placebo, 2.5 mg risedronate, or 5 mg risedronate per day. The duration of the trial was 3 years. The primary endpoint in this study was the reduction in hip fracture risk. Changes in bone density in the proximal femur were considered a secondary endpoint. In the women age 70 to 79 years, bone density at the femoral neck was 2.1% and 3.4% higher than placebo in the 2.5 mg and 5 mg risedronate groups, respectively. At the trochanter, bone density was 3.8% and 4.8% higher than placebo in the 2.5 mg and 5 mg risedronate groups. The actual changes from baseline are not cited in the *New England Journal of Medicine* publication. Hip fracture risk was statistically significantly reduced by 40% in the 70- to 79-year-old women for the two risedronate groups combined compared to the placebo group.

The original formulation of risedronate for the prevention or treatment of osteoporosis called for a dose of 5 mg daily. The effect of 35 mg and 50 mg of risedronate given only once a week compared to the 5 mg daily dose on lumbar spine bone density was reported in *Calcified Tissue International* by Brown et al. *(154)*. The participants in this trial were ambulatory women age 50 and older who were at least 5 years postmenopausal. They were required to have PA lumbar spine *T*-scores of –2.5 or poorer in the absence of a spine fracture or –2 or poorer with a spine fracture. Bone density was measured by DXA at the PA lumbar spine and proximal femur at 6 and 12 months. In addition to 1000 mg of elemental calcium a day, each woman received 5 mg risedronate daily, 35 mg risedronate once weekly, or 50 mg risedronate once weekly. At the end of 1 year, the average increase from baseline in lumbar spine bone density was 4.00%, 3.94%, and 4.25% for the 5 mg daily, 35 mg once weekly, and 50 mg once weekly risedronate groups, respectively. At the total hip, the increases from baseline were 2.51%, 2.35%, and 2.88% for the same three groups at the end of 12 months. At the femoral neck, there were increases of 2.05%, 1.92%, and 2.12% from baseline and at the trochanter there were increases of 3.34%, 3%, and 3.68% for the three dosage groups. The changes in bone density from baseline at all sites for all three groups were statistically significant.

Salmon Calcitonin

The results of the 5-year Prevent Recurrence of Osteoporotic Fracture (PROOF) study of nasal spray salmon calcitonin were reported by Chesnut et al. *(155)* in the *American Journal of Medicine* in 2000. Preliminary data from PROOF was reported at the 19th annual meeting of the American Society for Bone and Mineral Research in 1999 *(156)*.

One thousand two-hundred fifty-five women with an average age in their late 60s were randomized to receive placebo, 100, 200, or 400 IU of salmon calcitonin nasal spray daily *(155)*. All of the women also received 1000 mg of calcium and 400 IU of vitamin D daily. The women had at least one prevalent fracture and a BMD at the lumbar spine that was more than 2 SD below the young-adult mean value. BMD was measured at the lumbar spine and proximal femur with DXA at yearly intervals during the study. During the 5 years of the study, lumbar spine bone density remained stable in the placebo group. At the end of years 1 and 2, lumbar spine BMD increased significantly in all three nasal spray calcitonin groups compared to the placebo group. At the end of 3 years, however, only those women receiving 400 IU of nasal spray calcitonin had an increase in lumbar spine BMD that was significantly different from that seen in the placebo group. At the end of 5 years, there was no statistically significant difference in lumbar spine BMD between any of the nasal spray salmon calcitonin groups and the placebo group. The increase in lumbar spine bone density in all three nasal spray salmon calcitonin groups was statistically significant from baseline at all time points, however. At the end of the first year, the increase in lumbar spine BMD from baseline was between 1 and 1.5% for the three treatment groups. No significant effect on femoral neck or trochanteric bone density was reported for any of the groups. In the 200 IU nasal spray salmon calcitonin group only a statistically significant 33% reduction in the risk of spine fracture was documented. Significant reductions in fracture risk were not found for the 100 IU or 400 IU dose groups.

In study of 208 postmenopausal women with a distal forearm BMC 2 SD or more below the young-adult mean BMC, the response to nasal spray salmon calcitonin was evaluated at the end of 2 years with measurements of BMC at the distal forearm by SPA and at the PA lumbar spine by DXA (Hologic QDR-1000) *(157)*. The women received placebo, 50 IU, 100 IU, or 200 IU of nasal spray salmon calcitonin daily in addition to 500 mg of calcium. BMC increased in the salmon calcitonin treated women in a dose-dependent manner. At the end of 2 years, BMC in the lumbar spine had increased 3% in the women receiving 200 IU per day and 1% in the women receiving placebo. BMC at the distal radius declined in all groups approximately 1% at the end of 2 years.

The effectiveness of nasal spray calcitonin in preventing bone loss from the spine was evaluated in recently postmenopausal women by Reginster et al. *(158)*. Two hundred fifty-one women who were 6 months to 5 years postmenopausal were randomized to receive either placebo, 50 IU, or 200 IU of nasal spray salmon calcitonin daily for 5 consecutive days each week for 2 years. All of the women also received 500 mg of calcium daily. BMD measurements of the PA lumbar spine were obtained with DPA (Novo Lab 22A) every 6 months. At the end of 2 years, BMD in the lumbar spine decreased by 6.98% in the placebo group. In the 50 IU and 200 IU salmon calcitonin groups, BMD in the lumbar spine increased by 0.51% and 2.26%, respectively. The difference in BMD between both salmon calcitonin groups and the placebo group was statistically significant, whereas the difference between the two salmon calcitonin groups was not.

Sodium Fluoride

Sodium fluoride is a potent stimulator of osteoblastic bone formation. Its effect on BMD in the lumbar spine and proximal femur was evaluated by Riggs et al. *(159)* in 202 women with postmenopausal osteoporosis. Osteoporosis was defined as at least one prevalent vertebral fracture and a spine BMD below the normal range for premenopausal

women. The women received placebo or 75 mg of sodium fluoride daily and 1500 mg of calcium daily for 4 years. BMD of the PA lumbar spine and femoral neck were measured by DPA. The 33% radial site was measured by SPA. Women receiving placebo increased lumbar spine BMD by 0.4% per year, whereas the women receiving fluoride increased lumbar spine BMD 8.2% per year. At the femoral neck, women receiving placebo lost 0.9% per year, whereas women receiving sodium fluoride increased BMD 1.8% per year. At the radius, the fluoride-treated group had a decline in BMC of 1.8% per year, whereas the placebo group increased 0.4% per year. The difference between the rates of change in the fluoride-treated group and the placebo group was significant at these sites.

A different preparation of sodium fluoride and different regimen was evaluated by Pak et al. *(160)* in 110 Caucasian women with postmenopausal osteoporosis. These women were randomized to receive cyclic treatment with 25 mg of slow-release sodium fluoride or placebo twice daily for 12 months followed by 2 months withdrawal and 400 mg of calcium citrate twice daily continuously. BMD was measured at the PA lumbar spine and proximal femur by DPA and DXA and at the midradius by SPA (Norland). In this ongoing study, the average subject had completed more than two treatment cycles with only a few subjects having completed four cycles. In the placebo group, BMC in the lumbar spine did not change significantly over the first four cycles. In the slow-release sodium fluoride group however, BMC in the lumbar spine increased 4 to 6%. At the femoral neck the BMD did not change in the placebo group, whereas it increased in the slow-release fluoride group by 4.1% by the end of the first cycle and 2.1% by the end of the second cycle. The midradial BMD did not change significantly in either group.

Tamoxifen

In a small, uncontrolled trial, eight postmenopausal women beginning tamoxifen 10 mg orally twice a day after a diagnosis of breast cancer were followed every 6 months with BMD measurements of the PA spine with DPA (Lunar) *(161)*. At the end of 6 months, BMD in the lumbar spine had increased an average of 0.0456 g/cm^2 and at 12 months, 0.0565 g/cm^2. All eight subjects had increases in BMD in the lumbar spine.

The effect of tamoxifen on lumbar spine BMD and the 33% radial site was determined in 70 women receiving 10 mg twice daily after a diagnosis of breast cancer and compared to the findings in 70 women with similar stage breast cancer who served as controls *(162)*. BMD at the lumbar spine was measured with DPA (Lunar DP3) and at the 33% radius, by SPA (Lunar SP2). The women were followed for 2 years. Women receiving tamoxifen increased lumbar spine BMD 0.61% per year but lost BMD at the 33% radial site at a rate of 0.88% per year. The women not receiving tamoxifen lost BMD at both sites at a rate of 1.29% at the radius and 1% at the spine. The differences between the two groups were statistically significant at the spine but not at the 33% radial site.

Teriparatide

Teriparatide (recombinant human 1-34 parathyroid hormone) was evaluated in a placebo controlled, double-blind, randomized study of 1637 postmenopausal women *(163)*. To participate in the study, the women had to be at least 5 years postmenopausal and have two spine fractures or one spine fracture and a hip or spine *T*-score of –1 or poorer. All the women received 1000 mg of elemental calcium and 400 to 1200 IU of vitamin D.

After 2 weeks of daily placebo injections, the women were randomized to receive placebo, 20 or 40 μg of recombinant human 1-34 parathyroid hormone (rh PTH 1-34), injected subcutaneously daily. Bone density was measured at the PA lumbar spine, proximal femur, radius and total body with DXA at baseline, 12, and 18 months. Radiographs of the thoracic and lumbar spine was performed at baseline and at the end of the study. The study was stopped prematurely by the sponsor. As a consequence, the duration of therapy was approximately 18 months in all three groups. At the end of the study, the women receiving 20 μg of rh PTH 1-34 had an increase in PA lumbar spine BMD of 9.7% from baseline. The 40 μg rh PTH 1-34 group had an increase of 13.7% from baseline at the PA lumbar spine. At the femoral neck, the increases from baseline for the 20 and 40 μg rh PTH 1-34 groups were 2.8% and 5.1%, respectively, whereas the increases at the trochanter were 3.5% and 4.4% for the two groups. All of these changes were statistically significantly different from the changes seen in the placebo group. At the distal radius, the placebo group lost 1.6% from baseline by the time the study was terminated, whereas the 20 μg and 40 μg rh PTH 1-34 groups lost only 0.1% and 1.5%, respectively. There was a 65% reduction in the risk of new spine fractures seen with 20 μg rh PTH 1-34 treatment and a 69% reduction in the risk of new spine fractures seen with 40 μg rh PTH 1-34 treatment in this study.

The effects of teriparatide on bone density in men with osteoporosis was reported by Orwoll et al. *(164)* in the *Journal of Bone and Mineral Research* in 2003. Four hundred thirty-seven men with PA lumbar spine, total hip, or femoral neck BMD 2 or more SD below the young-adult mean were randomized to placebo, 20 μg, or 40 μg of teriparatide daily. The study was stopped after a median duration of 11 months. BMD was measured at the PA lumbar spine, proximal femur, and radius with DXA. Total body BMD and BMC was also measured with DXA. Lumbar spine BMD was significantly greater in the teriparatide groups than the placebo group by 3 months. By the end of the study, PA lumbar spine BMD had increased 5.97% in the 20 μg teriparatide group and 9.03% in the 40 μg teriparatide group compared to only 0.52% in the placebo group. At the femoral neck increases of 1.53% and 2.93% from baseline were seen in the 20 and 40 μg teriparatide groups, respectively, compared to 0.31% in the placebo group. There were no significant differences seen between the 20 μg teriparatide group and the placebo group at other skeletal sites. Total body BMC did increase significantly in the 20 μg teriparatide group compared to the placebo group. The increase in total body BMC was 0.64 g compared to a decline of 0.45 g in the placebo group.

Thyroid Hormone

BMD at the distal and 8-mm sites on the radius was measured with SPA (Nuclear Data ND 1100A) in 78 postmenopausal women who had been on thyroid hormone replacement for a minimum of 5 years *(165)*. The average age of the women was 64 years. Hypothyroidism in these women was initially caused by idiopathic hypothyroidism or primary autoimmune hypothyroidism. Forty-four of these women had persistently suppressed thyroid stimulating hormone (TSH) values, whereas 34 did not. One hundred two women served as controls. The women with nonsuppressed TSH values had *z*-scores at the 8-mm and distal radial sites of –0.07 and –0.03, whereas the women with suppressed TSH had *z*-scores of –0.25 and –0.20, respectively. The differences between the three groups were not statistically significant. The authors estimated that a suppressed TSH was associated with at most a 5% decrease in BMD.

Affinito et al. *(166)* also measured BMD at the distal radius in a study of 54 postmenopausal women with primary hypothyroidism and suppressed TSH levels during thyroid hormone replacement. Fifty-four healthy postmenopausal women served as controls. *Z*-scores at the distal radius in the women with suppressed TSH in this study were significantly decreased compared to the women in the control group in this study.

Guo et al. *(167)* conducted a prospective study of 64 postmenopausal women on thyroid hormone replacement. BMD was measured at the total body, PA lumbar spine and femoral neck with DXA (Lunar DPX). The average age of the women on thyroid hormone replacement was 61 years. The women were divided into three groups based on their diagnosis and TSH levels. Group 1 consisted of women on replacement with normal TSH levels. Group 2 consisted of women on replacement with suppressed TSH levels. Group 3 consisted of women with a history of thyroid cancer followed by thyroidectomy and suppressed TSH levels. Thirty-six healthy age-matched women served as controls. The women were followed for 2 years. After the baseline BMD measurements, the dose of thyroid hormone replacement was reduced in group 2 to return the TSH levels to normal. At baseline and at follow-up 2 years later, there was no significant difference in BMD at any of the sites between the four groups. In group 2, however, BMD significantly increased at the spine and femoral neck over 2 years suggesting that the reduction in the dose of thyroid hormone was beneficial.

Seventeen postmenopausal women with subclinical hypothyroidism were randomly assigned to receive thyroid hormone replacement or placebo for 14 months *(168)*. BMD was measured at the 33% radial site with SPA and at the lumbar spine with DXA (Hologic QDR-1000). In the thyroxine-treated group, the dosage was adjusted to maintain the TSH in the normal range. Over the 14-month period, BMD at the radius decreased in the treated group and the placebo group by 0.5% and 1.8%, respectively. The difference between the two groups was not significant. In the lumbar spine, the BMD increased 0.1% in the treated group and decreased 0.7% in the untreated group. This difference was again not significant. The author concluded that there was no detrimental effect on BMD of levothyroxine treatment that normalized TSH in postmenopausal women with subclinical hypothyroidism.

Tibolone

Tibolone is a synthetic compound with estrogenic, progestational, and androgenic activity. Its potential utility in preventing postmenopausal bone loss was reported 20 years ago *(169)*. In 1994, Rymer et al. *(170)* reported the results of a 2-year nonrandomized prospective study in which women between 6 and 36 months after menopause received either 2.5 mg of tibolone or no medication. BMD was measured in the PA lumbar spine and proximal femur with DXA (Hologic QDR-1000) at baseline, and again at 6, 12, and 24 months. Forty-six women in the tibolone group completed the study and 45 women in the control group completed the study. The average age of the subjects was 49.5 years. At the end of 2 years, women in the tibolone group had significant increases in bone density at the lumbar spine and the femoral neck, Ward's area, and the trochanter, whereas women in the placebo group had significant losses at those sites. On an individual basis, 39 of the women receiving tibolone increased bone density at the spine and 33 had increases in bone density in the femur. The average increase in lumbar spine BMD after 2 years in the tibolone-treated group was 2.5% and in the femoral neck, 3.5%. The control group had losses of 2.9% and 3.7% in the spine and femoral neck, respectively.

A comparison trial of tibolone 2.5 mg daily, estradiol 2 mg orally daily, and 50 μg of transdermal 17-β estradiol daily versus no medication was performed in 140 postmenopausal women with a median duration of menopause of 3 years *(171)*. BMD was measured at the lumbar spine, proximal femur, and total body using DXA (Hologic QDR-1000). At the end of 2 years, all three treatment regimens prevented bone loss, whereas the women in the control group lost BMD. There was no significant difference in BMD between the three treatment groups. In the control group, there was a loss of 3.4% from the lumbar spine, 2.2% from the total femur, 1.6% from the femoral neck, and no change in total body BMD at the end of 2 years.

In 2001, Gallagher et al. *(172)* reported the results of two large phase 3 trials of tibolone in the prevention of postmenopausal bone loss. Seven hundred seventy postmenopausal women participated in two separate but identically designed trials. To participate, the women had to be more than 1 but not more than 4 years postmenopausal and could not have osteoporosis. The women in the study received placebo, 0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg of tibolone for 2 years. BMD was measured with DXA every 6 months during the 2-year study. At L1–L4, BMD was statistically significantly better in all tibolone treatment groups at all time points. At the end of 2 years, the L1–L4 BMD had increased from baseline by 1.1%, 2%, and 2.6% in the 0.625 mg, 1.25 mg, and 2.5 mg tibolone groups, respectively. In the 0.3 mg tibolone group, L1–L4 BMD decline 0.4% at 2 years, whereas the placebo group had a decline of more than 2%. At the end of 2 years at the total hip, BMD was maintained in the 0.3 mg tibolone group and increased in the three other treatment groups in a dose-dependent fashion. Total hip BMD declined in the placebo group over 2 years. At the femoral neck however, only the 1.25 mg and 2.5 mg doses prevented bone loss over the 2-year period.

Changes in bone density over 8 years of treatment with 2.5 mg of tibolone were reported by Rymer et al. *(173)*. This was an open-label, nonrandomized study of 59 postmenopausal women who took 2.5 mg of tibolone daily for 8 years compared to an untreated control group of 51 women. Bone density was measured by DXA at the PA lumbar spine and proximal femur (Hologic QDR). After 8 years of continuous use, bone density increased 4.1% from baseline in the PA lumbar spine and 4.6% from baseline in the femoral neck in the women taking tibolone. During that same period, bone density declined from baseline in the control group by 7.5% in the PA lumbar spine and 6.7% in the femoral neck.

Zoledronic Acid

Zoledronic acid is a potent bisphosphonate, which is administered intravenously. It is approved by the FDA for use in the United States for the treatment of hypercalcemia of malignancy. The results of a phase 2 study of the effects of zoledronic acid on bone density and bone turnover were reported by Reid et al. *(174)* in the *New England Journal of Medicine* in 2002. Three hundred fifty-one women, 45 to 80 years of age, who were at least 5 years postmenopausal and who had a lumbar spine *T*-score of –2 or poorer participated in this study. All the women in the study received 1000 mg of elemental calcium daily as well as an intravenous infusion of saline or zoledronic acid every 3 months during the 1-year study. Zoledronic acid was given in a dose of 0.25 mg, 0.5 mg, or 1 mg every 3 months or 2 mg every 6 months or 4 mg at study start only. These five regimens were compared to saline placebo infusions. BMD was measured in the PA lumbar spine, total body, proximal femur, and nondominant forearm with DXA.

BMD increased in all the zoledronic acid treatment groups. At the end of 1 year, there was no difference in the increase in BMD between the zoledronic acid treatment groups, all of which had increases greater than 4%. These were statistically significant 4.3 to 5.1% greater gains in bone density than those seen in the placebo group in which lumbar spine BMD was maintained. At the femoral neck, all zoledronic acid treatment groups increased BMD similarly with differences of 3.1 to 3.5% at the end of 1 year compared to the placebo group, which lost 0.4%. The benefit of treatment at the distal radius and total body was not surprisingly less than that seen at the lumbar spine or femoral neck. Nevertheless, zoledronic acid treatment appeared to benefit BMD measured at the distal radius and total body as well.

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7 Selecting Patients for Bone Mass Measurements

Clinical Guidelines

CONTENTS

Physicians can accurately and precisely quantify the bone density at virtually any skeletal site with the densitometry techniques available today. But when should these technologies be used? In what clinical circumstances should physicians consider measuring the bone density?

Clinical guidelines for the use of bone mass measurements are available from major organizations that are knowledgeable in women's health and osteoporosis. As practice guidelines, they are intended to help the physician determine when a bone mass measurement may be useful in the care of individual patients. There is also an increasing number of risk-based assessment questionnaires that may be administered by a medical professional or self-administered by the patient to determine if a high probability of low bone density exists. Such patients would also be considered appropriate candidates for a bone mass measurement. In this chapter, the clinical guidelines from major organizations are reviewed and compared. Risk-based assessment questionnaires are examined in the next chapter.

CLINICAL GUIDELINES

Several national organizations have issued guidelines for the clinical use of bone densitometry, beginning in the late 1980s. Some of these guidelines cover a broad range of circumstances in clinical practice, whereas others are specific for postmenopausal osteoporosis.

1988 National Osteoporosis Foundation Guidelines

The first guidelines or indications for bone mass measurements from a national organization were released in 1988 by the National Osteoporosis Foundation (NOF). These guidelines or "clinical indications" were developed in response to a report from the Office of Health Technology Assessment (OHTA) of the Public Health Service that had been submitted to the Health Care Finance Administration (HCFA). The report from OHTA

concluded that the role of DPA and SPA in clinical practice had not been defined. The clinical indications from the NOF that were submitted to HCFA were published in 1989 in the *Journal of Bone and Mineral Research (1)*. The NOF pointed out that the methods that were available to measure bone mass or density were safe, accurate, and precise. They also noted that important clinical decisions could be influenced by the results of the measurements. The four clinical circumstances in which the NOF believed that sufficient experience existed to support the use of bone mass measurements were based primarily on experience with SPA and DPA, as DXA had only been approved for clinical use in 1988. The four clinical indications for bone mass measurements were:

- To diagnose significantly low bone mass in estrogen-deficient women in order to make decisions about HRT.
- To diagnose spinal osteoporosis in patients with vertebral abnormalities or roentgenographic osteopenia in order to make decisions about further diagnostic evaluation and therapy.
- To diagnose low bone mass in patients receiving long-term glucocorticoid therapy in order to adjust therapy.
- To identity low bone mass in patients with primary asymptomatic hyperparathyroidism in order to identify those at risk of severe skeletal disease who may be candidates for surgical intervention.

The NOF indications also noted the specific skeletal sites and techniques that should be used in these different circumstances. For an assessment of fracture risk in a postmenopausal woman, the NOF suggested that any site by any technique was appropriate. For the confirmation of spinal demineralization or the diagnosis of spinal osteoporosis, measuring the spine with DPA, DXA, or QCT was recommended. A measurement of the spine by DPA, DXA, or QCT was also recommended for the purposes of detecting bone loss from corticosteroids. To assess the effects of hyperparathyroidism on the skeleton a measurement of the spine by DXA, DPA, or QCT or a measurement of the radius by SPA was recommended.

DXA measurements of the forearm were not suggested as part of the evaluation of the patient with hyperparathyroidism as this capability was not in clinical use at the time. The serial assessment of bone density for therapeutic efficacy or disease effect was not mentioned in these indications because the indications were primarily based on the clinical experience with SPA and DPA. The precision of bone density measurements of the spine or proximal femur with DPA was not sufficient to make serial assessments feasible in most cases. In the text of the document, however, it was observed that the changes in bone density in the spine might be so rapid in the setting of corticosteroid-induced osteoporosis that serial assessment of spine bone density with DPA could be considered. Measurements of the forearm with SPA were also not thought to be useful for serial assessments of therapeutic efficacy. Although the precision of SPA measurements of the forearm was excellent, the changes in BMD at the forearm sites were thought to be too small to be detected in a clinically useful period of time.

The assessment of the estrogen-deficient woman with bone mass measurements specifically referred to making decisions about HRT. At the time of the 1988 NOF indications, there were no prescription alternatives to estrogen that were FDA-approved for the prevention of osteoporosis.

Finally, the NOF emphasized that these measurements should not be done if intervention decisions would not be affected by the result of the test. They noted that women who

received long-term ERT for reasons other than the prevention or treatment of osteoporosis did not need a measurement. The NOF also observed that measurements should not be done if sufficient quality control procedures were not in place to ensure the accuracy of the results.

1998 NOF Guidelines

In 1998, the NOF issued new guidelines for bone densitometry that were limited to the detection and management of postmenopausal osteoporosis *(2,3)*. The guidelines initially appeared in an extensive document on osteoporosis that was published in *Osteoporosis International (2)*. With some modification, they subsequently appeared in a document titled "Physician's Guide to Prevention and Treatment of Osteoporosis" *(3)*.

In the original 1998 document, extensive cost–benefit analyses were undertaken to determine the feasibility and benefits not only of measuring bone density but of treating women who were found to have a low bone mass. The authors of the paper insightfully noted that the conclusions were only as good as the evidence on which they were based and such evidence might change as new therapies became available or as more was learned about the pathophysiology of osteoporosis. In essence, however, the original 1998 NOF recommendations stated that it was cost-effective to assess bone density in all Caucasian women over the age of 60 regardless of other risk factors and in all Caucasian women between age 50 and 60 who had a strong risk factor for fracture. BMD testing was recommended for all women who had a vertebral fracture unless calcitonin was the only acceptable treatment option. In women with a nonvertebral fracture, testing was recommended for women age 60 even without other risk factors and women age 50 to 59 with other risk factors. The risk factors for fracture that were emphasized in this report included a history of fracture after age 40, a history of hip, spine, or wrist fracture in a first-degree relative, weight equal to or less than 127 lb, and current cigarette smoking. These risk factors were chosen because they were easy to determine in clinical practice and they were demonstrated as being independent predictors of hip fracture in the Study of Osteoporotic Fractures *(4)*. In order to help the clinician determine when it would be cost-effective to measure the bone density, nomograms were developed that were specific for the presence or absence of a prior spine fracture and the therapy being considered. The clinician would use the number of remaining risk factors from the list given above to determine if the patient should be tested. An example of such a nomogram is shown in Fig. 7-1. Another nomogram was provided for women with spine fractures in whom alendronate therapy was being considered. Nomograms for women with and without spine fractures and each of the remaining therapies that were approved for clinical use in 1998 were also provided.

The complexity of these guidelines made them unsuitable for widespread clinical use. In response, the NOF published guidelines tailored for the clinician *(3)*. In the introduction to the these guidelines, the NOF noted that the guidelines were primarily intended to be applied to postmenopausal Caucasian women because the data used to create the guidelines came from studies of that group. They also noted that their recommendations were based on measurements of bone density at the hip although they noted that BMD measurements at any site had value in predicting fracture risk. The NOF did not characterize any particular technique as being preferred, although measurements at the hip would, of necessity, require the use of DXA.

These clinical guidelines from the NOF in 1998 formed the cornerstone of subsequently released guidelines from other major organizations. The circumstances in which

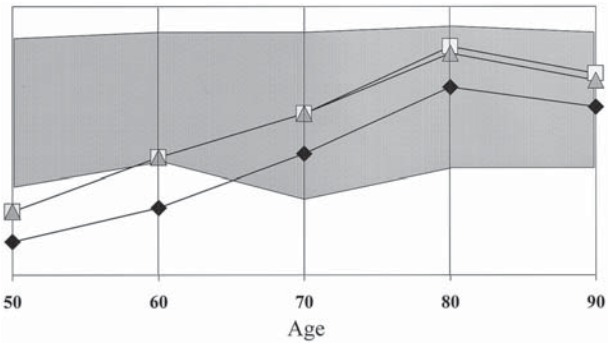

Fig. 7-1. Testing decision nomogram. If 5 years of alendronate therapy are being considered, a woman should undergo BMD testing if she falls into the shaded area based on her age and number of risk factors. ◆-no risk factors; ▲-1 risk factor; □-2 risk factors.
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the NOF recommended bone density testing in postmenopausal Caucasian women in 1998 were:

- All women under age 65 who have one or more additional risk factors for osteoporotic fracture.
- All women age 65 and older regardless of additional risk factors.
- Postmenopausal women who present with fractures.
- Women who are considering therapy if BMD testing would facilitate the decision.
- Women who have been on HRT for prolonged periods.

In all cases, the NOF emphasized that testing should never be done if the results would not influence treatment decisions.

The risk factors listed by the NOF in the clinical guidelines were numerous, but the same four risk factors used in the cost–benefit analyses were emphasized again as contributing to the risk of hip fracture: personal history of fracture as an adult, history of fracture in a first-degree relative, current cigarette smoking, and body weight less than 127 lb. The diseases and drugs noted by the NOF as being associated with an increased risk of osteoporosis are listed in Tables 7-1 and 7-2.

1996 Guidelines of the International Society for Clinical Densitometry

The guidelines from the International Society for Clinical Densitometry (ISCD) *(5)* were initially developed in 1994 during a meeting of an international panel of experts in bone densitometry and published in 1996. On the panel were 22 members from eight countries. The guidelines addressed both the use and interpretation of bone mass measurements in the prevention, detection, and management of all diseases characterized by low bone mass with an emphasis on osteoporosis. The guidelines provided a broad overview of how bone mass measurements should be used regardless of specific clinical circumstances in which they were employed. Although they did not specifically deal with patient selection, a review of the ISCD guidelines is included here because of their importance and their influence on the patient selection guidelines that followed. There were six major points on which the panel reached a consensus. Those points are summarized in Table 7-3.

Table 7-1
Diseases Associated with an Increased Risk of Generalized Osteoporosis in Adults

- Acromegaly
- Adrenal atrophy and Addison's disease
- Amyloidosis
- Ankylosing spondylitis
- Chronic obstructive pulmonary disease
- Congenital porphyria
- Cushing's syndrome
- Endometriosis
- Epidermolysis bullosa
- Gastrectomy
- Gonadal insufficiency
- Hemochromatosis
- Hemophilia
- Hyperparathyroidism
- Hypophosphatasia
- Idiopathic scoliosis
- Insulin-dependent diabetes mellitus
- Lymphoma and leukemia
- Malabsorption syndromes
- Mastocytosis
- Multiple myeloma
- Multiple sclerosis
- Nutritional disorders
- Osteogenesis imperfecta
- Parenteral nutrition
- Pernicious anemia
- Rheumatoid arthritis
- Sarcoidosis
- Severe liver disease, especially primary biliary cirrhosis
- Thalassemia
- Thyrotoxicosis
- Tumor secretion of parathyroid hormone-related peptide

Reproduced from ref. *3* with permission of the National Osteoporosis Foundation.

Table 7-2
Drugs Associated with an Increased Risk of Generalized Risk of Osteoporosis in Adults

- Aluminum
- Anticonvulsants
- Cigarette smoking
- Cytotoxic drugs
- Excessive alcohol
- Excessive thyroxine
- Glucocorticosteroids and adrenocorticotropin
- Gonadotropin-releasing hormone agonists
- Heparin
- Lithium
- Tamoxifen (premenopausal use)

Reproduced from ref. *3* with permission of the National Osteoporosis Foundation.

Table 7-3
Consensus Points from the International Society for Clinical Densitometry on the Clinical Utility of Bone Mass Measurements

1. Bone mass measurements predict a patient's future risk of fracture.
2. Osteoporosis can be diagnosed on the basis of bone mass measurements even in the absence of prevalent fractures.
3. Bone mass measurements provide information that can affect the management of patients.
4. The choice of the appropriate measurement site(s) for the assessment of bone mass or fracture risk may vary depending upon the specific circumstances of the patient.
5. The choice of the appropriate technique for bone mass measurements in any given clinical circumstance should be based on an understanding of the strengths and limitations of the different techniques.
6. Bone mass data should be accompanied by a clinical interpretation.

From ref. *5*.

The ISCD Guidelines are best appreciated if the scientific climate of the 1980s and early 1990s is understood. In the 1980s, medical conferences were awash in the "bone mass measurement controversy." This controversy largely centered on whether a measurement of bone mass or bone density could be used to predict fracture risk. In a decade in which DPA and SPA were the predominant techniques, bone densitometry was also not seen as useful for monitoring therapy. Indeed, therapeutic choices were viewed (rightly or wrongly) as being so limited, that early detection of disease with bone mass measurements was perceived as having little value. The situation was further compounded by a lack of agreement on the actual definition of osteoporosis itself. In the late 1980s and early 1990s, however, rapid developments in the field made most of these controversies moot.

In 1988, DXA was FDA-approved for clinical use. The enhanced precision of DXA, particularly at the spine, made monitoring the effects of disease or therapy practical. In 1993, several major fracture trials *(6–8)* were published and added to a growing body of literature that effectively lay to rest the bone mass measurement controversy. There was no longer any question that the risk of fracture could be predicted with a single bone mass measurement. In 1994, the WHO *(9)* published guidelines for the diagnosis of osteoporosis based on the measurement of bone density. Alendronate sodium and nasal-spray salmon calcitonin, approved in 1995, were dramatic additions to the therapeutic armamentarium. These developments profoundly changed the field of densitometry and osteoporosis, but they had still been poorly communicated to the practicing physician, the public, insurers, and politicians. The ISCD guidelines attempted to change that.

Another major goal of the ISCD guidelines was to point out that all bone mass measurement techniques have value when they are properly used. The bone densitometry industry is an intensely competitive industry. This competitiveness has, at times, been misperceived by those outside the industry as meaning that some technologies were inferior to others. ISCD wished to emphasize that the devices that were FDA-approved for the measurement of bone density do exactly what they purported to do. They can all be used to measure the bone density accurately and precisely. Assuming that all the techniques were available, the choice of which technique to use should be determined by the intent of the measurement. The intent of the measurement determined which site or sites should be measured and whether the primary need was accuracy or precision at that site. Once these determinations were made, a particular technique might be preferable to another in that specific circumstance but not necessarily in every circumstance that may follow. Another major emphasis of the ISCD guidelines was that the appropriate measurement site was determined by the intent of the measurement. One skeletal site was not appropriate for all of the potential uses of bone mass measurements. ISCD also strongly recognized the need for strict quality control of the machines and training for the operators. The guidelines also emphasized the need for an interpretation of the numeric data by a physician trained in densitometry.

1996 American Association of Clinical Endocrinologists' Guidelines

In 1996, the American Association of Clinical Endocrinologists (AACE) developed guidelines for the prevention and treatment of osteoporosis *(10)*. As part of these guidelines, BMD measurements were discussed. The specific clinical circumstances in which AACE believed that bone mass measurements were appropriate were virtually identical to the original guidelines from the NOF published in 1988, although they were clearly

updated to reflect DXA's more precise measurements and the increase in available therapies. The clinical circumstances in which AACE believed that bone mass measurements were appropriate were:

- Risk assessment in perimenopausal or postmenopausal women who are concerned about osteoporosis and willing to accept available intervention.
- In women with X-ray findings that suggest the presence of osteoporosis.
- In women beginning or receiving long-term glucocorticoid therapy, provided intervention is an option.
- For perimenopausal or postmenopausal women with asymptomatic primary hyperparathyroidism in whom evidence of skeletal loss would result in parathyroidectomy.
- In women undergoing treatment for osteoporosis, as a tool for monitoring the therapeutic response.

These guidelines reflect the increase in available therapeutic options beyond HRT for the prevention or treatment of osteoporosis. With the availability of nasal spray calcitonin and alendronate sodium, a woman's choices for the prevention or treatment of this disease were no longer limited to HRT. The superior precision of DXA measurements also offered the ability to follow therapeutic efficacy over time with bone mass measurements.

Because these guidelines were for the prevention and treatment of postmenopausal osteoporosis only, the AACE guidelines for the use of densitometry dealt only with women. There was also a concerted effort to emphasize in these guidelines that bone mass measurements should be done only if the outcome of the measurement would directly influence a clinical decision to intervene in some manner. Although this was a statement that could be made for any clinical test, AACE chose to emphasize this in these guidelines.

AACE also noted that a measurement of the spine, hip, radius or calcaneus could be used for fracture risk assessment. They did not note whether they were recommending a global or site-specific fracture risk assessment.[1] Although it was observed that under ideal circumstances, a measurement of both the spine and hip would be performed at a baseline evaluation and again should follow-up be indicated, AACE recommended a bone density study of the hip as the preferred site for the first measurement.

2001 AACE Guidelines

The 2001 guidelines *(11)* from AACE are an update of the 1996 guidelines. Additional reports in the medical literature published between 1996 and January 2001 were reviewed in preparation for the 2001 guidelines. The 2001 guidelines for bone density testing were part of an extensive treatise on the pathophysiology, detection, and management of osteoporosis. Guidelines for bone density testing were given in two contexts: as part of the specific assessment for postmenopausal osteoporosis and as part of a variety of different clinical circumstances.

In 2001, AACE recommended that all women age 65 and older undergo an assessment for postmenopausal osteoporosis that included a bone density measurement. They also recommended assessments in adult women who presented with a history of fracture not caused by severe trauma and in postmenopausal women who had risk factors for osteoporosis such as body weight less than 127 lb (57.6 kg) or a family history of spine or hip fracture.

[1] *See* Chapter 10 for a discussion of global and site-specific fracture risk predictions.

Unlike the 1996 recommendations, AACE recommended in 2001 that DXA measurements of the spine or proximal femur or QCT measurements of the spine be used for the diagnosis of osteoporosis and for monitoring changes in bone density. If the patient had a normal bone density, AACE recommended that a follow-up measurement be considered every 3 to 5 years. For women in an osteoporosis prevention program, ACCE recommended a follow-up measurement every 1 to 2 years until stability of the bone density was demonstrated. For women undergoing treatment for osteoporosis, a yearly bone mass measurement was recommended until stability was demonstrated. Once stability was demonstrated, an interval of 2 years was recommended between measurements. AACE recommended that the measurement of bone density at peripheral sites not be used for diagnosis or monitoring but instead limited to assessment of fracture risk.

The broader recommendations for the use of bone densitometry in clinical practice were very similar to the recommendations issued in 1996. There was some change in the wording and the recommendations were expanded to include women 40 years of age and older with fractures and all women age 65 and older. The 2001 recommendations are as follows:

- For risk assessment in peri- and postmenopausal women with risk factors for fractures and willingness to consider intervention.
- In women with X-ray findings suggestive of osteoporosis.
- In women beginning or already receiving long-term glucocorticoids or other drugs associated with bone loss.
- In all adult women with symptomatic hyperparathyroidism, other diseases or nutritional conditions associated with bone loss if management would be affected by the outcome of the test.
- For establishing skeletal stability and monitoring therapeutic response in women receiving treatment for osteoporosis.
- In all women 40 years of age and older who have sustained a fracture.
- In all women age 65 and older.

Guidelines from the European Foundation for Osteoporosis and Bone Disease

The European Foundation for Osteoporosis and Bone Disease (EFFO) published in 1996 some of the most practical guidelines yet for the clinical application of bone density measurements *(12)*. Some of the clinical circumstances in which the EFFO believed that bone mass measurements should be considered are shown in Table 7-4. Like AACE, the EFFO was careful to emphasize that bone mass measurements should not be done if the result would not affect the clinical decision-making process.

In contrast to the 1996 AACE guidelines, the EFFO guidelines do not direct the physician to perform a baseline measurement at the hip regardless of the reason for the measurement. The EFFO guidelines, like the ISCD guidelines, noted that the site of the measurement should be determined by the intent of the measurement. Although the EFFO observed that the hip may be less affected by changes of osteoarthrosis in the elderly and was the preferred site for a site-specific hip fracture risk assessment, they also observed that changes in BMD from therapeutic interventions were more likely to be documented in the spine. The EFFO also noted that the hip, wrist, or spine sites could be used for global fracture risk assessments in women around the time of menopause. Although the EFFO recommended scanning only one site initially, they acknowledged

Table 7-4
Indications for Bone Mass Measurements from the EFFO Guidelines

1. Presence of strong risk factors
   a. Premature menopause (<45 years)
   b. Prolonged secondary amenorrhea
   c. Primary hypogonadism
   d. Corticosteroid therapy (>7.5 mg/day for 1 year or more)
   e. Conditions associated with osteoporosis
      i. Anorexia nervosa
      ii. Malabsorption
      iii. Primary hyperparathyroidism
      iv. Post-transplantation
      v. Chronic renal failure
      vi. Osteogenesis imperfecta
      vii. Neoplasm
      viii. Hyperthyroidism
      ix. Prolonged immobilization
      x. Cushing's syndrome
2. Radiographic evidence of osteopenia and/or vertebral deformity
3. Previous fragility fracture, for example of the hip, spine, wrist, or upper humerus
4. Significant loss of height or thoracic kyphosis
5. Monitoring of treatment
   a. Hormone replacement treatment in patients with secondary osteoporosis
   b. Other agents, e.g. bisphosphonates, calcitonin, fluoride salts, vitamin D, and its metabolites

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that there might be clinical circumstances in which two sites were necessary in order to assess sites that are predominantly cortical or predominantly trabecular bone.

The EFFO guidelines noted that the interval between BMD measurements for the detection of bone loss over time would vary with the anticipated rate of loss from the disease process. In some circumstances, the interval could be as short as 6 months. In others, the interval would be 2 to 3 years. In monitoring changes in BMD from a therapeutic intervention, the EFFO noted that the interval between measurements would again be determined by the agent being used and the site being measured. This statement reflects the combined effect of the expected rate of change from a particular agent at a given site and the precision of the measurement at that site.[2] They noted that the usual interval for such measurements is 1 to 2 years. The monitoring of women on HRT that was prescribed *for postmenopausal hormone replacement* was not recommended except in the case of complicating factors that might increase the woman's risk for secondary osteoporosis. If HRT was prescribed specifically *for the treatment of osteoporosis*, the EFFO did recommend periodic monitoring because of the variability in response to treatment.

2002 ACOG Recommendations for Bone Density Screening for Osteoporosis

In a press release *(13)* on February 28, 2002, the American College of Obstetricians and Gynecologists (ACOG) announced long-awaited recommendations for the use of bone densitometry. ACOG, like the NOF and AACE, recommended that all postmenopausal women 65 years of age and older be screened for osteoporosis. Similarly, they

[2] *See* Chapter 11 for a discussion of the relationship between precision and rate of change in determining the interval between measurements.

Table 7-5
ACOG: 2001 Recommendations for Bone Density Screening for Osteoporosis. Diseases and Conditions Associated with an Increased Risk for Osteoporosis in Which BMD Testing May Be Useful in Both Pre- and Postmenopausal Women

• Endometriosis	• Hemophilia	• Lymphoma
• Leukemia	• Eating disorders	• Nutritional disorders
• Rheumatoid arthritis	• Multiple sclerosis	• Tobacco use
• Lithium therapy	• Heparin therapy	

From ref. *15*.

also recommended screening in postmenopausal women under the age of 65 with one or more risk factors. The risk factors ACOG noted in the press release were a personal history of fracture as an adult, Caucasian race, a history of alcoholism, and impaired eyesight after correction.

ACOG also noted that bone density testing might be useful in both pre- and postmenopausal women with diseases or conditions associated with an increased risk for osteoporosis. The diseases and conditions emphasized in the press release are listed in Table 7-5. ACOG recommended that repeat testing for screening purposes should not occur more often than every 2 years. DXA was described by ACOG as the gold standard for bone density testing.

2002 North American Menopause Society Recommendations

The North American Menopause Society (NAMS) published a comprehensive review of postmenopausal osteoporosis in the journal *Menopause* in 2002 *(14)*. Included in the review were recommendations for bone density testing in the specific context of osteoporosis prevention and management. NAMS noted that measurement of BMD is the preferred method for diagnosing osteoporosis and that DXA is the "technological standard" for measuring BMD. NAMS stated that the total hip was the preferred region of interest to evaluate, particularly when measuring bone density in women over 60 because of the increased likelihood of degenerative calcification in the spine that would affect spine measurements.[3] Nevertheless, spine measurements were described as useful in early postmenopausal women because of the faster rate of bone loss at that site compared to the rate seen at the proximal femur. Citing a report from the International Osteoporosis Foundation (IOF) published in 2000 *(15)*, NAMS stated that they generally supported the use of the total hip or femoral neck for the diagnosis of osteoporosis rather than other skeletal sites.

The NAMS recommendations, like those of the NOF, ACOG, and AACE included measuring bone density in all women age 65 years and older. They also recommended measuring bone density in postmenopausal women under the age of 65 who had at least one of the following risk factors: a nonspine fracture after menopause, weight less than 127 lb, or a history of a first-degree relative with a spine or hip fracture. NAMS also recommended BMD measurements in premenopausal women who experienced fractures deemed to be low trauma fractures and those with known causes of bone loss. In all cases, testing should only be done if the results would influence treatment decisions.

[3] *See* Chapter 2 for a discussion of the effect of dystrophic calcification on the measurement of BMD in the spine.

Recommendations were also made that dealt with the frequency of repeat testing, depending on the clinical circumstances. In women who were not receiving a pharmacologic intervention for osteoporosis, NAMS stated that repeat testing should not be performed for 3 to 5 years. In those women who were receiving treatment, repeat testing should not be performed for 2 years. NAMS stated that peripheral sites should not be used to monitor therapy. Instead, they noted that peripheral site measurements should be used only for fracture risk assessments. Diagnosis and monitoring should only be done using the spine or proximal femur.

2002 US Preventive Services Task Force Recommendations

In September 2002, the US Preventive Services Task Force (USPSTF) issued recommendations for bone density testing when screening for postmenopausal osteoporosis *(16)*. Like the recent guidelines from the NOF, AACE, NAMS, and ACOG that preceded the release of these recommendations, the USPSTF recommended that women age 65 and older be routinely screened for osteoporosis. Unlike previous guidelines that also recommended testing for postmenopausal women younger than age 65 who had risk factors for osteoporosis, the USPSTF limited their recommended for screening in younger postmenopausal women to those women ages 60 to 64 who were at high risk for osteoporosis. They made no comment on screening for postmenopausal women younger than age 60. The USPSTF also noted that there was no data to determine an upper age limit for screening.

In making these recommendations, the USPSTF did not direct the clinician to use a specific bone density technology or skeletal site. They also noted that the risk factors that should be considered in deciding whether to test the younger postmenopausal woman were difficult to identify. Body weight less than 154 lb (70 kg), increasing age, and no current use of estrogen were identified as strong predictors of low bone density.

The recommendations to screen women age 65 and older and women 60 to 64 at high risk for osteoporosis were classified by the USPSTF as grade B recommendations. A grade B recommendation means that the USPSTF recommends that clinicians routinely provide such services to their patients based on finding fair evidence that the service is beneficial in improving outcomes and that such benefit outweighs any potential harm. The evidence supporting these recommendations was characterized as fair on the USPSTF scale of good, fair, and poor. A characterization of fair indicates that the USPSTF believed that the evidence was sufficient to determine the effect of the service on health outcomes but was limited by one or a number of factors.

The evidence reviewed by the USPSTF predominantly came from searches of MEDLINE spanning 1966 to May 2001, HealthSTAR spanning 1975 to May 2001, and Cochrane databases *(17)*. No studies were identified that directly linked screening for postmenopausal osteoporosis using risk factors or bone densitometry to a reduction in osteoporotic fractures. It was primarily for this reason that the evidence for the screening recommendations from the USPSTF was characterized as fair rather than good. Numerous studies were identified that evaluated the associations between risk factors and low bone density and fractures as well as studies documenting the predictive ability of bone densitometry for fracture risk. The USPSTF also reviewed published trials of the therapeutic agents approved by the FDA for either the prevention or treatment of postmenopausal osteoporosis or both.

Based on their review, the USPSTF estimated the effectiveness of screening 10,000 women with densitometry in reducing hip and spine fractures. The results are shown in

Table 7-6
Screening for Osteoporosis in 10,000 Postmenopausal Women: Hip and Vertebral Fracture Outcomes by 5-Year Age Intervals

	Age Group					
Variable	*50–54*	*55–59*	*60–64*	*65–69*	*70–74*	*75–79*
Base-case assumptions						
Prevalence of osteoporosis	0.0305	0.0445	0.065	0.120	0.2025	0.285
Relative risk of hip fracture with treatment	0.63	0.63	0.63	0.63	0.63	0.63
Relative risk for vertebral fracture with treatment	0.52	0.52	0.52	0.52	0.52	0.52
Adherence to treatment	0.7	0.7	0.7	0.7	0.7	0.7
Results, *n*						
Identified as high risk (osteoporotic)	305	445	650	1200	2025	2850
Hip fractures prevented	1	2	5	14	39	70
NNS to prevent one hip fracture	7446	4338	1856	731	254	143
NNT to prevent one hip fracture	227	193	121	88	51	41
Vertebral fractures prevented	5	7	22	40	95	134
NNS to prevent one vertebral fracture	1952	1338	458	248	105	75
NNT to prevent one vertebral fracture	60	60	30	30	21	21

NNS, number needed to screen for benefit; NNT, number needed to treat.
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Table 7-6. To create this table, age-specific prevalence rates for osteoporosis and treatment effects based on clinical trial results were considered and an adherence to therapy rate of 70% was assumed. Available treatments were assumed to reduce the risk of hip fractures by 37% and spine fractures by 48%. The outcomes in Table 7-4 also assume that bone density is measured at the femoral neck using DXA. Within this framework, 1200 women would be identified as being osteoporotic based on WHO criteria and subsequently treated. In the next 5 years, such treatment would prevent 14 hip fractures and 40 spine fractures, resulting in a number needed to screen to prevent 1 hip fracture of 731 and a number needed to screen to prevent 1 spine fracture of 248. These projections clearly depend on the prevalence of osteoporosis in a given age range, the effectiveness of the therapy and the rate of adherence to the prescribed therapy.

The USPSTF is an independent panel of experts in primary care *(18)*. The first panel was convened in 1984 by the US Public Health Service. Its mission was to create age-, gender and risk-based recommendations for services to be used in primary care using evidence-based medicine. In 1998, the Agency for Healthcare Research and Quality (previously known as the Agency for Healthcare Policy and Research) convened the third USPSTF panel. The members of the panel are experts representing various specialties of medicine who are selected from nominees based on their expertise in preventive and evidence-based medicine and primary care. Guidelines produced by the USPSTF panel are not considered official statements from the Agency for Healthcare Research and Quality, the Department of Health and Human Services or the US Public Health Service.

Guidelines for Bone Density Testing in Men

Determining when testing is appropriate in men has become increasingly important with the advent of prescription pharmacologic therapy for the treatment of osteoporosis in men. The prevalence of osteoporosis in men, although not as great as that in women, is high. In one study *(19)*, the prevalence of osteoporosis in a population-based sample of 348 men was 19% when osteoporosis was defined as 2.5 SD or more below the average peak BMD for men. The major risk factors for osteoporosis in men are not dissimilar from those seen in women: cigarette smoking, advancing age, risk of falls, and the presence of diseases or the use of medications known to affect bone metabolism *(20–22)*. Heavy alcohol consumption is considered a major risk factor in men, more so than in women. Other risk factors include a sedentary lifestyle, lifelong low calcium intake, and low body weight.

At the present time, prudent recommendations *(23)* for bone density testing in men do not differ considerably from the 1998 clinical guidelines for bone density testing in women from the NOF. Testing in men is recommended in the following circumstances:

- Men with low trauma fractures.
- Men with prevalent spine deformities.
- Men with radiographic evidence of osteopenia.
- Men with medical conditions associated with an increased risk of bone loss such as hyperparathyroidism or overt hypogonadism.
- Men receiving medications associated with an increased risk of bone loss such as corticosteroids.

Recommending BMD testing in men on the basis of age alone, such as the recommendation to test women age 65 and older regardless of other risk factors, is more

Table 7-7
A Comparison of Major Guidelines for Bone Density Testing for the Detection of Osteoporosis in Women

	Women ≥ age 65	*Postmenopausal Women ≤ age 64 and at least one risk factor*	*Postmenopausal Women with Fractures*	*Technique for Diagnosis*	*Site for Diagnosis*[a]	*Against Using Peripheral Sites for Monitoring*
NOF 1998	√	√	√	DXA	Hip Preferred	—
WHO 1999	√[b]	√[b]	√[c]	DXA	Hip Preferred	—
IOF 2000	—	—	—	—	Total Hip	—
AACE 2001	√	√	√[c]	DXA/QCT	Spine, Proximal Femur	√
ACOG 2002	√	√	√	DXA	—	—
NAMS 2002	√	√	√	DXA	Total Hip Preferred, Femoral Neck or Spine	√
USPSTF 2002	√	√[d]	—	—	—	—
ISCD 2002	—	—	—	DXA[e]	PA Spine, Hip (not Ward's Area)	√

[a] The term hip indicates that a specific region in the proximal femur was not specified.
[b] The WHO noted that hypogonadism, possibly to include all postmenopausal women, was justification for a measurement.
[c] Consideration was limited to low trauma fractures.
[d] This recommendation was limited to postmenopausal women age 60 to 64.
[e] Methodologies other than DXA were not considered in these guidelines.
—Indicates no comment.

controversial than the clinical circumstances described above. In general however, authorities suggest that measuring bone density in men age 70 and older is an appropriate strategy.

In 2002, ISCD *(24)* published a position paper on the diagnosis of osteoporosis in men and non-Caucasian women. Although the focus of this paper was the applicability of the WHO criteria for the diagnosis of osteoporosis in Caucasian women to these other groups, recommendations were made for bone density testing in men. ISCD recommended bone density testing in the following groups of men:

- Men 70 years of age or older regardless of other risk factors.
- Men with a prior history of fragility fracture.
- Men with conditions known to increase the risk of bone loss and/or fracture such as hypogonadism, corticosteroid treatment, hyperparathyroidism, alcohol abuse, anticonvulsant use, and prior gastrectomy.

1999 World Health Organization Task Force Recommendations for Men and Women

An interim report *(25)* from the WHO Task Force for Osteoporosis was published in 1999 in which recommendations for bone density testing for both men and women were made. Bone density measurements were recommended if there was the following:

- Radiographic evidence of osteopenia or vertebral deformity.
- Loss of height or thoracic kyphosis.
- Previous low trauma fracture.
- Prolonged corticosteroid therapy.
- Hypogonadism.
- Chronic disorders associated with osteoporosis.
- A maternal history of hip fracture.
- A BMI less than 19 kg/m^2.
- A low calcium intake.

HOW DO THE GUIDELINES COMPARE?

There is far more unanimity among the guidelines from the various organizations than there are differences. The four clinical circumstances in which bone mass measurements might be performed originally proposed to HCFA by the NOF in 1988 were reiterated in the 1996 guidelines from ISCD, EFFO, and AACE. The 1996 guidelines from ISCD, EFFO, and AACE also noted the utility of DXA in the serial assessment of bone density. There was general agreement that hip fracture risk was best assessed by measuring the hip if the technology required to perform the hip measurement was available. Nevertheless, the 1988 NOF and 1996 ISCD and EFFO guidelines all noted the utility of multiple skeletal sites, with the choice of site determined by the intent of the measurement. The 1996 EFFO and ISCD guidelines stated that measurements of the spine, hip, and radius could all be used for global fracture risk assessments.

All of the guidelines emphasized to some degree that the measurement should not be performed if a decision to intervene would not be affected by the measurement. Both the NOF and ISCD emphasized the need for strict quality control procedures in the performance of densitometry.

A comparison of the major recommendations found in the more recent guidelines is shown in Table 7-7. The most glaring contrast between the guidelines published in 1996

or earlier and the later guidelines is the emphasis on the proximal femur as the preferred baseline measurement site. In contrast, whereas the 1996 guidelines from AACE recommended the proximal femur as the preferred measurement site, the 2001 guidelines noted that either the spine or proximal could be used. The preference for hip bone density measurements for diagnosis or fracture risk assessment is based on the ability of the hip bone density measurement to predict both spine and hip fracture risk and the relative lack of dystrophic changes at the hip that would affect the accuracy of the measurement. Although the hip can be used for follow-up measurements of bone density to assess therapeutic efficacy, this is not always clinically practical. The precision of proximal femur testing combined with the rates of change seen in the regions of interest in the proximal femur with currently available therapies result in a minimum wait of 2 to 3 years before efficacy can be assessed. Guidelines from the EFFO in 1996 noted that the spine, because of the greater percentage of trabecular bone, was more likely to demonstrate a greater response to therapeutic intervention than other sites. The precision of PA spine testing is also generally superior to that of proximal femur testing and equal to that of total hip testing. This combination of superior or equal precision and a greater expected magnitude of change makes the spine the preferred site for serial assessment of therapeutic efficacy. The dramatic improvement in the precision of the trochanteric region of interest in the proximal femur seen with the newer fan-array DXA devices has given rise to a potential exception to the previous statement. Because the rate of change in the trochanteric ROI is similar to that seen in the PA spine, the use of the trochanteric ROI in the proximal femur for monitoring with the newer fan-array DXA devices may be as useful as the PA spine.

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8

Selecting Patients for Bone Mass Measurements

Self-Assessment Indices

CONTENTS

Self-assessment indices are questionnaires or nomograms that utilize risk factors for low bone mass or osteoporosis to identify women who are likely to have a low bone density. Women who are identified in this fashion should be considered candidates for a bone density measurement. Although a woman can have a low bone density in the absence of any identifiable risk factors, these indices are useful in a variety of ways. They can help select those women who are less likely to have a low bone density as well as those who are more likely. Because most of these indices can be self-administered by the patient, they foster patient education and awareness and encourage the patient to initiate the discussion of bone density testing and osteoporosis with the physician.

In evaluating the utility of any one of these indices, it is useful to evaluate the process by which the index was created. In general, risk factors are identified and bone density measured in an initial group, called the development cohort. Regression analyses[1] are performed to determine which risk factors are significant predictors of having a predetermined level of bone density. Once the index is developed, it is then tested in a second group, called the validation cohort. Important measures of the utility of the index are the sensitivity, specificity, likelihood ratios, and the area under the receiver

[1] *See* Chapter 3 for a discussion of regression analysis, sensitivity and specificity, ROC curves, and likelihood ratios.

operating characteristic curve (AUROC or AUC). Before using any index, the physician should determine if the development or validation cohort are similar to the population of patients in which the physician intends to use the index. It is also important to remember that most indices are designed to identify individuals likely to have a bone density that is at or below a specific level at one skeletal site only. Finally, determining what level of sensitivity and specificity is acceptable for these instruments is at least in part, a philosophical decision. A high sensitivity will ensure that most women with a low BMD are referred for testing. A high specificity will ensure that most women with a BMD not considered low are not referred for testing. In the former case, more women with a low BMD who might benefit from treatment will be identified. In the latter case, more unnecessary studies may be avoided.

SIMPLE CALCULATED OSTEOPOROSIS RISK ESTIMATION

The Simple Calculated Osteoporosis Risk Estimation (SCORE) index was based on an analysis of the relationship between more than 350 variables and osteoporosis *(1)*. The development cohort for SCORE consisted of community-dwelling women, 45 years of age and older, who were recruited from October 1994 to February 1995. There were 1279 postmenopausal women in this cohort. Eighty-nine percent of these women were Caucasian and their average age was 61.5 years. Each woman in this original development cohort completed a self-administered questionnaire to determine the presence or absence of factors possibly or probably associated with osteoporosis. Proximal femur and PA spine bone density studies were performed with DXA.

Through statistical analysis, the initial list of more than 350 variables was reduced to 123. The data was further evaluated at that point, and any variable for which more than 4% of the responses from the questionnaires were missing was eliminated from consideration. This resulted in the number of variables considered for inclusion in a model to predict BMD being reduced to 101.

Multivariate linear regression[2] was used to develop the model for predicting the BMD *T*-score from the candidate variables. Statistically significant predictor variables were retained in the final model and the screening characteristics were determined for the model by calculating the specificity for the cutpoint value of probability that resulted in 90% sensitivity. The linear regression model was then simplified and the regression coefficients for each significant variable were reduced to integers. These integers are summed to give the SCORE, as shown in Table 8-1. For example, a 60-year-old Caucasian woman who weighs 120 lb, with no history of rheumatoid arthritis, a history of wrist fracture at age 57, and no history of estrogen use would have a SCORE of 16.[3]

As shown in Table 8-2, the SCORE threshold of 6 resulted in 90% sensitivity for identifying women with a femoral neck *T*-score of –2 or less. The specificity at this cutpoint was 50%. When sensitivity is plotted against 1-specificity for the linear regression model, the AUC for the resulting ROC is 0.811. The AUC is a measure of the probability that the predicted probability of low bone density is greater for women who have a low BMD between any two randomly paired low BMD and non-low BMD

[2] *See* Chapter 3 for a discussion of linear regression.

[3] The example is calculated as follows: +5 for race, 0 for no history of rheumatoid arthritis, +4 for the history of wrist fracture after age 45, +(3 × 6) for age, +1 for history of no estrogen use, and – (1 × 12) for weight. The sum is 16.

Table 8-1
Coefficients for Calculating SCORE

Variable	*Score*	*If Woman*
Race	5	is NOT Black
Rheumatoid arthritis	4	HAS Rheumatoid Arthritis
History of fractures	4	for EACH TYPE (wrist, rib, hip) of nontraumatic fracture after age 45 (maximum score—12)
Age	3	times first digit of age in years
Estrogen	1	if NEVER received estrogen therapy
Weight	–1	times weight divided by 10 and truncated to integer

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Table 8-2
Sensitivity and Specificity of SCORE for Various Threshold Values and Levels of BMD at the Femoral Neck Calculated Using Manufacturer's Reference Data

Threshold	*Prediction of BMD ≤ –2 SD*		*Prediction of BMD ≤ –2.5 SD*		*Prediction of BMD ≤ –1 SD*	
SCORE	*Sensitivity*	*Specificity*	*Sensitivity*	*Specificity*	*Sensitivity*	*Specificity*
0	0.993	0.124	0.996	0.103	0.980	0.199
1	0.986	0.167	0.992	0.140	0.963	0.256
2	0.976	0.203	0.992	0.176	0.948	0.305
3	0.966	0.257	0.992	0.223	0.924	0.368
4	0.942	0.340	0.974	0.294	0.872	0.447
5	0.925	0.417	0.954	0.361	0.831	0.529
6	0.894	0.497	0.936	0.433	0.776	0.602
7	0.816	0.578	0.883	0.520	0.694	0.678
8	0.737	0.672	0.822	0.614	0.616	0.787
9	0.674	0.746	0.769	0.692	0.540	0.845
10	0.604	0.824	0.708	0.772	0.456	0.902

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women. An AUC of around 0.8 is considered acceptable for a diagnostic test *(2)*. This graph is shown in Chapter 3, Fig. 3-8 as part of the discussion of ROC curves. In the worked example of SCORE noted above, the SCORE of 16 is above the SCORE threshold of 6 for a high probability of a bone density *T*-score of –2 or less at the femoral neck. As a result, the woman should be considered for bone density testing.

To validate the SCORE model, a second group of 259 women were recruited of whom 208 were postmenopausal. Of these women, 94% were Caucasian and their average age was 63.1 years. Bone density was again measured with DXA and the SCORE questionnaire was completed. The sensitivity, specificity, and AUC for SCORE in both the development and validation cohorts are shown in Table 8-3.

Table 8-3
Summary of Results in Development and Validation Cohorts for SCORE Threshold of 6 for the Identification of a BMD of –2 or Less at the Femoral Neck

Cohort	n[a]	*Sensitivity*	*95% CI*	*Specificity*	*95% CI*	*AUC*
Development	1102	0.89	0.86–0.92	0.50	0.47–0.52	0.77
Validation	185	0.91	0.81–0.96	0.40	0.30–0.52	0.72

[a] Number of women with no missing responses on all variables used in the predictor.

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The SCORE questionnaire performed well in both the development and validation cohorts. Sensitivities of 0.89 and 0.91 indicate that 89 and 91% of the women in the two cohorts with femoral neck *T*-scores of –2 or less were at or above the SCORE threshold of 6 and would have been appropriately referred for bone density testing. In order to achieve this high degree of detection, the lower specificities of 0.50 and 0.40 in the 2 cohorts must be accepted. Of the women in the 2 cohorts 50 to 60% with femoral neck *T*-scores greater than –2 would also be referred for testing because their test scores were at or above the SCORE threshold of 6.

The initial publication of the design of the SCORE questionnaire and its utility was greeted with skepticism. Prior to the development of SCORE, most attempts to use clinical risk factors to select women for bone density testing had not resulted in adequate sensitivity and specificity. The questionnaire itself appeared deceptively simple in its final form, belying the very complex statistical analysis of more than 350 variables. It was also noted that 24% of the women in the validation cohort had rheumatoid arthritis. This cast doubt on the applicability and validity of the SCORE questionnaire to the general population in which such a high percentage of rheumatoid arthritis would not be expected. Finally, the femoral neck *T*-scores used in the development and validation phase of SCORE were based on the manufacturer's reference databases, not the NHANES III database *(3)*. A Lunar DXA device was used in slightly more than half the cases in both cohorts with a Hologic or Norland DXA device used in the remaining cases. It was thus initially unclear how the adoption of the NHANES III database *T*-scores might affect the choice of the SCORE threshold for identifying individuals with a high probability of low bone mass at the femoral neck.

Other researchers attempted to validate the SCORE questionnaire in different study populations. Cadarette et al. *(4)* utilized the SCORE questionnaire in a population of 398 postmenopausal women with an average age of 64.5 years. Of the 398 women, 86.7% were Caucasian. Bone density was measured at the femoral neck and PA lumbar spine with a Hologic DXA device and *T*-scores were calculated using the manufacturer's reference data. The original SCORE threshold of 6 was used to identify those women who had a high probability of having a *T*-score of –2 or less at the spine, femoral neck, or both. The sensitivity and specificity for identifying women with a low BMD at either the spine or femoral neck in this study were 0.90 and 0.32, respectively. This means that 90% of the women with a low BMD at either the PA spine or femoral neck would be referred for bone density testing. Conversely, 68% of women with a BMD not considered low at either site would also be referred for testing, but 32% would not. When the analysis

Table 8-4
Sensitivity and Specificity for Various SCORE Thresholds in Two Age Groups

Group	*n*	*SCORE cutpoint*	*Sensitivity*	*Specificity*
50–59 years	183	6	0.96	0.51
		7	0.85	0.65
		8	0.74	0.77
60–69 years	124	8	0.90	0.20
		9	0.77	0.39
		10	0.72	0.58

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was restricted to identifying women with a low BMD at the femoral neck only, the sensitivity and specificity at a SCORE threshold of 6 were 0.904 and 0.29, respectively.

In a similar study, Von Mühlen et al. *(5)* studied 1013 postmenopausal Caucasian women who were part of the Rancho Bernardo osteoporosis study. The average age of these women was 72.5 years. Bone density was measured using a Hologic DXA device and *T*-scores were calculated for the femoral neck using the manufacturer's reference data. At the original SCORE threshold of 6, the sensitivity was an extremely high 0.98 but the specificity was only 0.125. The authors concluded that in these women who were much older than the original SCORE development and validation cohorts, the questionnaire had limited value for selecting women for a bone density measurement.

In 2000, Ungar et al. *(6)*, writing in the *Journal of Clinical Densitometry*, published the results from the use of the SCORE questionnaire in 307 postmenopausal women. The average age of the women was 58.4 years and 91% were Caucasian. The questionnaire was self-administered and the women then underwent PA lumbar spine and proximal femur bone density testing with either a Lunar or Hologic DXA device. PA spine *T*-scores were derived from the manufacturer's databases but the femoral neck *T*-scores were derived using the NHANES III reference database. Women with a *T*-score of –2.0 or lower at either skeletal site were considered as having low BMD.

Table 8-4 lists the sensitivity and specificity for different SCORE thresholds by age range for the 307 women in this study. At the original threshold of 6, the sensitivity and specificity for women aged 50 to 59 years were 0.96 and 0.51, respectively. In the older women, a SCORE threshold of 8 was required to achieve a sensitivity of 0.90. At this sensitivity however, the specificity was only 0.20. The AUC for the older women was also poor at 0.594. The authors concluded that SCORE performed better in women in their fifties compared to women in their sixties and that SCORE thresholds higher than 6 were required in older women.

OSTEOPOROSIS RISK ASSESSMENT INSTRUMENT

The Osteoporosis Risk Assessment Instrument (ORAI) questionnaire was developed by Cadarette et al. *(7)* using information obtained at the baseline visit for women participating in the Canadian Multicentre Osteoporosis Study[4] (CaMos). There were 926 par-

[4] CaMos is a population-based cohort study in which risk factors for osteoporosis, BMD, and osteoporotic fracture are being evaluated over a 5-year period.

Table 8-5
Demographic Characteristics of the Original ORAI Cohorts

Variable	*Development Cohort* n = *926*	*Validation Cohort* n = *450*
Mean age, years	62.8	63.5
Race (%)		
White	879 (94.9)	423 (94.0)
Asian	27 (2.9)	14 (3.1)
Other	20 (2.2)	13 (2.9)
BMD PA lumbar spine or femoral neck *T*-Score		
> –1	538 (58.1)	268 (59.6)
≥ –2	210 (22.7)	105 (23.3)
≥ –2.5	101 (10.9)	54 (12.0)

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Table 8-6
Performance Characteristics of Clinical Risk Assessment Algorithms in the Development Cohort of the ORAI by Number of Variables in the Algorithm

Number of Variables	*Sensitivity %*	*Specificity %*	*AUC*
6	91.9	46.6	0.803
5	91.4	47.5	0.802
4	91.9	44.5	0.803
3	90.0	45.1	0.789
2	93.8	40.5	0.779
1	80.5	53.6	0.713

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ticipants in the development cohort and 450 in the validation cohort. The characteristics of these women are shown in Table 8-5.

Information on risk factors was obtained from questionnaires that the women completed on enrollment in CaMos. The relationship between each risk factor and a low BMD at either the spine or femoral neck was evaluated using logistic regression techniques. The variables that were the best predictors of low BMD at either skeletal site were considered for inclusion in the final model to predict low BMD at either site. The six variables were age, weight, current estrogen use, menopause, physical activity, and previous minimal trauma fracture at age 45 or older. Models were tested that included from one to six variables. The sensitivity, specificity and AUC for these models are shown in Table 8-6. The sensitivity of the three variable model containing age, weight, and estrogen use was similar to the sensitivity of the models containing four, five and six variables. Although the sensitivity of the model containing only the two variables of age and weight was similar to the more complex models, the specificity was much lower. As a result, only the three variables of age, weight, and estrogen use were included in the final model.

Table 8-7
Scoring System for the ORAI[a]

Variable	*Score*	*Variable*	*Score*
Age, years		Weight, kg	
≥75	15	< 60	9
65–74	9	60–69	3
55–64	5	≥ 70	0
45–54	0		
Current estrogen use			
No	2		
Yes	0		

[a] Women with a score of 9 or greater would be selected for bone densitometry.
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Scores were assigned to the various risk factors by rounding the odds ratio for low BMD for that risk factor to the nearest integer. To ensure that few women with a low BMD at either site would be missed, threshold scores for recommending BMD testing were chosen to ensure 90% sensitivity. When the three-variable ORAI was tested in the validation cohort, its performance was similar to that seen in the development cohort. The sensitivity for identifying women with a PA lumbar spine or femoral neck *T*-score of –2 or poorer was 93.3% and the specificity was 46.4%.

The scoring system for the ORAI is shown in Table 8-7. A score of 9 or greater indicates that a woman should be referred for testing. As a consequence of the scoring system, all women age 65 and older would be referred for testing. All women age 45 or older who weigh less than 60 kg (132 lb) would also be selected for testing. ORAI would also select women aged 55 to 64 years who weight 60 to 70 kg and who are not currently taking estrogen.

THE STUDY OF OSTEOPOROTIC FRACTURES SIMPLE USEFUL RISK FACTOR SYSTEM

The Study of Osteoporotic Fractures Simple Useful Risk Factor System (SOFSURF) is a risk factor-based statistical model for the prediction of a total hip BMD *T*-score of –2.5 or less in non-black women age 67 years and older *(8)*. Risk factor and bone density data from 8070 women in the very large Study of Osteoporotic Fractures (SOF) were used to develop this prediction model. Weight and age were again strong predictors of total hip *T*-score as was seen in the development of the SCORE and ORAI instruments although those instruments focused on different skeletal sites and/or regions of interest. The scoring system for SOFSURF is shown in Table 8-8. In this development cohort, 85% of the women with a SOFSURF score greater than 3 had a total hip *T*-score of –2.5 or poorer. The AUC for detecting this level of BMD at the total hip was 0.75.

ABONE

The ABONE instrument was proposed by Weinstein et al. *(9)* in 1999. ABONE is a mnemonic for age (A), bulk (B), and never estrogens (ONE). In the creation of the

Table 8-8
The SOFSURF Scoring System

Variable	*Score*
Weight < 150 lb	1
Current smoking	1
History of fracture after age 50	1
Weight < 130 lb[a]	2
Age > 65	0.2 for each year above 65

[a] This is in addition to the 1 point awarded for weight less than 150 lb.
From ref. *8*.

ABONE criteria, 1346 Caucasian, postmenopausal women underwent DXA testing of the spine and proximal femur and completed a risk factor questionnaire. Their average age was 62.2 years and they were an average of 16.2 years postmenopausal. Multivariate regression analysis was performed using the PA lumbar spine, total hip, and femoral neck *T*-score to determine which risk factors were independent predictors of osteoporosis. Osteoporosis was defined using WHO criteria[5] and the NHANES III database[6] was used to calculate *T*-scores at the proximal femur. Among the potential risk factors that were evaluated were past or current use of steroids, thyroid replacement, heparin, oral contraceptives, estrogen, and alcohol. Caffeine intake, calcium intake, calcium supplementation, exercise, smoking history, family history of osteoporosis, and history of hysterectomy or oophorectomy were also evaluated.

The independent variables related to osteoporosis at the spine, total hip, and femoral neck were age and weight. Lack of postmenopausal estrogen use and lack of oral contraceptive use for at least 6 months were independent predictors for osteoporosis at any of the three sites.

In a subsequent publication *(10)*, Weinstein et al. extended these observations to an additional 264 women. The addition of these 264 women increased the total number of women studied to 1610 but did not change the average age or years postmenopausal. Multivariate regression analysis was again performed to determine which independent variables were significant predictors of osteoporosis. Age and years past menopause were positive predictors, whereas weight was a negative predictor. Lack of either postmenopausal estrogen use or oral conceptive use for at least 6 months was also a significant predictor of osteoporosis. Ninety-five percent confidence intervals were calculated for age and weight to determine the best cutpoints for screening purposes. Based on these analyses, Weinstein and colleagues suggested that postmenopausal women greater than 65 years of age who weigh less than 140 lb at menopause or have never used estrogens for more than 6 months be referred for bone density testing. A scoring system that awards 1 point for weight less than 140 lb at menopause or never use of estrogens for more than 6 months was proposed such that any 65-year-old woman with an ABONE score of 1 or 2 would be referred for testing.

[5] *See* Chapter 9 for a discussion of the WHO criteria for the diagnosis of osteoporosis based on measurement of the bone density.

[6] *See* Chapter 5 for a discussion of the NHANES III proximal femur database.

Table 8-9
Risk Factors Evaluated in the Development of the OSTA Questionnaire

- Age
- Height
- Weight
- Race
- Height loss
- History of fracture
- Age at menopause
- History of rheumatoid arthritis
- Calcium supplementation
- Dietary calcium intake
- Smoking history
- Time spent in recreational physical activity
- History of being bedridden
- Sunlight exposure
- Estrogen use
- Thyroid hormone use
- Corticosteroid use

Adapted with permission of the publisher from Koh LKH, Sedrine WB, Torralba TP, et al. A simple tool to identify Asian women at increased risk of osteoporosis. Osteoporos Int 2001;12:699–705. ©Springer-Verlag

THE OSTEOPOROSIS SELF-ASSESSMENT TOOL

Koh and colleagues *(11)* developed the original Osteoporosis Self-Assessment Tool for Asians (OSTA) based on a study of 860 non-Caucasian, postmenopausal women from eight Asian countries. Risk factors were captured from a self-administered questionnaire and bone density was measured by DXA in the proximal femur. Proximal femur *T*-scores were based on the manufacturer's reference data for Asian women. Statistical analysis was performed to determine which risk factors were independent predictors of BMD. The risk factors that were captured are listed in Table 8-9. These independent predictors were combined in a multivariable model from which risk factors were dropped one at a time until only statistically significant variables remained in the model. An index was developed from the variables in the final model to identify those women with a high probability of having a femoral neck *T*-score of –2.5 or less.

The final model included 11 variables that were significantly and independently associated with femoral neck bone density: age, weight, current estrogen use, current thyroid hormone use, any fracture after age 45, spine fracture after age 45, Chinese or Thai ethnicity, and being from Malaysia, Hong Kong, or Taiwan. Each of these variables was assigned a value based on the regression coefficient for that variable in the statistical model. The index values for all 11 variables were then added for each woman.

The sensitivity and specificity for an OSTA cutpoint of –1 were 95% and 47%, respectively. The AUC was 0.85. When thyroid hormone use and the three countries were dropped from the model, the AUC was still 0.83. Dropping Chinese and Thai ethnicity and current estrogen use lowered the AUC to only 0.80. Finally, dropping a history of any fracture or spine fracture after age 45 still resulted in an AUC of 0.79. This left only age and weight in the final index. Using an OSTA cutpoint of –1 with only age and weight in the model, the sensitivity was 91% and the specificity was 45% for a femoral neck *T*-score –2.5 or less in the development cohort. The two-variable index was validated in a cohort of 1123 Japanese women. A cutpoint of –1 resulted in a sensitivity of 98% and a specificity of 29% in this group.

The OSTA score is calculated by subtracting age in years from weight in kilograms, multiplying the result by 0.2 and truncating to an integer. For example, a 64-year-old

Table 8-10
Performance of the OSTA Index in the Development and Validation Cohorts by Risk Category

	Asian Development Cohort		*Japanese Validation Cohort*	
Index Score	n *(%)*	n *(%) with* T ≤ –2.5	n *(%)*	n *(%) with* T ≤ –2.5
< –4	62 (8%)	38 (61%)	281 (25%)	123 (44%)
–1 to –4	417 (52%)	62 (15%)	562 (50%)	56 (10%)
> –1	318 (40%)	10 (3%)	280 (25%)	4 (1%)

Adapted with permission of the publisher from Koh LKH, Sedrine WB, Torralba TP, et al. A simple tool to identify Asian women at increased risk of osteoporosis. Osteoporos Int 2001;12:699–705. ©Springer-Verlag

Asian woman who weighs 56 kg would have an OSTA score of –1.[7] Using age and body weight to calculate the OSTA score, the authors identified three categories of risk. The low-risk category included women with an OSTA score greater than –1. The women in the intermediate risk category had scores of –1 to –4 and the women in the high risk category had scores less than –4. Table 8-10 gives the total percentage of women in each group and the percentage with femoral neck *T*-scores of –2.5 or less for both the development and validation cohorts.

The OSTA index is easily transformed into a nomogram as shown in Fig. 8-1A. Women in the high and medium-risk category should be referred for bone density testing. It must be kept in mind that the cut point shown here is based on the original study of Asian women and is specific for predicting a *T*-score of –2.5 at the femoral neck. As will be seen, different cutpoints appear to be necessary if this index is to be used in other populations as well as for predicting different *T*-scores at other skeletal sites.

In 2002, Koh *(12)* reported the performance characteristics of the OSTA index in an additional group of 294 normal Singapore women with an average age of 59. The OSTA index calculated for each woman ranged from –10 to 7. The original OSTA cutpoints of –1 and –4 were again used to establish high, moderate and low-risk categories. In this group, the index had a sensitivity of 90%, a specificity of 58% and an AUC of 0.82 for predicting a femoral neck *T*-score or –2.5 or poorer.

Koh *(13)* also attempted to utilize the OSTA index in 98 Asian men with an average age of 61 years. The calculated OSTA index values for these men ranged from –7 to 8. Using male Asian reference values to establish a *T*-score of –2.5 or poorer at the femoral neck, the original OSTA cutpoint of –1 resulted in a sensitivity of only 50% and a specificity of 78%.

Hochberg et al. *(14)* utilized the OSTA index to predict an osteoporotic femoral neck *T*-score in 140 Asian women who participated in the Fracture Intervention Trial in the United States. Utilizing an OSTA index cutpoint of 0[8] or less for the prediction of an osteoporotic femoral neck *T*-score based on reference data for Asian women, the sensitivity was 96% and the specificity was 37%. The positive likelihood ratio (LR+) was 1.52 and the negative likelihood ratio (LR-) was 0.12.

[7] The OSTA score is calculated as follows: $(56 - 64) \times 0.2 = -1.6$. This value is truncated to an integer resulting in an OSTA score of –1.

[8] Note that the original OSTA index cut point value for women was –1 or below, not 0 or below.

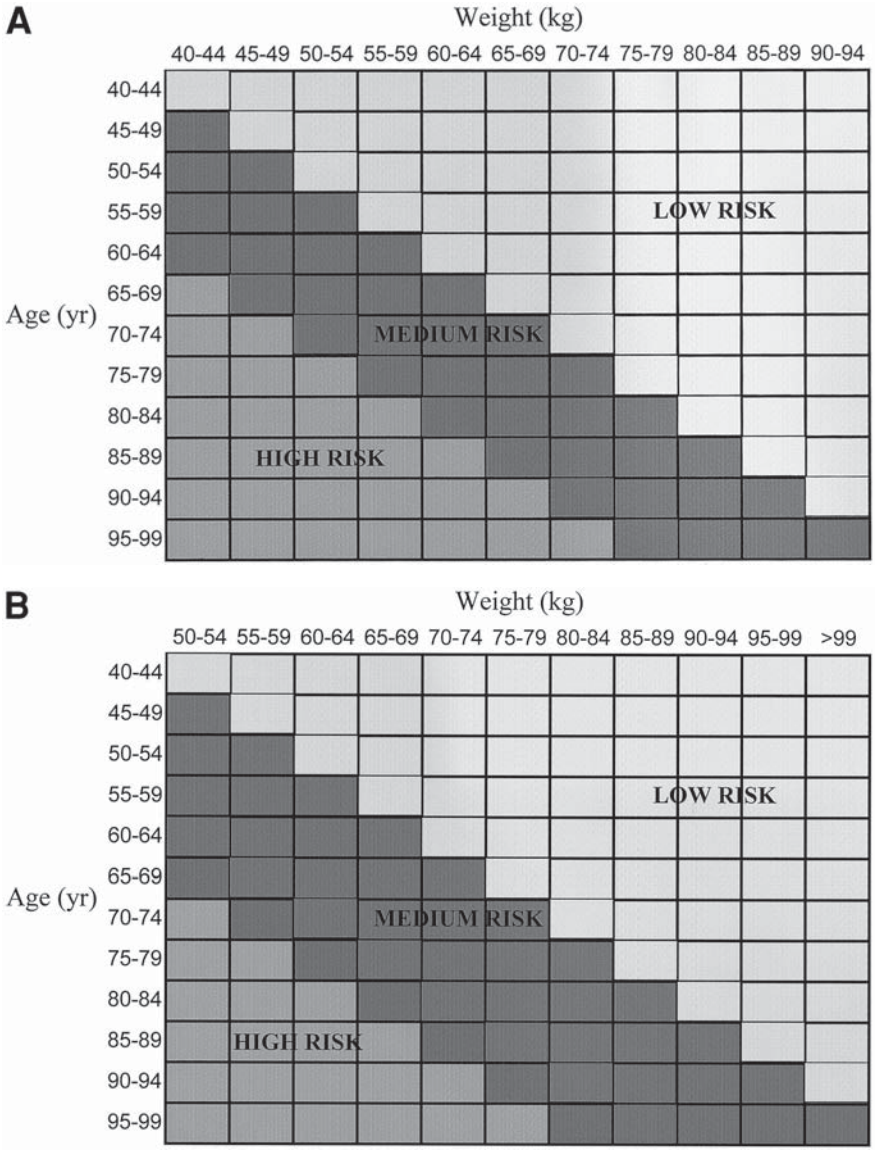

Fig. 8-1. (A) The OSTA nomogram for Asian women. **(B)** The OST nomogram for Caucasian women. The cells are shifted to the right, reflecting the effects of weight. Women in the high- and medium-risk categories should undergo BMD testing because of a sufficiently high probability of osteoporosis at the femoral neck. These nomograms are found on the accompanying CD-ROM.

The OSTA index has also been utilized in Caucasian women. In this context, the name is shortened to the Osteoporosis Self-Assessment Tool (OST). Ben Sedrine and Reginster *(15)* reported the use of the OST index in 4035 Caucasian Belgian women with an average age of 61 and an overall prevalence of osteoporosis of 19%. Using the original OSTA index cutpoints of –1 and –4 to establish high-, moderate-, and low-risk

Table 8-11
Performance Characteristics of 154 lb (70 kg) Weight Criterion for Osteopenia and Osteoporosis at the PA Lumbar Spine and Femoral Neck

Site	*Sensitivity*	*Specificity*	*PPV*	*NPV*
PA Lumbar Spine				
Osteopenia	0.81	0.46	0.64	0.67
Osteoporosis	0.89	0.38	0.33	0.91
Femoral Neck				
Osteopenia	0.80	0.43	0.60	0.67
Osteoporosis	0.94	0.36	0.21	0.97

PPV, positive predictive value; NPV, negative predictive value.

Adapted with permission of the publisher from Micha Isson K, Bergström R, Mallmin H, Holmberg L, Wolk A, Ljunghall S. Screening for osteopenia and osteoporosis: selection by body composition. Osteoporos Int 1996;6:120–126. ©Springer-Verlag

groups for a femoral neck *T*-score of –2.5 or poorer, 90% of the 3.4% of women in the high-risk group were found to have osteopenia or osteoporosis. Of the 4035 women, 30% were in the moderate-risk group. Of these women, 73% had either osteoporosis or osteopenia at the femoral neck. The authors noted that the prevalence of osteopenia and osteoporosis at the femoral neck was sufficiently high in the moderate-risk category to justify referral for a bone mass measurement when the OST index value was –1 or lower. This is the upper boundary of the moderate-risk group shown in the nomogram in Fig. 8-1A.

WEIGHT SELECTION CRITERIA

The use of weight alone as a criterion for selecting women for bone mass measurements was proposed in 1996 by Michaëlsson et al. *(16)*. In this study reported in *Osteoporosis International*, only anthropomorphic measures were considered in predicting which individuals were likely to have a low bone density. The measures included height, weight, BMI, waist-to-hip ratio, lean tissue mass, and fat tissue mass. Bone density was measured by DXA at the PA lumbar spine and femoral neck. Lean and fat tissue mass were determined using DXA total body studies. *T*-scores were calculated using the manufacturer's reference database for US Caucasian women. Osteopenia and osteoporosis were defined using WHO criteria for diagnosis. One hundred seventy-five women were studied, of whom 106 were postmenopausal. Their average weight was 148.6 lb (67.4 kg). The women were divided into tertiles based on weight. The sensitivity, specificity, and positive and negative predictive values for osteopenia and osteoporosis were calculated for the cutpoints between weight tertiles. The best sensitivity and negative predictive value was obtained for the weight cutpoint between the second and third tertile of 154 lb (70 kg). These are shown in Table 8-11. The authors suggested that women weighing 154 lb or less should undergo bone density measurements, whereas women weighing more than 154 lb could reasonably be excluded from testing.

THE FRACTURE INDEX

The FRACTURE Index was developed by Black et al. *(17)* to identify women at high risk of osteoporotic fracture based on clinical risk factors with or without a bone density

measurement. This is not exactly the same as a risk-assessment tool to identify women with a high probability having of low bone mass. Nevertheless, women identified by this fracture risk assessment tool as being at high risk for fracture based on clinical risk factors alone would certainly be considered for bone density testing. For this reason, the FRACTURE Index is included in this discussion.

The FRACTURE Index is based on data that was obtained from 7782 women, aged 65 years and older, who participated in the Study of Osteoporotic Fractures (SOF).[9] Women in this trial provided complete medical histories and underwent physical examinations as well as anthropomorphic measurements and assessments of neuromuscular function. Bone density studies were performed with DXA of the proximal femur. Fracture assessments were performed every 4 months. Spine radiographs were obtained an average of 3.7 years apart and total time for hip and nonvertebral fracture follow-up was 5 years.

To derive the index, the investigators considered previously identified *(18)* risk factors for hip fracture as well as other clinically identifiable risk factors. Some 20 different variables were initially considered in a logistic regression analysis. The final statistical model included those variables that were statistically significant for the prediction of hip fracture and were easily assessed in clinical practice. An additive scoring system was developed based on the final model. The scoring system is shown in Table 8-12.

The same risk factors were used in the FRACTURE Index with or without a bone density measurement. As noted in Table 8-12, the maximum score without a bone density measurement was 11. With a bone density measurement, the maximum possible score was 15. The sensitivity and specificity were determined for all the possible scores for the index both with and without a bone density measurement as well as the AUC.

For the model without a BMD measurement, the AUC was 0.714. For the model with a BMD measurement, the AUC was 0.766. In the model without a bone density measurement, which is clearly the most relevant model to the discussion here, a score of 4 of higher[10] resulted in a sensitivity of 66% and a specificity of 66.3% for hip fracture. In the model that included a bone density measurement, a score of 6 or higher resulted in a sensitivity of 78.6% and a specificity of 61.7%.

The FRACURE Index was validated in 6679 women with an average age of 80.5 years who participated in the EPIDOS study.[11] The women were divided into quintiles based on the FRACTURE Index score. Quintiles were derived for scoring both with and without the BMD measurement. As was seen in the SOF development cohort, the risk of hip fracture increased progressively with increasing FRACTURE Index values for both types of scoring. Without a BMD measurement, women with a FRACTURE Index value of 7 to 10 had a 10.4% risk of hip fracture. With a BMD measurement, those women who had FRACTURE Index values of 11 to 14 had a hip fracture risk of 14.1%.

[9] SOF is a prospective study of 9704 women at least 65 years of age. Caucasian women make up 99.7% of the study population.

[10] The score of 4 is used as a dichotomous cutpoint. The sensitivity and specificity given here are for all scores of 4 or higher considered as a group, whereas a second group would be all scores of 3 or lower. The specificity and sensitivity for an exact score of 4, 5, or 6, and so on, would be different.

[11] EPIDOS is a prospective study of risk factors for hip fracture in France. There were 7575 women aged 75 and older recruited for the study during 1992 and 1993 and followed every 4 months for the duration of the study. The data presented here is based on a mean follow-up of 4 years.

Table 8-12
The FRACTURE Index Scoring System

	Point Value
1. What is your current age?	
Less than 65	0
65–69	1
70–74	2
75–79	3
80–84	4
85 or older	5
2. Have you broken any bones after age 50?	
Yes	1
No/Don't know	0
3. Has your mother had a hip fracture after age 50?	
Yes	1
No/Don't know	0
4. Do you weight 125 lb or less?	
Yes	1
No	0
5. Are you currently a smoker?	
Yes	1
No	0
6. Do you usually need to use your arms to assist yourself in standing up from a chair?	
Yes	2
No/Don't know	0
If you have a current bone density (BMD) assessment, then answer the next question	
7. BMD results: Total Hip *T*-score	
T-score ≥ –1	0
T-score between –1 and –2	2
T-score between –2 and –2.5	3
T-score < –2.5	4

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The FRACTURE Index was also useful in identifying women at high risk of spine and other nonspine fractures in both the development and validation cohorts. The authors noted that risk factors other than BMD assessments were predictive of fracture but that the BMD measurement itself had additional predictive ability. As a consequence, they recommended BMD testing prior to initiating therapy whenever possible. The authors noted that age was the most important single component of the FRACTURE Index, in keeping with what has been found with other risk indices. Based on these findings, the authors recommended that postmenopausal women with a FRACTURE Index score of 4 or higher, in the absence of a BMD test, undergo additional evaluation. In the context of selecting women for bone density testing, it would seem reasonable to conclude that a FRACTURE Index score of 4 or higher is justification for a bone density measurement.

COMPARING THE PERFORMANCE OF SELF-ASSESSMENT QUESTIONNAIRES

Several studies *(19–22)* have compared the performance characteristics of the various indices. Cadarette and colleagues *(19)* compared the performance of the ORAI index to that of SCORE, ABONE, the 1998 NOF guidelines[12] and the body weight criterion in a population of 2365 postmenopausal women age 45 and older who were participating in the CaMos study. These women were otherwise healthy women who had not taken HRT or any other bone-sparing agent or who had taken HRT for 5 years or more. The average age was 66.4 years and the average weight was 152 lb (69 kg). Bone density was measured at the femoral neck and *T*-scores were calculated using the manufacturer's reference data for Canadian women in which the mean and SD were 0.857 g/cm^2 and 0.125 g/cm^2, respectively.[13] To compare the performance of the 1998 NOF guidelines to the risk indices, the authors converted the NOF guidelines to an index scoring system in which 1 point was awarded for age 65 or older, weight less than 127 lb (57.6 kg), personal history of minimal trauma fracture after age 50, family history of fracture, and current cigarette smoking. In keeping with the intent of the 1998 NOF guidelines, a score of 1 or greater would trigger a referral for bone density testing.

The performance characteristics of each index for identifying women with femoral neck *T*-scores at various levels are shown in Table 8-13. The original cut point[14] recommended by the creators of each index was used in this calculation. In this comparison, the performance characteristics of SCORE and ORAI were the best at all bone density levels. When the comparison was restricted to femoral neck *T*-scores at or below –2.5, SCORE, ORAI, and the weight criterion were equivalent based on the AUC. SCORE, ORAI, and the NOF guidelines selected 94% or more of the women with femoral neck *T*-scores below –2 and 96% of the women with femoral neck *T*-scores at or below –2.5. Of these three indices, ORAI had the highest specificity. ABONE and the weight criterion decision rules missed 20% of the women with femoral neck *T*-scores below –2 in this study suggesting that they were not useful for this purpose. The authors suggested that because the ORAI index had superior specificity to SCORE and the NOF guidelines and greater simplicity when compared to SCORE, the ORAI index was the most useful.

SCORE, ORAI, SOFSURF, and OST were compared by Hochberg et al. *(22)* in a study of 17,572 Caucasian women ranging in age from 45 to 93 years who were initially screened for participation in FIT *(23)*. Twenty-one percent of these women had osteoporosis at the femoral neck using the WHO criteria of a *T*-score of –2.5 or poorer and the NHANES III proximal femur database. At approximately 90% sensitivity, both OST and SOFSURF had an acceptable 46% specificity for the prediction of an osteo-porotic *T*-score at the femoral neck. The cutpoints, sensitivities, specificities, and LRs are shown in Table 8-14. The cutpoints for OST used in this study have been shifted up by one unit compared to those used in the original OSTA index for Asian women. The shift in the cutpoint for SCORE represents the effect of using the NHANES III reference database for the calculation of proximal femur *T*-scores and the prediction of a lower *T*-score than called for in the development of the SCORE index.

[12] *See* Chapter 7 for a discussion of the 1998 NOF guidelines.

[13] The mean and SD at the femoral neck in the NHANES III non-Hispanic white female database are 0.858 g/cm^2 and 0.120 g/cm^2, respectively.

[14] NOF guidelines 2; SCORE ≥ 6; ORAI ≥ 9; ABONE ≥ 2; Weight < 154 lb (70 kg).

Table 8-13
Performance Characteristics of Various Self-Assessment Risk Indices for Identifying Women Age 45 and Older Who Are Below Various Levels of Bone Density at the Femoral Neck

	Index	*Sensitivity*	*Specificity*	*AUC*
T-Score < –1	NOF	87.9	25.6	0.64
	SCORE	90.6	30.8	0.72
	ORAI	83.2	43.7	0.71
	ABONE	64.4	64.2	0.67
	Weight	64.1	61.9	0.68
T-Score < –2.0	NOF	93.7	19.8	0.67
	SCORE	97.5	20.8	0.77
	ORAI	94.2	31.9	0.76
	ABONE	79.1	52.7	0.71
	Weight	79.6	52.2	0.74
T-Score ≤ –2.5	NOF	96.2	17.8	0.70
	SCORE	99.6	17.9	0.80
	ORAI	97.5	27.8	0.79
	ABONE	83.3	47.7	0.72
	Weight	87.0	47.6	0.79

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Table 8-14
Performance Characteristics of 4 Self-Assessment Risk Indices for the Prediction of Femoral Neck *T*-Scores of –2.5 or Less in 17,572 Caucasian Women Screened for FIT

Index	*Cutoff*	*Sensitivity*	*Specificity*	*LR +*	*LR –*
OST	< 1 vs ≥ 1	89%	46%	1.65	0.24
ORAI	> 10 vs ≤ 10	92%	26%	1.24	0.31
SOFSURF	> 1 vs ≤ 1	86%	46%	1.60	0.30
SCORE	> 11 vs ≤ 11	89%	39%	1.45	0.30

Adapted with permission of the publisher from Hochberg MC, et al. Osteoporos Int 2002;13:S111. ©Springer-Verlag

The original development and validation cohorts for SCORE were utilized again in a comparison study of SCORE, ORAI, OST, and SOFSURF by Geusens et al. *(21)*. As noted previously, in the original publication of the development and validation of the SCORE index femoral neck *T*-scores were calculated using the manufacturer's reference database instead of the NHANES III database *(1)*. In this study, *T*-scores at the femoral neck were recalculated using NHANES III. The various indices were calculated as described in the original publications *(1,7,8,11)*. A single cutpoint was chosen for each index that provided approximately 90% sensitivity for the prediction of an osteoporotic femoral neck *T*-score of –2.5 or poorer. The sensitivity and specificity was also calculated for the same cutpoint for prediction of a femoral neck *T*-score of –2 or poorer. This resulted in slightly lower sensitivity and slightly higher specificity for the *T*-score of –2 or poorer. The results for the 1102 women from the SCORE cohorts are shown in Table 8-15.

Table 8-15
Sensitivity and Specificity by Femoral Neck *T*-Score for Four Risk Indices from the Original SCORE Cohorts

		T-*Score* ≤ –2.5		T-*Score* ≤ –2.0	
Index	*Cutpoint*	*Sensitivity*	*Specificity*	*Sensitivity*	*Specificity*
OST	< 2	88%	52%	84%	59%
ORAI	> 8	90%	52%	82%	58%
SCORE	> 7	89%	58%	80%	65%
SOFSURF	> –1	92%	37%	88%	42%

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Table 8-16
Percentage of Individuals in Risk Index Categories with Femoral Neck *T*-Scores of –2.5 or Poorer or –2.0 or Poorer Using NHANES III Reference Data

	FIT Screening Population		*Rotterdam Study Population*	
Risk Index Category	T-*Score* ≤ –2.5	T-*Score* ≤ –2.0	T-*Score* ≤ –2.5	T-*Score* ≤ –2.0
Background Prevalence	21%	43%	19%	39%
OST				
>1 (low risk)	4%	16%	4%	16%
–3 to 1 (moderate risk)	23%	48%	22%	45%
< –3 (high risk)	57%	79%	57%	79%
ORAI				
<9 (low risk)	4%	17%	7%	21%
9 to 17 (moderate risk)	16%	37%	16%	36%
>17 (high risk)	41%	68%	46%	70%
SCORE				
<7 (low risk)	4%	15%	1%	4%
7 to 15 (moderate risk)	21%	46%	16%	35%
>15 (high risk)	51%	74%	38%	66%
SOFSURF				
<0 (low risk)	3%	11%	5%	16%
0 to 4 (moderate risk)	18%	40%	17%	39%
>4 (high risk)	53%	77%	51%	74%

Adapted with permission of the publisher from ref. *21*.

The risk indices were compared by Geusens et al. *(21)* in three other study populations as well: 3374 Caucasian women age 55 and older from the Rotterdam Study *(24)*, 4204 postmenopausal women age 50 to 80 from a Netherlands clinic study, and 23,833 postmenopausal women age 55 to 81 years who were screened for FIT. Femoral neck *T*-scores were calculated using the NHANES III reference data for the Rotterdam cohort and FIT cohort. *T*-scores for the PA lumbar spine in the SCORE cohort and the Netherlands clinic study cohort were calculated using the manufacturer's reference data.

The prevalence of femoral neck *T*-scores at or below –2.5 or –2.0 for the Rotterdam cohort and FIT cohort by risk index category is shown in Table 8-16. All four risk

Table 8-17
Prevalence of Low Spine BMD by OST Category and *T*-Score Cutoff

	SCORE Cohort		*Netherlands Clinic Sample*	
Risk Index Category	T-*Score* ≤ *–2.5*	T-*Score* ≤ *–2.0*	T-*Score* ≤ *–2.5*	T-*Score* ≤ *–2.0*
Background Prevalence	17%	25%	17%	29%
OST				
>2 (low risk)	7%	11%	7%	15%
–3 to 2 (moderate risk)	21%	30%	23%	37%
< –3 (high risk)	38%	52%	50%	63%

Adapted with permission of the publisher from ref. *21*.

indices produced similar prevalences by risk category. The prevalence of PA lumbar spine *T*-scores for the SCORE cohorts and Netherlands clinic cohort by risk category is shown in Table 8-17. In order to obtain a sensitivity of 90% with the OST questionnaire for the prediction of a *T*-score of –2.5 or poorer at the PA lumbar spine, it was necessary to use a higher cutpoint than that for the femoral neck. The OST nomogram in Fig. 8-1B reflects the higher cutpoints for medium and high risk for Caucasian women in the FIT cohort for a femoral neck *T*-score of –2.5.

The authors of this study *(21)* noted that all four indices performed well. Additionally, the re-evaluation of the original SCORE cohorts using NHANES III femoral neck reference data for the calculation of the *T*-score and SCORE's performance in the Rotterdam and FIT cohorts further validates the utility of the SCORE questionnaire. Nevertheless, the simplicity of the OST index may make it the most suitable for widespread clinical use.

SUMMARY

All of these indices in their final form appear deceptively simple. In virtually all cases, however, hundreds of risk factors were actually evaluated using complex statistical analyses before the final index was developed. The indices rely on easily obtained information and each is dependent on weight and age (with the exception of the weight criterion) to some degree. The OST index in particular is easily reduced to a nomogram as shown in Fig. 8-1. Such a nomogram can be marked by the patient and brought to medical personnel for review. These indices are not intended to replace clinical judgment. They are also not intended to supplant the carefully crafted guidelines from various organizations discussed in Chapter 7. Nevertheless, the use of such indices can aid appropriate patient identification for bone densitometry and promote osteoporosis awareness and education. In using any risk index, however, the choice of the cutpoint is critical, as the cutpoint is specific for a given level of bone density at a particular skeletal site.

The SCORE questionnaire was originally developed to identify with 90% sensitivity those women with a high probability of having a femoral neck *T*-score of –2 or poorer at the femoral neck, using the manufacturer's reference data. A value of 6 on the SCORE index was determined as the appropriate cut point. Lowering the *T*-score to –2.5 and implementing the NHANES III reference data predictably altered the cutpoint to 7 or better in order to achieve 90% sensitivity in the same population as demonstrated by Geusens et al. *(21)*. Similarly the cutpoint for OST was adjusted from the original value

to achieve 90% sensitivity with the lower femoral neck *T*-score, different reference database and Caucasian rather than Asian population. Only the ORAI index was originally designed to identify women with low bone density at either the spine or femoral neck. The other indices primarily focused on the femoral neck. Nevertheless, it would appear that both SCORE and OST may be useful in identifying women with low bone density at the PA lumbar spine.

The use of these indices to create categories of low, moderate, and high risk provides more flexibility in identifying patients who potentially have low bone density and in deciding whom to test. The prevalence of low bone density in even the moderate risk categories is sufficiently great to justify the measurement of bone density.

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9 Diagnosing Osteoporosis

CONTENTS

Many disease processes can affect skeletal mass. As the use of densitometry has become more widespread, an increasing number of diseases[1] have been recognized as causing a decline in bone density. Nevertheless, the use of densitometry to diagnose osteoporosis remains the most common application of densitometry to disease states.

In 1991 *(1)* and again in 1993 *(2)*, Consensus Development Conferences attempted to clarify the clinical definition of osteoporosis. The NOF, the National Institutes of Health (NIH), and the European Foundation for Osteoporosis and Bone Disease sponsored these conferences. The definition of osteoporosis from the 1993 conference reflected only minor modifications from the 1991 conference. At the 1993 Consensus Development Conference *(2)* it was agreed that osteoporosis was:

> *...a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.*

The 1993 definition emphasized that both mass and architecture contributed to bone strength. The presence of a fracture was not required before a diagnosis of osteoporosis was appropriate. Fracture, as an outcome of skeletal fragility, was separated from the disease, osteoporosis. This was similar to the approach taken with hypertension and hypercholesterolemia. Hypertension reflects the measurement of a quantity, the blood pressure, which has reached a level that places the individual at risk for the undesirable outcome of stroke. Hypercholesterolemia refers to the measurement of a quantity, cholesterol, which has reached a level that places the individual at risk for the undesirable outcome of myocardial infarction. In both cases, the occurrence of the outcome is not required before the diagnosis of disease is made. In a strict sense, hypertension and hypercholesterolemia are not diseases in and of themselves. They are risk factors for the undesirable outcomes of stroke and myocardial infarction. They have been *made* dis-

[1] *See* Chapter 6 for discussion of diseases affecting bone density.

eases. Some would call this the "medicalization of risk factors." It is extremely useful, however, because quantifying those risk factors allows the clinician to determine the need for pharmacologic intervention. In the cases of hypercholesterolemia and hypertension, however, the diagnostic threshold, the threshold constituting unacceptable risk, and the intervention threshold tend to be one and the same. The implication of the Consensus Conferences' definition of osteoporosis is also that the thresholds for diagnosis, unacceptable risk, and intervention would be the same. Unfortunately, the Consensus Conferences' definition lacked the specificity necessary to be implemented clinically. The level of low bone mass, architectural deterioration, or increased risk of fracture that was necessary for a diagnosis of osteoporosis was absent from the definition. Even in 1991 and 1993, bone density could be measured in all of its infinite variations. Quantifying architectural deterioration remains a challenge even today. Disagreement still abounds on how best to define fracture risk. So the question remains when using densitometry to diagnosis osteoporosis: "How low is too low?"

GUIDELINES OF THE STUDY GROUP OF THE WHO FOR THE DIAGNOSIS OF OSTEOPOROSIS

In an extensive report published in 1994 *(3)*, a WHO study group composed of 16 internationally known experts in the field of osteoporosis proposed criteria for the diagnosis of osteoporosis based on a specific level of bone density. The focus of the WHO study group was the study of world populations rather than the diagnosis of osteoporosis in individuals. While endorsing the prior 1991 and 1993 Consensus Development Conferences' definition of osteoporosis, the WHO recognized that their proposed criteria did not include any assessment of microarchitectural deterioration. The WHO attempted to reconcile the prevalence of the disease that would be created depending on the level of bone density chosen with published lifetime fracture risk estimates. The study group noted that a cut-off value of 2.5 SD or more below the average value for healthy young women for bone density at the PA spine or proximal femur or for bone mineral content at the midradius would result in 30% of all postmenopausal women being labeled as osteoporotic. Fifty percent or more of these women will have sustained a fracture of the spine, femur, forearm, humerus, or pelvis. The diagnostic categories established by the study group of the WHO are shown in Table 9-1. Although the table refers to values of bone density in terms of the number of SD below the average value for a healthy young adult, the values could also be expressed as the *T*-score or young-adult *z*-score, because these terms are used synonymously. These guidelines for diagnosis were proposed for Caucasian women only. They were not originally intended to be applied to women of other races or to men. This is being done in clinical practice however, in the absence of any other diagnostic guidelines for these groups.

The WHO study group recognized that an individual might be categorized differently depending on the site at which they are assessed. The WHO cautioned that "individuals will be categorized differently according to the site and technique of measurement, and the equipment and the reference population used." They also emphasized that the use of bone density measurements for the diagnosis of osteoporosis should not be confused with the use of the technology for the prediction of fracture risk, cautioning that it was "important to distinguish between the diagnostic and prognostic use of bone mineral density measurement." They correctly pointed out that bone density values were risk

Table 9-1
World Health Organization Criteria for the Diagnosis of Osteoporosis in Caucasian Women

Diagnostic Category	*Diagnostic Thresholds*
Normal	Less than or equal to 1 SD below the young-adult mean
Osteopenia or low bone mass	More than 1 SD below but less than 2.5 SD below the young-adult mean
Osteoporosis	2.5 SD or more below the young-adult mean
Severe or established osteoporosis	2.5 SD or more below the young-adult mean with fragility fracture(s)

factors for fracture as well as being used as criteria for the diagnosis of disease but that these two uses of the values were really quite distinct. The study group noted the analogy to hypertension and hypercholesterolemia described above. Although no other authoritative body has published proposed diagnostic levels of bone density for osteoporosis, a slightly higher cut-off level has been equated with the diagnosis of osteoporosis in the United States. In approving certain medications for the management or treatment of osteoporosis, the US FDA has recommended the use of these drugs in individuals with a bone density that is more than 2 SD below that of the young adult. In essence, this equates a diagnosis of osteoporosis with a bone density that is more than 2 SD below that of the young adult, in contrast to the lower cut-off proposed by the WHO of 2.5 SD or more below that of the young adult.

The WHO Criteria, as they have come to be called, have been widely misquoted. In the original publication of the guidelines, as well as subsequent publications discussing them, confusion has arisen regarding the SD cutpoints for normal and osteoporosis. The cut points shown in Table 9-1 are correct *(4)*. A normal bone density includes a bone density that is 1 SD below the average value for a young adult (*T*-score of –1). Similarly, an osteoporotic bone density is considered present when the bone density is 2.5 SD or more below the average value for a young adult (*T*-score of –2.5 or poorer). In some publications, a bone density *T*-score of –1 or –2.5 has been erroneously considered osteopenic. Osteopenia refers to a bone density *T*-score *between* –1 and –2.5.

THE 1999 WHO AND 2000 IOF RECOMMENDATIONS

The 1994 WHO Criteria did not direct physicians to measure bone density at a specific site for the diagnosis of osteoporosis. An interim report *(5)* from the WHO Task-Force for Osteoporosis was published in 1999 in which it was stated that DXA of the proximal femur was preferred for diagnostic bone density measurements, particularly in elderly individuals. Physicians were not directed in this report, however, to limit the application of the WHO Criteria for diagnosis to BMD measurements made at the proximal femur.

In 2000, the IOF *(6)* recommended that only bone density measured at the total femur be used for the diagnosis of osteoporosis based on the WHO Criteria. In 2002 however, the ISCD *(7)* stated that the WHO Criteria could be utilized with bone density measurements at the PA spine, total femur, femoral neck, or trochanter. They also stated that the WHO Criteria should not be applied to measurements of bone density made at any peripheral site *(8)*. These positions strongly suggest that other skeletal sites, regardless of the technique by which they are measured, cannot be used for the diagnosis of osteoporosis.

The rationale behind these positions is both understandable and unfortunate and in no small way, reflects the confusion predicted by the WHO study group in 1994. Such positions also require that the identification of individuals at risk for fracture remain a separate issue from the diagnosis of osteoporosis because these positions would otherwise deny the established predictive ability of peripheral sites for fracture.

THE CLINICAL DILEMMA

The WHO Criteria were established to enable the WHO to study the prevalence of osteoporosis in large populations. Their intent was not to establish bone density criteria for the diagnosis of osteoporosis in individuals. As noted earlier, the WHO study group chose a cutpoint based on the number of SDs below the young normal mean value that would result in a prevalence of osteoporosis that roughly coincided with published estimates of fracture risk. They chose the statistical device of the SD to avoid using specific levels of bone density or bone content that would be different for each technique and/or device. The bone density data that was considered in the creation of these guidelines came from the PA lumbar spine, proximal femur, and midradius as measured by DPA, DXA and SPA. The WHO did not create only two classifications indicating the presence or absence of disease, but instead created four: normal, osteopenia, osteoporosis, and severe osteoporosis. The classifications actually recognized a gradient of fracture risk although only the last two were designated as representative of disease.

Despite the warnings from the WHO study group that application of the criteria to individuals would result in a different diagnosis depending on the site measured, technique, and reference population used, the clinical community embraced the WHO Criteria for use in individuals. The criteria provided the specificity that was lacking in the Consensus Conferences' definition of osteoporosis, enabling the use of densitometry for diagnosis. In the clinical application of these criteria, however, several issues immediately became apparent.

In addition to the three sites considered by the WHO (PA spine, proximal femur, and midradius), densitometrists can measure bone density at the phalanges, calcaneus, distal radius, distal and proximal forearm (radius and ulna combined), lateral spine, tibia, and total body. In addition to the three techniques that were responsible for the bulk of the bone density data considered by the WHO (SPA, DPA, and DXA), QUS, QCT, RA, and radiogrammetry can be employed to measure a variety of sites. For each site, on each device, from each manufacturer, data from a different population of individuals has been used to create the reference database. The peak bone density and SD are specific for that population, at that skeletal site, as measured by that device. The number of skeletal sites, devices, and techniques used today far exceed the number considered by the WHO. Although the WHO carefully considered both prevalence and fracture risk in choosing a cut point of 2.5 SD below the young-adult mean BMD or BMC, such considerations of prevalence and risk have largely been lost with the proliferation of devices, techniques, and sites. A measured value that is 2.5 SD below the young-adult mean value at some site by some technique may reflect only the variability in the bone density in the population rather than a specific level of fracture risk.

There is no question that low bone density is predictive of fracture. This is essentially true, irrespective of where or how the bone density is measured *(9–12)*. What we call low, however, is based on impressions created from comparisons to the reference database; specifically, the number of SDs below the young adult average value or the

T-score. How likely one is to be considered "low" is clearly dependent on the site, the technique, and the reference database. In the large prospective observational trial called the National Osteoporosis Risk Assessment (NORA), bone density and fracture data was evaluated in 149,524 white women *(12)*. Bone density was measured in the phalanges with DXA (accuDEXA, Schick Technologies, Long Island City, NY), heel with SXA (Osteoanalyzer, Norland, a CooperSurgical Company, Ft. Atkinson, WI), heel with QUS (Sahara, Hologic, Inc., Bedford, MA), and forearm with DXA (pDEXA, Norland, a CooperSurgical Company, Ft. Atkinson, WI). After only 1 year of follow-up, 2259 women reported 2340 new fractures. All of the measurements, regardless of site, device or technique, predicted fracture equally well. Women with *T*-scores of –2.5 or less had a 2.15- to 3.94-fold increase in fracture risk compared with women with normal bone densities. Of note, however, was that the likelihood of having a *T*-score of –2.5 or less was dependent on where and how the bone density was measured. Only 2.9% of the women had a *T*-score of –2.5 or less based on QUS at the heel, compared to 4.1% based on SXA of the heel, 9.4% based on DXA of the forearm and 12% based on DXA of the phalanges. The *T*-scores in NORA were derived from the manufacturers' reference databases.

Differences in the percentages of women diagnosed with osteoporosis depending on the measurement site and technique have been extensively documented. In 1996, Greenspan et al. *(13)* reported that the percentage could vary from 19 to 66% depending on the measurement site, even when all the sites were measured by the same DXA device. Varney et al. *(14)* published similar findings in 1999, with diagnostic percentages for osteoporosis of 4% at the trochanter, 6% at the total hip, 17% at the femoral neck, 34% at Ward's area, 20% at the PA lumbar spine, 12% at the ultradistal radius, and 27% at the 33% radius. This problem was highlighted by Faulkner et al. *(15)*, who plotted the change in *T*-score by age in women for various skeletal sites as measured by different devices, using the manufacturer's reference databases. This graph is shown in Fig. 9-1. As the graph clearly shows, the *T*-scores for an average 60-year-old woman ranged from a *T*-score of –0.7 at the heel by QUS to –2.5 at the spine by QCT. Such a woman could be diagnosed as normal, osteopenic, or osteoporotic depending on where and how the measurement was made.

The effect of different reference databases on diagnosis was discussed in Chapter 5. In addition to issues of reference databases, the multitude of sites and techniques adds considerations of different rates of bone loss and biologically different measures of bone density. The peripheral site data from NORA suggest a threefold difference in the likelihood of being diagnosed "osteoporotic" using WHO Criteria, depending on the site that is measured and the technique that is used. In recognition of this dilemma, investigators have attempted to determine *T*-scores or *T*-score ranges at nonspine, nonproximal femur sites that would identify similar percentages of individuals as osteopenic or osteoporotic based on WHO Criteria at the spine and proximal femur itself.

Peripheral Site T-*Score Equivalents for the Diagnosis of Osteopenia and Osteoporosis*

Attempts to determine site, device, and manufacturer-specific *T*-scores or *T*-score ranges at peripheral sites to identify women who are osteopenic or osteoporotic at the spine or proximal femur generally involve the calculation of sensitivity, specificity and area under the receiver operating characteristic curve (AUC) as discussed in Chapter 3.

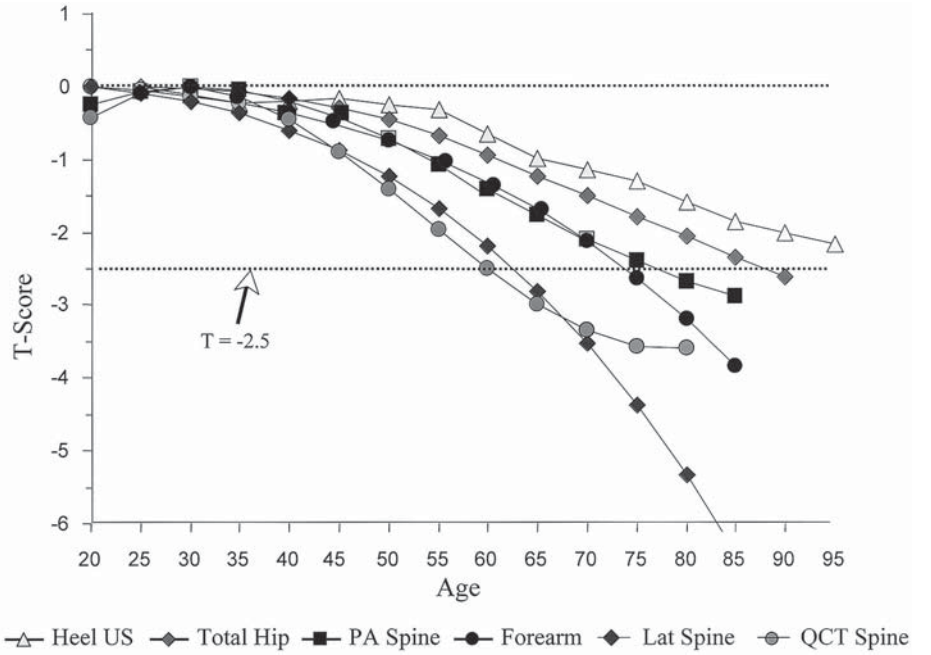

Fig. 9-1. The *T*-score regression on age for women by site and device, from the reference databases of the various manufacturers. The expected *T*-score for an average 60-year-old woman ranges from –0.7 at the heel by QUS to –2.5 at the spine by QCT. Reproduced with permission of the publisher from ref. *15*.

In a study from Pouillès et al. *(16)*, 234 women, ranging in age from 45 to 60 years, underwent DXA studies of the PA lumbar spine and proximal femur (Lunar DPX-IQ) and pDXA forearm studies (Norland pDEXA). The average peak BMD and SD for each skeletal site was determined from studies of a group of young, healthy women, rather than from the manufacturers' reference databases. At the PA lumbar spine, the young-adult mean BMD and SD were 1.180 ±0.12 g/cm^2. The values at the femoral neck were 0.990 ±0.11 g/cm^2. At the forearm, the values for the distal region of interest were 0.347 ±0.05 g/cm^2 and at the proximal region, 0.816 ±0.06 g/cm^2. Using the WHO Criteria of less than or equal to –2.5 SD below the young-adult mean bone density for a diagnosis of osteoporosis, 17.5% of the women were osteoporotic at the spine and femoral neck combined. Fourteen percent were osteoporotic based on measurements at the proximal forearm and only 3.4% were osteoporotic based on measurements at the distal forearm. The authors then determined the number of SD below the young-adult mean BMD or *T*-score that would be required at the distal and proximal forearm for 95% sensitivity in diagnosing osteoporosis or a combination of osteopenia and osteoporosis at the spine and proximal femur. At the distal forearm, a *T*-score of –0.74 was required for 95% sensitivity for the diagnosis of osteoporosis at the central sites. The corresponding specificity was 59.5% and the AUC was 0.80. At the proximal forearm, the *T*-score cutpoint was –0.73 with a corresponding specificity of 46.7% and an AUC of 0.75. To detect both osteopenic and osteoporotic bone densities at the central sites, a *T*-score of +1.06 was required at the distal forearm and +0.53 at the proximal forearm for 95% sensitivity. The corresponding specificities were 23.3% and 23.4%, respectively.

In 115 women (average age 61 years), Varney et al. *(14)* measured bone density at the PA spine and proximal femur with DXA (Hologic QDR 4500A), at the phalanges with DXA (Schick accuDEXA), and at the heel with QUS (Hologic Sahara). Using the WHO Criteria of a *T*-score of –2.5 to diagnose osteoporosis, 28% of the women were osteoporotic based on measurements at the spine, total hip, and femoral neck combined. Forty-nine percent were osteopenic and 23% were normal. The authors determined that a *T*-score of –1.9 or less was necessary to diagnose a similar percentage of women as osteoporotic using QUS of the heel, using the estimated heel BMD in g/cm^2 as provided by the software. A *T*-score of –1.4 or less for phalangeal DXA was required to diagnose a similar percentage of women as osteoporotic. At these *T*-score thresholds, the sensitivity and specificity were 56 and 78% for QUS and 56 and 80% for phalangeal DXA, respectively. The authors also determined the equivalent *T*-score range for osteopenia for the two devices. For QUS of the heel, a similar percentage of women were diagnosed as osteopenic when osteopenia was defined as a *T*-score between –1.9 and +0.3. For DXA of the phalanges, the equivalent osteopenic range was between –1.4 and +0.4. The sensitivities and specificities for the two ranges were 86% sensitivity and 48% specficity and 89% sensitivity and 59% specificty, respectively.

T-score thresholds for phalangeal DXA were also determined by Mulder et al. *(17)*. One hundred twenty-three women (average age 64.6 years) underwent PA spine, proximal femur, and forearm DXA measurements (Hologic QDR-4500) and phalangeal DXA measurements (Schick accuDEXA). In contrast to the definition used by Varney et al. *(14)*, the authors of this study defined osteoporosis as a *T*-score of –2.5 or poorer at the femoral neck only. A *T*-score of –2.5 at the finger had a sensitivity of only 35% for osteoporosis at the femoral neck although the specificity was 88%. Better sensitivity was obtained with a phalangeal *T*-score of –1.0. At this *T*-score, the sensitivity for femoral neck osteoporosis was 85% although specificity fell to 49%. This phalangeal *T*-score threshold also had excellent sensitivity for femoral neck *T*-scores of –2 or poorer. Here the sensitivity was 82% with a specificity of 56%.

Fiter et al. *(18)* suggested that a *T*-score of –1.65 provided a better combination of sensitivity and specificity for phalangeal DXA for the diagnosis of osteoporosis at the PA lumbar spine or femoral neck. In a study of 230 postmenopausal women (average age 58.4 years), BMD was measured at the PA lumbar spine and femoral neck with DXA (Hologic QDR 1000) and at the middle phalanx with DXA (Schick accuDEXA). Applying the WHO Criteria, the prevalence of osteoporosis was 33% based on measurements of the PA lumbar spine and femoral neck. At the middle phalanx, however, the prevalence of osteoporosis using the WHO threshold of 2.5 SD below the young-adult mean value was only 18%. Based on an AUC analysis, the authors determined that the optimum sensitivity and specificity for the middle phalangeal DXA measurement for diagnosing osteoporosis at the PA lumbar spine and femoral neck was a *T*-score of –1.65. At this *T*-score, the sensitivity was 75% with a specificity of 77%. The AUC was 0.822.

Optimum *T*-score thresholds for a different heel QUS device were determined by Damilakis et al. *(19)*. Bone density was measured at the PA lumbar spine, femoral neck, and total hip with DXA (Hologic QDR 1000) and at the heel with QUS (Ubis 3000, DMS, France) in 333 women, 42 to 79 years of age. Using the WHO Criteria of a *T*-score of –2.5 or poorer, osteoporosis was found in 14% of the women at the spine, 13% at the femoral neck, and 10% at the total femur, for an average prevalence of 12%. Using a *T*-score of –2.5 or less based on the QUS measurement at the heel for BUA

resulted in only 1.5% of the women being diagnosed as osteoporotic. The SOS *T*-score of –2.5 resulted in a diagnosis of osteoporosis in only 8.4%. In order to achieve a similar percentage of women diagnosed as osteoporotic as seen at the central sites by DXA, the *T*-score thresholds for BUA and SOS had to be adjusted to –1.8 and –2.2, respectively. The authors also used sensitivity, specificity and AUC analyses to determine the optimum *T*-score thresholds for BUA and SOS for detecting osteoporosis at the femoral neck. In that analysis, the optimum *T*-score for BUA was –1.3. The sensitivity and specificity at this *T*-score was 68% and 83%, respectively with an AUC of 0.82. The optimum *T*-score threshold for SOS was –1.5. The sensitivity and specificity for the *T*-score of –1.5 was 63% and 79%, respectively. The AUC was 0.75. The difference between the AUC for the optimum BUA and SOS *T*-score thresholds was statistically significant, suggesting that BUA was a better predictor of low femoral neck bone density than was SOS.

Fordham et al. *(20)* attempted to define an optimum *T*-score threshold for the heel measured by DXA in 443 women with a mean age of 60 years. Bone density was measured at the PA lumbar spine and femoral neck with DXA (Lunar DPX-L) and with DXA at the heel (Lunar PIXI). Using the manufacturer's reference database, osteoporosis was considered to be present if either the PA lumbar spine or femoral neck *T*-score was –2.5 or less. Based on sensitivity, specificity, and AUC analyses, the optimum heel *T*-score threshold for identifying women who were osteoporotic at the spine or femoral neck was –1.3 or poorer for the entire group. At this *T*-score, the sensitivity was 69.6% and the specificity was 82.6%. The AUC was 0.836. The authors also noted that the sensitivity and specificity varied by age. In women age 50 to 64, a heel DXA *T*-score of –1.3 or poorer had a sensitivity and specificity of 68% and 85%, respectively, with a false-negative rate of 13%. In women age 65 and older, however, the same *T*-score threshold resulted in a sensitivity and specificity of 71% and 68%, respectively, with a false-negative rate of 40%.

Pacheco et al. *(21)* also attempted to determine the optimum *T*-score threshold for BMD measured at the calcaneus by DXA for the diagnosis of osteoporosis at the PA lumbar spine, total femur, or femoral neck. Bone density was measured in 204 Caucasian women age 20 and older at the heel (Lunar PIXI) and at the PA lumbar spine and proximal femur (Lunar DPX-L and Hologic QDR 4500). Osteoporosis was defined using the WHO Criteria for the diagnosis of osteoporosis and femoral neck *T*-scores were calculated using the NHANES III reference database. At a *T*-score of –2.5 at the calcaneus, the sensitivity for osteoporosis at any of the three central sites was only 20.3% although the specificity was 97.1%. As in the study from Fordham et al. *(20)*, the optimum *T*-score threshold at the calcaneus for the diagnosis of central osteoporosis based on a ROC analysis appeared to be a *T*-score of –1.3, which the authors noted coincided with a calcaneal BMD of 0.390 g/cm^2 on the Lunar PIXI.

Using a different heel DXA device (Norland Apollo), Sweeney et al. *(22)* measured bone density in the calcaneus in 119 women with an average age of 51.6 years. Bone density was also measured at the PA lumbar spine and femoral neck with DXA (Norland Eclipse). Using the established WHO Criteria for the diagnosis of osteopenia and osteoporosis at the spine, 30% of the women were osteopenic and 17% were osteoporotic. At the femoral neck, 41% were osteopenic and 21% were osteoporotic. At the heel, 32% were osteopenic and only 2% were osteoporotic. The authors attempted to identify the heel DXA *T*-score threshold that would identify women with spine or femoral neck

Table 9-2
Equivalent *T*-Scores and *T*-Score Ranges at Peripheral Sites by Specific Devices for Osteopenia and Osteoporosis at the PA Lumbar Spine and/or Proximal Femur

		Osteopenia		*Osteoporosis*	
Device	*Site/ROI*	*Equal Prevalence*	*Optimum Sensitivity*	*Equal Prevalence*	*Optimum Sensitivity*
pDEXA[a]	Distal		≤ +1.06		≤ –0.74
	Proximal		≤ +0.53		≤ –0.73
accuDEXA	Phalanges	–1.4 to +0.4[b]		≤ –1.4[b]	≤ -1.0[c]/ ≤ –1.65[d]
Sahara[b]	Heel BMD	–1.9 to +0.3		≤ –1.9	
UBIS[e]	Heel BUA			≤ –1.8	≤ –1.3
	Heel SOS			≤ –2.2	≤ –1.5
PIXI[f,g]	Heel				≤ –1.3
Apollo[h]	Heel		≤ 0.0*		≤ 0.0*

Note. The reader is referred to the text for specific definitions of optimum sensitivity and osteoporosis for the various studies as well as the methodology used for the diagnosis of osteoporosis.

*Optimum sensitivity for detecting osteopenia and osteoporosis combined.

[a] From ref. *16*.
[b] From ref. *14*.
[c] From ref. *17*.
[d] From ref. *18*.
[e] From ref. *19*.
[f] From ref. *20*.
[g] From ref. *21*.
[h] From ref. *22*.

T-scores of –1 or less. Using a heel *T*-score of –1 or less resulted in a sensitivity of 58% and specificity of 88% for identifying women with a low bone density at the spine. The same heel *T*-score threshold resulted in a sensitivity of 51% and specificity of 93% for identifying women with a low bone density at the femoral neck. The authors were particularly interested in maximizing sensitivity in women age 40 to 65. They noted that a heel DXA *T*-score of 0.0 or less resulted in 100% sensitivity for low bone density at the femoral neck and 85% sensitivity for low bone density at the spine in this age group.

These observations have prompted organizations like the IOF and ISCD to recommend against the use of peripheral sites for the diagnosis of osteoporosis in general and specifically when the WHO Criteria are used. This is despite the recognized fact that bone density at peripheral sites is predictive of fracture and that considerations of bone density at the midradius were included in the development of the WHO Criteria. It would also seem to be contradictory to the intent of the 1991 and 1993 Consensus Conferences' *(1,2)* definition of osteoporosis in which osteoporosis was defined as a disease of "low bone mass...characterized by an increase in bone fragility and susceptibility to fracture." If the measurement of bone density at peripheral sites is predictive of fracture and therefore indicative of bone fragility and increased susceptibility to fracture, bone density at peripheral sites should be used to diagnose osteoporosis. Clearly, however, the application of the specific *T*-score thresholds originally proposed by the WHO for the diagnosis of osteopenia and osteoporosis to the results from the myriad of sites, devices, and techniques available today is not appropriate.

Changing the Definition of Osteoporosis

There has been considerable debate as to whether *T*-scores and the WHO Criteria should be retained or whether entirely new approaches to quantitatively defining osteoporosis should be pursued. The 1991 and 1993 Consensus Conferences' *(1,2)* definition of osteoporosis and even the 2000 Consensus Conference *(23)* definition[2] ultimately define osteoporosis as a state of increased risk for fracture. It would be preferable for the diagnostic threshold for osteoporosis to coincide with the level of bone density that constitutes an unacceptable level of fracture risk, no matter what skeletal site or technique might be used for the measurement.

Lu et al. *(24)* compared the diagnostic agreement for osteoporosis between two normal reference population approaches and a risk-based approach in 7671 women from the Study of Osteoporotic Fractures (SOF). Bone density was measured at eight different regions of interest using a combination of DXA and SPA: the PA lumbar spine, total femur, femoral neck, trochanter, Wards' area, calcaneus, distal radius, and proximal radius. The first reference population approach utilized a *T*-score of –2.5 based on the manufacturers' reference databases for the diagnosis of osteoporosis. The second reference population approach used a SD score of –1, when the reference BMD was the mean BMD for 65-year-old women from the SOF population. The risk-based approach defined osteoporosis as a spine and/or hip fracture risk greater than 14.6% based on age and BMD. The best diagnostic agreement for osteoporosis among the eight different regions of interest was 69% using the risk-based approach. The poorest agreement of 25% was seen when young-normal reference data was used. Black *(25)*, writing for a joint committee of the NOF and ISCD, proposed the development of risk-based *T*-score equivalents, based on the 5-year hip fracture risk in women aged 70–74 with femoral neck *T*-scores of less than –2.5. Blake and Fogelman *(26)* also suggested a hip fracture risk-based threshold approach. Conceptually, a risk-based definition of osteoporosis is far more clinically relevant than the population-based *T*-scores approach in use now. The development of such a definition is far from clear-cut, however. Decisions must be made as to the type of risk suitable to define the disease. Should it be global or all fracture risk? Or should it be only hip fracture risk or spine fracture risk? Should the expression of risk be the current fracture risk, the 5- or 10-year fracture risk or lifetime fracture risk? And finally, what level of risk is unacceptable? All of these issues remain to be decided. At present, the recommendations to limit the use of the WHO Criteria for diagnosis to the PA lumbar spine, total femur, femoral neck, and trochanter are reasonable. Nevertheless, a move to a risk-based definition of osteoporosis would serve the needs of the densitometrist and patient far better than a population-based approach and would enhance the utility of all measurement sites and devices. At present, however, none of the proposed risk-based approaches has supplanted the WHO Criteria in clinical practice.

DIAGNOSING OSTEOPOROSIS IN MEN

The issues surrounding the appropriate criteria for the diagnosis of osteoporosis in men are not substantially different than those for women. The WHO Criteria were

[2]At this NIH Consensus Conference osteoporosis was defined as a "skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture."

Table 9-3
Percentage of Men Over the Age of 50 at or Below the Indicated *T*-Score Using Male Reference Data

T-*Score*	*Femoral Neck*	*Total Femur*	*DXA Spine*	*Total Forearm*	*Heel Ultrasound*	*QCT Spine*
–3.5	1%	0%	0%	1%	0%	8%
–3.0	4%	1%	1%	3%	2%	16%
–2.5	9%	4%	4%	8%	5%	28%
–2.0	20%	9%	11%	16%	13%	45%
–1.5	36%	20%	23%	29%	26%	62%
–1.0	55%	36%	40%	46%	44%	77%

Adapted from ref. *27* with permission of the publisher.

derived from data on women and were intended to be applied only to women. Once again, in the absence of other criteria, they have been applied to bone density measurements in men as well. There is some controversy as to whether a *T*-score of –2.5, at any skeletal site by any technique, is appropriate for a diagnosis of osteoporosis in men. Additionally, whether the *T*-score that is used for a man should be calculated by using a female reference database rather than a male reference database has also been raised. Ultimately, the question once again becomes "What does the diagnosis of osteoporosis mean?" If it is meant to imply a certain level of fracture risk that is imparted by the bone density alone, then a sex-specific *T*-score calculation may not be necessary or appropriate. The choice of the *T*-score threshold for the diagnosis of osteoporosis in men would depend on the magnitude of risk that is deemed synonymous with disease.

These issues were addressed by Faulkner and Orwoll *(27)* in the *Journal of Clinical Densitometry* in 2002. Using the manufacturers' reference databases for several skeletal sites and techniques, US population estimates for the year 2000 and the WHO *T*-score cutpoints for women, they calculated the prevalence of osteoporosis in men age 50 and over. Calculations were done using both male and female reference databases. The results are shown in Tables 9-3 and 9-4. Using the same approach as the WHO, they then attempted to determine the *T*-score at each site/device that matched the prevalence of osteoporosis with a reported lifetime fracture risk estimate of 13%. As shown in Table 9-5, regardless of whether male or female reference databases were used, the *T*-score cutpoint at every site with the exception of the spine by QCT, was better than –2.5. If a *T*-score cutpoint of –2.5 was used, regardless of whether it was based on male or female reference values, the lifetime fracture risks would be underestimated. In contrast, a *T*-score of –2.5 at the spine by QCT overestimated the lifetime fracture risk.

In this same study, Faulkner and Orwoll examined the expected decline in *T*-scores in men by site and technique with age. This relationship is shown in Fig. 9-2. This is similar to previously published findings in women *(15)*. In Fig. 9-2, the decline in *T*-scores at the spine by QCT was the largest, falling below a *T*-score threshold of –2.0 by age 75. *T*-scores at other skeletal sites did not fall below –2 until the ninth decade. From the graph, it can be seen that *T*-scores for a man age 65 could range from –0.6 to –1.9, depending on the site and technique used for the measurement.

Table 9-4
Percentage of Men Over the Age of 50 At or Below the Indicated *T*-Score Using Female Reference Data

T-*Score*	*Femoral Neck*	*Total Femur*	*DXA Spine*	*Total Forearm*	*Heel Ultrasound*	*QCT Spine*
–3.5	0%	0%	0%	0%	0%	12%
–3.0	1%	0%	0%	0%	1%	22%
–2.5	6%	1%	2%	0%	3%	37%
–2.0	9%	3%	5%	0%	8%	54%
–1.5	19%	7%	12%	1%	18%	71%
–1.0	34%	16%	24%	2%	34%	84%

Adapted from ref. *27* with permission of the publisher.

Table 9-5
***T*-Scores Thresholds at Different Skeletal Sites for Men Older than Age 50 that Best Correspond to Lifetime Risk for Osteoporotic Fracture**

T-*Score*	*Femoral Neck*	*Total Femur*	*DXA Spine*	*Total Forearm*	*Heel Ultrasound*	*QCT Spine*
Male Norms	–2.3	–1.8	–1.9	–2.1	–2.0	–3.1
Female Norms	–1.7	–1.2	–1.5	–0.5	–1.7	–3.4

Adapted from ref. *27* with permission of the publisher.

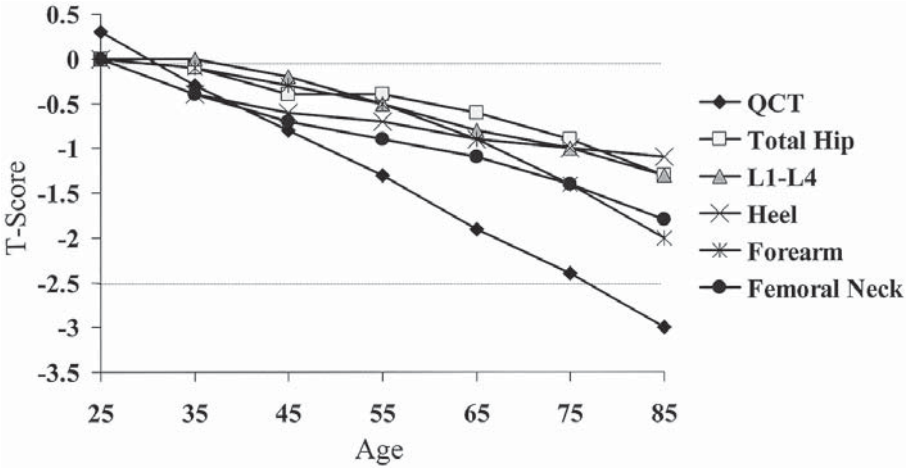

Fig. 9-2. The *T*-score regression on age for men by site and device, from the reference databases of the various manufacturers. The expected T-score for an average 65-year-old man ranges from –0.6 at the total femur by DXA to –1.9 at the spine by QCT. Reproduced with permission of the publisher from ref. *27*.

In 2002, ISCD *(28)* stated that osteoporosis in men should be defined as a *T*-score of –2.5 or poorer below the young normal mean for *men*. This is in contrast to the recommendation of the IOF *(6)* in 2000 in which a *T*-score of –2.5 based on a *female* reference database was recommended as the diagnostic criteria for osteoporosis in men. An analysis of data from the European Prospective Osteoporosis Study (EPOS) study *(29)* suggests that the IOF recommendation may actually be more appropriate when the primary issue is the implication for fracture risk from any given level of bone density. Using BMD and fracture data from 3461 men and women, the EPOS investigators determined that for any given age and spine bone density, the risk of spine fracture was similar in men and women. Incident spine fractures were more common in women than in men simply because, for any given age, bone density in women is lower than in men. Similarly, De Laet et al. *(30)*, using mathematical models and data obtained from the Rotterdam study, suggested that hip fracture risk in men is lower than that in women overall, but appeared to be similar at the same level of femoral neck BMD. They noted that to capture the same proportion of hip fractures in men as in women, the BMD level must be higher than that for women and that the use of gender-specific *T*-scores would accomplish this. But because absolute risk for fracture is more relevant for intervention decisions, they proposed that the same levels of BMD be used for intervention decisions in men and women. As a consequence, if a given level of bone density in a woman would prompt an intervention to prevent fracture, that same level of bone density should prompt intervention in a man, regardless of the sex-specific *T*-scores. In an editorial in 2001 in the *Journal of Bone and Mineral Research*, Melton et al. *(31)* agreed that the absolute risk of fracture in men and women with the same BMD was similar although they also noted that relatively few men will reach the lowest levels of bone density that are associated with the greatest fracture risks in women. The authors observed that men are generally older than women at any given level of low bone density. Nevertheless, they concluded that it was not yet clear whether a female standard for the diagnosis of osteoporosis or risk assessment could reasonably be applied to men.

As noted earlier, these issues regarding the appropriate use of bone density to diagnosis osteoporosis in men are similar to those for women. Conceptually, the 1991, 1993, and 2000 Consensus Conferences' definitions remain clinically relevant, linking the diagnosis of osteoporosis to an increased risk of fracture. How best to express this quantitatively remains at issue. In some cases however, the *T*-score reflects more of the variability in bone density at a specific site when measured by a specific technique in a specific population than it reflects fracture risk. As a result, the diagnosis of osteoporosis and the prediction of fracture risk using bone densitometry must currently remain separate processes.

ADDITIONAL CONSIDERATIONS IN SITE SELECTION FOR DIAGNOSIS

As noted in Chapter 2, the PA lumbar spine is commonly affected by dystrophic calcification in older adults, increasing the measured BMD and *T*-score. In particular, after the age of 60, the percentage of women having osteophytes in the lumbar spine is estimated at 61% *(32)*. Calcification of the aorta, facet sclerosis, and intervertebral disk calcification can all have a significant effect on bone density measured at the PA lumbar spine *(33–38)*. As a consequence, for diagnosis, the PA lumbar spine is less useful in individuals age 60 and over. This age cutoff is somewhat arbitrary but generally appro-

priate. In individuals under age 60, the PA lumbar spine is an entirely appropriate skeletal site for the diagnosis of osteoporosis with bone densitometry.

In the proximal femur, the total hip, femoral neck, and trochanter are all useful sites. The proximal femur is less affected by dystrophic changes than the PA spine, but it is not entirely free of such affects. Although the hip joint itself is not measured in a DXA proximal femur study, severe osteoarthritis of the hip joint can affect the bone density of the proximal femur *(39,40)*. Therefore, if severe unilateral osteoarthritis is known or suspected, the proximal femur on the unaffected side should be measured. If this is not possible, the trochanteric region becomes the preferable region of interest in the proximal femur as the effects of osteoarthritis of the hip joint are most notable in the femoral neck and Ward's area, both of which are included in the total hip region of interest.

If either hip has been fractured or undergone surgical instrumentation, it is not suitable for diagnostic assessment by densitometry. An additional consideration is the presence of scoliosis. In a study from Hans et al. *(41)*, femoral neck bone density averaged 4.2% lower on the side of the spine convexity in a small study of 15 women with scoliosis. Consequently, the measurement of the proximal femur on the side of the convexity in scoliotic patients may provide the "worst case" bone density between the two femurs.

New developments in densitometry applications have made possible the rapid study of both proximal femurs. Although this may be desirable in specific circumstances, the question has arisen as to whether study of both proximal femurs should always be done when a proximal femur bone density measurement is performed to diagnose osteoporosis. Bone density in the various regions of the right and left femurs in individuals has consistently been found to be highly correlated when measured by DXA *(42–45)*. Similarly, the average absolute differences in bone density in g/cm^2 between the right and left proximal femoral regions have been small and generally not statistically significantly different. Based on comparisons of both femurs in 198 women with an average age of 32.6 years, Bonnick et al. *(42)* found that the average difference was 0.7%, 0.2%, and 1.9% for the femoral neck, Ward's area, and trochanter, respectively. Only the difference observed at the trochanter was statistically significant, but all the differences were well within the precision error for the region of interest. Rao et al. *(43)* evaluated 131 women with an average age of 61 years. No significant difference was found between the femoral neck BMD in the right and left femur in this study as well, with a mean difference of about 1%. The differences in BMD between the right and left femur at Ward's area and the trochanter were statistically significant but small, averaging 2 to 2.5%. In a very large study of 2372 women with an average age of 56.6 years, Petley et al. *(44)* did find a statistically significant difference between the right and left proximal femurs in the femoral neck, but again, the difference was quite small and not clinically relevant. The mean BMD of the right femoral neck in this study was 0.840 g/cm^2, whereas the mean BMD in the left femoral neck was 0.837 g/cm^2. The mean difference was 0.003 g/cm^2. The maximum difference observed in this study was 0.249 g/cm^2. Based on these findings, all of these authors concluded that there was little justification for the *routine* measurement of both proximal femurs in clinical practice. In a study of 61 women from Mazess et al. *(45)*, however, it was noted that 32% of the women had differences between the right and left femoral necks of 0.5 SD and that 5% of the women had differences that exceeded 1 SD. In those 5% of women, a difference of 1 SD, or an entire *T*-score unit, could clearly affect not only the assignment of diagnostic category but treatment decisions as well. Nevertheless, it is difficult to justify routine measurement of both femurs

in all women on this basis. It is possible that a difference of even 0.5 SD could alter the assignment of diagnostic category when the WHO Criteria are employed. If such an alteration will reasonably affect decisions to intervene, then the measurement of both femurs may be justified.

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10 Predicting Fracture Risk

CONTENTS

The risk of any outcome can be expressed in a variety of different ways, as was noted in Chapter 3. The more commonly used measures of risk are prevalence, incidence, absolute and relative risk, and odds ratios. All of these measures can be employed in the specific context of the assessment of fracture risk. In densitometry, other measures of risk are employed as well such as the fracture threshold, lifetime risk, and remaining lifetime fracture probability. These are quantitative measures of risk. Qualitative fracture risk assessments may also be useful. Although there is no question that a measurement of bone density can predict fracture risk, none of the measures used clinically to express fracture risk is ideal. A physician should ultimately use whichever expression of risk best conveys the implications for fracture based on the patient's BMD.

THE PREVALENCE OF FRACTURE AT DIFFERENT LEVELS OF BMD

Prevalence describes the ratio of the number of individuals with a disease at a given point in time in a particular population to the number of individuals who are at risk for the disease. Prevalence can be used to answer the question of how common a disease is in a population that is at risk for the disease. In the context of this volume, prevalence is used to answer the question, "How common is fracture at a given level of BMD?" This question was addressed by Mazess *(1)* in a study of 590 Caucasian women ages 50 to 89 years who underwent PA spine and proximal femur bone density studies with DPA. Approximately 25% of these women had spine or hip fractures. The prevalence of either spine or hip fracture or both at varying levels of BMD at L2–L4 or the femoral neck is shown in Tables 10-1 and 10-2. This type of risk assessment can be useful to a physician who is trying to determine the clinical significance of any given level of BMD in his or her patient, even if the patient has not yet fractured. Because the data shown in Tables 10-1 and 10-2 were based on measurements made with DPA, the ranges for spine BMD and for femoral neck BMD (depending on the type of DXA device) should be adjusted

Table 10-1
The Prevalence of Spine or Hip Fracture or Both at Varying Levels of Spine BMD Measured with DPA

L2-L4 BMD (g/cm²)	*N*	*Spine Fracture %*	*Hip Fracture %*	*Either/Both %*
> 1.10	100	6.0	3.0	7.0
1.00–1.09	111	9.9	5.4	13.5
0.90–0.99	159	17.0	6.3	22.0
0.80–0.89	134	23.1	9.7	29.9
0.70–0.79	49	40.8	12.2	44.8
0.60–0.69	20	50.0	15.0	60.0

Adapted with permission from ref. *1*.

Table 10-2
Prevalence of Spine or Hip Fracture or Both at Varying Levels of Femoral Neck BMD Measured with DPA

Femoral Neck BMD (g/cm²)	*N*	*Spine Fracture %*	*Hip Fracture %*	*Either/Both %*
> 0.80	133	3.8	0.0	3.8
0.70–0.79	178	10.6	3.4	12.9
0.60–0.69	164	21.3	10.4	31.1
0.50–0.59	89	32.6	29.2	51.7
0.40–0.49	26	38.5	46.2	76.9

Adapted with permission from ref. *1*.

downward in order to compare DXA measurements to this data. The equations for converting DPA data to DXA data are given in Chapter 5 and again in Appendix II.

FRACTURE RISK PREDICTION

Site-Specific and Global Fracture Risk Prediction

Fracture risk predictions fall into two general categories. The prediction may be a site-specific fracture risk prediction or it may be a global fracture risk prediction. A site-specific fracture risk prediction is the prediction of the risk of fracture at a specific site. For example, the prediction of spine fracture risk is a type of site-specific fracture risk prediction. Similarly, the prediction of hip fracture risk is a type of site-specific fracture risk prediction. Site-specific fracture risk prediction does *not* necessarily mean that the measurement is being performed at a specific site. A global fracture risk prediction is the prediction of the risk of having any and all types of osteoporotic fractures. Again, the terminology does not imply the measurement of bone density at a particular site.

Relative Risk Fracture Data

The studies that conclusively established the predictive capabilities of bone mass measurements for fracture risk generally reported the data as the increase in relative risk

per SD decline in bone density. In Chapter 3 it was noted that relative risk is the best indicator of the strength of the relationship between a risk factor (in this case, low bone mass or density) and an outcome (fracture). It is understandable, therefore, that much of the information in the medical literature about the prediction of fracture risk from bone mass measurements is presented in the form of relative risk values. Relative risk is calculated from absolute risk data that is collected during prospective fracture trials. The ratio of the absolute risk for fracture between two groups constitutes the *relative* risk for fracture between the two groups. A relative risk of 1 implies that there is no difference in risk between the groups. It is possible that both groups have an increased absolute risk, but the risk of one group is no greater than the risk of the other group. Relative risk data thus obscures the actual magnitude of the absolute risk for either group. For example, if the absolute risk for fracture in group A is 50% compared to the absolute risk for fracture of 25% in group B, the relative risk of group A compared to group B is 2 (50% ÷ 25% = 2). This would be interpreted to mean that the risk in group A is twofold greater than that of group B. The relative risk would also be 2, however, if the absolute risk in group A was 2% and the absolute risk in group B was 1% (2% ÷ 1% = 2). The interpretation is unchanged. Group A has a twofold greater risk of fracture than group B.

Relative risk data can be used to establish which skeletal sites have the best predictive power for certain types of fracture risk predictions. The site that has the greatest increase in relative risk for fracture per SD decline in bone mass or density will be the skeletal site that has the best predictive power for that type of fracture risk prediction.

Global Fracture Relative Risk Data

The sites on the forearm have been used in several classic fracture trials to assess global fracture risk as well as site-specific assessments of spine, hip, or forearm fracture risk. Hui et al. *(2)* evaluated radial bone mass in 386 community-based women and 135 retirement home-based women using SPA (Norland-Cameron). Bone mass was measured at the midradius at baseline and the women were subsequently followed for the development of nonspine fractures for 1 to 15 years. During that time, 89 women had 138 nonspine fractures of various types. The statistical analysis revealed that for each SD decline in bone mass at the midradius, the relative risk for any type of nonspine fracture was 2.2 in the community-based women and 1.5 in the retirement-home women.

Gardsell et al. *(3)* also used the radius to evaluate global fracture risk in a study of 332 women over an average period of 14.6 years. The distal and midradius were measured using SPA. During the follow-up period, 100 women had one or more fragility fractures. The relative risk for fracture measured at the distal radius was 2.6 and at the midradius, 3.2.

The lumbar spine, femoral neck, and trochanter are also useful for global fracture risk prediction. In a study of 304 women, aged 30 to 94 years, who were followed for a median of 8.3 years, 93 women experienced 163 new fractures *(4)*. Bone mass was measured at baseline at five sites that included the PA lumbar spine, femoral neck, and trochanter by DPA and the distal and midradius by SPA. The relative risk for all fractures measured at the spine, femoral neck, and trochanter was 1.5, 1.6, and 1.5, respectively, when only those fractures that resulted from mild to moderate trauma were considered. The midradius was also predictive of global fracture risk for fractures resulting from mild to moderate trauma with a relative risk of 1.5.

Table 10-3
Age-Adjusted Increase in Relative Risk for Fracture for Global Fracture Risk Prediction Per SD Decrease in Bone Mass Measured at Various Skeletal Sites

Site	*Global Fracture RR*
AP lumbar spine	1.5,[b] 1.35[b]
Total femur	1.40[b]
Femoral neck	1.6,[b] 1.41[b]
Trochanter	1.5,[b] 1.38[b]
Midradius	1.5,[a] 1.32,[b] 3.2[a]
Distal radius	1.42,[b] 2.6[a]
Calcaneus	1.51[b]

[a] Per SD decrease in BMC
[b] Per SD decrease in BMD
From refs. *2–5*.

Other studies have quantified the increase in relative risk per SD decline in bone mass or density measured at different skeletal sites for the prediction of global fracture risk. In the Study of Osteoporotic Fractures *(5)*, a 1 SD decrease in BMC at the midradius resulted in an age-adjusted increase in relative risk of 1.3 and at the distal radius, 1.4. Measurements of BMD at the lumbar spine and femoral neck were also predictive of global fracture risk with comparable relative risk values of 1.35 and 1.41, respectively. The calcaneus was equally predictive of global fracture risk with a relative risk of 1.51 for each SD decline in bone density. In another study *(6)* of 1098 women followed for an average of 4.5 years, a decrease of 2 SD in BMC at the proximal radius resulted in an increase in relative risk of 2.8 for any type of nonspine fracture. The relative risk values for global fracture risk prediction are summarized in Table 10-3.

Site-Specific Spine Fracture Relative Risk Data

Several sites are useful for the site-specific prediction of spine fracture risk. In the study by Melton et al. *(4)* the increase in relative risk for spine fracture resulting from mild to moderate trauma for each SD decline in BMD or BMC was statistically significantly different from 1 at the spine itself, but also at the femoral neck, trochanter, and midradius. The relative risk values were 2.2, 2, 1.7, and 2.5, respectively. The greatest increase in relative risk of 2.5 was actually seen at the midradius, suggesting that this was the preferred site to measure for spine fracture risk prediction. However, a statistical analysis suggested that each of these four sites actually performed equally well.

Data presented in abstract form at the 19th annual meeting of the American Society for Bone and Mineral Research suggests that the phalanges and metacarpals as measured by radiographic absorptiometry can be useful predictors of spine fracture risk. In a study *(7)* of 251 women whose average age at baseline was 74 years, 18 spine fractures occurred during an average follow-up of 2.7 years. Based on RA measurements of the phalanges, the increase in relative risk per SD decline in BMD was 3.4. In another study *(8)* of 509 postmenopausal women with an average age of 74 at baseline, 37 fracture spine fracture cases were observed during an average follow-up of 2.7 years. The relative risk for spine fracture from RA of the metacarpals in this study was 1.9.

Site-Specific Hip Fracture Relative Risk Data

Different skeletal sites for site-specific hip fracture risk prediction have been evaluated in several studies. In the study from Melton et al. *(4)* noted above, 10 fractures of the proximal femur from mild to moderate trauma occurred during the study. Statistically significant increases in relative risk for hip fracture could be determined for BMD measured at the femoral neck, trochanter, and distal radius. The increases in relative risk for hip fracture from BMD measured at the spine or midradius did not reach statistical significance. In what is considered a sentinel study for determining hip fracture risk, Cummings et al. *(9)* evaluated 8134 women aged 65 and over. During an average follow-up period of 1.8 years, 65 hip fractures occurred (33 femoral neck, 32 intertrochanteric). BMD was measured at the lumbar spine and proximal femur with DXA (Hologic QDR-1000) and at the distal and midradius and os calcis with SPA (OsteoAnalyzer). Within the proximal femur, the total femur, femoral neck, trochanter, intertrochanter, and Ward's triangle were measured. All of these sites had statistically significant increases in relative risk for hip fracture for each SD decline in BMD. In this study, the sites in the proximal femur were clearly stronger predictors of hip fracture than the PA lumbar spine or radial sites. The os calcis[1] was also an excellent predictor of hip fracture risk being out-performed by the proximal femur regions of interest by the narrowest of margins. The age-adjusted increases in relative risk for hip fracture in the total femur, femoral neck, Ward's, trochanteric, and intertrochanteric regions were all very similar. They were 2.7, 2.6, 2.8, 2.7, and 2.5, respectively. The increase in relative risk at the os calcis was 2. Both the lumbar spine and distal radius had a relative risk of 1.6 per SD decline in BMD, whereas the midradius had a relative risk of 1.5 per SD decline.

In the previously described study from Hui et al. *(2)*, 30 hip fractures occurred in the retirement-community women. Based on measurements of the midradius with SPA in this group, the relative risk for hip fracture per SD decline in bone mass was 1.9.

Phalangeal bone density also appears to be useful as a predictor of hip fracture risk. During NHANES I between 1971 and 1975, 3481 subjects underwent radiographic photodensitometry studies of the hand *(10)*. At baseline, the ages of the subjects ranged from 45 to 74. During the follow-up period through 1987, 72 hip fractures occurred. The relative risk for hip fracture as calculated from radiographic photodensitometry measurements of the middle phalanx of the small finger was 1.57 for all subjects. When the analysis was restricted to Caucasian women, the relative risk was 1.56. The radiographic photodensitometry films were re-analyzed using the more modern technique of RA. When the films were analyzed in this manner, the relative risk for each SD decline in RA bone density was 1.81 for all subjects and 1.79 for Caucasian women only. Table 10-4 summarizes the increases in relative risk per SD decline in bone mass for site-specific fracture risk prediction when the bone mass is measured at different skeletal sites.

Applying Relative Risk Data in Clinical Practice

The values for relative risk discussed above were derived from specific study populations. The characteristics of each study population such as the mean age and the mean and SD for BMD make the increase in relative risk per SD decline in BMD unique for that population. Applying such relative risk data to an individual patient and utilizing the SD for the reference population supplied by the densitometry manufacturer to

[1] Os calcis and calcaneus are used interchangeably.

Table 10-4
Increase in Age-Adjusted Relative Risk for Spine or Hip Fracture Per SD Decrease in Bone Mass as Measured at Various Skeletal Sites

Site	*Spine Fracture RR*	*Hip Fracture RR*
AP lumbar spine	2.2[b]	1.6[b]
Total femur		2.7[b]
Femoral neck	2.0[b]	2.6,[b] 2.8[b]
Ward's		2.8[b]
Trochanter	1.7[b]	2.7,[b] 2.4[b]
Distal radius		1.6,[b] 3.1[b]
Midradius	2.5[a]	1.5,[b] 1.9[a]
Calcaneus		2.0[b]
Phalanges	3.4[c]	1.8[c]
Metacarpals	1.9[c]	

[a] Per SD decrease in BMC
[b] Per SD decrease in BMD
[c] Per SD decrease in RA units
From refs. *2,4,7–10.*

calculate the relative risk for the patient in question is clearly an extrapolation of the data that may not be appropriate. In addition, relative risk values are generally calculated as age-adjusted values. Age adjustment means that the effect of age has been accounted for or eliminated statistically such that only the effect of bone density on risk remains. These considerations profoundly affect the densitometrist's ability to use relative risk data in clinical practice.

The calculation of a patient's relative risk for various types of fracture using standard scores on the densitometry printout and published relative risk data is not difficult. The relationships between absolute risk, relative risk, and the magnitude of the SD decline in bone density that were discussed in Chapter 3 are the key to this calculation and its interpretation. For example, in the spine bone density study shown in Fig. 10-1, the L1–L4 BMD is 0.814 g/cm^2. The *T*-score of –2.12 indicates that the L1–L4 BMD is 2.12 SD below the average peak BMD of the young adult. The *z*-score of –0.08 indicates that the L1–L4 BMD is 0.08 SD below the average BMD predicted for this woman's age. How does a physician calculate the global fracture relative risk or site-specific spine fracture relative risk? The age-adjusted increases in relative risk for fracture from Melton et al. *(4)* can be used to calculate these values. Melton et al. found that for each SD decline in bone density when measured at the spine, the increase in relative risk for *any* type of low to moderate trauma fracture was 1.5. Therefore, the relative risk for global fracture in this patient compared to the individual who still has an average peak bone density, based on this measurement of bone density at the lumbar spine, is $1.5^{2.12}$ or 2.4. This is the increase in relative risk per SD decline in bone density raised to the power of the *T*-score. Compared to the individual who has a spine bone density that would be predicted for the patient's age, her global fracture relative risk would be $1.5^{0.08}$ or 1.03. This is the increase in relative risk raised to the power of the *z*-score. *Strictly speaking, neither of these calculations is correct, although it is the best that can be done with the data at hand.*

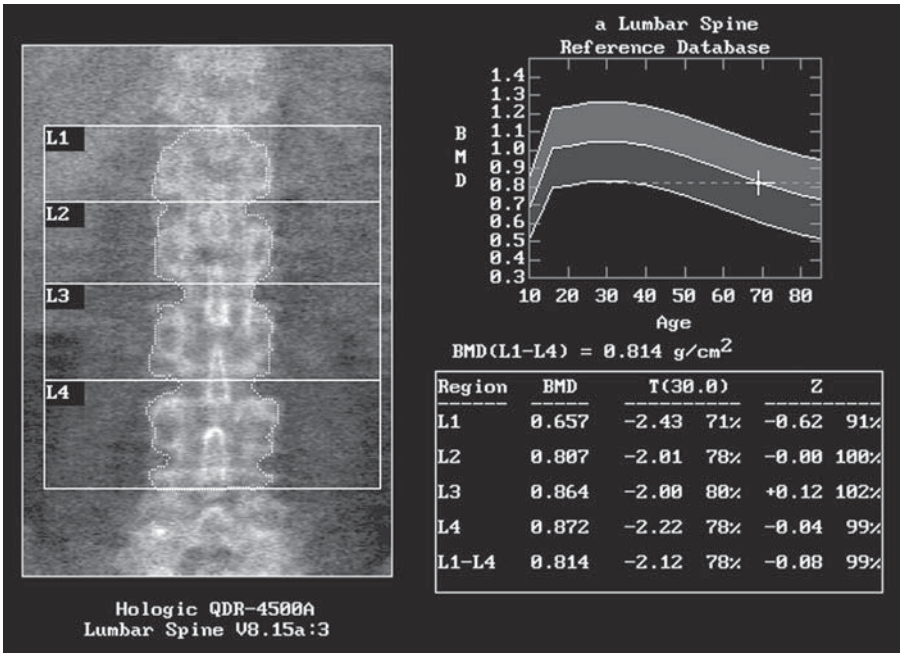

Fig. 10-1. Hologic QDR PA lumbar spine study in a 70-year-old Caucasian woman. The L1–L4 BMD is 0.814 g/cm^2. The *T*-score is –2.12 and the *z*-score is –0.08. The correct diagnosis is osteopenia. The patient also meets the NOF guidelines for prescription intervention in osteoporosis. Use of relative risk fracture data with either the *T*- or *z*-score will lead to very different impressions of this patient's fracture risk.

The reason that neither calculation is correct is because the strict interpretation of the 1.5 relative risk for global fracture per SD decline in spine BMD from the Melton study *(4)* is that an individual in the Melton study has a 1.5-fold higher risk for global fracture than another individual in the same study who has a BMD that is 1 SD higher. There is nothing here that a densitometrist can really use to quantify fracture risk in his or her individual patient. Because the data are age-adjusted, and the BMD study mean and SD are unique for the study population, the use of the individual patient's *T*- or *z*-score is not correct. The use of the patient's *z*-score is probably the better of the two standard scores on the bone density printout with which to use relative risk data but in this case, might clearly lead to confusion. The patient would be diagnosed as osteopenic using WHO Criteria[2] and meet the NOF Guidelines for prescription intervention and yet the use of the *z*-score with relative risk fracture data might lead the physician to conclude that she is not at increased risk for fracture.

Relative risks for site-specific spine fracture prediction are calculated in a similar fashion. Using an increase in relative risk per SD decline in BMD of 2.2 for spine fracture when measured at the spine, the calculation would be $2.2^{2.12}$ or $2.2^{0.08}$, depending on the comparison the physician wishes to make.

[2] *See* Chapter 9 for a discussion of the WHO Criteria for the diagnosis of osteoporosis.

Global fracture relative risk data for BMD measurements made at other sites can be calculated using data from Melton et al. *(4)* as well as other authors *(2,3,5)*. Similarly, the relative risk for a site-specific spine fracture risk prediction can be calculated from bone density measured at other sites using data from Melton et al. *(4)* and others *(2,7,8)*. The data from Cummings et al. *(9)* are most commonly used for the calculation of relative risk for site-specific hip fracture risk prediction.

Lifetime Risk of Fracture

In 1992, Black et al. *(11)* proposed a method for calculating a woman's lifetime risk for hip fracture. The prediction was based on the woman's bone mass at menopause expressed as a percentile for her age, estimations of bone mass at subsequent ages and then estimating her risk for hip fracture at each age. The risk of hip fracture at each age was based on two factors: the risk of fracture at a particular age derived from population-based data and the risk of fracture at a particular bone mass from prospective fracture trials. Based on a review of the literature at the time, an increase in relative risk for hip fracture of 1.65 for each SD decline in bone mass at the radius was used in the calculation of risk based on the level of bone mass. Using this method, the lifetime risk of hip fracture for a 50-year-old Caucasian woman whose midradial bone mass was at the 10th percentile was 19%. If her bone mass was at the 90th percentile, her lifetime risk of hip fracture was 11%. The gradient of risk, therefore, between the 90th and 10th percentile was 1.7 (19% ÷ 11% = 1.7). This model is obviously dependent on the value chosen for the increase in relative risk per SD decline in bone mass. The authors noted if the increase in relative risk was 2 instead of 1.65, the lifetime risks for the 10th and 90th percentiles would be 21 and 9%, respectively. The gradient of risk would therefore increase to 2.3.

In 1993, Suman et al. *(12)* developed a nomogram for predicting lifetime risk of hip fracture that was derived from the model developed by Black et al. *(11)* This nomogram is shown in Fig. 10-2.The *z*-scores utilized in the nomogram are based on the mean and SD for bone mass for 50-year-old Caucasian women. Like the concept of remaining lifetime fracture probability that is discussed next, lifetime fracture risk goes beyond the prediction of current fracture risk. A young individual with a slightly low bone mass and low current fracture risk will be identified as having a higher lifetime fracture risk. Similarly, an older individual with a low bone mass and high current fracture risk may have a lower lifetime fracture risk because of a shorter life expectancy.

Cummings et al. *(13)* published lifetime fracture risk data for hip fracture based on the femoral neck bone density *T*-score. These data are shown in Table 10-5. The risk of hip fracture used to determine lifetime hip fracture risk was derived from data from the Study of Osteoporotic Fractures in which the relative risk for hip fracture was 2.6 per SD decline in bone density at the femoral neck *(9)*. The femoral neck *T*-scores are based on NHANES III reference data *(14)*. Using Table 10-5, a 60-year-old Caucasian woman with a femoral neck *T*-score of -2.0 would have a lifetime hip fracture risk of 27%. An 80-year-old Caucasian woman with the same femoral neck *T*-score would have a lifetime hip fracture risk of 24%.

10-Year Fracture Probability

Lifetime fracture risk predictions appropriately emphasize that current fracture risk predictions may be misleading in the context of the need for preventive interventions. Nevertheless, lifetime fracture risk predictions have been criticized for emphasizing a

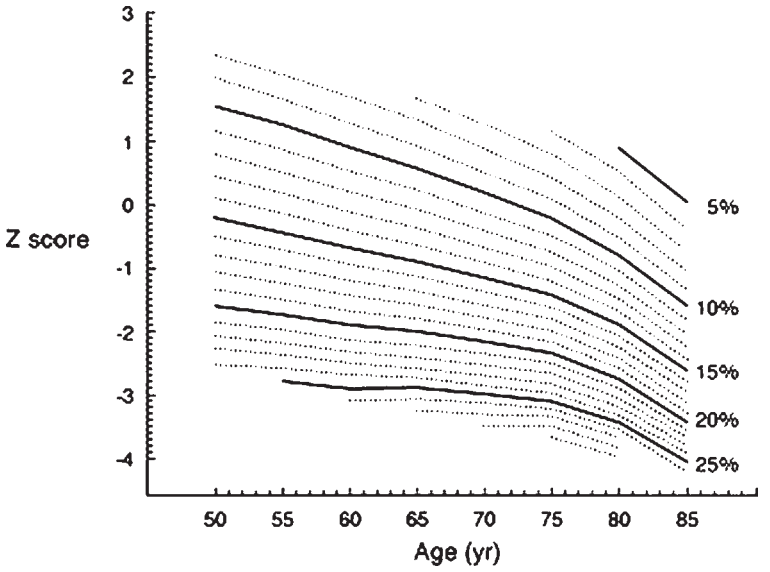

Fig. 10-2. Lifetime hip fracture risk as predicted from age and radial bone density. *Z*-scores are based on the average BMD of the 50-year-old woman. Reprinted with permission from ref. *12*.

Table 10-5
Lifetime Risk (%) of Hip Fracture for White Women Based on Age and *T*-Score at the Femoral Neck

	Femoral Neck Bone Density T-*Score*							
Age, years	*–3.5*	*–3.0*	*–2.5*	*–2.0*	*–1.5*	*–1.0*	*–0.5*	*0*
50	49	41	33	27	21	16	13	10
60	47	40	33	27	21	17	13	10
70	46	39	33	27	21	17	13	10
80	41	35	30	24	20	16	12	10

Adapted with permission of the publisher from Cummings SR, Bates D, Black DM. Clinical use of bone densitometry. JAMA 2002;286:1889–1897. ©American Medical Association

time frame that is too long to be clinically useful. Experts have argued that most patients will not take a preventive medication over a lifetime. Therefore, looking at their risk over a shorter period of time better assesses their need for and potential benefit from an intervention. In response, 5- and 10-year fracture probabilities are beginning to appear. Using fracture and mortality data from Malmö, Sweden, Kanis et al. *(15)* determined the 10-year probability of global and site-specific fractures. Tables 10-6 through 10-9 reflect the 10-year probability of fracture based on the patient's age and femoral neck *T*-score. The femoral neck *T*-score was again based on NHANES III 1995 reference data for Caucasian women *(14)*. The relative risk of fracture at the hip and proximal humerus used to calculate 10-year fracture probabilities was 2.6 per SD decline in bone density at the femoral neck. Relative risk per SD decline in femoral neck bone density for spine fracture was assumed to be 1.8, for forearm fracture, 1.4, and for global fracture, 1.6.

Table 10-6
Ten-Year Probability (%) of Sustaining Any Type of Osteoporotic Fracture (Hip, Spine, Shoulder, Forearm) in Men by Age and *T*-Score at the Femoral Neck

	T-*Score*									
Age	*+1*	*+0.5*	*0*	*–0.5*	*–1.0*	*–1.5*	*–2.0*	*–2.5*	*–3.0*	*–4.0*
45	1.5	1.9	2.3	2.8	3.4	4.2	5.1	6.3	7.7	11.4
50	1.8	2.2	2.7	3.4	4.2	5.1	6.3	7.7	9.4	14.0
55	1.9	2.4	3.0	3.7	4.6	5.7	7.0	8.6	10.6	16.0
60	2.5	3.0	3.6	4.4	5.4	6.5	7.9	9.5	11.5	16.7
65	3.0	3.6	4.3	5.1	6.2	7.4	8.8	10.4	12.4	17.4
70	3.4	4.2	5.1	6.1	7.4	9.0	10.9	13.1	15.7	22.4
75	4.1	5.1	6.3	7.8	9.6	11.8	14.4	17.5	21.2	30.4
80	5.3	6.4	7.7	9.2	11.1	13.3	15.8	18.7	22.2	30.3
85	5.3	6.3	7.5	8.8	10.4	12.2	14.3	16.7	19.5	26.1

Adapted from Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fracture according to BMD and diagnostic thresholds. Osteoporos Int 2001;12:989–995 with permission of the publisher. ©Springer-Verlag

Table 10-7
Ten-year Probability (%) of Sustaining Any Osteoporotic Fracture (Hip, Spine, Shoulder, Forearm) in Women by Age and *T*-Score at the Femoral Neck

	T-*Score*									
Age	*+1*	*+0.5*	*0*	*–0.5*	*–1.0*	*–1.5*	*–2.0*	*–2.5*	*–3.0*	*–4.0*
45	1.8	2.3	2.8	3.5	4.3	5.4	6.6	8.1	10.0	15.0
50	2.4	3.0	3.8	4.7	5.9	7.4	9.2	11.3	14.1	21.3
55	2.6	3.3	4.1	5.3	6.7	8.5	10.7	13.4	16.8	26.0
60	3.2	4.1	5.1	6.5	8.2	10.4	13.0	16.2	20.2	30.6
65	4.0	5.0	6.3	8.0	10.0	12.6	15.6	19.3	23.9	35.5
70	4.3	5.5	7.1	9.0	11.5	14.6	18.3	22.8	28.4	42.3
75	4.2	5.4	7.0	9.1	11.8	15.2	19.4	24.5	30.8	46.2
80	4.6	6.0	7.7	9.9	12.7	16.2	20.5	25.6	31.8	46.4
85	4.5	5.8	7.4	9.4	12.0	15.3	19.1	23.8	29.4	42.7

Adapted from Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fracture according to BMD and diagnostic thresholds. Osteoporos Int 2001;12:989–995 with permission of the publisher. ©Springer-Verlag

Tables 10-6 and 10-7 are 10-year global fracture risk predictions for women and men. Tables 10-8 and 10-9 are 10-year site-specific fracture risk predictions for women and men based on *T*-scores that define WHO diagnostic categories of osteopenia and osteoporosis. The *T*-score thresholds of –1 and –2.5 correspond to femoral neck bone densities measured on Hologic DXA of 0.740 g/cm^2 and 0.577 g/cm^2 for both the men and women. The authors suggest that the similar 10-year probabilities of hip and spine fracture at the WHO diagnostic thresholds add to the belief that the use of *T*-scores derived in women are applicable to men. Kanis et al. also point out that 10-year risks based on measurement of BMD at sites other than the femoral neck by DXA or by other techniques would be different. They noted that although data on fracture rates and

Table 10-8
Ten-Year Probability (%) of Fracture at the Sites Shown by Age and Diagnostic Category in Men

	Forearm Fracture		*Hip Fracture*		*Spine Fracture*		*Shoulder Fracture*		*Any of These Fractures*	
Age	*< –1*	*< –2.5*	*< –1*	*< –2.5*	*< –1*	*< –2.5*	*< –1*	*< –2.5*	*< –1*	*< –.25*
45	1.9	2.7	1.2	3.3	1.6	3.0	0.8	1.1	4.7	7.6
50	1.8	2.5	2.0	5.2	2.2	4.0	0.7	1.0	5.7	9.2
55	1.9	2.8	1.9	5.2	2.6	4.9	0.6	0.9	6.4	10.4
60	2.3	3.2	2.6	6.2	3.0	5.1	1.0	1.3	7.6	11.6
65	2.0	2.7	4.1	8.8	3.5	5.7	1.7	2.3	8.8	13.0
70	1.2	1.7	6.2	13.7	4.8	8.0	2.0	2.7	10.8	16.2
75	1.5	2.1	9.5	21.4	5.6	9.7	1.9	2.6	14.1	21.5
80	1.7	2.3	11.0	21.2	6.0	9.7	2.4	3.1	16.6	23.2
85	1.3	1.6	9.6	16.9	5.2	7.7	2.8	3.5	16.0	21.4

Note: The diagnostic category is based on the *T*-score at the femoral neck, using the 1995 NHANES III reference data for non-Hispanic white women.

Adapted from Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fracture according to BMD and diagnostic thresholds. Osteoporos Int 2001;12:989–995 with permission of the publisher. ©Springer-Verlag

Table 10-9
Ten-Year Probability (%) of Fracture at Sites Shown in Women by Age and Diagnostic Category

	Forearm Fracture		*Hip Fracture*		*Spine Fracture*		*Shoulder Fracture*		*Any of These Fractures*	
Age	*< –1*	*< –2.5*	*< –1*	*< –2.5*	*< –1*	*< –2.5*	*< –1*	*< –2.5*	*< –1*	*< –2.5*
45	3.6	5.2	0.8	2.2	1.1	2.1	1.2	1.7	6.1	9.9
50	5.1	7.3	1.1	2.9	1.9	3.5	1.6	2.3	8.6	13.9
55	5.8	8.4	2.0	5.1	2.5	4.6	1.7	2.5	10.3	16.8
60	6.7	9.3	3.3	7.8	3.6	6.4	2.8	4.0	13.2	20.5
65	7.5	10.2	5.0	10.9	5.3	9.0	4.0	5.4	16.8	24.9
70	7.9	10.6	8.3	16.7	6.7	10.9	4.8	6.5	20.7	29.8
75	8.0	10.4	11.8	21.5	6.9	10.7	5.3	7.0	23.6	32.6
80	7.6	9.5	14.6	23.8	7.1	10.2	5.7	7.2	26.6	34.4
85	6.1	7.4	14.7	21.9	6.9	9.4	6.4	7.8	26.7	33.1

Note: The diagnostic category is based on the *T*-score at the femoral neck, using the 1995 NHANES III reference data for non-Hispanic white women.

Adapted from Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fracture according to BMD and diagnostic thresholds. Osteoporos Int 2001;12:989–995 with permission of the publisher. ©Springer-Verlag

mortality from Sweden are robust, fracture rates are high and mortality is low compared to other parts of the world.

Another approach to 10-year fracture risk, which also suggests levels for intervention, has been proposed using guidelines developed by the NIH *(16)* for the detection and treatment of high cholesterol in the prevention of heart disease *(17)*. These guidelines defined high risk for heart disease as a 10-year risk greater than 20%. Moderate risk was a 10-year risk from 10 to 20% and low risk, a 10-year risk of less than 10%.

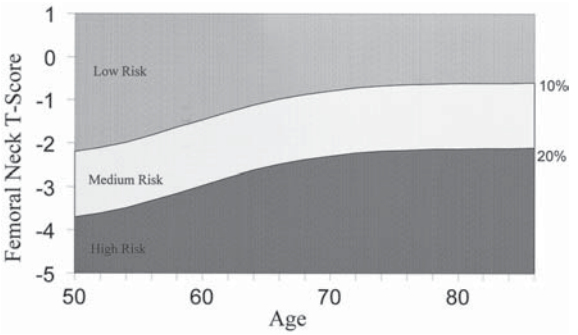

Fig. 10-3. Ten-year global fracture risk stratified by risk probabilities of 10 and 20% based on age and femoral neck *T*-score. Reproduced courtesy of Dr. Ken Faulkner, GE Medical Systems, Madison, WI.

In an analogous fashion, the 10-year risk for all fractures (global fracture risk) for any given age and BMD that corresponds to 10 and 20% can be calculated and presented in graphic form as shown in Fig. 10-3. Interestingly, at age 65, a 20% 10-year risk for all fractures occurs at a *T*-score of –2.5. A *T*-score of –1 at age 65 results in a 10% 10-year fracture risk.

Remaining Lifetime Fracture Probability

Remaining lifetime fracture probability (RLFP) is a type of *future* global fracture risk prediction that was proposed by Ross et al. *(18)*. The concept of RLFP is based on the exponential increase in fracture risk as BMD declines and decreased survival after age 75. Therefore, although a 50-year-old woman and an 80-year-old woman may both have the same low bone density, their RLFP will be quite different. Because the expected life span of the 80-year-old woman is much shorter than that of the 50-year-old, the RLFP for the 80-year-old will be less. RLFP is calculated based on the individual's current age and bone density, life expectancy, and anticipated rate of bone loss. These values are entered into a statistical model that predicts the number of osteoporotic fractures that the individual is expected to experience in her lifetime. For example, if the RLFP is 5, the individual is expected to suffer five osteoporotic fractures in her lifetime if no intervention is undertaken to slow the anticipated rate of bone loss and she lives a normal life span. The site(s) of the fractures cannot be specified. RLFP is a global fracture risk prediction. RLFP is one of the most concrete and easily understood modalities for expressing future fracture risk.

The fracture incidence and bone loss rate data on which the RLFP model was originally based were derived from the Kuakini Osteoporosis Study. The original implementation of RLFP was based on measurements of bone mass at the calcaneus. Bone density measurements performed at other sites had to be converted to an equivalent calcaneal measurement. Using nomograms, the physician could find the calcaneal BMC on one scale and the patient's age on a second scale *(19)*. By connecting the two values, the physician could find the RLFP on a third scale. RLFP predictions have now been recalculated for DXA measurements of the axial and appendicular skeleton and are available on the internet at www.medsurf.com. After entering the patient's age, menopausal age, skeletal site measured, type of equipment used, and BMD, the RLFP calculation is presented as shown in Fig. 10-4. In this RLFP analysis, the RLFP was

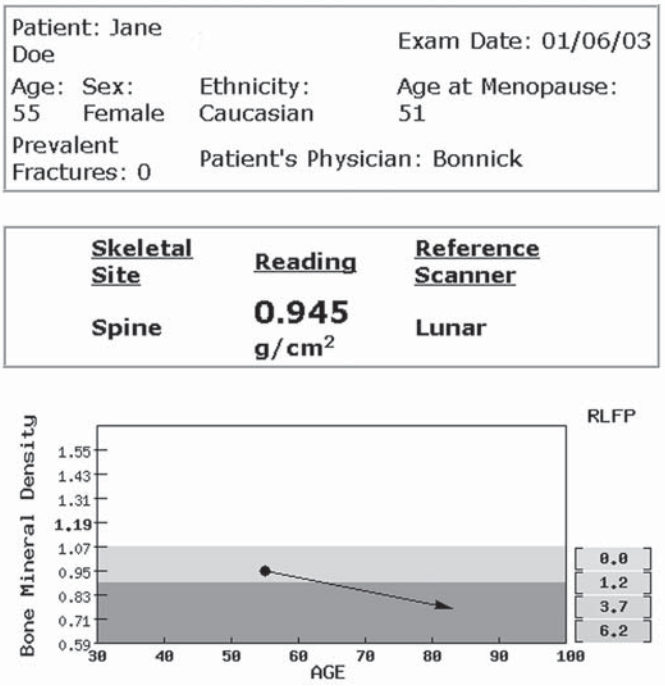

Fig. 10-4. The remaining lifetime fracture probability (RLFP) calculation from www.medsurf.com. At age 55 with a PA lumbar spine BMD of 0.945 g/cm^2 on a Lunar DXA device, the RLFP is 3.82. Reproduced courtesy of Dr. Richard Wasnich, Honolulu, HI.

3.82, indicating that the patient is expected to suffer 3.82 osteoporotic fractures in her lifetime without intervention. The probability of fracture in the next year is predicted to be only 1.5% but her 10-year fracture probability is 10.2%. It is also possible to calculate the effects on the RLFP of an intervention that reduces fracture risk or bone loss by a specified amount. In this case, a intervention that halts bone loss would reduce the RLFP to 0.76. Alternatively, an intervention that permanently reduces fracture risk by 50% is expected to reduce the RLFP to only 0.33. As noted above, the sites of the future fractures are not specified.

RLFP is based on a statistical model. When the RLFP model is applied to the US population, the estimates of vertebral and nonvertebral fracture incidence are comparable to actual observations of fracture incidence *(20)*. This observation provides an external validation of the theory and application of RLFP.

The Fracture Threshold

Many experts in the field object strenuously to the concept of a fracture threshold, noting that it is more appropriate to emphasize the existence of a gradient of risk for fracture with risk increasing as the bone density declines. They correctly observe that there is no arbitrary level of bone density above which no one fractures and below which everyone fractures. Nevertheless, the concept of a fracture threshold can be useful in the clinical setting. It suggests a "cut-off" level of bone density above which it is desirable

to stay in order to keep fracture risk at a minimum. It also emphasizes that bone density need not be returned to "normal" levels to reduce the risk of fracture.

In 1982, Riggs et al. *(21)* proposed a fracture threshold for BMD in the spine and proximal femur based on studies of 205 subjects (123 women, 82 men). Of these 205 subjects, 31 (26 women, 5 men) had hip fractures and 84 women had vertebral fractures. BMD was measured with the older technique of DPA in the PA lumbar spine and proximal femur. The fracture threshold was defined as the 90th percentile for BMD in the proximal femur for subjects with hip fracture and in the spine for women with spine fracture. For women, the fracture threshold was 0.95 g/cm^2 at the femoral neck, 0.92 g/cm^2 at the intertrochanteric region, and 0.97 g/cm^2 at the lumbar spine.

Ross et al. *(22)* proposed that the fracture threshold be defined as the BMC or BMD at which the risk of fracture doubled in comparison to premenopausal women. This recommendation was based on a prospective study of 1098 women who participated in the Kuakini Osteoporosis Study beginning in 1981. These women underwent BMC and BMD measurements at the proximal and distal radius and os calcis yearly with SPA and, beginning in 1984, lumbar spine BMD measurements with DPA. Four hundred eight women had spine films at baseline and were used to calculate spine fracture incidence during 4 years of follow-up. Spine fracture prevalence was calculated based on data from subjects who had fractures prior to the first bone density measurement. The authors looked at a variety of ways to define the fracture threshold and the BMC or BMD levels at the various sites that resulted. These considerations are shown in Table 10-10. They observed that the levels of BMC and BMD that corresponded to the 10th percentile of young normals, the 80th percentile of prevalent spine fracture cases, or an absolute risk of fracture of 5% per decade also coincided with the level of BMC and BMD that resulted in a doubling of fracture risk in comparison to premenopausal women. They concluded that this level of bone density was the most appropriate definition of the fracture threshold.

Vega et al. *(23)* calculated a fracture threshold for femoral neck and trochanteric hip fractures based on cross-sectional data from 75 women with atraumatic fractures of the proximal femur and 51 age-matched nonfractured controls. The average age of the women was 70.1 years. In the hip fracture group, there were 36 femoral neck fractures and 39 trochanteric fractures. BMD was measured at the lumbar spine and proximal femur with DPA (Lunar DP3) and at the midradius with SPA. The average BMD and SD in the femoral neck of the femoral neck fracture patients were 0.624 g/cm^2 and 0.055 g/cm^2, respectively. For the trochanteric fracture patients, these values in the femoral neck were 0.548 g/cm^2 and 0.066 g/cm^2. The authors defined the fracture threshold as the mean BMD plus 2 SD at the femoral neck as calculated from the BMD measurements in the fracture group. For fractures of the femoral neck, this value was 0.73 g/cm^2. For trochanteric fractures, this value was 0.68 g/cm^2. Using a spine fracture threshold of 0.97 g/cm^2 from Riggs et al. *(21)*, the authors observed that 94% of the patients with trochanteric fracture and 74% of the patients with femoral neck fracture had spine BMD values that were also below the spine fracture threshold.

The fracture threshold concept can also be utilized to assess the benefit of any particular therapy. For example, a 57-year-old woman may have a bone density that is currently above the fracture threshold at a particular site. It is anticipated, however, that her bone density will fall below the fracture threshold in the future at a point in time that will be determined by the rate of bone loss. Using statistical models, it can be anticipated that if the patient loses BMD at a rate of 1% per year, she will fall below the fracture threshold

Table 10-10
A Comparison of Different Definitions for the Fracture Threshold

Definition	*Proximal Radius (g/cm)*	*Distal Radius (g/cm)*	*Calcaneus (g/cm^2)*	*Lumbar Spine (g/cm^2)*
Based on Young Normals				
10th Percentile	0.78	0.76	0.33	0.97
2 SD Below Mean	0.71	0.66	0.28	0.90
Based on Postmenopausal Women				
10th Percentile	0.59	0.52	0.22	0.74
2 SD Below Mean	0.49	0.42	0.17	0.60
Based on Prevalent Fracture Cases				
80th Percentile	0.78	0.75	0.33	0.94
Based on Incident Fracture Cases				
95th Percentile	0.78	0.67	0.31	0.94
Based on Increased Fracture Risk				
Absolute Risk of 5% per Decade	0.78	0.74	0.32	0.97
Doubling of Risk Relative to Age 45	0.77	0.78	0.32	0.94
Reference Values (mean and SD)				
Young Normals[a]	0.88 ± 0.08	0.89 ± 0.11	0.41 ± 0.07	1.13 ± 0.12
Postmenopausal Women[b]	0.73 ± 0.11	0.70 ± 0.13	0.31 ± 0.08	0.92 ± 0.15

[a] Premenopausal women, ages 30–45. Mean age 38 years, $n = 128$.
[b] Postmenopausal women, mean age 64. $N = 1083$.
Reprinted with permission from ref. *22*.

by age 64. If the rate of bone loss is reduced to 0.5%, she will not reach the fracture threshold until age 72 gaining 8 years of relative protection from fracture.

Qualitative Risk Assessments

Qualitative fracture risk assessments are descriptions of risk as being low, moderate, or high or as not increased, increased, or markedly increased. At its most basic, a qualitative assessment of fracture risk may be a statement of "not at risk" versus "at risk." This is an assessment of current fracture risk. In 2002, the Canadian Panel of the ISCD recommended that bone density reports contain a qualitative assessment of fracture risk *(24)*. Thresholds for moderate and high fracture risk or increased and markedly increased fracture risk are generally the same as the WHO diagnostic categories of osteopenia and osteoporosis. These types of qualitative assessments of risk are commonly seen on computer-generated printouts of bone density data. Caution must be used however as such assessments are inappropriate in individuals under age 50. In deciding whether a quantitative or qualitative assessment of risk is necessary or sufficient, the physician must decide what difference such an assessment may make in the management of the patient. Will treatment be considered if the risk is increased, regardless of the magnitude of the increase? If so, a qualitative assessment will suffice. Will the magnitude of the increase motivate the physician to treat or the patient to accept treatment? If so, a quantitative assessment of risk may be more powerful than a qualitative assessment.

Table 10-11
Age-Adjusted Odds Ratios (and 95% CI) for Osteoporotic Fracture Per 1 SD Decrease in BMD by Skeletal Site Measured for Rochester, Minnesota Men and Women Depending on the Criterion Used for Establishing Normal Means and SDs

	Skeletal Site				
Study Group and Criterion	*Total Hip*	*Femoral Neck*	*Trochanter*	*PA Spine*	*Total Wrist*
20–29 year *male* criteria					
Women	2.20 (1.50, 3.22)	2.25 (1.44, 3.51)	2.06 (1.38, 3.08)	1.67 (1.18, 2.36)	1.77 (1.27, 2.47)
Men	1.29 (0.97, 1.72)	1.10 (0.82, 1.48)	1.34 (1.00, 1.78)	1.15 (0.89, 1.48)	1.51 (1.12, 2.03)
20–49 year *male* criteria					
Women	2.66 (1.66, 4.29)	2.70 (1.56, 4.65)	2.48 (1.50, 4.10)	1.79 (1.21, 2.66)	1.67 (1.24, 2.26)
Men	1.38 (0.97, 1.97)	1.12 (0.78, 1.62)	1.44 (1.01, 2.07)	1.17 (0.88, 1.56)	1.45 (1.11, 1.90)
20–29 year *female* criteria					
Women	2.40 (1.57, 3.68)	2.43 (1.49, 3.95)	2.21 (1.42, 3.42)	1.66 (1.18, 2.33)	1.56 (1.20, 2.03)
Men	1.33 (0.97, 1.83)	1.11 (0.80, 1.54)	1.38 (1.01, 1.88)	1.14 (0.89, 1.47)	1.38 (1.09, 1.74)
Premenopausal *female* criteria					
Women	2.37 (1.56, 3.61)	1.28 (1.50, 4.08)	2.19 (1.42, 3.38)	1.61 (1.17, 2.23)	1.54 (1.20, 1.99)
Men	1.33 (0.97, 1.82)	1.11 (0.80, 1.55)	1.37 (1.00, 1.87)	1.14 (0.90, 1.44)	1.37 (1.09, 1.72)

Adapted with permission of the American Society for Bone and Mineral Research from ref. *26*.

PREDICTING FRACTURE RISK IN MEN

The number of studies reporting fracture risk in men based on the decline in bone density has increased in recent years. As in so many of the studies on women, the increase in fracture risk is generally reported as the relative risk for fracture per SD decline in bone density. Other studies have reported absolute risk. The findings from these studies have led to two apparently contradictory conclusions: women have a greater increase in relative risk for fracture per SD decline in BMD than do men but the absolute risk for fracture at any given level of BMD is the same in women and men *(25)*. In Table 10-11, the age-adjusted relative risk values for fracture in men and women age 35 years and older from a population-based case-control study in Rochester, Minnesota are shown *(26)*. The relative risks differ depending on the reference population used. Note that the relative risk for any type of fracture in men was 1.1 per SD decline in femoral neck BMD when the reference population was 20- to 29-year-old men. The same relative risk value in women was 2.4 when the reference population was 20 to 29 year old women. An important difference in the calculation of these relative risk values was that the SD in men of 0.109 g/cm^2 was much smaller than the 0.119 g/cm^2 SD seen in women. In other studies in which the relative risks per SD decline in bone density have been similar, the magnitude of the SD in men and women was also similar. This suggests that the SD itself has a significant effect on the apparent sex-specific relative risk for fracture. This would be true even if the absolute risk for fracture at any given BMD was the same. Data from the Hawaii Osteoporosis Study do, in fact, suggest that the absolute risk for spine fracture is the same in men and women for any given level of calcaneal BMD *(27)*. In an analysis of data *(28)* from the EPOS[3] study, the use of a common SD of 0.1 g/cm^2 resulted in a relative risk for spine fracture when bone density was measured at the PA lumbar spine of 1.4 in men and 1.5 in women. When bone density was measured at the femoral neck and the same SD of 0.1 g/cm^2 was used, the relative risk for spine fracture was 1.5 in men and 1.8 in women. In the Rotterdam study, as reported by De Laet et al. *(29)*, hip fracture incidence was only slightly higher in women than in men for any given level of femoral neck BMD. De Laet et al. *(30)* concluded that hip fracture risk is the same in men and women at the same bone density. The distribution of bone density levels at any given age in men also suggests two conclusions. First, at any given level of low BMD, men are likely to be older than women. This means that fewer men will reach the same low levels of BMD than will women. Second, the average age of men who experience hip fractures will be younger than that of women. De Laet et al. *(30)* suggested that sex-specific SDs were appropriate when the primary goal was to identify a similar proportion of men who would fracture compared to women. This would suggest the use of sex-specific relative risk values. If, however, the ultimate goal of fracture risk prediction is the identification of individuals who would benefit from intervention, the same absolute BMD threshold that signals unacceptable risk would be appropriate in both men and women. Note that in the 10-year fracture risk tables for *men* from Kanis et al. *(15)* in Fig. 10-7, the *T*-scores were derived using NHANES III femoral neck BMD data for *women*. In 2000, the Scientific Advisory Board of the International

[3] EPOS is the European Prospective Osteoporosis Study and is a continuation of the European Vertebral Osteoporosis Study (EVOS). EVOS is a study of the prevalence of fracture in men and women conducted at 36 centers in 19 countries in Europe.

Osteoporosis Foundation (IOF) *(31)* recommended that the diagnosis of osteoporosis in men be based on a *female T*-score of –2.5 at the hip. In 2002, the ISCD *(32)* recommended the continued use of sex-specific SDs (*T*-scores) for men. Given, however, that relative risk data are poorly used with *T*- and *z*-scores from densitometry reports and that absolute risk is the more relevant quantity, an approach that advocates the same BMD thresholds for varying levels of risk seems more appropriate for clinical decisions that may result in interventions.

USING SKELETAL MORPHOMETRY FROM DENSITOMETRY TO PREDICT FRACTURE RISK

Densitometry has primarily been a quantitative measurement technique. The first skeletal images from a densitometer, such as that seen in Fig. 1-7, were only vaguely reminiscent of the actual bone. The poor image quality had little effect on the ability to quantify the bone density, which was the primary purpose of the various techniques. With the advent of DXA and QCT, skeletal imaging as a potential application of densitometry became possible. Continued improvements in the technology combined with modern computer capabilities have resulted in spine images with sufficient clarity to diagnose fracture. The physical dimensions of the vertebrae and proximal femur can be measured from densitometry images using morphometric software applications. Recognition of a vertebral fracture may result in a different diagnosis than would otherwise result based on the bone density alone. In addition, the presence of vertebral fracture and proximal femur geometry have been recognized as independent predictors of fracture risk.

Vertebral Morphometry and Fractures

The Relationship Between Prevalent Spine Fractures and Future Fracture Risk

A number of studies have demonstrated that the presence of a spine fracture is predictive of future fractures, independent of bone density *(33–39)*. The strongest association is between existing spine fractures and future spine fractures with estimates of the increase in risk from only one prevalent spine fracture of 3- to 11.1-fold. One of the first such studies was from Ross et al. *(33)*. This study was performed in the same group of women from the Kuakini Osteoporosis Study who were described earlier in the discussion of the definition of a spine fracture threshold. In this study, the presence of one vertebral fracture at baseline resulted in a fivefold increase in the risk for new vertebral fractures. If two vertebral fractures were present at baseline, the risk for new vertebral fractures increased 12-fold.

In a second study, Ross et al. *(35)* evaluated 380 postmenopausal women with an average age of 65 who were participants in a multicenter trial of etidronate therapy for postmenopausal osteoporosis. In this study, the presence of one or two spine fractures at baseline increased the risk of future spine fractures 7.4-fold.

Nevitt et al. *(34)* evaluated the effect of the number and location of prevalent spine fractures on future fracture risk using data from the Fracture Intervention Trial (FIT), a placebo-controlled, randomized trial of alendronate therapy in postmenopausal osteoporosis. Data from 6082 women were included in this analysis, roughly half of whom were receiving a placebo. Vertebral fractures at baseline were found in 1950 women. Four hundred sixty-two new vertebral fractures occurred in 344 women during an aver-

age of 3.8 years of follow-up. Nevitt et al. found that the presence of just one vertebral fracture at baseline resulted in a threefold increase in the risk for new vertebral fractures compared to women without a vertebral fracture at baseline. This was true even after adjustment for age, total hip BMD, and weight. Prevalent spine fractures appeared to be stronger predictors of incident spine fractures in the upper spine than in the lower spine.

Data obtained during the Study of Osteoporotic Fractures, a prospective study of 9704 women aged 65 and older, were analyzed by Black et al. *(36)* to determine the effect of prevalent spine fracture on future fracture risk. Seven thousand two hundred thirty-eight women had technically adequate films for morphometric evaluation of spine fracture at baseline and after an average follow-up of 3.7 years. Prevalent spine fractures were present at baseline in 1915 women. Two or more deformities were seen in 797 and four or more, in 211. Over the follow-up period, 389 women developed new vertebral fractures. The risk for new vertebral fracture increased as the number of prevalent vertebral fractures increased. In women with one prevalent vertebral fracture, the relative risk for new vertebral fracture was 3.2. For women with three or more prevalent vertebral fractures, the relative risk of new vertebral fracture was 10.6 even after adjustment for age.

In a population-based epidemiologic study *(37)* of vertebral fracture incidence between 1985 and 1994 in Rochester, Minnesota, 820 residents (619 women, 201 men) were diagnosed as having one or more vertebral fractures. The residents were followed until death or the last clinical contact during the study period. The average age at the time of the first vertebral fracture was 67.3 years for women and 55.5 years for men. Compared to fracture incidence rates expected in the general population, the observed rate was almost three times higher in individuals age 35 or older with a prior vertebral fracture. The increase in risk for new vertebral fractures was 12.6-fold higher for both sexes combined and 11.1-fold higher for women alone.

Prevalent vertebral fractures have also been shown to be predictive of nonvertebral fractures. Two hundred fifty subjects (225 women, 25 men) with an average age of 74 years were evaluated for the presence of vertebral deformity at baseline and the subsequent development of nonvertebral fracture during a follow-up period of 3 years *(38)*. During this period, 39 subjects suffered nonvertebral fractures of which 10 were hip fractures, 17 were forearm fractures, and 13 were at a variety of other skeletal sites. Of the 39 subjects who developed nonvertebral fractures, 27 had spine deformities at baseline. Spinal deformities were graded as mild or severe based on the number of vertebrae affected and/or the degree of deformity. After adjusting for age, sex, and BMD in the femoral neck (DXA), subjects with severe spinal deformities at baseline had a fourfold increase in the risk of nonvertebral fracture (RR 4.1; 95% CI 1.3 to 12.4). Subjects with mild spinal deformities had a relative risk of 1.5 for the development of nonvertebral fractures but this increase in relative risk was not significant at the 95% CI.

In the study from Black et al. *(36)* utilizing data from the Study of Osteoporotic Fractures, prevalent spine fractures were also predictive of nonspine fractures in general and hip fractures, specifically. The risk of any nonspine fracture was increased 1.9-fold, whereas the risk of hip fracture was increased 3.8-fold. The authors could not show a statistically significant increase in the risk for wrist fracture based on the finding of a prevalent spine fracture. In the Rochester, Minnesota population-based study from Melton et al. *(37)*, the finding of a prevalent spine fracture resulted in a 2.3-fold increase in the risk for hip fracture. Unlike the study from Black et al., Melton and colleagues did find a significant increase in the risk of distal forearm fracture of 1.6.

Klotzbuecher et al. *(39)* reviewed the available literature in 2000 to summarize the known associations between prevalent fracture and future fracture risk of all types. They performed a literature search that spanned 1966 through 1999, identifying 15 publications that reported associations between prevalent spine fractures and subsequent fractures. Based on this review, Klotzbuecher et al. concluded that prevalent spine fracture increases the risk for future spine fracture 4.4-fold (95% CI 3.6 to 5.4). The risk of subsequent hip fracture was increased 2.3-fold (95% CI 2.0 to 2.8) and the risk of subsequent wrist fracture was increased 1.4-fold (95% CI 1.2 to 1.7). The authors noted that in 5 of the 15 studies reviewed, the associations between prevalent spine fracture and subsequent fracture were reduced by only 20% or less when adjustments were made for BMD. Nevertheless, BMD was also a strong predictor of future fractures, independent of prior fractures. Klotzbuecher et al. concluded that BMD and prevalent fractures were complementary in the prediction of future fracture risk.

Diagnosing Vertebral Fractures

The assessment of fracture risk is clearly incomplete without an assessment for vertebral fracture. It is estimated that only 33% of vertebral fractures are symptomatic *(40)*. Of those fractures that are not clinically symptomatic, 78% remain unrecognized *(41)*. A more aggressive effort to evaluate patients for vertebral fracture is clearly indicated. The lack of a clear "gold standard" for defining the types of vertebral deformities that are the result of bone fragility and thus fractures, remains controversial. Semiquantitative and quantitative approaches for defining vertebral fractures are used clinically. Either can be applied to plain radiographs as well as densitometric spine images.

Vertebral Fracture Assessment with Genant's Semiquantitative Technique

Genant's semiquantitative technique relies on the expertise of the observer rather than direct measurements of the physical dimensions of the vertebrae *(42)*. Based on the physical appearance, vertebrae are characterized as being normal or deformed. The types of deformation are mild (grade 1), moderate (grade 2), and severe (grade 3). Deformed vertebrae are also described based on the shape of the deformation as wedged (anterior fracture), biconcave (middle fracture), or crushed (posterior fracture). These deformities are illustrated in Fig. 10-5. Although physical measurements are not made with this technique, a grade 1 deformity roughly corresponds to a 20 to 25% reduction in the anterior, middle, or posterior height of the vertebra and a 10 to 20% reduction in vertebral area. A grade 2 deformity is the result of a 25 to 40% reduction in any of the three heights and a reduction in vertebral area of 20 to 40%. A grade 3 deformity occurs when there is a 40% reduction in any of the three heights and a 40% reduction in vertebral area. An expert in the Genant semiquantitative technique also brings to bear knowledge of vertebral deformities caused by various disease processes other than fracture. This adds an invaluable qualitative aspect to the evaluation of vertebral fracture with this technique. This technique has been traditionally used with plain radiographs of the spine but semiquantitative vertebral fracture assessment can be performed with fan-array DXA spine images as well.

Quantitative Techniques

Quantitative techniques rely on physical measurements to diagnose vertebral fracture. Reference points are placed on each vertebral body. A common method is the placement of six points, one point at each corner of the vertebral body and one point at the midpoint

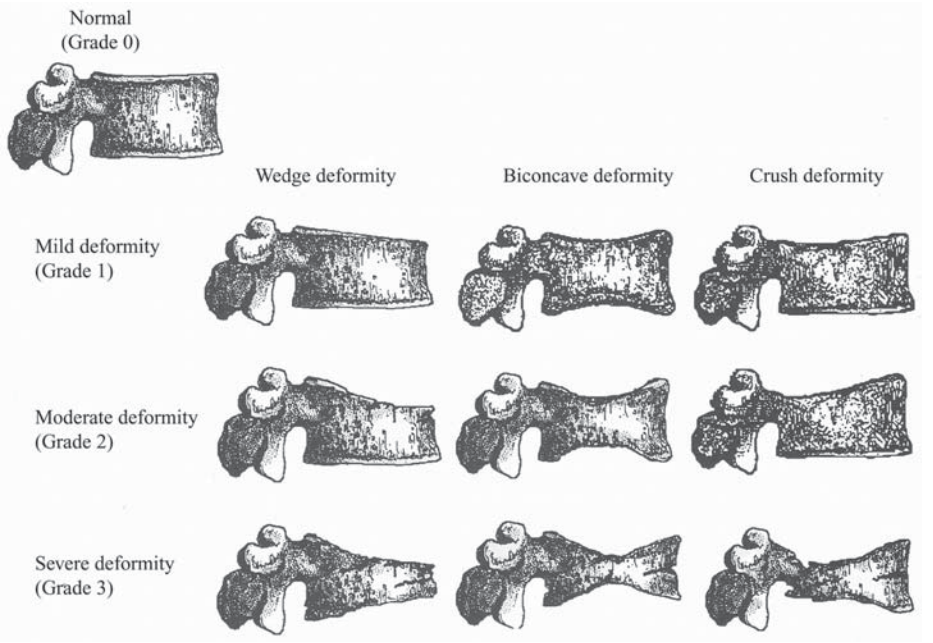

Fig. 10-5. Genant's semiquantitative vertebral fracture grading system. Reproduced courtesy of Dr. Harry Genant, San Francisco, CA.

of each of the endplates. Using these points, the anterior, mid-, and posterior heights (h_a, h_m, and h_p, respectively) of the vertebra are measured. The vertebral area is calculated as the polygon area defined by the six points. In addition to the heights themselves, the anterior–posterior height ratio (h_a/h_p) and the midposterior height ratio (h_m/h_p) are calculated. Other ratios include the wedge index ($I_w = h_p/h_a$) *(43)* and the biconcavity index (h_m/h_a) *(44)*. These measurements were originally made from plain radiographs. In recent years, measurements were made from digitized films. With the advent of fan-array DXA spine imaging and morphometry software, quantitative vertebral morphometry can be performed by the densitometrist as well.

Different criteria have been proposed for the diagnosis of prevalent or incident fracture based on quantitative morphometry. Several authorities have proposed that a prevalent fracture is present if there is a 15% or greater reduction in the h_a/h_p or h_m/h_p ratio or the ratio of the posterior height of one vertebra to the posterior height of an adjacent vertebra (h_p/h_{pa}) when compared to the mean value for a normal population *(45–47)*. A more stringent 20% reduction in these ratios has been proposed as well. A reduction of 3 SD in the h_a/h_p or h_m/h_p compared to normative data to define vertebral fracture was proposed by Ross et al. and Eastell et al. *(48,49)*. McCloskey and Kanis *(50,51)* also proposed utilizing a 3 SD reduction in any of the ratios combined with reductions in ratios calculated using a predicted posterior height. These morphometric definitions of vertebral fracture require comparisons to normative reference data for a population. Heights may also be adjusted for body size using the dimensions of the fourth thoracic vertebra (T4). In other words, the h_p for T12 can be adjusted or normalized for size by dividing it by the h_p at T4 in the individual. The resulting posterior dimension for T12 is then abbreviated

nh_p, reflecting the normalization for size. Minne et al. *(52)* proposed defining vertebral fracture as being present when any of the three normalized heights was below the third percentile of the normal range. Because vertebrae are expected to have slightly different shapes depending on the vertebral level, individual heights must be compared to normal values that are specific for that vertebral level.

The definition of incident fractures tends to be more straightforward. When plain radiography is used to capture images of the vertebrae it is imperative that the same radiographic technique be used to avoid artifactual changes in the vertebral shapes. When this is done, a decrease of 15% in the h_a, h_m, or h_p from the baseline film is indicative of an incident fracture. A reduction of 20 to 25% has also been proposed for the definition of an incident fracture *(53)*. An even more stringent criterion is a reduction of 20 to 25% in any of the three heights with a minimum absolute reduction of 4 mm *(54)*.

Performance Comparisons of Semiquantitative and Quantitative Techniques

Quantitative techniques rely heavily on the accuracy of point placements as well as comparisons to reference databases. Point placement can be subjective and affected by the deformity itself or patient positioning. Differences of opinion exist regarding the validity and design of reference databases for vertebral morphometry, just as they do for bone densitometry. Genant's semiquantitative technique is based on the visual recognition of quantitative changes in vertebral shape as well as knowledge of disease processes that cause deformities other than fracture. The performance of these techniques in identifying vertebral fractures have been compared in several studies *(55–60)*. In order to compare the techniques, a gold standard for the diagnosis of vertebral fracture was generally created by a consensus reading of radiographs by experts. When done in this manner, the semiquantitative and quantitative approaches generally perform equally well but the threshold chosen for identifying fracture by quantitative morphometry profoundly effects the agreement between the two techniques. The combination of a semiquantitative and quantitative technique may be better than either alone. Spine imaging with fan-array densitometry combined with precise, computerized measurements enable the densitometrist to utilize both.

Fan-Array Spine Imaging with DXA

Fan-array DXA spine imaging is one of the newer applications for DXA. The spine can be imaged from T4 to L5 in the lateral or PA projection. DXA spine imaging can be performed in seconds to minutes, depending on the scan mode, but always at a fraction of the radiation exposure of conventional spine radiographs.

Lateral spine images, such as the image shown in Fig. 10-6, can be evaluated using Genant's semiquantitative method. Morphometric software can also be used to define and measure vertebral heights, as shown in Fig. 10-7. This technique is called morphometric X-ray absorptiometry (MXA) in contrast to the use of conventional radiographs for morphometric measurements, which is called morphometric radiography (MXR). In 1998, Rea et al. *(61)* evaluated 161 postmenopausal women for fracture using conventional lateral spine radiographs and fan-array lateral spine imaging. Both image types were evaluated using Genant's semiquantitative method. The sensitivity for moderate and severe (grade 2 and 3, in the Genant method) vertebral fractures for analyzable vertebrae on the DXA spine images was 91.9%. When mild (grade 1) fractures were included, the sensitivity dropped to 77.4%. The specificity was extremely high, however,

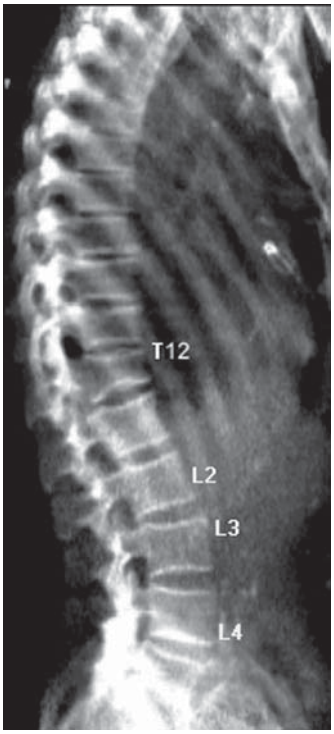

Fig. 10-6. A lateral spine DVA™ image from a Lunar Prodigy showing a grade 2 fracture at T12. Case courtesy of GE Medical Systems, Madison, WI.

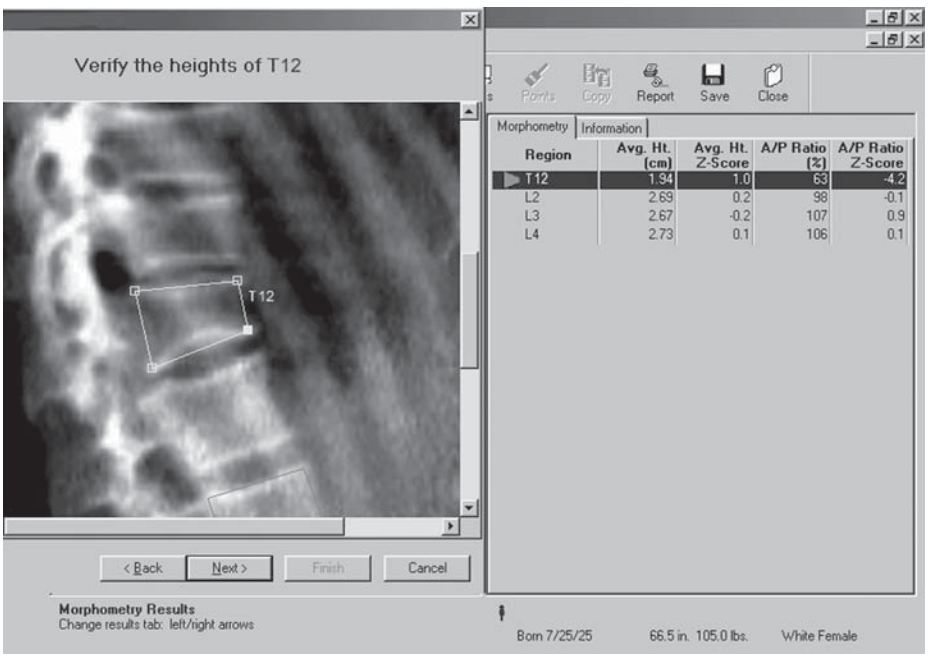

Fig. 10-7. Computerized morphometric analysis of vertebral heights for T12, as seen in Fig. 10-6. Case courtesy of GE Medical Systems, Madison, WI.

at 98.4% in analyzable vertebrae. As a result, the negative predictive value of DXA spine imaging for vertebral fractures was excellent. Even when mild fractures were included, the negative predictive value for spine fractures from the DXA spine images was 97.5%, suggesting that DXA spine imaging was an excellent means of excluding the diagnosis of vertebral fracture. The agreement in fracture diagnoses between the visual assessment of DXA spine images and the semiquantitative assessment of standard spine radiographs for vertebrae that could be evaluated with both techniques was 96.3%.

Although DXA spine imaging spans T4 to L4, it is not uncommon for the uppermost thoracic vertebrae to be poorly visualized. In the study by Rea et al. *(61)*, 94.9% of the vertebrae could be evaluated. T4 and T5 were the most common vertebrae that were too poorly visualized to be evaluated. In a study by Schousboe et al. *(62)* in which 342 women underwent DXA lateral spine imaging, 92.1%, or 4096 of the 4446 vertebrae studied, could be evaluated. In this study, T4 to T6 were less likely to be adequately visualized. The inability to consistently evaluate T4 to T6 on lateral DXA spine images does not present a significant problem in osteoporotic fracture identification. Several studies have demonstrated that the majority of fractures occur below these levels. The most common locations for vertebral fractures would appear to be T11 to L1, followed by T7 and T8 *(34,59,62,63)*. In studies that have utilized DXA spine imaging for spine fracture diagnosis, a surprising percentage of women with nonosteoporotic bone densities have been found to have fractures. In the study by Schousboe et al. *(62)*, 27.4% of the patients age 60 and older with osteopenic bone densities according to WHO Criteria were found to have vertebral deformities consistent with a diagnosis of fracture on DXA spine images. Of the patients age 60 and older with osteoporotic bone densities, 42% were found to have vertebral deformities as well. In this study, the diagnosis of fracture on the DXA image was based primarily on Genant's semiquantitative method. Faulkner et al. *(64)* evaluated 231 women with a mean age of 65 with DXA spine imaging utilizing proprietary morphometric software in which a diagnosis of spine fracture was based on a reduction in vertebral height or height ratio of 3 SD or more from the expected mean value. Using this definition of prevalent fracture, more than 50% of the women were found to have vertebral fractures. Based on bone density at the PA lumbar spine or proximal femur, 46.7% of the women had osteopenia and 26.4% had osteoporosis. Of the women with osteopenia, 49.1% were found to have spine fractures. More than 72% of the women with osteoporosis were also found to have spine fractures based on MXA measurements.

MXA, like densitometry, is a quantitative measurement technique. Like densitometry, the utility of MXA can be assessed in part, by its reproducibility or precision. The long-term precision of MXA was evaluated by Ferrar et al. *(65)* in a population-based sample of 48 postmenopausal women (average age 65 years) and in 50 postmenopausal women with osteoporosis (average age 67 years). Spine imaging was performed with a Hologic QDR 4500 A on two occasions. Precision was calculated for the population-based sample over a 2-year period. One-year precision was calculated for the osteoporotic women. In both groups, use of the "compare" option resulted in better precision. In the population-based sample, the RMS-SD was 0.60 mm with the "compare" option and 0.87 mm without the "compare" option for vertebral heights. The RMS-SD for height ratios in this group was 0.03 and 0.18, with and without "compare." Precision was poorer in the osteoporotic group with RMS-SD of 0.77 mm and 1.59 mm for vertebral heights, again with and without the "compare" option, respectively. Ferrar et al. concluded that the long-term precision of MXA was comparable to that of MXR. Rea et al. *(66)* also evaluated

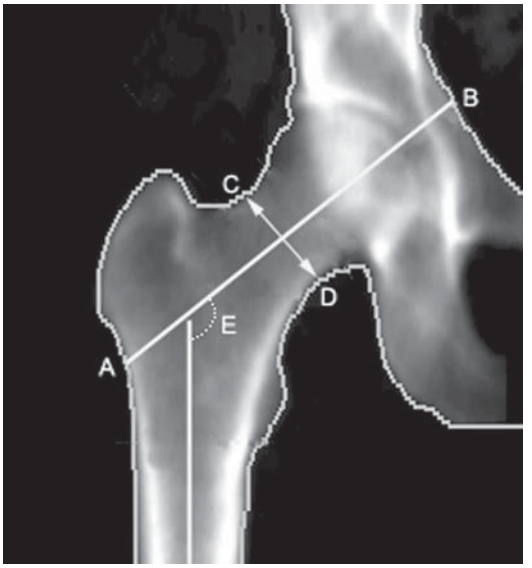

Fig. 10-8. The proximal femur image showing the HAL **(A-B)**, femoral neck width **(C-D)**, and neck-shaft angle **(E)**.

the long-term precision of MXA and compared it to that of MXR. Although these authors concluded that the precision of MXA was not as good as that of MXR, they noted, as did Ferrer et al. *(65)*, that the precision errors for both techniques were substantially smaller than the 20 to 25% reduction in vertebral height often used as a criteria for the diagnosis of incident vertebral fracture.

Proximal Femur Morphometry

Interest in the measurement of the dimensions and geometry of the proximal femur as part of the assessment of fracture risk was spurred by the initial recognition of hip axis length as an independent predictor of hip fracture risk. Other measures have come under scrutiny as predictors of hip fracture risk as well. These are measures such as the neck-shaft angle and femoral neck width as well as segments of the hip axis length.

Hip Axis Length

Hip axis length (HAL) has been demonstrated to be a predictor of hip fracture risk that is independent of BMD *(67)*. As part of the Study of Osteoporotic Fractures, 8074 women aged 65 and older were evaluated with DXA (Hologic QDR-1000) measurements of the proximal femur. HAL was measured in 134 women without fractures and in 64 women who experienced hip fractures during 1.6 years of follow-up. A goniometer was used to measure HAL from the computer printout. HAL was defined as the distance from the inner pelvic brim to the outer edge of the greater trochanter along the femoral neck axis as shown in Fig. 10-8. Odds ratios for BMD and the risk of hip fracture and for HAL and the risk of hip fracture were calculated. For femoral neck BMD, each SD *decline* in BMD resulted in a 2.7-fold increase in the risk of hip fracture. For HAL, each SD *increase* in length resulted in a 1.9-fold increase in the risk of femoral neck fracture and a 1.6-fold increase in the risk of trochanteric fracture.

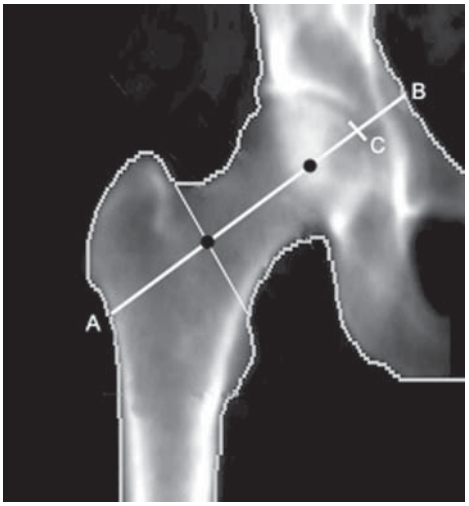

Fig. 10-9. The proximal femur showing the HAL **(A-B)** and its segments: the femoral neck axis length or FNAL **(A-C)**, and the intertrochanteric-head distance (■ - ●).

In 1994, Faulkner et al. *(68)* proposed automating the measurement of HAL on proximal femur bone density studies. Faulkner et al. re-analyzed the 198 proximal femur studies for which HAL had been determined manually *(67)*, with modified proximal femur analysis software using a QDR-1000/W (Hologic, Inc.). The correlation between the manual and automated measurements was 0.98. The precision of the automated HAL measurement was determined as the average SD from three measurements on each of 33 women. This value was 0.07 cm or 0.68%.

Duboeuf et al. *(69)* also found that HAL was a significant predictor of femoral neck fracture risk with an odds ratio of 1.64 based on an analysis of proximal femur studies from the EPIDOS[4] study. Unlike Faulkner et al. *(67)*, however, these authors concluded that HAL was not a significant predictor of trochanteric fracture. Other authors have attempted to partition the HAL into segments, to determine if any particular segment of HAL was more predictive of hip fracture than HAL itself. One such segment is the femoral neck axis length (FNAL), which is a segment of HAL that spans the base of the greater trochanter to the apex of the femoral head as shown in Fig. 10-9. Center et al. *(70)* measured the FNAL in 260 men and women from the Dubbo Osteoporosis Epidemiology Study[5] from proximal femur DXA studies in which the analysis software included a ruler that could be a manipulated for the measurement. In this study, FNAL was significantly correlated with current and maximum height. When FNAL was adjusted for current and maximum height, however, no difference was seen between hip fracture patients and nonfractured patients in the FNAL. Center et al. concluded that the FNAL had very little utility in improving hip fracture risk prediction.

[4] EPIDOS is a multicenter prospective study of 7575 women living at home, age 75 to 95 years, in France. The data in this study are from 320 women from the Lyon and Montpellier centers.

[5] The Dubbo Osteoporosis Epidemiology Study is a case-control study involving 1902 men and women who were recruited between 1989 and 1993.

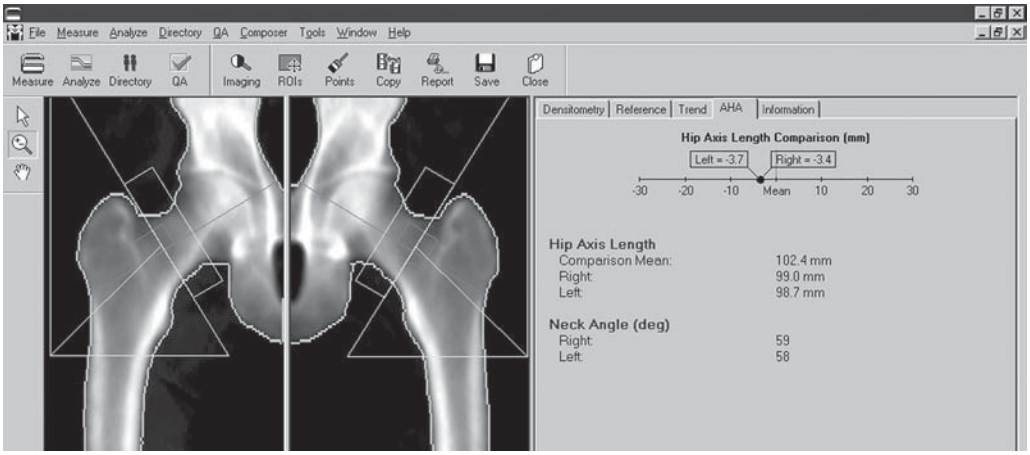

Fig. 10-10. A Lunar Prodigy DualFemur® study with the HAL measurement. The HAL in both femurs is slightly shorter than predicted for height.

Bergot et al. *(71)* evaluated HAL and seven different segments of HAL, including the FNAL, from proximal femur DXA scans acquired on a Hologic QDR 1000/W. Comparisons of measurements in 49 women with nontraumatic hip fractures to measurements in 49 age-matched women and 49 age- and BMD-matched women were made to determine which HAL segments best discriminated between the three groups of women. The best discriminators between women with hip fractures and all nonfractured women were femoral neck BMD and HAL. Femoral neck BMD and HAL were also the best discriminators between the women with hip fracture and the nonfractured, age-matched women. The best discriminator between fractured women and low BMD-matched, nonfractured women was a different segment of HAL called the intertrochanter-head center distance, defined by the line that begins at the center of the femoral head and ends at the intertrochanteric line, shown in Fig. 10-9. FNAL was not useful in discriminating between the groups. The authors noted that the intertrochanter-head center distance is more difficult to measure than HAL because of the imprecision in marking the center of the femoral head. Normal values, as well as the magnitude of risk imparted by increases in the intertrochanter-head center distance, must be established. This particular segment of HAL remains a focus of research interest.

HAL has been suggested as a possible explanation for the difference in hip fracture rates among various races. Cummings et al. *(72)* demonstrated that the mean HAL of predominantly US-born Asian and Black women was significantly shorter than that of Caucasian women. Both Asian and Black women are known to have a lower risk of hip fracture than Caucasian women. Nakamura et al. *(73)* demonstrated that the FNAL, a component of HAL, was significantly shorter in Japanese women than in Caucasian women, noting that hip fracture rates in Japanese are approximately half that seen in Caucasians. HAL is simple to measure and is now offered as an automated measurement commercially on proximal femur bone density studies. Figure 10-10 is a DualFemur® DXA study performed on a Lunar Prodigy showing the HAL measurement. The scale indicates the patient's value in comparison to the mean value predicted for height.

Although this is clearly a nonmodifiable risk factor, HAL can be useful for hip fracture risk stratification. Using the Lunar Prodigy, Bonnick and Lewis *(74)* reported RMS-SD and RMS-%CV precision values for HAL measurements of the left femur of 0.7 mm or 0.67% in women age 20 to 49 and 0.6 mm or 0.53% in women age 50 to 70.

The Femoral Neck-Shaft Angle

The femoral neck-shaft angle is another geometric measure that has been studied as a predictor of hip fracture risk. This angle is indicated by the letter "E" in Fig. 10-8. The studies to date have provided mixed results on the utility of this measure. Several studies *(75–78)* have found significantly greater femoral neck-shaft angles in hip fracture patients than in controls while others *(67,71,79)* have not. In the study from Bergot et al. *(71)*, the neck-shaft angle was not different in the hip fracture patients compared to the low-BMD nonfractured patients or the age-matched controls. The neck-shaft angle was 127.1° in the fracture patients compared to 127.2° in the low-BMD nonfractured patients and 125.6° in the age-matched control group. In contrast, in a study from Partanen et al. *(78)*, the neck-shaft angle was statistically significantly greater in a group of 70 postmenopausal women with hip fractures (mean age 74.9 years) compared to a control group of 40 postmenopausal women (mean age 73.7) without hip fractures. In the fracture group, the mean neck-shaft angle was 133.7° compared to a mean of 128.3° in the control group. Partanen et al. also found that the neck-shaft angle was significantly greater in the 46 women with cervical fractures than in the 24 women with trochanteric fractures. The neck-shaft angle in the cervical fracture group was 135.7° compared to 130.3° in the trochanteric fracture group.

Femoral Neck Width

Femoral neck width is measured at the narrowest part of the femoral neck as indicated by line C–D in Fig. 10-8. An increase in neck width from periosteal bone apposition has been postulated as a response to a decrease in bone density. The result of the width increase should be an increase in the cross-sectional moment of inertia (CSMI). This would potentially compensate for the reduction in endosteal bone and theoretically reduce the risk of hip fracture. If this is so, the increase in femoral neck width in the presence of a low bone density should indicate a reduction in fracture risk compared to individuals with an average or reduced neck width and the same low bone density. Nevertheless, Bergot et al. *(71)* did not find a statistically significant difference in neck width between hip fracture patients and age- and BMD-matched nonfractured controls. The absolute neck width was slightly greater in the age- and BMD-matched nonfractured control group compared to the hip fracture patients at 3.20 cm compared to 3.17 cm. In this study, the femoral neck width was greater in both the fracture group and age- and BMD-matched nonfractured group compared to the age-matched controls but again, not statistically significantly so. Other investigators *(75,76)* have found a significant increase in femoral neck width in fracture patients compared to controls.

The Upper Femoral Neck

The upper femoral neck is a relatively new region of interest in the proximal femur. It is the superior half of the traditional femoral neck region of interest as shown in Fig. 10-11. Yoshikawa et al. *(80)* suggested that there was a greater decrease in bone density in the superior region of the femoral neck in women. They suggested that this would

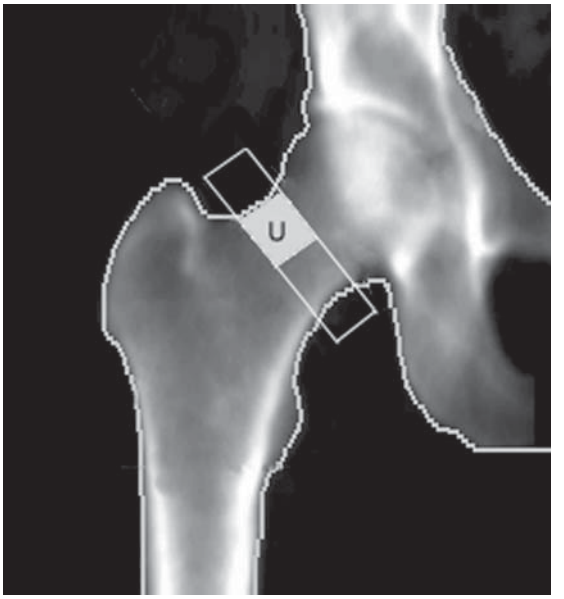

Fig. 10-11. The upper neck region of interest in the proximal femur.

cause the center of mass to move in such a way as to place greater stress on the femoral neck, increasing the risk of fracture. The upper femoral neck region of interest was compared to the entire femoral neck region and to the lower femoral neck region for the prediction of neck and trochanteric hip fracture in the study from Duboeuf et al. *(69)*. In this study, upper femoral neck BMD was highly predictive of femoral neck fracture with an odds ratio of 2.8 for each SD decline in bone density and outperformed the more traditional total femoral neck measurement. The lower femoral neck BMD was not predictive of femoral neck fracture. All three regions were predictive of trochanteric fracture and hip fracture in general.

Hip Strength Analysis

Yoshikawa et al. *(80)* developed algorithms to calculate the CSMI as well as other measures of hip strength. Yoshikawa et al. noted that although BMD was an important predictor of hip fracture risk, BMD accounted for only 50% of the bone strength estimated from the CSMI. This suggested that the CSMI reflected elements of bone strength not captured in the measurement of BMD. In 2002, Crabtree et al. *(81)* reported the application of a test version of proprietary DXA software (GE Medical Systems) designed to assess hip strength. The subjects for this study were 68 women age 60 and older who had recently suffered a hip fracture and 800 women age 60 and older without a hip fracture originally recruited as part of the EPOS study. All subjects underwent standard proximal femur DXA studies (Lunar DPX). The hip strength analysis (HSA) software uses the proximal femur DXA study to calculate measures reflecting the geometry and bone distribution within the proximal femur. In addition to standard measurements of proximal femur BMD, the program calculated the upper and lower femoral neck BMD, HAL, Cstress, and Fall Index (FI). Cstress reflects the compressive

stress from a fall on the greater trochanter. Typical units are N/mm^2. The calculation of the CSMI is necessary to calculate Cstress. The FI is a dimensionless quantity that reflects the resistance to fracture from forces generated during a fall on the greater trochanter. In this study, HAL was significantly longer in the fracture patients than in the controls. Cstress was also significantly greater in the fracture patients than in the controls. The FI was significantly lower in the fracture patients than in the controls. Femoral neck BMD, whether measured as a total, upper, or lower neck value, was significantly lower in the fracture patients than in the controls. Unlike the earlier study from Duboeuf et al. *(69)*, Crabtree et al. could not show that the upper femoral neck BMD was a better predictor of femoral neck fracture than total femoral neck BMD. The authors then attempted to develop a statistical model for the prediction of hip fracture status. They found that the combination of Cstress, age, and BMI in the model resulted in an area under the curve (AUC) of 0.875. The use of femoral neck BMD alone resulted in an AUC of 0.827. The difference between these two areas was statistically significant. Femoral neck BMD alone was better than Cstress alone, but the addition of femoral neck BMD to the model containing Cstress, age, and BMI did not improve the model's ability to predict hip fracture status. The authors concluded that HSA could enhance the prediction of hip fracture risk.

COMBINING CLINICAL RISK FACTORS WITH BMD TO PREDICT FRACTURE RISK

BMD is one of many risk factors for fracture, albeit a major one, rivaled only by a prior fragility fracture. Pharmacological bone active agents are prescribed to favorably affect bone to modify an individual's fracture risk. They cannot reasonably be expected to modify nonbone clinical risk factors for fracture, such as the risk of falling, family history of fracture, or smoking. Nevertheless, nonbone or nondensity-related risk factors for fracture can be combined with knowledge of the patients bone density to more precisely determine the patient's actual fracture risk. As noted previously, age is commonly combined with bone density for fracture risk prediction. Leslie et al. *(82)* developed a clinical risk factor inventory primarily using data from the Study of Osteoporotic Fractures. They combined this inventory with age and BMD to produce a prediction of 5-year and lifetime hip fracture risk as well as a prediction of the number needed to treat to prevent a hip fracture, assuming a 50% reduction in risk from a therapeutic intervention. The authors caution that this predictive model has not been validated clinically and that the predictions may not be valid for non-Caucasian women. The risk factors are also weighted toward the prediction of hip fracture, rather than other types of fracture. This prediction model is available on the internet at http://apps.sbgh.mb.ca/fracture/. The user must enter the patient's age and bone density *z*-score (not *T*-score) and relative risk for fracture per SD decline in bone density. If no relative risk is entered in the space provided, a relative risk of 2.6 will be assumed, which is appropriate for hip fracture risk when bone density is measured at the proximal femur. If a nonfemoral site is measured, the appropriate relative risk value should be entered for the prediction of hip fracture at that site. The user checks the relevant risk factors from the list and then clicks on "calculate." The 5-year and lifetime hip fracture risks are presented based on age; age and clinical risk factors; and age, clinical risk factors, and BMD. The calculation from the web site is shown in Fig. 10-12.

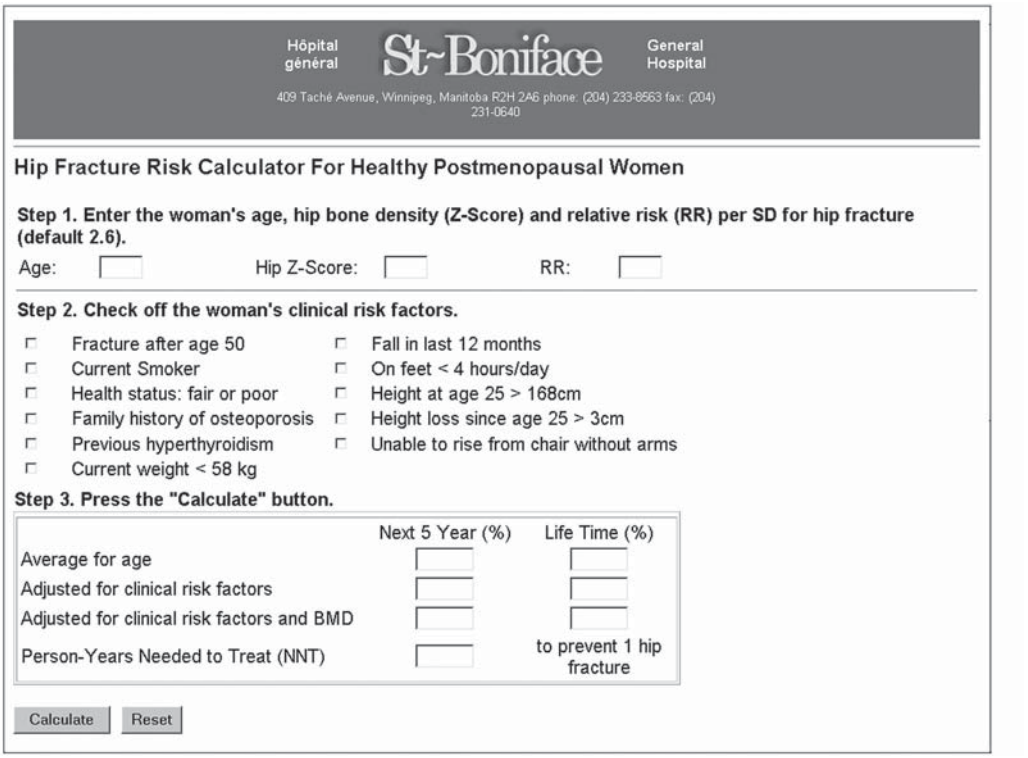

Fig. 10-12. Five-year and lifetime hip fracture risk calculation as seen at http://apps.sbgh.mb.ca/fracture/ based on age, hip bone density *z*-score and risk factors. Reproduced with permission of Dr. William Leslie, St. Boniface General Hospital, Winnipeg, Manitoba.

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11 Monitoring Changes in Bone Density

CONTENTS

In following changes in bone density in individuals, a densitometrist is generally interested in disease progression or therapeutic efficacy. As densitometry has become more widespread, the awareness of the number of diseases with effects on skeletal density has also increased. Nevertheless, monitoring changes in bone density is still primarily done to assess therapeutic efficacy of bone active agents. An increase in bone density, or, depending on the agent, stabilization of the bone density is considered an appropriate surrogate for efficacy of the agent in reducing fracture risk. Although effects on bone density are not the only means by which therapeutic agents may reduce fracture risk, meta-analyses of the relationship between changes in bone density and spine fracture risk have consistently demonstrated a statistically significant relationship between increasing bone density and declining spine fracture risk *(1,2)*. The same can be said of nonspine fractures and bone density, in which the relationship appears to be even stronger *(3)*. This does not negate any potential effects of therapeutic agents on nondensity factors in reducing fracture risk. It simply means that changes in bone density remain the best surrogate marker for fracture risk reduction in clinical practice. To properly follow changes in bone density and interpret the results, the densitometrist must be thoroughly familiar with the concept of precision, which was introduced in Chapter 3.

THE CONCEPT OF PRECISION

Precision is the attribute of a quantitative measurement technique like bone densitometry that refers to the ability to reproduce the same numerical result in the setting of no real biologic change when the test is repeatedly performed in an identical fashion. Like all quantitative tests in clinical medicine, no bone densitometry technique is perfectly reproducible. This is true even when the bone density test is performed in exact accordance with the manufacturer's recommendations every time. If the test is

not consistently performed in accordance with the manufacturer's recommendations, the technique becomes less reproducible.

The precision of bone density testing assumes great importance when the technique is used to follow changes in bone density over time. Because densitometry is not perfectly reproducible, the results on any given patient are not expected to be identical, even if the bone density in the patient has not actually changed. The only way that a physician can know that a real biological change has occurred is to know if the precision error of the technique has been exceeded. This means that the precision must be quantified by performing a precision study. The precision, expressed as the root-mean-square SD (RMS-SD) with the same units as the measurement or the root-mean-square %CV (RMS-%CV), is then used to determine the minimum change in bone density that constitutes a real biological change. This is called the least significant change (LSC). The LSC can then be used to determine the minimum interval between follow-up measurements.

PERFORMING A PRECISION STUDY

The results of three PA lumbar spine DXA bone density measurements are shown in Table 11-1. Mrs. B., whose bone density studies were previously discussed in Chapter 3 in the explanation of the mean, variance, and SD, is the patient whose results are shown in the table. Remember that these measurements on Mrs. B. were all performed within a few minutes of each other, with only enough time between studies to allow Mrs. B. to get off the scan table and be repositioned by the technologist. The same technologist positioned Mrs. B. perfectly for all three studies and also analyzed all three studies according to the manufacturer's recommendations. The mean or average value for these three studies was 1.021 g/cm^2.

Note that the numerical results of the three studies are not identical, even though each study was performed perfectly and no biological change could have occurred in Mrs. B. in the brief period that elapsed between tests. This reflects the imperfect precision of bone densitometry. In looking at Mrs. B.'s measurements in Table 11-1 it is reasonable to ask, by how much do each of the three measurements vary from the mean value? This can be found by subtracting each of the three measurements from the mean value, as shown in Equations 1 through 3.

$$\text{Scan 1: } 1.011 - 1.021 = -0.010 \text{ g/cm}^2 \quad (1)$$

$$\text{Scan 2: } 1.030 - 1.021 = 0.009 \text{ g/cm}^2 \quad (2)$$

$$\text{Scan 3: } 1.022 - 1.021 = 0.001 \text{ g/cm}^2 \quad (3)$$

The question then becomes, what is the representative variation from the mean for each of these measurements? An intuitive approach would be to find the average difference by adding the three differences found in equations 1 through 3 and dividing the sum by 3. This is neither mathematically correct nor possible, because the sum of the differences is 0, which cannot be divided. Instead, the formula in equation 4 is used. The three differences are squared, to remove the minus signs. After squaring, they are added and the resulting total is divided by the number of measurements minus 1 (or in this case, 2). Then the square root is taken. The resulting value is the SD for the set of three measurements on Mrs. B. The SD has the units of the measurement, g/cm^2, and is the appropriate expression of the representative variability about the mean for the

Table 11-1
Results from a Series of Three PA Lumbar Spine DXA Studies on Patient, Mrs. B.

PA Spine DXA Studies	
Study 1	1.011 g/cm^2
Study 2	1.030 g/cm^2
Study 3	1.022 g/cm^2
Mean	1.021 g/cm^2
SD	0.010 g/cm^2
CV	0.010
%CV	1.0%

three measurements on Mrs. B. The SD is also the appropriate expression of the precision of the three measurements.

$$SD_B = \sqrt{\frac{\sum_{i=1}^{n_B} \left(X_{iB} - \bar{X}_B\right)^2}{n_B - 1}} \tag{4}$$

In Equation 4, n_B is the number of measurements on Mrs. B., X_{iB} is the actual value of the *i*th measurement and $\bar{X}_B$ (pronounced X bar) is the mean BMD value for Mrs. B. The sum of the squared differences is divided by n-1 rather than n because, in this case, only two of the three measurements actually contribute independently to the calculation of the mean. In other words, if the average value and two of the three measured values that were used to calculate the average were known, the third measured value could always be determined mathematically. The third value is thus not independent. In the example presented, the SD for the set of three measurements on Mrs. B. is 0.010 g/cm^2 as shown in Table 11-1.

Now that the SD and mean value for the three measurements on Mrs. B. are known to be 0.010 g/cm^2 and 1.021 g/cm^2, respectively, one can ask what proportion or percentage of the mean does the SD represent? This is found by dividing the SD by the mean as shown in Equation 5. This quantity is called the coefficient of variation (CV). When multiplied by 100 and expressed as a percentage, it is called the percent coefficient of variation (%CV) as shown in Equation 6. The CV and %CV are alternative expressions of the precision of the measurement. For Mrs. B., the CV was 0.010 (after rounding) and the %CV, 1.0%.

$$CV = \frac{SD}{\bar{X}} \tag{5}$$

$$\%CV = \frac{SD}{\bar{X}}(100) \tag{6}$$

Although the SD, CV, or %CV for Mrs. B. could be used in determining significant changes in PA lumbar spine bone density over time for Mrs. B., calculating individual precision values for every patient in a clinical practice that might be followed with bone densitometry is not practical. It is necessary to establish representative precision values for each skeletal site used for monitoring at a bone densitometry facility. This is done by performing a short-term precision study.

Table 11-2
Combination of Number of Patients and Scans Per Patient for 30 Degrees of Freedom in a Precision Study

Number of Patients	*Number of Scans per Patient*
1	31
5	7
10	4
15	3
30	2

Short-Term Precision Studies

A separate precision study must be done for each skeletal site that might be used in following a patient. The precision for multiple regions within a skeletal site, such as the five regions of interest within the proximal femur, can be determined from a single proximal femur precision study.

The number of individuals and number of scans per individual needed for a precision study is determined by the degrees of freedom necessary to achieve the narrowest confidence limits for the precision estimate that are practical. Remember that one of the measurements on an individual will not contribute independently to the calculation of the mean for that individual. The number of measurements that do independently contribute are called the degrees of freedom (df) for the study. For statistical validity, it is recommended that a short-term precision study have 30 df *(4)*. Thirty df are chosen to ensure that the upper limit for the 95% CI of the precision value is no more than 34% greater than the calculated precision value. If only one person is studied, 31 tests must be performed to obtain 30 df because one test will not contribute independently to the calculation of the mean. If 15 patients are studied, three tests per patient must be done because again, only two of the three tests per patient will be independent ($15 \times 2 = 30$). The specific combinations of the number of patients and number of scans per patient that are recommended for a short-term precision study are shown in Table 11-2. A short-term precision study should be completed in 2–4 weeks. All the scans on any one patient can be completed on the same day if desired.

The following is the method for determining short-term precision as recommended by Gluer et al. *(5)*. Using the combination of 15 patients and three scans each for the sake of example, the average value, SD, and CV should be found for each of the 15 sets of three measurements, just as was done for the set of three measurements on Mrs. B. Rather than reporting the arithmetic mean of the 15 SDs or 15 CVs (adding the 15 values and dividing by 15) as the precision value, the RMS-SD or the RMS-CV is calculated as shown in Equations 7 and 8. The RMS-SD and RMS-CV are preferred to the arithmetic mean SD and CV because the latter quantities tend to underestimate the Gaussian error.[1]

[1] The Gaussian distribution is the symmetrical bell-shaped curve that is obtained from a plot of values of a variable in which the variation in the value is caused by several independent factors. It was named after Gauss, the individual who originally described it. If the variation in the value of a variable is primarily from only one factor, the distribution will not be a symmetrical bell-shaped curve. Instead, it may be skewed in one direction or the other.

Table 11-3
The Measured and Mean PA Lumbar Spine Values for 15 Patients in a Short-Term Precision Study

Patient	*Scan 1*	*Scan 2*	*Scan 3*	*Mean*
1	1.011	1.030	1.022	1.021
2	0.925	0.940	0.918	0.928
3	1.164	1.160	1.170	1.165
4	0.999	1.010	1.008	1.006
5	0.900	0.920	0.905	0.908
6	0.955	0.960	0.960	0.958
7	1.000	1.010	1.150	1.053
8	0.875	0.849	0.869	0.864
9	0.898	0.920	0.901	0.906
10	1.111	1.009	1.100	1.073
11	0.964	0.949	0.960	0.958
12	1.000	0.985	0.992	0.992
13	1.200	1.185	1.205	1.197
14	1.165	1.170	1.180	1.172
15	0.909	0.915	0.904	0.909

Note: All values are in g/cm^2

$$SD_{RMS} = \sqrt{\frac{\sum_{i=1}^{m} \left(SD^2\right)}{m}} \tag{7}$$

$$CV_{RMS} = \sqrt{\frac{\sum_{i=1}^{m} \left(CV^2\right)}{m}} \tag{8}$$

In Equations 7 and 8, m is the number of patients. Using these equations, the 15 SDs or 15 CVs would be squared, summed, and then divided by the number of patients, 15. Then the square root is taken resulting in the RMS-SD or RMS-CV for the group of 15 patients. The RMS-CV can be expressed as a percentage, the RMS-%CV, by multiplying by 100.

In the following example, the short-term precision for the PA lumbar spine was calculated after three PA lumbar spine studies were performed on each of 15 patients within 4 weeks. The same technologist scanned all of the patients. Between each scan, the patient was repositioned. The individual values and the average value for each of the 15 patients are listed in Table 11-3. In all, 45 PA spine studies were performed (15 patients × 3 scans/patient = 45 scans).

Mathematical Procedures Used to Calculate Precision

Step 1

The mean or average BMD, SD, CV, and %CV for the set of three scans for each of the 15 patients must be calculated. These results are shown in Table 11-4. Note that patient 1 in Table 11-3 and 11-4 is Mrs. B., for whom this calculation was made earlier.

Table 11-4
The Mean, Standard Deviation (SD), Coefficient of Variation (CV), and % Coefficient of Variation (%CV) for Each of 15 Patients in a Short-Term Precision Study

Patient	*Mean*[a]	*SD*[a]	*CV*	*%CV*
1	1.021	0.010	0.010	1.0%
2	0.928	0.011	0.012	1.2%
3	1.165	0.005	0.004	0.4%
4	1.006	0.006	0.006	0.6%
5	0.908	0.010	0.011	1.2%
6	0.958	0.003	0.003	0.3%
7	1.053	0.084	0.080	8.0%
8	0.864	0.014	0.016	1.6%
9	0.906	0.012	0.013	1.3%
10	1.073	0.056	0.052	5.2%
11	0.958	0.008	0.008	0.8%
12	0.992	0.008	0.008	0.8%
13	1.197	0.010	0.009	0.9%
14	1.172	0.008	0.007	0.7%
15	0.909	0.006	0.006	0.6%

[a] Mean and SD values are in g/cm^2.

Step 2

Although the precision for each of the 15 patients is now known, the precision for the group as a whole must now be calculated. This is done by finding the RMS-SD or RMS-CV for the group of 15 patients, using equations 7 and 8.

Using Equation 7, each of the 15 SDs is squared. The 15 squared SDs are summed beginning with Mrs. B. who is patient 1 and continuing through the total number of patients, *m*, which in this case is 15. The sum is divided by *m*, the number of patients or 15. Finally, the square root is taken. This is the RMS-SD in g/cm^2 and is the precision for the entire group. For the short-term precision study illustrated in Tables 11-3 and 11-4, the RMS-SD is 0.027 g/cm^2.

Because the precision may also be expressed as the CV, the RMS-CV for the entire group of 15 patients is determined using equation 8. The steps are analogous to those described for equation 7 and the calculation of the RMS-SD, except that the CV for each set of scans is used instead of the SD.

Using Equation 8, each of the 15 CVs that have been previously calculated are squared and then added. This sum is divided by the number of patients, *m*, and then the square root is taken. This is the RMS-CV for the entire group. To convert this value to the RMS-%CV, the RMS-CV is multiplied by 100. The RMS-%CV for the group of 15 patients is 2.61%.

The average BMD for the entire group used to determine the precision should be stated in addition to the RMS-SD, RMS-CV, or RMS-%CV. The average BMD for the group of 15 patients is found simply by adding all 45 values and dividing by 45. This value is 1.007 g/cm^2. The average BMD for the group should be stated because the precision may not be as good in osteopenic or osteoporotic populations as it is in normal

populations. When the precision is expressed as a CV or %CV, part of the poorer precision in groups with a lower average BMD is a function of the smaller denominator in the calculation of the CV for each patient. For example, in the group of 15 patients with an average BMD of 1.007 g/cm^2 shown in Tables 11-3 and 11-4, the precision was found to be 0.027 g/cm^2 when the RMS-SD was used and 2.61 % when the RMS-%CV was used. If a precision study was done in a different group of 15 individuals and the RMS-SD for this group was also 0.027 g/cm^2, it would be correct to conclude that the precision was equal in the two groups. However, if the average BMD in the second group was lower, the RMS-%CV would appear to be poorer.

Part of the poorer precision may be real however. As the bones become progressively demineralized and the BMD falls, the precision may not be as good as the precision in individuals with higher levels of BMD. In ideal circumstances, a precision study would be performed on different groups of individuals in which the average BMDs of the various groups spanned normal to osteoporotic values. The appropriate precision value could then be applied in clinical circumstances based on the BMD of the patient in question. Another approach is to perform a precision study in each individual patient that will be followed. Neither are clinically practical suggestions. It is therefore important to remember that the precision value obtained in a short-term study of young, normal individuals represents the best possible precision. Nevertheless, this is an excellent population to test the basic skills of the technologist in positioning and analysis. If a young, healthy population is not representative of the patient population in whom the precision values would be used, a second precision study should be performed using individuals who more closely resemble the patient population in age and BMD.

Most authorities agree that precision should be expressed as the RMS-SD in the units of the measurement. Nevertheless, use of the arithmetic mean SD as well as the arithmetic mean %CV remains common in the literature. The arithmetic mean SD, CV and %CV will appear better than their RMS counterparts.

Long-Term Precision Studies

A long-term precision study in which patients are followed over the course of at least 1 year would be preferable to a short-term precision study, but is logistically much more difficult to do. The calculation of the precision value is also different, requiring the use of a statistical technique called linear regression because biological changes would be expected to occur during the longer time frame. Instead of the SD, a different quantity called the standard error of the estimate is calculated and used to express precision *(6)*. Because of the longer time involved, the possibility of other errors in the test increases, such as errors from machine drift and differences in operator techniques. Consequently, long-term precision estimates tend to be poorer than short-term precision estimates. Although a long-term precision study is a more appropriate reflection of the relevant circumstances in clinical practice, the logistical difficulties of performing such a study make it impractical to do.

APPLYING THE PRECISION VALUE TO SERIAL MEASUREMENTS

Assume that a postmenopausal woman, Mrs. C., underwent a PA lumbar spine bone density study and her physician elected to begin a bone active therapy for the treatment of osteoporosis. Her baseline study revealed a BMD of 0.734 g/cm^2. How long should the

Table 11-5
Z' Values for Various Levels of Statistical Confidence

Statistical Confidence Level	*Z' Value*
99%	2.58
95%	1.96
90%	1.65
85%	1.44
80%	1.28

physician wait before repeating the PA spine bone density study in the hope of seeing a significant change in BMD? When the repeat bone density study was performed, the PA spine bone density was 0.760 g/cm^2. This represented an absolute increase of 0.026 g/cm^2 or 3.54% from baseline. Was this a statistically significant increase given that the technology cannot perfectly reproduce the results of any bone density test even when there has been no real change in the BMD? Answering these questions begins with establishing the precision value for PA lumbar spine bone density testing and then using this value to determine the least significant change (LSC).

The Determination of LSC

Once the precision of the measurement at any given skeletal site is known, the magnitude of the change in bone density at that site that indicates real biological change can be determined. This is called the LSC. To determine the LSC, a decision must be made as to what level of statistical confidence is needed and how many measurements will be done at baseline and follow-up. Ideally, 95% statistical confidence is chosen, but 80% statistical confidence is generally more than adequate for clinical decisions. The formula for determining the LSC is as follows:

$$LSC = Z'(Pr)\sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \tag{9}$$

where *Z'* (pronounced Z prime) is the value chosen based on the desired level of statistical confidence, *Pr* is the precision value as either the RMS-SD or the RMS-CV, n_1 is the number of baseline measurements and n_2 is the number of follow-up measurements. *Z'* values are chosen from tables of such values usually found in statistical or mathematical texts. *Z'* values for various levels of confidence are shown in Table 11-5.

For any precision value and any number of baseline and follow-up measurements, the magnitude of the change needed for statistical significance, the LSC, will be less at lower levels of statistical confidence. The magnitude of the LSC can also be reduced for any level of statistical confidence by increasing the number of measurements performed at baseline and follow-up. In clinical practice, one measurement is commonly done at baseline and again at follow-up. When 1 is substituted for both n_1 and n_2 in Equation 9, the sum under the square root sign becomes 2 as shown in Equation 10.

$$LSC = Z'(Pr)\sqrt{\frac{1}{1} + \frac{1}{1}} = Z'(Pr)\sqrt{2} \tag{10}$$

The situation then, of one measurement at baseline and one measurement at follow-up effectively changes equation 10 to equation 11, used for the calculation of the ${}_{1x1}$LSC:

$$ {}_{1x1}LSC = Z'(Pr)1.414 \tag{11} $$

If two measurements are done at baseline and again at follow-up, the sum under the square root sign in equation 9 becomes 1 as shown in equation 12 for the calculation of the ${}_{2x2}$LSC.

$$ {}_{2x2}LSC = Z'(Pr)\sqrt{\frac{1}{2}+\frac{1}{2}} = Z'(Pr)\sqrt{1} \tag{12} $$

This effectively changes the equation for the calculation of the ${}_{2x2}$LSC to:

$$ {}_{2x2}LSC = Z'(Pr)1 = Z'(Pr) \tag{13} $$

Thus, for any level of statistical confidence, the magnitude of the LSC is reduced by performing duplicate measurements at baseline and follow-up rather than single measurements because the product of the Z' and precision values is being multiplied by only 1 instead of 1.414. The LSC is effectively reduced by approximately 30%.

If the Z' values shown in Table 11-5 for 95% and 80% are substituted in the formulas for the ${}_{1x1}$LSC and the ${}_{2x2}$LSC the formulas become:

$$ {}_{1x1}LSC^{95} = 1.96(Pr)1.414 = 2.77(Pr) \tag{14} $$

$$ {}_{1x1}LSC^{80} = 1.28(Pr)1.414 = 1.81(Pr) \tag{15} $$

$$ {}_{2x2}LSC^{95} = 1.96(Pr)1 = 1.96(Pr) \tag{16} $$

$$ {}_{2x2}LSC^{80} = 1.28(Pr)1 = 1.28(Pr) \tag{17} $$

For example, if the RMS-SD precision of PA lumbar spine DXA studies at a facility was determined to be 0.015 g/cm^2, this value would be substituted in Equation 14 if 95% confidence was desired and one measurement was performed both at baseline and follow-up. In that case, the changes in Equation 14 are reflected in Equations 18 and 19.

$$ {}_{1x1}LSC^{95} = 2.77(Pr) = 2.77\left(0.015\ \text{g/cm}^2\right) \tag{18} $$

$$ {}_{1x1}LSC^{95} = 0.042\ \text{g/cm}^2 \tag{19} $$

For 80% confidence, the precision value of 0.015 g/cm^2 is substituted in equation 15, resulting in an LSC of 0.027 g/cm^2. The RMS-%CV can be substituted in a similar fashion for the precision value in equations 14 through 17 to give the LSC as a percent change from baseline for the various levels of confidence and numbers of measurements.

The timing of the repeat measurement is a direct consequence of the LSC. The follow-up measurement(s) should be done when enough time has passed for the LSC to be achieved. Therefore, once the magnitude of the LSC has been determined, the time required between measurements is:

$$ \text{Time Interval} = \frac{\text{LSC}}{\text{Expected rate of change per year}} \tag{20} $$

Table 11-6
The Interval Between BMD Measurements Required to Obtain the $_{1x1}LSC^{95}$ for Various Levels of Precision and Expected Rates of Change

		Interval Between BMD Measurements	
Precision as % CV	*% Change/Year*	*Months*	*Years*
0.5	1	16.7	1.39
	3	5.60	0.46
	5	3.30	0.28
1.0	1	33.2	2.77
	3	11.0	0.92
	5	6.70	0.55
1.5	1	50.0	4.16
	3	16.6	1.39
	5	10.0	0.83
2.0	1	66.5	5.54
	3	22.2	1.85
	5	13.3	1.11
2.5	1	83.2	6.93
	3	27.7	2.31
	5	16.6	1.39

The expected rate of change per year for the various therapeutic agents or disease states is determined from the available literature. For example, if the average increase in bone density after 1 year of therapy with some agent is 0.03 g/cm^2 and the LSC in equation 19 of 0.042 g/cm^2 is used, the time interval required is:

$$\text{Time Interval} = \frac{0.042 \text{ g/cm}^2}{0.03 \text{ g/cm}^2\text{/yr}} = 1.4 \text{ yr} \quad (21)$$

The follow-up measurement should not be made for 1.4 years because it will take at least that long before the LSC can be expected to be reached. The LSC and expected rate of change can also be given as percentages. To calculate the LSC as a percentage change from baseline, the RMS-%CV value must be used as the precision value rather than the RMS-SD.

It is clear then, that the time interval required to see a significant change is not only dependent on the precision at a site but the expected rate of change at that site as well. Therefore, if the precision at a particular site is excellent but the anticipated rate of change is very slow, the required time interval may be far too long to be acceptable for clinical purposes. Table 11-6 illustrates the interaction between precision and rate of change and the time interval to the LSC at the 95% confidence level for one measurement at both baseline and follow-up. Precision tends to be the best, and therefore the precision values the lowest, at the PA lumbar spine, total hip, proximal radius, and heel. Rates of changes at these sites may be quite different however. The preferred skeletal site for monitoring any particular therapy or disease state will be the site that provides the combination of superior precision and greatest rate of change.

A Case in Point

This case study illustrates the application of the precision and LSC values in clinical practice in order to answer the questions posed earlier in this chapter about Mrs. C., the postmenopausal women who has begun therapy for the treatment of osteoporosis. Assume that the precision for PA lumbar spine studies at a bone densitometry facility was previously determined to be 1.5%. This is the RMS-%CV that was calculated from a study of 15 people, each of whom underwent three studies of the PA lumbar spine.[2] Such a precision study provides 30 df. This means that the calculated precision of 1.5%, at a statistical confidence level of 95%, is at worst actually 34% higher than that or 2.01% [(1.5% × 34%) + 1.5%]. At this same facility, the precision for femoral neck bone density studies was established as 2.4%. At 95% confidence, the worst this precision figure might actually be is 3.2%.

Mrs. C., who has a recent diagnosis of osteoporosis, has just received a prescription for a potent antiresorptive agent as treatment for her osteoporosis. Her physician has requested that she have repeat bone density studies to assess the effectiveness of the therapy. When should Mrs. C.'s bone density studies be repeated? The follow-up measurements to assess therapeutic efficacy should not be made until sufficient time has passed to allow the LSC to be reached.

There are several factors to be considered in answering what would seem to be a straightforward question. First, what magnitude of change in bone density at the PA lumbar spine and femoral neck is expected over the course of 1 year with the particular agent that has been prescribed for Mrs. C.? How many measurements will be done at both baseline and follow-up? And finally, what level of statistical confidence is required for the clinical decision-making process. Ninety-five percent confidence is the most stringent criterion but 80% confidence is often more than sufficient.

For this example, assume that the therapeutic agent in question has been shown to produce an average increase of 5% from baseline in PA lumbar spine bone density and 2% in femoral neck bone density during the first year of treatment. One measurement of the PA lumbar spine and femoral neck has already been made and no additional baseline measurements are planned. Only one measurement of either the PA lumbar spine or femoral neck or both is planned at the time of follow-up. The time to the ${}_{1x1}\text{LSC}$ for both 95% and 80% confidence can be calculated.

The first step is to find the ${}_{1x1}\text{LSC}$ for 80% confidence and the ${}_{1x1}\text{LSC}$ for 95% confidence for each of the skeletal sites using the precision values that have been previously established. Equations 14 and 15 can be used to find these values by substituting the RMS-%CV precision values of 1.5% for the PA lumbar spine and 2.4% for the femoral neck into each of the equations. For the lumbar spine, the ${}_{1x1}\text{LSC}^{95}$ is 4.16% and the ${}_{1x1}\text{LSC}^{80}$ is 2.72%. At the femoral neck, the ${}_{1x1}\text{LSC}^{95}$ is 6.65% and the ${}_{1x1}\text{LSC}^{80}$ is 4.34%. Given the anticipated rate of change from the chosen therapeutic agent, the length of time it will take to equal or exceed any of these values is the earliest time that the follow-up study at either site should be performed.

If the average increase in PA lumbar spine bone density with this agent is 5% in the first year, then the ${}_{1x1}\text{LSC}^{95}$ of 4.16% should be exceeded within 1 year. Using equation

[2] Although the RMS-SD is preferred to the RMS-%CV, the change in bone density from baseline seen with various therapeutic agents is generally given as a percentage in the medical literature, necessitating the use of the RMS-%CV for the calculation of the time to the LSC.

20, the exact time can be determined to be 0.8 years. The $_{1x1}LSC^{80}$ at the lumbar spine can be reached even more quickly, by 0.54 years. At the femoral neck, however, given that the average increase in bone density is only 2% in the first year and the precision is slightly poorer than at the PA lumbar spine, the $_{1x1}LSC^{95}$ of 6.65% would not be reached for 3.33 years. Even the $_{1x1}LSC^{80}$ of 4.34% will not be reached for 2.17 years. It would be reasonable then to advise repeating only the PA lumbar spine bone density study in 1 year in anticipation of seeing a change in bone density sufficiently great to conclude that a significant change has occurred with 95% statistical confidence. Repeating the proximal femur bone density study in 1 year would not be reasonable because a significant change in bone density would probably not be detected then, given the precision of testing at the femoral neck and the relatively small anticipated change at that site.

One year later, Mrs. C. returns for her repeat PA spine bone density study. At the time of her original study, her L1–L4 PA lumbar spine bone density study was 0.734 g/cm^2. On her repeat study, the L1–L4 BMD was 0.760 g/cm^2. Is this a significant change? For the change to be significant, the LSC must be equaled or exceeded. In this example, the LSC has been given as a percentage, so the percent increase from baseline for Mrs. C. must be calculated. In order to do this, the baseline BMD value is subtracted from the follow-up value. This difference is divided by the baseline value and multiplied by 100 to express it as a percentage. The formula and the practical application are shown in Equations 22 through 24.

$$\%\ \text{Change from Baseline} = \frac{\text{Follow-up BMD} - \text{Baseline BMD}}{\text{Baseline BMD}} \times 100 \tag{22}$$

$$\%\ \text{Change from Baseline} = \frac{0.076\ \text{g/cm}^2 - 0.734\ \text{g/cm}^2}{0.734\ \text{g/cm}^2\text{/yr}} \times 100 \tag{23}$$

$$\%\ \text{Change from Baseline} = 3.54\% \tag{24}$$

The percent change from baseline of 3.54% does not equal or exceed the $_{1x1}LSC^{95}$ of 4.16% so the change cannot be said to significant at the 95% confidence level. It does exceed the $_{1x1}LSC^{80}$ of 2.72% however, so the change can be said to be significant at the 80% confidence level.

MORE SOPHISTICATED ISSUES OF STATISTICAL CONFIDENCE FOR THE MEASURED CHANGE

Determining the Level of Confidence for Any Change and Precision

In its 2002 position statement, the International Society for Clinical Densitometry (ISCD) *(7)* recommended that the LSC be calculated for 95% confidence and that changes in bone density be considered significant only if they equaled or exceed this value. This is a stringent requirement. It is imperative to know how confident one can be that a real change has occurred, but the level of statistical confidence necessary to influence clinical decisions is generally not required to be 95%. For example, 80% is often more than adequate. If the change in BMD has not equaled or exceeded the LSC for 95% or even 80% confidence, the question then becomes how confident can one be that there has been a real change in the BMD? It is possible to calculate the level of confidence for any given precision value and change in BMD. This is essentially done by using Equation 9.

Table 11-7
Levels of Statistical Confidence[a] for Various Combinations of Precision and Change in BMD

Change in	*Precision (g/cm²)*									
BMD (g/cm²)	*0.005*	*0.010*	*0.015*	*0.020*	*0.025*	*0.030*	*0.035*	*0.040*	*0.045*	*0.050*
0.005	52	28	19	14	11	9	8	7	6	6
0.010	84	52	36	28	22	19	16	14	12	11
0.015	97	71	52	40	33	28	24	21	19	17
0.020	100	84	65	52	43	36	31	28	25	22
0.025	100	92	76	62	52	44	39	34	31	28
0.030	100	97	84	71	60	52	46	40	36	33
0.035	100	99	90	78	68	59	52	46	42	38
0.040	100	100	94	84	74	65	58	52	47	43
0.045	100	100	97	89	80	71	64	57	52	48
0.050	100	100	98	92	84	76	69	62	57	52
0.055	100	100	99	95	88	81	73	67	61	56
0.060	100	100	100	97	91	84	77	71	65	60
0.065	100	100	100	98	93	87	81	75	69	64
0.070	100	100	100	99	95	90	84	78	73	68
0.075	100	100	100	99	97	92	87	82	76	71
0.080	100	100	100	100	98	94	89	84	79	74
0.085	100	100	100	100	98	95	91	87	82	77
0.090	100	100	100	100	99	97	93	89	84	80
0.095	100	100	100	100	99	97	95	91	86	82
0.100	100	100	100	100	100	98	96	92	88	84

[a] Confidence levels are in %.
Table created by and reproduced courtesy of Ken Faulkner, PHD.

The measured change, no matter what it is, is considered the LSC. Since the precision of the measurement and the number of measurements made at baseline and follow-up are also known, the equation can be solved for Z'. Once that is done, the confidence level can be determined. That is what has been done in the Statistical Confidence Calculator spreadsheet on the CD that accompanies this book. Table 11-7, from Dr. Ken Faulkner, is this type of calculation in tabular form for specific combinations of precision and change in BMD. For example, if the RMS-SD precision is 0.010 g/cm^2 and the measured change in BMD is 0.015 g/cm^2, the physician may be 71% confident that a real change in BMD has occurred. Whether the confidence is sufficient to warrant clinical consideration is a matter of judgment on the part of the physician.

The Confidence Interval (CI) for the Change in BMD Between Two Measurements

Once it has been determined that a measured change in BMD is significant at some level of statistical confidence, the question remains as to what the actual change in BMD really is. As noted in the example above, with a precision of 0.010 g/cm^2 and a measured change of 0.015 g/cm^2, a physician may be 71% confident that a real change has occurred. The physician cannot be 71% confident that a change of 0.015 g/cm^2 has actually occurred. Because there is some statistical uncertainty in both the baseline and follow-up measurements, there is also uncertainty in the magnitude of the measured change.

Table 11-8
Confidence Intervals for the Measured Change in BMD for Different Values of Precision

Confidence	*Precision, %CV*				
Interval	*1%*	*1.25%*	*1.5%*	*1.75%*	*2.0%*
99	±3.65	±4.56	±5.48	±6.39	±7.30
95	±2.77	±3.46	±4.16	±4.85	±5.54
90	±2.33	±2.91	±3.50	±4.08	±4.66
85	±2.04	±2.55	±3.06	±3.57	±4.08
80	±1.81	±2.26	±2.72	±3.17	±3.62

Note: All values are in %.

So how can the range of values in which the true change may lie be calculated? Table 11-8 illustrates the range of values for 99%, 95%, 90%, 85%, and 80% CIs for a change in BMD between two measurements at various levels of precision. The values shown in the table for the various levels of precision and confidence are added and subtracted from the actual measured change. For example, if the precision of testing is 1.5% and the measured change is 3%, the actual range of change for the 95% CI is 3% ± 4.12% or –1.12% to +7.12%. Because the range of possible values contains 0, the measured change of 3% with a precision of 1.5% is not statistically significant at the 95% CI. On the other hand, if the precision is 1.25% and the change between two measurements is 4%, the 95% CI for the change is 4% ± 3.46% or 0.54% to 7.46%. This range of values does not contain 0 and therefore the change of 4% is significant at the 95% CI. Obviously, this is a very wide confidence interval. It is perhaps disconcerting to note that although the measured change is statistically significant, the actual change may range from as little as 0.54% to as much as 7.46%. The 85% CI is narrower. In this case, the range of values is 4% ± 2.76% or 1.24% to 6.76%. Defining these ranges is certainly less important than recognizing whether the measured change is statistically significant.

THE IMPORTANCE OF PRECISION

When properly performed, bone density measurements are the most precise quantitative measurements in use in clinical medicine today. But it should be clear that until precision studies are performed at a facility, the LSC cannot be determined for any level of statistical confidence, making the interpretation of serial studies impossible. The calculations necessary to determine precision are somewhat tedious but not complex. Such calculations are simple with a relatively inexpensive statistical calculator. On the CD-ROM that accompanies this book, a precision calculator program is included that utilizes Microsoft® Excel. A similar program is available from the ISCD.[3] Precision studies do not need to be done on a regular basis, but they should be done at least once.

[3]At website www.iscd.org an Excel spreadsheet is available at no cost for download that allows the physician to enter the bone density values obtained during a precision study. The precision is calculated automatically by formulas imbedded in the spreadsheet. The spreadsheet can only be used with Microsoft® Excel.

They should be repeated if a new technologist begins scanning or if there is a major equipment change. The patients who participate in precision studies to derive the values that will be used clinically should be representative of the patient population that will be subsequently monitored with the technique. If a densitometry facility employs two or more technologists who are equally likely to perform a patient's bone density study on any given day, then the precision study should be performed by all of the technologists because this will be more representative of what is likely to occur in actual practice. It should be anticipated that the precision will not be quite as good as when only one technologist performs all the studies. It is not uncommon for precision studies to be performed with healthy young adults of normal body size and normal bone density. This type of precision study should be done to allow the technologist to test his or her skills in positioning and analysis. The precision value that results from such a study should not be used as the representative precision value for the facility, unless that is the type of patient the facility sees.

Which Skeletal Sites Should Be Used for Monitoring?

There are four basic rules that govern the choice of skeletal site for the purposes of monitoring the effects of disease or drugs on the skeleton.

1. Measure the skeletal site or type of bone (trabecular or cortical) that you expect to be affected.
2. Of the sites potentially affected, measure the site at which the greatest change in BMD is expected.
3. Of the sites potentially affected, measure the site at which you can measure the BMD with the best precision.
4. Peripheral sites are not used for monitoring by any technique.

Rule 1 is simply common sense. If a disease, drug, or procedure is not known to affect bone density in a particular region of the skeleton, it makes no sense to monitor that region. Rule 1 does require the densitometrist to know what the anticipated effect of a disease, drug, or procedure on the skeleton may be. The review of the effects of diseases, drugs, and procedures on the skeleton in Chapter 6 is intended to help in this regard. Knowing at which skeletal site the greatest effect is likely to be seen, as required by rule 2, is necessary to pick the skeletal site at which a change in BMD is most likely to be detected. This is because a certain magnitude of change is necessary to equal or exceed the LSC as discussed earlier. In addition, the greater the magnitude of the change, the sooner the change can be detected, making monitoring a more efficient process. Better precision, as required by rule 3, also increases the likelihood of detecting a significant change and detecting it more quickly. Table 11-6, illustrates the relationship between rate of change, precision, and the time to the LSC. Ideally, the site that is chosen for monitoring is the site with the greatest anticipated rate of change and the best precision. Peripheral sites are not used for monitoring, regardless of the technique by which they are measured. Precision is generally excellent at peripheral sites but the anticipated rates of change are too slow to make monitoring clinically useful. As a practical matter then, rule 4 means that the skeletal sites used for monitoring are the spine and proximal femur.

As noted in Chapter 2, the spine and proximal femur are both weight-bearing, central sites. The spine is part of the axial skeleton while the proximal femur is part of the appendicular skeleton. In considering the requirements of rules 1 and 2 however, the percentages of cortical and trabecular bone within the spine and various regions in the proxi-

mal femur are most pertinent. The area or size of the various regions of interest is relevant to rule 3. The PA spine is generally considered to be 66% trabecular bone. In the proximal femur, the regions of interest with the greatest percentage of trabecular bone are Ward's area and the trochanteric region. The exact percentage of trabecular bone in Ward's area is not defined but it is considered highly trabecular. The percentage of trabecular bone in the trochanteric region is approximately 50%. The greatest rates of change are usually seen in skeletal regions that contain higher percentages of trabecular bone. This is because trabecular bone has a much higher metabolic rate than cortical bone. Precision however, is often a function of the size of the area being measured. The larger the size, the better the precision tends to be. The greatest area is found in the PA spine by considering three or four of the lumbar vertebrae as one block. In the proximal femur, the greatest area is in the total femur region, followed by the trochanteric region.

In a position statement *(7)* from the ISCD published in 2002, the PA lumbar spine was described as the preferred site for monitoring. The total femur region of interest was an alternate choice when the PA spine could not be measured for any reason. In recommending the PA lumbar spine as the preferred choice, ISCD panel members noted that the PA lumbar spine provided the best combination of magnitude of change and precision. In the original publication there was no recommendation to use L1–L4 in preference to L2–L4. The precision of L1–L4 has rarely been compared to the precision of L2–L4. The area of L1–L4 will clearly be greater than that for L2–L4, and in general, the greater the area, the greater the precision will be. There is a point, however, past which further increases in area will not have a significant effect on improving precision. In a precision study in which the precision at L1–L4 was compared to that of L2–4 on the Lunar Prodigy, Bonnick and Lewis *(8)* found excellent precision for both L1–L4 and L2–L4. In women aged 50 to 70, the RMS-SD and RMS-%CV values were 0.012 g/cm^2 and 1.1% for both combinations of vertebrae. In a younger group of women aged 20 to 49 years, the RMS-SD and RMS-%CV values were 0.009 g/cm^2 and 0.7% for L1–L4 and 0.011 g/cm^2 and 0.9% for L2–L4. Although these differences are statistically significant, their clinical significance is doubtful. It would seem then, that either L1–L4 or L2–L4 is appropriate for monitoring purposes in the PA lumbar spine.

The total femur was recommended by ISCD because of its greater area in the proximal femur. This does indeed result in excellent precision at the total femur. In the precision study from Bonnick and Lewis *(8)*, the precision of the total femur on the Lunar Prodigy was 0.007 g/cm^2 or 0.7% in younger women (RMS-SD and RMS-%CV, respectively). In the group of older women, the precision was 0.006 g/cm^2 and 0.7%. Rates of change at the total femur tend to be slow. They are often less than those seen in the femoral neck, a region with a much smaller area and certainly less than those seen in the trochanteric region. This slower rate of change is, in part, offset by the excellent precision, enabling the physician to detect a significant change in bone density within a reasonable period of time. The trochanteric region of interest, however, potentially offers a reasonable alternative to the PA lumbar spine for monitoring. Rates of change in the trochanteric region of interest are often similar to those seen in the PA lumbar spine because of its similar trabecular composition. The area of the trochanteric region is greater than that of the femoral neck although not as great as that of the total femur. With the advent of fan-array DXA scanning, the precision of trochanteric measurements has been dramatically improved. The precision of the trochanteric region of interest on the Lunar Prodigy was 0.008 g/cm^2 and 0.9% (RMS-SD and RMS%CV, respectively) in younger women and

0.009 g/cm^2 and 1.3% in the older women *(8)*. Note that these RMS-SD values are even smaller than those seen at the PA lumbar spine and comparable to those seen at the total femur. The combination of rate of change and precision at the trochanter make it a suitable site for monitoring in the proximal femur and a reasonable choice if the PA lumbar spine cannot be monitored.

How Frequently Should Measurements Be Repeated?

The frequency with which measurements should be made is determined by the time to the LSC, as discussed earlier. The time to the LSC is determined by the anticipated rate of change and the precision at the skeletal site being measured as well as the number of measurements made at baseline and at follow-up and the desired level of statistical confidence for the measured change. In the ISCD position *(7)* statement on serial bone density measurements, it was noted that an interval of less than 1 year was rarely indicated when measurements were made at the PA lumbar spine. It was also noted that an interval of 2 years at the total femur might not be sufficient to demonstrate a statistically significant change. Both of these statements are correct. The precision of PA lumbar spine bone density measurements is sufficiently good when combined with the rates of change generally seen at the PA lumbar spine to justify repeat measurements at the end of 1 year in anticipation of seeing a significant change in most circumstances, even at the 95% confidence level. Despite superb precision at the total femur, the slower rates of change generally seen at this site may preclude seeing a significant change even after 2 years. The same statement would be true regarding the femoral neck region of interest. The potentially superb precision of the trochanteric region of interest with the newer DXA devices combined with rates of change comparable to those seen in the PA lumbar spine suggest that monitoring of the trochanteric region could be done in many cases at an interval of 1 year.

Once it has been determined that the bone density is stable or has significantly changed, the frequency with which testing should be repeated is unclear. In the context of assessing therapeutic efficacy of bone active agents, there is no evidence to date that suggests that therapeutic efficacy, once established, may subsequently be lost. As a consequence, the frequency of monitoring in this circumstance must be left to the discretion of the densitometrist. The frequency of repeat bone density studies in individuals not receiving therapy is discussed in Chapter 12. Guidelines from major organizations on these issues are also reviewed in Chapter 7.

Regression to the Mean and Monitoring

In an article in the *Journal of the American Medical Association* in 2000, Cummings et al. *(9)* raised the issue of whether regression to the mean (RTM) invalidated serial bone density measurements in clinical practice. The statistical concept of RTM was explained in Chapter 3. Cummings et al. used bone density data from the Fracture Intervention Trial of alendronate in postmenopausal women as well as data from the Multiple Outcomes of Raloxifene Evaluation trial in postmenopausal women. They limited their analysis to data obtained during the first 2 years of each trial in women who were compliant with the medication. They analyzed bone density data at the proximal femur in women by treatment assignment (active medication versus placebo). The average change in bone density at the end of 1 year was calculated for each treatment assignment group. The women were then divided into subgroups based on their actual change in bone density during the first

year. At the end of the second year, the change in bone density in each of the subgroups was compared to the change in bone density seen at the end of the first year in the same subgroups. The results were identical, regardless of treatment assignment or clinical trial. The subgroups that gained bone density during the first year of the trial tended to lose bone density during the second. Conversely, the subgroups that lost bone density during the first year gained bone density during the second. The subgroups that had the greatest initial gains tended to show the greatest subsequent losses. The converse was again true in that the subgroups that had the greatest initial losses tended to have the greatest subsequent gains. Cummings et al. correctly noted that their observations were due to RTM. They further noted however, that their "findings raise questions about the value of monitoring BMD during treatment." They suggested that because of RTM, individuals who appear to lose bone density during the first year of a therapy are likely to gain density during the second. Similarly, individuals who gain bone density during the first year of therapy will likely lose it during the second. These predictions would indeed make monitoring irrelevant if they were correct. They are not correct, however. As noted in Chapter 3, RTM is a statistical phenomenon that is created by a particular study design and analysis. The study design and analysis presented by Cummings et al. met all the necessary requirements to create RTM. First, a variable was measured on two separate occasions. In this case, the variable was the change in bone density during the first year and the change in bone density during the second year. Second, the value of the variable could change. The magnitude of the change in BMD during each of the 2 years could change because of the effects of therapy or simply because of precision errors. Third, subgroups were defined based on high or low values at the time of the first measurement. Here subgroups were indeed defined based on the change in bone density at the end of the first year. Having met these three conditions, the results of the Cummings' analysis were predictable. No matter what the change in the subgroup at the end of the first year, the change in that subgroup at the end of the second year would return toward or regress to the mean change at the end of the first year for the entire group. In other words, the conditions necessary to see RTM were created in this analysis and RTM was indeed observed. This is not clinically relevant, however. As noted in Chapter 3, RTM is a statistical phenomenon, not a biologic one *(10)*. It is also a group phenomenon, not an individual one. As a consequence, RTM has no relevance in following changes in BMD in individuals in clinical practice. The statistical issue of importance in serial bone density measurements is precision.

A FINAL CONSIDERATION

All of these careful considerations may be rendered moot, however, if the follow-up study is performed on a different manufacturer's bone densitometer. Even a different device from the same manufacturer is less desirable than using the exact same densitometer for the follow-up study as was used for the baseline study.[4] Under ideal circumstances, the same technologist would perform both the baseline and follow-up study. Although sometimes difficult, it is the responsibility of the densitometrist to ensure that the follow-up study is performed under the exact conditions of the baseline study. Serial measurements made on devices from different manufacturers cannot be interpreted with

[4] *See* Chapter 5 for a discussion of BMD data obtained different devices from the same manufacturer.

any degree of clinical accuracy. The conversion equations described in Chapter 5 cannot be used for this purpose, as there is still too great a margin for error. The use of a different device for the follow-up study even though it is from the same manufacturer of the device used for the baseline study has the potential to increase the precision error and therefore, increase the LSC. The magnitude of any increase is difficult to quantify in clinical practice. As a consequence, it is desirable to avoid this situation if at all possible.

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12 Reporting Densitometry

CONTENTS

The computer-generated printouts from densitometry devices have become increasingly sophisticated as the field of densitometry itself has matured. Skeletal images are clearer on the printouts with improvements in both image resolution and printer resolution. In addition to the measured skeletal parameters from the device, World Health Organization (WHO) Criteria *(1)* diagnoses, fracture risk assessments, and colorful graphic comparisons of the patient's BMD to their peers are commonly found. The addition of WHO diagnostic categories and fracture risk assessments to the densitometry printout is a departure from earlier practices in which such *clinical interpretations* of the numerical data were deemed inappropriate in the absence of a physician's review of the data. In fact, such densitometry computer-generated assessments are still inappropriate in the absence of a careful review by the densitometrist. It is also absolutely necessary that the densitometrist offer clinical guidance to the referring physician based on the densitometry findings. Such guidance is far beyond the scope of the computer-generated printout.

ELEMENTS OF DENSITOMETRY REPORTS REQUESTED BY PRIMARY CARE PHYSICIANS

In 2001, Merck & Co. Inc. *(2)* conducted focus groups with primary care physicians to determine what was both wanted and needed in reporting the results of densitometry. When asked to rate the extent to which they used either the technical report (the com-

puter-generated printout) or the summary report (the physician interpretation) for clinical decisions, primary care physicians assigned a score of 86 out of a possible 100 points to the summary report. According to these physicians, the top five components of the ideal report were risk factor identification, *T*-score, diagnosis, fracture risk assessment, and treatment recommendations. It was also noted that comparisons to prior studies should be made when appropriate. In a separate focus group, physicians emphasized that the ideal report would only be one page long!

US DENSITOMETRY CENTER REPORTING PRACTICES

Based on a national survey of densitometry reporting practices, it is clear that the needs of primary care physicians are not being met. In 2002, Fuleihan et al. *(3)* summarized the reporting practices of 270 densitometry centers in the United States. These were centers that were listed in the National Osteoporosis Foundation (NOF) database of US densitometry centers who responded to a questionnaire on densitometry reporting practices. At 71% of the 270 centers, the PA spine and proximal femur were routinely measured. Thirteen percent of the centers measured only one site routinely, and 11% measured the spine, proximal femur, and forearm routinely. In reporting the results of the studies, 89.6% included *T*-scores and 55.9% included *z*-scores as well. At 7.1% of the centers, *T*-scores were not reported and at 38.9%, *z*-scores were not reported. Only 64% of the centers mentioned the WHO Criteria for diagnosis and only 70% provided assessments of fracture risk. Of the centers reporting fracture risk, 65% based the risk assessment on the *T*-score, whereas only 6% utilized the *z*-score. Fourteen percent utilized both standard scores and 15% utilized neither standard score. In reporting fracture risk, 80% of the centers did not apply any age restriction to this assessment. Fracture risk assessments were limited to individuals over age 50 in only 7.5% and to individuals over age 65 in only 5%.

The findings from Fulheihan et al. continued to be disheartening in the realm of clinical guidance. Only 57% of the responding centers recommended patient evaluations for secondary causes of bone loss. The criteria for making such recommendations also varied. A *T*-score of less than –2.5 was used by 25% of the centers and a *z*-score less than –2 was used in 18%. When specific tests were recommended, the most common recommendations included a measurement of serum calcium, parathyroid hormone (PTH) and thyroid stimulating hormone (TSH). Fifty-six percent recommended nonprescription interventions such as calcium, vitamin D, and exercise for the prevention of osteoporosis and only 52% recommended such interventions as part of therapy. Only 51% of the centers recommended prescription interventions for the prevention of osteoporosis, whereas only 58% made recommendations for prescription interventions for treatment. In contrast, 74% of the centers did recommend a follow-up bone density measurement, with most recommending follow-up after one year. A detailed report, which included recommendations for an evaluation for secondary causes of bone loss and treatment options, was employed by only 28% of the 270 centers. In summarizing the results of this study, the authors correctly concluded that densitometry reporting in the United States often failed to include clinical information necessary to assist physicians in the care of their patients and that such reporting was often not evidence-based. They noted that these issues must be addressed to optimize the clinical utility of densitometry.

RECOMMENDATIONS FROM THE CANADIAN PANEL OF THE ISCD FOR BONE DENSITY REPORTING

Although there is no widespread consensus on the essential elements that should be found in a densitometry report, the Canadian Panel of the ISCD *(4)* issued guidelines for reporting of densitometry studies in 2002. The panel noted that a report should contain the following five elements:

1. Comments on technical issues potentially affecting the accuracy of the study such as artifacts, degenerative changes, fractures, etc.
2. *T*-score and the corresponding WHO diagnosis.
3. *Z*-score, if relevant, such as a *z*-score of –2 or less accompanied by recommendations for aggressive evaluation of secondary causes of bone loss.
4. Qualitative assessment of fracture risk.
5. When relevant, serial BMD changes, stating the in vivo precision in the units of the densitometer and the statistical significance of the change in BMD.

REPORTING THE DIAGNOSIS

The Canadian Panel linked the reporting of *T*-scores with the assignment of a diagnostic category utilizing the WHO Criteria, thus fulfilling two of the primary care physician's requested elements for the ideal report. Although the WHO Criteria are in widespread use, it is still desirable to state that these are the criteria being used. It is also important to state the skeletal site from which the *T*-score is derived for this purpose. This is because, as noted in Chapter 9, both the IOF *(5)* and the ISCD *(6)* recommend limiting the use of the WHO Criteria to specific skeletal sites. For example, the statement regarding diagnosis might read:

This patient has osteoporosis according to World Health Organization Criteria based on the T*-score of –2.6 at the femoral neck.*

Such a statement is appropriate for a postmenopausal woman. If the study has been performed in a man, the statement should be amended to reflect that the WHO Criteria were originally intended to be used in postmenopausal women only. The controversy surrounding the use of the WHO Criteria in men was discussed in Chapter 9. Until this controversy is resolved, an amended statement should be used. Such a statement might read as follows:

When the World Health Organization Criteria for postmenopausal women are utilized, this man has osteoporosis based the T*-score of –2.6 at the femoral neck.*

In utilizing the WHO Criteria, it is important to note that modifiers such as mild, moderate, or severe are not used to describe the diagnostic category of osteopenia or low bone mass. In addition, severe osteoporosis should be used to describe only those individuals with a bone density 2.5 or more SD below the young-adult mean value and who have a presumed fragility fracture.

One of the limitations of the WHO Criteria is that the WHO Criteria do not allow for an individual with an osteopenic bone density *T*-score and presumed fragility fracture to be called osteoporotic. In such a case, it would be reasonable to point out that this individual certainly meets the conceptual definition of osteoporosis as proposed by the

1991 and 1993 Consensus Development Conferences *(7,8)*.[1] In this circumstance a statement might read:

> *Although this patient does not meet the quantitative definition of osteoporosis established by the World Health Organization, low bone density and fracture evidence of skeletal fragility meet the diagnostic criteria for osteoporosis proposed by the 1991 and 1993 Osteoporosis Consensus Development Conferences.*

The preceding statement is somewhat awkward but extremely important. These patients have proven that their skeletons are sufficiently fragile to fracture. They are at greater risk for future fracture than their bone density alone implies because of the presence of a fracture. Even so, if they are not diagnosed as osteoporotic, they may not be considered as having a disease and therefore may go untreated.

REPORTING FRACTURE RISK

The previous discussion highlights the clinical dilemma of the densitometrist in explaining what these numbers mean, because the level of bone density that constitutes a diagnosis of osteoporosis is not necessarily the same level of bone density that constitutes an unacceptable level of risk for fracture. The prediction of fracture risk is therefore a separate statement.

It is not clear why the Canadian Panel chose to emphasize reporting qualitative assessments of fracture risk instead of quantitative assessments. Nevertheless, for the referring physician, the overriding issue may certainly be whether the patient is at increased risk of fracture or not. The exact magnitude of any increase in risk may be less important. There is no agreement as yet as to the ideal form that a quantitative assessment of fracture risk should take. There are certainly a growing number of quantitative assessments from which to choose. Relative risk data, whether used with the *T*-score or *z*-score is poorly understood and not particularly useful clinically. Instead, global or site-specific fracture risk predictions such as RLFP, 10-year, or lifetime fracture risks are both intuitive and useful.[2] The presence of a fracture and/or multiple clinical risk factors can be combined into a quantitative assessment of risk or they can simply be noted to increase the risk beyond the stated projections. The overriding goal in any of these approaches is to ensure that the magnitude of the risk is recognized so that appropriate interventions are recommended. Typical statements, depending on the modality chosen for expressing fracture risk for a 60-year-old postmenopausal woman with a femoral neck *T*-score of –2.0 are as follows:

> *The patient's RLFP or the number of osteoporotic fractures she is expected to experience in her lifetime is 5.48.*
>
> *The patient's lifetime risk of hip fracture is 27%.*
>
> *The patient's 10-year probability of having any type of osteoporotic fracture is 13%.*

As noted in the study from Fuleihan et al. *(3)*, many densitometry centers do not employ any age restriction on fracture risk predictions. This is inappropriate. Such pre-

[1] *See* Chapter 9 for a discussion of the 1991 and 1993 Consensus Conferences' definition of osteoporosis.

[2] *See* Chapter 10 for a discussion of these methods for predicting fracture risk.

dictions should be reserved for women age 60 and older and probably for men of the same age as well. This is the age group in which the relationship between bone density and fracture risk has been studied. Fracture risk predictions should not be made in otherwise healthy young adults because there is no data to support doing so. It is also clear that for any given level of bone density, the risk of fracture is markedly less in these individuals than in older individuals.

RECOMMENDING EVALUATIONS FOR SECONDARY CAUSES OF BONE LOSS

The Canadian Panel's recommendation to comment on the *z*-score when it was less than –2 and to aggressively recommend an evaluation for secondary causes of bone loss is entirely appropriate. This was not listed in the top five elements of a report requested by primary care physicians but this is all the more reason that such statements should be included in densitometry reports. Statements reminding physicians to exclude secondary causes of bone loss are always appropriate in individuals with a low bone mass, regardless of the *z*-score. In postmenopausal women, estrogen-deficient bone loss is a diagnosis of *exclusion*. It is incumbent on the physician to prove that nothing else could have caused the apparent bone loss. In men, a search for secondary causes is equally important. Densitometrists may use the *z*-score to determine how aggressively to recommend such an evaluation, but the recommendation should always be made in some form. Statistically, a *z*-score of –2 or poorer is grounds for making an aggressive recommendation. A more aggressive recommendation could include not only a differential diagnosis of causes of bone loss but suggestions for specific tests to exclude such causes as well. Such statements should always be prefaced with the phrase "if clinically indicated." The referring physician may be able to exclude many of the differential diagnoses based on his or her historical knowledge of the patient or based on previous tests. It should be made clear that the decision to pursue additional testing belongs to the referring physician.

A routine recommendation for an evaluation for secondary causes may be worded as follows:

Secondary causes of bone loss should be excluded clinically.

More detailed and aggressive recommendations can be made based on published findings from studies of patients with osteoporosis such as those from Johnson et al. *(9)* and Tannenbaum et al. *(10)*. In 1989, Johnson et al. *(9)* evaluated 180 individuals (173 women, 7 men) with osteoporosis. In this study, osteoporosis was defined as two atraumatic spinal compression fractures or as a PA lumbar spine bone density 10% or more below the age-matched predicted value. After a thorough medical evaluation, 83 of the 180 individuals were found to have additional diagnoses that could potentially contribute to the development of osteoporosis. These diagnoses are shown in Table 12-1. A total of 128 diagnoses were identified in the 83 patients. In 11% of the 180 patients, the diagnosis was previously unknown. In the study from Tannenbaum et al. *(10)*, 173 postmenopausal women with osteoporosis at the PA lumbar spine, proximal femur, and/or forearm based on WHO Criteria were evaluated for secondary causes of osteoporosis. Patients with previously known causes of secondary osteoporosis were excluded from the study. The findings from this study are shown in Table 12-2. The types and percentages of abnormal laboratory tests used to identify these individuals are shown in Table 12-3.

Table 12-1
Contributing Diagnoses[a] in 83 of 180 Patients with Osteoporosis

Endocrine		Gastrointestinal	
Glucocorticoid use	(26)	Lactase deficiency	(4)
Premature menopause	(17)	Gluten-sensitive enteropathy	(3)
Low serum 25-OH vitamin D	(10)	Malabsorption/surgery	(2)
Hyperthyroid	(7)		
Iatrogenic	(5)		
Diabetes	(5)	Other	
Hyperparathyroid	(3)	Chemotherapy	(8)
Paget's disease	(3)	Scoliosis	(7)
Polycystic ovary	(1)	Rheumatoid arthritis	(5)
Hyperprolactinemia	(1)	Poliomyelitis	(4)
Malignancy		Kidney stones	(4)
Multiple myeloma	(2)	Alcohol abuse	(4)
Breast cancer	(2)	Prolonged bedrest	(3)
Acute leukemia	(1)	Poor nutrition	(2)
Sarcoma	(1)	Seizure disorder with phenytoin	(1)
Hodgkin's disease	(1)	Sarcoidosis	(1)

[a] Numbers in parentheses indicate the number of diagnoses ($N = 128$).

Osteoporosis was defined as a PA lumbar spine BMD 10% or more below the age-matched mean BMD or two or more atraumatic spinal compression fractures.

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Table12-2
Secondary Contributors to Osteoporosis[a] Identified in 173 Otherwise Healthy Women with Osteoporosis

	Prevalence	
Disorder	*No.*	*% of 173 patients*
Hypercalciuria	17	9.8
Renal (7)		
Idiopathic (6)		
Undefined (4)		
Malabsorption	14	8.1
Relative calcium malabsorption (11)		
Celiac sprue (3)		
Hyperparathyroidism (HPT)	12	6.9
1° HPT (1)		
2° HPT due to inadequate calcium intake (6)		
Unexplained 2° HPT (5)		
Vitamin D deficiency (<30 nmol/L)	7	4.1
Exogenous hyperthyroidism	4	2.3
Cushing's disease	1	0.6
Hypocalciuric hypercalcemia	1	0.6
Total number of new diagnoses	56	
Patients with at least one new diagnosis	55	32.4

[a] Osteoporosis was defined by applying WHO Criteria to bone density measured at the PA spine, proximal femur or forearm.

Numbers in parentheses indicate the number of patients with that diagnosis.

Adapted from Tannenbaum C, Clark J, Schwartzman K, et al. Yield of laboratory testing to identify secondary contributors tro osteoporosis in otherwise healthy women. J Clin Endocrinol Metab 2002;87: 4431–4437 with permission of the publisher. ©The Endocrine Society

Table 12-3
Frequency of Laboratory Abnormalities in 173 Women

Lab Test	*No. of Abnormal Tests (%)*	*No. of Abnormal Tests Contributing to a New Diagnosis*
Elevated PTH	27 (15.6)	27/27
Hypocalciuria	22 (12.7)	12/22
Hypercalciuria	17 (9.8)	17/17
Low 25-OH vitamin D	9 (4.6)	9/9
Low thyroid stimulating hormone	4 (2.5)	4/4
High urine cortisol	4 (3.7)	1/4
Anemia	5 (2.9)	0/5
Monoclonal peak (SPEP/IPEP)	3 (2.1)	0/3
Hypercalcemia	3 (2.0)	2/3
Leukopenia	2 (1.6)	0/2
Total	96 (6.6)	72

Adapted from Tannenbaum C, Clark J, Schwartzman K, et al. Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. J Clin Endocrinol Metab 2002; 87:4431–4437, with permission of the publisher.

Based on this information, the most cost-effective laboratory strategy was determined to identify patients with secondary causes of bone loss. The authors concluded that a strategy that involved measurement of serum calcium, PTH, 24-hour urine calcium, and TSH (in women receiving thyroid hormone) detected 85% of all of the observed disorders at an average cost of $272 per diagnosis or $75 per patient screened.

Using the data from these studies, a more detailed recommendation to exclude secondary causes of bone loss may read as follows:

> *Estrogen-deficient bone loss is a diagnosis of exclusion. Therefore, secondary causes of bone loss should be excluded clinically. Such causes may include, but are not limited to, hyperparathyroidism, hyperthyroidism, hypercalciuria, Cushing's disease, rheumatoid arthritis, multiple myeloma, malabsorption, alcoholism, and use of medications such as corticosteroids, lithium, excessive thyroid hormone, anticonvulsants, and GnRH agonists.*

An even more aggressive and specific recommendation to exclude secondary causes of osteoporosis reads as follows:

> *Estrogen-deficient bone loss is a diagnosis of exclusion. Therefore, secondary causes of bone loss should be excluded clinically. Such causes may include, but are not limited to, hyperparathyroidism, hyperthyroidism, hypercalciuria, Cushing's disease, rheumatoid arthritis, multiple myeloma, malabsorption, alcoholism, and use of medications such as corticosteroids, lithium, excessive thyroid hormone, anticonvulsants, and GnRH agonists. If clinically indicated, a laboratory evaluation that includes a serum calcium, serum PTH, 24-hour urinary calcium excretion, and serum TSH (in patients receiving thyroid hormone) should be performed. Other tests that may be useful are a CBC,[3] SPEP,[4] IPEP,[5] 25-OH vitamin D,[6] urine cortisol and/or antigliadin and antiendomysial antibodies.[7]*

[3] Complete blood count.
[4] Serum protein electrophoresis.
[5] Immuno protein electrophoresis.
[6] 25-hydroxy vitamin D.
[7] These antibodies may be present in cases of nontropical sprue.

TREATMENT RECOMMENDATIONS

There are two aspects to treatment recommendations: whom to treat and how to treat them. The NOF Guidelines *(11)* for the treatment of postmenopausal osteoporosis are extremely useful as well as clear. In 1998, the NOF recommended that prescription medications be considered for women with a bone density *T*-score of less than –1.5 in the presence of other risk factors and in women with a bone density *T*-score less than –2, regardless of other risk factors. It is relatively straightforward then, to make a statement such as:

The patient meets (or does not meet) National Osteoporosis Foundation guidelines for prescription intervention to prevent or treat osteoporosis.

To recommend specific treatments is a more difficult undertaking. The Canadian Panel *(4)* did not recommend the inclusion of such recommendations in a densitometry report. It is clear, however, that primary care physicians want suggestions in this regard *(2)*. Given the diverse specialties of physicians involved in densitometry, some physicians may be more comfortable than others in making such recommendations. It should be possible, however, for any physician to remind the referring physician of the desirability of nonprescription interventions such as calcium, vitamin D, and exercise and to list the currently approved prescription interventions for the prevention and/or treatment of osteoporosis. A general statement regarding nonprescription interventions might be as follows:

It is recommended that the patient obtain her RDA[8] for calcium and vitamin D as well as participate in a regular program of weight-bearing and strength-training exercise.

In osteoporotic individuals, some restrictions on exercise are appropriate to avoid increasing the risk for fractures or falls. An appropriate cautionary note might read:

The patient should avoid exercises or activities that involve repeated or resisted trunk flexion (such as traditional sit-ups), high impact aerobics (such as running or jumping rope), and activities in which the risk of falls is increased (such as exercising on slippery floors or trampolines or step aerobics).

Based on the patient's age, the physician may make more specific recommendations for calcium and vitamin D intake such as this recommendation for a 60-year-old woman:

It is recommended that the patient obtain 1200 mg of elemental calcium and 400 IU of vitamin D per day.

Prescription interventions are best summarized rather than specifically recommended, as decisions regarding the feasibility of any one intervention should be left to the referring physician. It is important to distinguish between agents that are recommended for prevention, treatment, or both and to note the doses recommended for each. The following statements address these concerns:

The following antiresorptive medications are FDA-approved for the prevention and treatment of postmenopausal osteoporosis: alendronate, 5 mg po daily or 35 mg po once weekly for prevention and 10 mg po daily or 70 mg po once weekly for treatment;

[8] RDA is a widely understood abbreviation for recommended dietary allowance. New terminology has been introduced by the National Academy of Science (NAS) in which the RDA is one of four possible intake amounts under the broad heading of the Dietary Reference Intake (DRI). Strictly speaking, the NAS recommendation for calcium is not an RDA but instead is one of the other amounts called an Adequate Intake (AI) value. Nevertheless, the term RDA is commonly used.

risedronate, 5 mg po daily or 35 mg po once weekly for either indication; raloxifene in a dose of 60 mg po daily for either indication. Several forms of estrogen replacement are approved for the prevention of postmenopausal osteoporosis. The minimum effective dose is specific for the preparation. Salmon calcitonin is approved for treatment in women more than 5 years postmenopausal in a dose of 100 IU injected subq daily or 200 IU in one nasal spray daily. The anabolic agent teripartide is approved for the treatment of postmenopausal osteoporosis in women who are at high risk for fracture for a period of no more than 2 years at a dose of 20 μg injected subq daily.

This statement clearly refers to therapies for women. If the nature of the report requires only a discussion of treatment, comments regarding preventive doses can be eliminated. If the issue is solely prevention, comments regarding treatment can be eliminated for the sake of brevity. For the treatment of osteoporosis in men, the following summary is appropriate:

Alendronate, in a dose of 10 mg po daily (a dose of 70 mg po once weekly can be considered) is approved for the treatment of osteoporosis in men. Teriparatide in a dose of 20 μg injected subq daily for period of no more than 2 years is indicated to increase bone density in men with primary or hypogonadal osteoporosis.

In the specific circumstance of corticosteroid-induced osteoporosis, alendronate and risedronate are approved for use in both men and women.

Statements such as those noted above are lengthy but specific enough to be useful while still leaving final treatment decisions in the hands of the referring physician. If the densitometrist knows that such a statement would not be appreciated or needed by the referring physician, it is not necessary to include it in the report.

RECOMMENDING A FOLLOW-UP DENSITOMETRY STUDY

The timing of a follow-up study is based on the specific circumstances of patient management. If a prescription medication is started, either for prevention or treatment, the timing of the repeat study and the skeletal site to be used for that measurement are determined by the anticipated effects of the drug on the skeleton and the precision of the measurement at the chosen skeletal site.[9] To address all possible contingencies becomes quite difficult. As noted in Chapter 7, several organizations have attempted to provide general guidelines in this regard. As a rule, the PA lumbar spine is the site of choice to monitor all currently available therapies. Significant changes at the PA lumbar spine from either of the bisphosphonates or teriparatide may be seen after one year. A more appropriate interval if raloxifene is used is 2 to 3 years. The longer interval would also be appropriate for salmon calcitonin. If the proximal femur is chosen as the site to monitor, a longer interval is required because of the effect of the combination of the rate of change and precision at the skeletal site. The minimum interval for proximal femur measurements to assess efficacy is 2 years. In general, proximal femoral measurements are less useful for monitoring raloxifene and salmon calcitonin. Consequently, if therapy is begun, it is reasonably safe to recommend that the PA lumbar spine bone density study be repeated at an interval to be determined by the choice of therapy. From the standpoint of Medicare *(12)* reimbursement, however, a follow-up bone density study to assess treatment efficacy cannot be performed any earlier than 23 months after the baseline measurement.[10]

[9] *See* Chapter 11 for a discussion of monitoring changes in bone density.

[10] *See* Appendix VI for the provisions of the Bone Mass Measurement Act of 1997.

Table 12-4
Follow-Up Time in Healthy Peri- and Postmenopausal Women, Not Selected by Risk Factors

T-Score of the Spine or Neck (lowest)	*Suggested Action*
>0	Consider repeating the scan in 5 years
–0.5 to 0	Scan again after 3 years
–1 to –0.5	Scan again after 1 year

Adapted from ref. *13* with the permission of the American Society for Bone and Mineral Research.

The timing of repeat measurements, if any, in peri- and postmenopausal women with normal bone densities who may not be utilizing any prescription intervention for bone loss is less clear. Abrahamsen et al. (13) suggested that the timing of such measurements should be based on the measured BMD, rather than on a fixed interval approach. The authors utilized 5-year data from 925 women participating in the Danish Osteoporosis Prevention Study[11] (DOPS) to determine the maximum interval between studies in women with normal baseline *T*-scores to identify women whose *T*-scores had fallen below –1 at follow-up. The threshold of a *T*-score of less than –1 was chosen, because at that point, the patient would be considered osteopenic and according to the authors, a potential candidate for intervention. The suggested intervals are shown in Table 12-4. The authors noted that women with co-existing diseases or other risk factors for bone loss may be restudied sooner than recommended in the table. Therefore, if the lowest bone density *T*-score is –0.4 at the PA lumbar spine in an otherwise healthy woman, a statement such as the following could be included in the densitometry report:

A repeat PA lumbar spine study is recommended in 3 years.

ASSESSMENT OF RISK FACTORS

Clinical risk factors (nonbone density factors) clearly increase the risk of both fracture and bone loss. For this reason, it is reasonable for the densitometrist to assess them, in order to provide a more complete assessment of fracture risk and knowledgeable recommendation for follow-up and intervention. Such assessments are generally done with self-administered questionnaires. Although a list of all such risk factors would be unmanageably long, it is a relatively simple matter to construct a questionnaire that addresses the most significant and common risk factors for bone loss and fractures. Positive findings can then be noted in the densitometry report and statements regarding fracture risk, selection for treatment or timing of follow-up studies can be amended accordingly. A sample questionnaire is shown in Appendix XIII and is also available on the CD-ROM that accompanies this book. Depending on the particular patient population most often seen at a facility, modifications to the questionnaire should be made as the densitometrist deems appropriate.

[11] DOPS is a 20-year multicenter study of risk factors for osteoporosis in women ages 45 to 58 years who are peri- or postmenopausal.

REPORTING SERIAL STUDIES

When the results of a follow-up bone density study are reported, the primary interest is in the magnitude and significance of the change in BMD between studies, rather than the diagnostic category or prediction of fracture risk from the follow-up study. It is also imperative that the technical aspects of the baseline and follow-up study be identical. The report should indicate the equipment type, software versions, and dates for both studies and the regions of interest that are being compared at baseline and follow-up. The precision of testing at the densitometry facility for the skeletal site(s) in question should be stated, as well as the average BMD for the population in whom the precision study was done. Ideally, the precision should be expressed as the RMS-SD.[12] The absolute magnitude of the change, the percent change from baseline and the statistical confidence level for the change should be reported. These values can be calculated with the statistical confidence calculator on the accompanying CD-ROM. This type of information can be presented efficiently in either a tabular or narrative format. In the narrative format, a sample statement might be:

The patient underwent baseline and follow-up DXA studies of the PA lumbar spine on 2/5/02 and 2/10/03, respectively. A Lunar Prodigy, software version 6.7, was used for both studies. At baseline, the L2–L4 BMD was 0.945 g/cm^2. At follow-up, the L2–L4 BMD was 0.987 g/cm^2. This represents an absolute change from baseline of 0.042 g/cm^2 or 4.44%. The precision of L2–L4 PA lumbar spine BMD testing at this facility is 0.011 g/cm^2 in postmenopausal women with an average L2–L4 BMD of 0.904 g/cm^2. Therefore, the statistical confidence level for the change in bone density in this patient is 99%.

THE CHALLENGE IN REPORTING DENSITOMETRY RESULTS

The knowledge that a densitometrist must bring to bear on the quantitative assessment of bone density to interpret the findings and place them in the appropriate clinical context is considerable. But the conclusions must be carefully crafted in the most succinct fashion possible. Long reports are simply not read. Vague statements will not be understood or appreciated. At present, it is not sufficient to simply say that the patient does or does not have osteoporosis or is or is not at increased risk for fracture. For the densitometry report to be useful it must be accurate, clear, and complete but also concise. Even though some have said that densitometrists should restrict their statements to a simple review of the numbers, referring physicians want and require more from the experienced densitometrist to better serve their patients' needs.

The best format for conveying this information is a matter of opinion. Narrations in the form of a letter may evoke a sense of frustration on the part of the busy clinician who feels he or she must search the letter for information relevant to the care of the patient. Shorter narrations that are followed by numbered conclusions may result in only the numbered conclusions being read. Any important information contained in the narration may be lost. It would also seem clear that the longer the letter or the greater the number of conclusions, the less likely it is that the pertinent information will be

[12] *See* Chapters 3 and 11 for a discussion of the RMS-SD.

read. Addressing these issues at present is primarily a matter of trial and error and personal opinion. To meet the needs and requests of the primary care physician regarding reporting and to ensure that all the relevant information is reviewed and understood is a challenge. With these issues in mind, a reporting format that combines a very brief narrative paragraph describing pertinent technical issues with a brief series of numbered conclusions that clearly address the specific clinical issues raised by primary care physicians would seem to be the best approach. The issues addressed by the numbered conclusions should be clearly identified and always given in the same order, from report to report. For example, Figs. 12-1A and B are a PA lumbar spine and proximal femur bone density study on a 67-year-old Caucasian woman. Prior to undergoing the study, the woman completed the patient questionnaire found in Appendix XIII. From the questionnaire, it was noted that she had never taken hormone replacement, she weighed only 105 lb, and her mother had osteoporosis. This was her first bone density study. The patient was referred by her physician for testing because she met the NOF Guidelines for testing described in Chapter 7. The report from the densitometrist to the referring physician might read as follows:

January 15, 2003

Dear Dr. Smith:

Ms. Jane Doe, dob 2/7/35, underwent PA lumbar spine and proximal femur DXA bone density studies on a Lunar Prodigy, software version 5.5 on 1/15/03. No technical difficulties were encountered. A review of the bone density images did not suggest fracture, degenerative change or artifact that would affect the interpretation of the numerical results.

1. *Diagnosis: Osteoporosis, based on the* T*-score of –3.3 at L2–L4, applying World Health Organization Criteria for the diagnosis of osteoporosis.*
2. *Fracture Risk: Markedly increased.*
3. *Historical risk factors: Postmenopausal estrogen deficiency, low body weight, family history of osteoporosis.*
4. *Recommendations:*
   a. *Secondary causes of bone loss should be excluded clinically.*
   b. *The patient meets National Osteoporosis Foundation guidelines for prescription intervention to treat osteoporosis. She should obtain 1200 mg of elemental calcium and 400 IU of vitamin D per day. The following antiresorptive medications are FDA-approved for the treatment of postmenopausal osteoporosis: alendronate, 10 mg po daily or 70 mg po once weekly; risedronate, 5 mg po daily or 35 mg po once weekly; and raloxifene in a dose of 60 mg po daily. Salmon calcitonin is approved for treatment in women more than 5 years postmenopausal in a dose of 100 IU injected subq daily or 200 IU in one nasal spray daily. The anabolic agent teripartide is approved for the treatment of postmenopausal osteoporosis in women who are at high risk for fracture for a period of no more than 2 years at a dose of 20 μg injected subq daily.*
   c. *A repeat PA lumbar spine bone density study is recommended in 1 year to assess therapeutic efficacy if prescription therapy is initiated.*

Sincerely,

Your name.

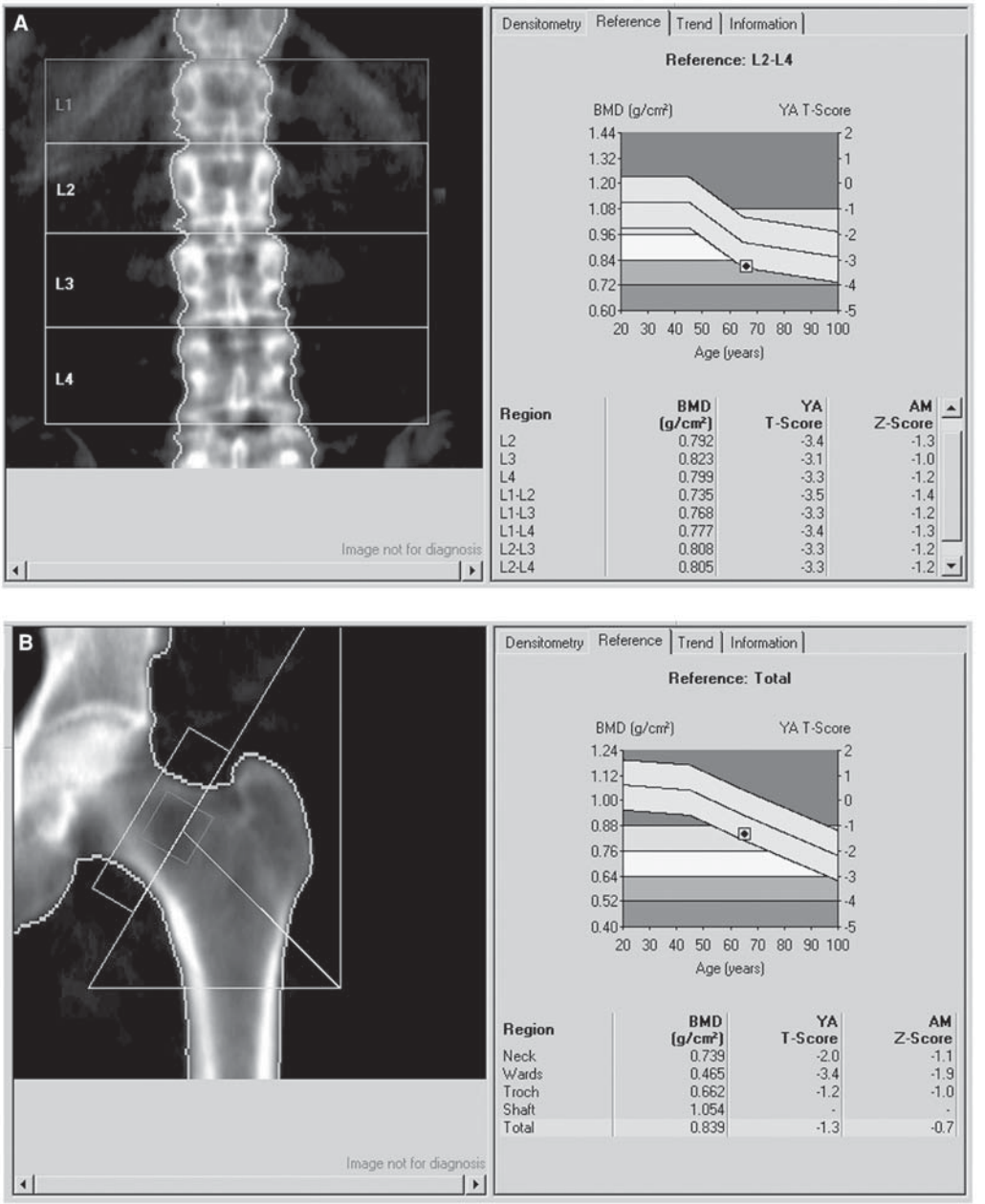

Fig. 12-1. (A) Lunar Prodigy PA lumbar spine study. **(B)** Lunar Prodigy proximal femur study on the same 67-year-old Caucasian woman.

This report is actually only one page long, using standard margins and line spacing. Headings and phrases are underlined for emphasis to ensure that they are read. In future reports, the same format would be followed, which helps the physician learn where to look for the pertinent clinical information and ensures that nothing of importance is overlooked. In this particular report, the lengthiest section is the reiteration of therapeutic

options for the treatment of postmenopausal osteoporosis. As noted earlier, if you know that the referring physician does not need or would not appreciate this type of reminder, it can be omitted.

If other reporting formats have been found to be useful or more appropriate for a particular practice they should certainly be used. The densitometrist is responsible for device quality control, skeletal site selection, scan frequency, precision issues, data analysis, diagnosis, fracture risk assessment, therapeutic recommendations, and assessments of therapeutic efficacy. But the success or failure of the densitometrist and the promise of the marvelous technologies that we use ultimately resides in the accuracy, clarity and completeness of the reports that we send to the physicians who have asked for our assistance in the care of their patients. It is a privilege to be asked; it is a challenge that we must not fail.

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13 FDA-Approved Densitometry Devices

CONTENTS

The devices discussed in this chapter are available in the United States for clinical use. The specifications were provided by the manufacturers and are subject to change without notice as devices are continually upgraded to reflect advances in the technology. The categories of information provided by each manufacturer may vary slightly. All categories are not relevant to every device. This listing of devices is not intended to reflect all devices in use in the United States. Every attempt was made to ensure the accuracy of the information. The manufacturer should be contacted for the latest specifications. The devices are grouped by type and listed alphabetically by model name.

COMPUTER-ENHANCED RADIOGRAMMETRY

Sectra Osteoporosis Package™ IDS5™ Workstation Clinical Application

- Manufacturer: Sectra Pronosco, Herlev, Denmark
- Technique: Computerized radiogrammetry utilizing a standard digitized X-ray image of the hand as part of an integrated PACS workstation
- Skeletal application(s): Metacarpals of the index, long, and ring fingers
- Results:
  BMD estimate (g/cm^2)
  Metacarpal Index
  T-score, *z*-score
  Graphical representation of the *T*- and *z*-score
  Graphical representation of the Metacarpal Index
- Patient Scan time: Not applicable
- Analysis time: 5 seconds
- Precision: 0.35%
- Radiation exposure: 1 μSv limited to the hand during plain film acquisition
- Operation: Data from a hand image is analyzed and stored in a PACS system. The hand image data file is opened for viewing on the IDS5 workstation. The radiogrammetry analysis is begun with a mouse click and complete in approximately 5 seconds. The report can then be printed. The system is equipped with an internet update feature for reference databases and DICOM modality on-line support.

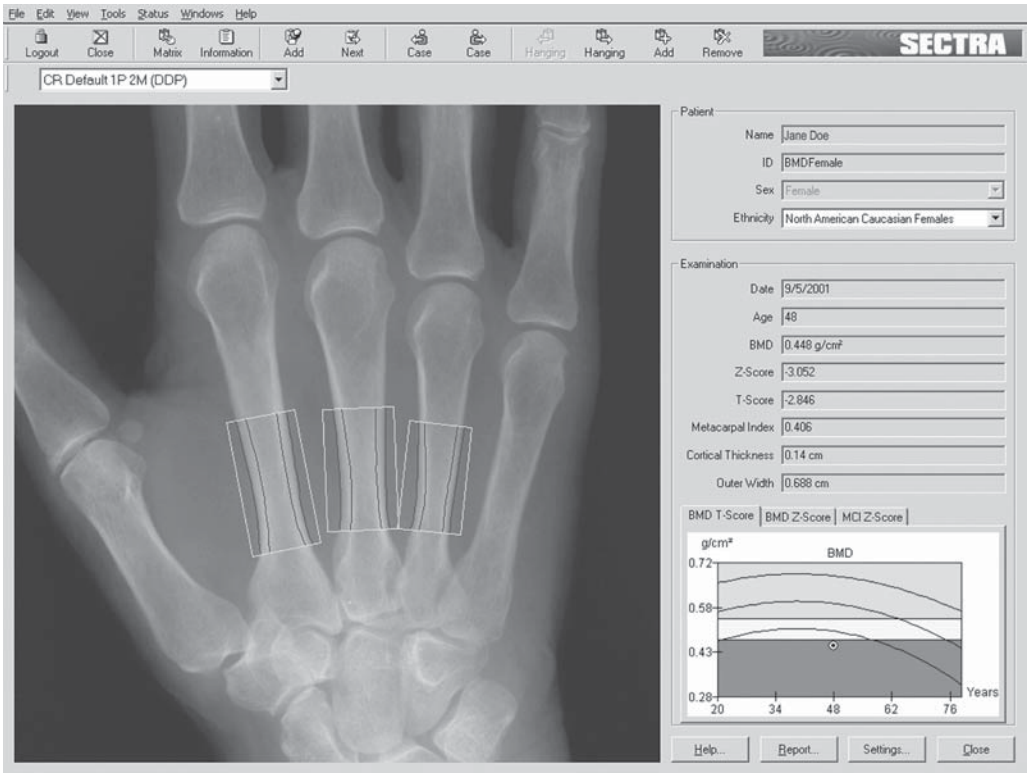

Fig. 13-1. Sectra Osteoporosis Package™ IDS5™ Workstation Clinical Application. The analysis is performed as part of an integrated PACS workstation. Photograph courtesy of Sectra Pronosco, Denmark.

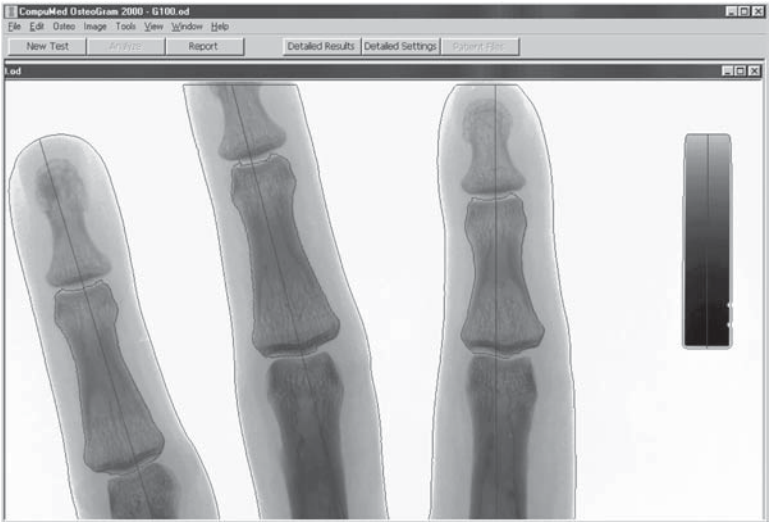

Fig. 13-2. The CompuMed Automated Osteogram® Analysis System. The system consists of the computer, monitor, mouse, flatbed scanner, and analysis software to perform computer-assisted radiographic absorptiometry of the phalanges, as shown here. Photograph courtesy of CompuMed Inc., Los Angeles, CA.

COMPUTER-ENHANCED RADIOGRAPHIC ABSORPTIOMETRY

Automated OsteoGram®

- Manufacturer: CompuMed Inc., Los Angeles, CA
- Technique: RA utilizing plain films of the hand with a computerized analysis. The system consists of an HP® minitower computer with OsteoGram® software installed, 15-in flat panel display monitor, AGFA DuoScan T1200 scanner, keyboard, and mouse.
- Skeletal application(s): Middle phalanges of the index, long, and middle fingers
- Results:
  BMD in arbitrary RA units
  T-score and *z*-score
  Diagnostic classification based on WHO Criteria
- Patient Scan time: Not applicable
- Analysis time: Approximately 1 minute, excluding film digitization time
- Precision: < 1%
- Quality control: Automated system checks to ensure quality and accuracy of image digitization.
- Operation: Two hand films are taken. Data is entered into the computer program with the computer keyboard. The plain film is scanned into the computer and then analyzed by proprietary software installed on the computer. The results are then printed.
- Accessories provided:
  SCSI interface connector
  CMI/AGFA Ortho 400 Green Cassette with the OsteoGram® film template mounted with the reference wedge
  Mouse pad
  Clinical overview CD
  Procedure video
  Instruction manual

MetriScan™

- Alara, Inc., Hayward, CA
- Technique: RA with storage phosphor technology
- Skeletal application(s): Middle phalanges of the index, long, and ring fingers
- Scan time: 1 second
- Results:
  Estimated phalangeal BMD in arbitrary RA units
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  Diagnostic classification based on WHO Criteria
- Precision: 1.1%
- Radiation exposure: 0.0001 mrem/scan (0.001 μSv/scan)
- Dimensions: 16 × 16 × 16 in (40.6 × 40.6 × 40.6 cm)
- Weight: 41.5 lbs (18.8 kg)
- Environmental operating temperature: 64°F to 95°F (18° to 35°C)
- Environmental operating humidity: 5 to 80%, noncondensing
- Scatter radiation: 0.0001 mrem/scan (0.001 μSv/scan) at 1 m
- Quality control: Automated

Fig. 13-3. The Alara MetriScan™. This is a self-contained X-ray unit used to perform radiographic absorptiometry of the phalanges. Photograph courtesy of Alara Inc., Hayward, CA.

- Operation: Unit is self-contained and does not require a standard hand film. Data input from keypad on unit. Separate HP DeskJet 697C or 710C printer or printer as specified by Alara, Inc. for results output.

CENTRAL X-RAY DENSITOMETERS

Delphi™

- Manufacturer: Hologic, Inc., Bedford, MA
- Technology: DXA
- Skeletal regions studied:
  PA lumbar spine
  Proximal femur
  Forearm
  IVA™ lateral spine imaging (T4–L4)
  Dual Hip™
  Whole body (on Delphi with Whole Body)
- Scan time (in the 60 Hz scan mode):
  PA lumbar spine and proximal femur 15 seconds
  Forearm 30 seconds
  Whole body 6.8 minutes
  Single energy IVA™ 10 seconds (for 15-in scan length)
- Results:
  BMD (g/cm^2)
  BMC (g)

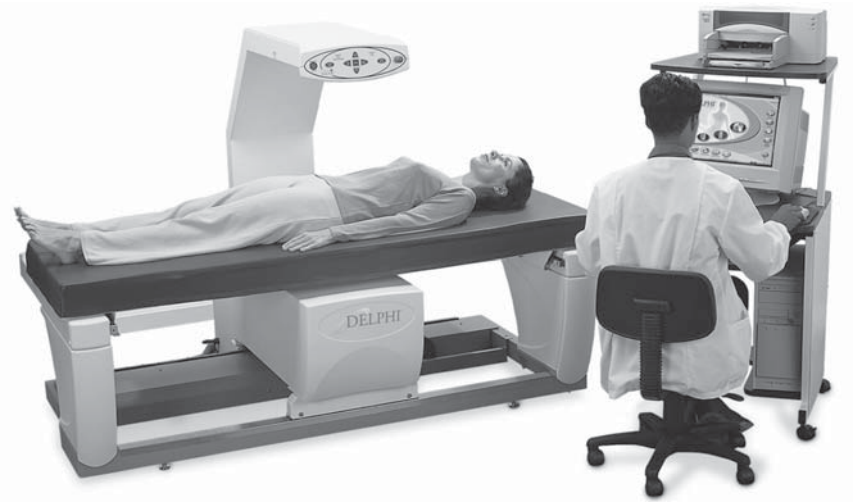

Fig. 13-4. The Hologic Delphi™. A central fan-array dual-energy X-ray absorptiometry. Photograph courtesy of Hologic, Inc., Bedford, MA.

Area (cm^2)
T-score and *z*-score
sBMD (mg/cm^2)
NHANES III reference data for hip
Trend reports for serial monitoring

- Precision: Less than 1.0%
- Radiation dose (in the 60 Hz scan mode):
  PA lumbar spine and proximal femur 5 mR
  Forearm 10 mR
  Whole body 1.5 mR
  IVA™ 7 mR (15-in scan length)
- Dimensions:
  Delphi™ 76 × 49.5 × 28 in (193 × 126 × 71 cm)
  Delphi™ with Whole Body 79.5 × 48 × 28 in (202 × 122 × 71 cm), 119 × 59 × 28 in (302 × 150 × 71 cm) table extended
- Weight:
  Delphi™ 650 lb (296 kg)
  Delphi™ with Whole Body 680 lb (310 kg)
- Recommended dedicated floor space: 8 × 8 ft (2.4 × 2.4 m)
- Scatter radiation: Less than 1.0 mR/hr (0.01 mSv/hr) measured at 6.6 ft (2 m) from the examination table for most scan modes
- Operating environmental temperature: 60° to 90°F (15° to 32°C)
- Operating environmental relative humidity: 20 to 80%, noncondensing
- X-ray source: Switched pulse at 140 kVp and 100 kVp for dual energy; 140 kVp for single energy IVA™
- X-ray beam geometry: Fan
- Detectors: Multi-element detector array

- Scan path: Linear
- Quality control: Self-calibrating with Hologic Automatic Internal Reference system and automated quality control program
- Operation: IBM-compatible Pentium computer, Windows 98®-based operating system, HP DeskJet® printer, 17-in monitor
- Accessories provided:
  Anthropomorphic spine phantom
  Medical imaging printer
- Options: Magneto optical disk storage; HP LaserJet® B&W printer; flat panel monitor; whole body, body composition analysis and quantitative morphometry software; modem or network options

Discovery™

- Manufacturer: Hologic, Inc., Bedford, MA
- Technology: Dual energy X-ray absorptiometry
- Models: C_i, W_i, C, W, SL, and A
- Skeletal regions studied:
  PA lumbar spine, all models
  Proximal femur, all models
  Forearm, all models
  Dual Hip™, all models
  IVA™, on models C, W, SL, and A
  CAD*fx*, on models C, W, SL, and A
  Whole body, on models W_i, W, and A
- Scan time on models C_i and W_i (in the 60 Hz scan mode):
  PA lumbar spine and proximal femur 30 seconds
  Forearm 30 seconds
  Whole body 6.8 minutes (model W_i only)
- Scan time on models C, W, SL, and A (in the 60 Hz scan mode):
  PA lumbar spine and proximal femur 10 seconds
  Forearm 30 seconds
  Single-energy IVA™ 30 seconds
  Whole Body 6.8 minutes (model W); 180 seconds (model A)
- Results:
  BMD (g/cm^2)
  BMC (g)
  Area (cm^2)
  T-score and *z*-score
  NHANES III reference data for hip
  Diagnosis using World Health Organization Criteria
  Fracture Risk Assessment
  Vertebral Fracture Assessment (with IVA™)
  Trend reports for serial monitoring
- Precision: <1.0%
- Radiation dose (in the 60 Hz scan mode):
  Models C_i and W_i PA lumbar spine and proximal femur 0.10 mGy
  Models C, W, SL, and A PA lumbar spine 0.007 mGy

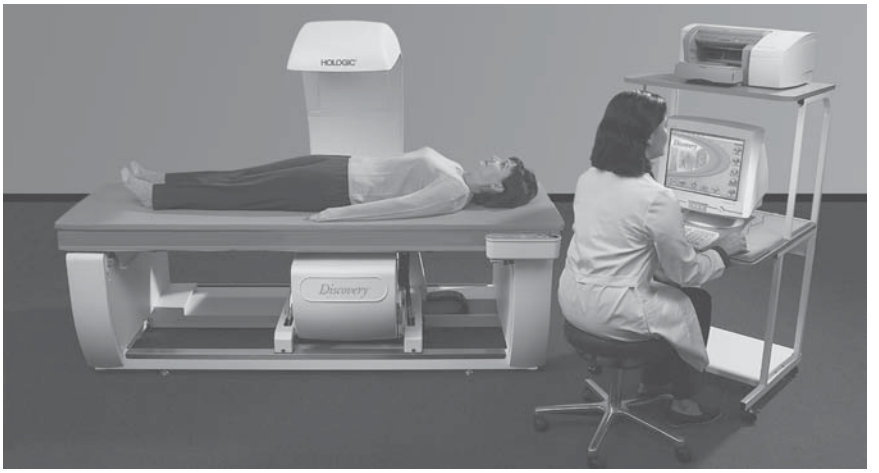

Fig. 13-5. The Hologic Discovery™. The newest model in the Hologic central, fan-array dual energy X-ray absorptiometer scanner line. Six models are available. Photograph courtesy of Hologic, Inc., Bedford, MA.

Models C, W, SL, and A Proximal femur 0.07 mGy
Models C_i and W_i Forearm 0.010 mGy
Models C, W, SL, and A Forearm 0.005 mGy
Models W_i and W Whole body 0.015 mGy (model A 0.01 mGy)
Models C, W, SL, and A IVA™ 0.07 mGy

- Dimensions:
  Models C_i and C 76 × 41 in (1.93 × 1.05 m)
  Models W_i, W, SL, and A 79.5 × 41 in (2.02 × 1.05 m)
  Models W_i and W, table extended 119 × 59 in (3.02 × 1.50 m)
  Model SL, table extended, and C-arm rotated 79.5 × 59 in (2.02 × 1.50 m)
  Model A, table extended, and C-arm rotated 119 × 59 in (3.02 × 1.50 m)
- Weight:
  Control console, all models, 150 lb (68 kg)
  Models C_i and C 650 lb (295 kg)
  Models W_i and W 680 lb (310 kg)
  Models SL and A 800 lb (365 kg)
- Recommended dedicated floor space: 8 × 8 ft (2.4 × 2.4 m) to 8 × 10 ft (2.4 × 3.1m), depending on model
- Scatter radiation: Less than 1.0 mR/hr (0.01 mSv/hr) measured at 6.6 ft (2.0 m) from the examination table for most scan modes
- Operating environmental temperature: 60° to 90°F (15° to 32°C)
- Operating environmental relative humidity: 20 to 80%, non-condensing
- X-ray source: Switched pulse with 140 kVp peak
- X-ray beam geometry: Fan
- Detectors: Multi-element detector array
- Quality control: Self-calibrating with Hologic Automatic Internal Reference system and automated quality control program

- Operation: IBM-compatible Pentium computer, QDR for Windows® XP Operating systems, HP DeskJet® printer, 17-in monitor, mouse, 56K modem, CD-RW drive
- Options: Magneto optical disk storage; HP LaserJet® B&W printer; 15-in flat panel monitor; modem or network options; IRIS package (includes DICOM, Physician's Report Writer); prosthetic hip software; and depending on model, decubitus lateral BMD, body composition and sub-region analysis software, small animal capability.

DPX-IQ™

- Manufacturer: GE Medical Systems, Madison, WI
- Technology: DXA
- Skeletal application(s):
  PA spine
  Proximal femur
  Total body with soft tissue quantification (with full size table only)
- Scan time:
  PA spine 2 minutes
  Proximal femur 2 minutes
  Total body 11 minutes
- Results:
  BMD (g/cm^2)
  BMC (g)
  Area (cm^2)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  sBMD (mg/cm^2) for L2–4 and total hip
  NHANES III total hip comparisons
- Precision:
  PA spine 0.5%
  Hip 1%
  Total body 0.5%
- Radiation dose:
  PA spine or proximal femur less than 3 mRem
  Total body 0.02 mRem
- Dimensions:
  Full-size table $95 \times 42 \times 52$ in ($242 \times 107 \times 133$ cm)
  Compact table $71 \times 40 \times 52$ in ($181 \times 100 \times 133$ cm)
- Weight:
  Full-size table 598 lbs (272 kg)
  Compact table 550 lbs (250 kg)
- Recommended dedicated floor space:
  Full-size table 9×7 ft ($2.\ 7 \times 2.1$ m)
  Compact table 7×7 ft (2.1×2.1 m)
- Operating environmental temperature: 65° to 80° F (18° to 27°C)
- Operating environmental relative humidity: 30 to 75%, noncondensing
- X-ray source: 134 KVp; 3.0 mA for PA spine and proximal femur studies (mA varies by skeletal site and scan mode)
- X-ray filtration: constant potential, cerium K-edge filter

- X-ray beam geometry: Pencil-beam
- Detectors: NaI
- Scan path: Rectilinear
- Quality control: Block phantom and aluminum spine phantom supplied by manufacturer
- Operation: IBM compatible desktop Pentium™ computer, SVGA monitor, printer
- Accessories provided:
  PA spine-positioning block
  Foot positioner for proximal femur studies
  Block phantom
  Aluminum spine phantom
- Options: Forearm, hand, lateral spine and orthopedics software; forearm positioner; lateral spine positioner; encapsulated spine phantom

DPX MD™

- Manufacturer: GE Medical Systems, Madison, WI
- Technology: DXA
- Skeletal application(s):
  PA spine
  Proximal femur
  DualFemur™ (not available on compact model)
  Total body (not available on compact model)
- Scan time:
  PA spine and proximal femur 2 minutes
  DualFemur™ 4 minutes
  Total body 8 minutes
- Results:
  BMD (g/cm^2),
  BMC (g),
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  sBMD (mg/cm^2)
  NHANES III reference data
  WHO diagnostic classification
- Precision:
  PA spine and total femur 1.0%
  DualFemur™ 0.7%
  Total body 0.5%
- Radiation dose:
  PA spine 1 mrem
  Femur 1 mrem
  Total body 0.02 mrem
- Dimensions:
  Full-size table $95 \times 42 \times 52$ in ($242 \times 107 \times 133$ cm)
  Compact table $71 \times 40 \times 52$ in ($181 \times 100 \times 133$ cm)
- Weight:
  Full-size table 598 lb (272 kg)
  Compact table 550 lb (250 kg)

- Recommended dedicated floor space:
  Full-size table 9 × 7 ft (2.7 × 2.1 m);
  Compact table 7 × 7 ft (2.1 × 2.1 m)
- Operating environmental temperature: 65° to 80° F (18° to 27°C)
- Operating environmental relative humidity: 30 to 75%, noncondensing
- X-ray source: 134 kV; 0.75 mA for PA spine, proximal femur, DualFemur™ (mA varies by skeletal site and scan mode)
- X-ray filtration: Constant potential, cerium K-edge filter
- X-ray beam geometry: Pencil
- Detectors: NaI
- Scan path: rectilinear
- Quality control: Automatic test program
- Operation: IBM-compatible computer, printer
- Accessories provided:
  PA spine positioner
  Proximal femur positioner
  DualFemur™ positioner
  Aluminum spine phantom
- Options: Lateral spine, Forearm/Hand, Pediatrics, Orthopedics and Small Animal software; encapsulated phantom

DPX MD+™

- Manufacturer: GE Medical Systems, Madison, WI
- Technology: DXA
- Skeletal application(s):
  PA spine
  Proximal femur
- Results:
  BMD (g/cm^2)
  BMC (g)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  sBMD (mg/cm^2)
  NHANES III reference data
  WHO diagnostic classification
- Precision:
  PA spine, proximal femur and total body 1%
  DualFemur™ less than 1%
- Radiation dose:
  PA spine and proximal femur 3 mrem
  Total body 0.02 mrem
- Dimensions:
  Full-size table 95 × 42 × 52 in (242 × 107 × 133 cm)
  Compact table 71 × 40 × 52 in (181 × 100 × 133 cm)

Fig. 13-6. The Lunar DPX Pro™. The newest model in the DPX series of central, pencil-beam, dual energy X-ray absorptiometers. This device is available in both a full-size and compact model. Photograph courtesy of GE Medical Systems, Madison, WI.

- Weight:
  Full-size table 598 lb (272 kg)
  Compact table 550 lb (250 kg)
- Recommended dedicated floor space:
  Full-size table 9 × 7 ft (2.7 × 2.1 m)
  Compact table 7 × 7 ft (2.1 × 2.1m)
- Operating environmental temperature: 65° to 80° F (18° to 27°C)
- Operating environmental relative humidity: 30 to 75%, noncondensing
- X-ray source: 134 kV; 0.75 mA for PA spine, proximal femur, DualFemur™
- X-ray filtration: Constant potential, cerium K-edge filter
- X-ray beam geometry: pencil
- Detectors: NaI
- Scan path: rectilinear
- Quality control: Automatic test program
- Operation: IBM-compatible computer, printer
- Accessories provided:
  PA spine positioner
  Proximal femur positioner
  Aluminum spine phantom
- Options: DualFemur™ with positioner (not available on compact model), total body with body composition (not available on compact model); encapsulated phantom

DPX-NT™

- Manufacturer: GE Medical Systems, Madison, WI
- Technology: DXA
- Skeletal application(s):
  - PA spine
  - Proximal femur
  - DualFemur™
  - Total body with body composition
- Scan time:
  - PA spine 1 minute
  - Proximal femur 2 minutes
  - DualFemur™ 4 minutes
  - Total body 8 minutes
- Results:
  - BMD (g/cm^2)
  - sBMD (mg/cm^2)
  - *T*-score and *z*-score
  - NHANES III reference data
  - WHO diagnostic classification
- Precision:
  - PA spine 1%
  - Proximal femur 1%
  - Total body 1%
  - DualFemur™ less than 1%
- Radiation dose:
  - PA spine 3 mrem
  - Proximal femur 3 mrem
  - Total body 0.02 mrem
- Dimensions: 95 × 42 × 52 in (242 × 107 × 133 cm)
- Weight: 598 lb (272 kg)
- Recommended dedicated floor space: 9 × 7 ft (2.7 × 2.1 m)
- Operating environmental temperature: 65° to 80° F (18° to 27°C)
- Operating environmental relative humidity: 30 to 75%, noncondensing
- X-ray source: 134 kV; 1.5 mA for PA spine, proximal femur, DualFemur™ (mA varies by skeletal site and scan mode)
- X-ray filtration: Constant potential, cerium cerium K-edge filter
- X-ray beam geometry: Pencil
- Detectors: NaI
- Scan path: rectilinear
- Quality control: Automated QA program
- Operation: IBM-compatible computer running Windows NT
- Accessories provided:
  - PA spine positioner
  - Proximal femur positioner
  - DualFemur™ positioner
  - Aluminum spine phantom
- Options: Encapsulated phantom

Excell™

- Manufacturer: Norland, a CooperSurgical Company, Ft. Atkinson, WI
- Technology: DXA
- Standard application(s):
  - PA spine
  - Proximal femur
- Scan time:
  - PA spine less than 1.5 minutes
  - Proximal femur less than 2 minutes
- Results
  - BMD (g/cm^2)
  - BMC (g)
  - Length (cm)
  - Percent young reference and percent age-matched comparisons
  - *T*-score and *z*-score
  - sBMD (mg/cm^2) for L2–L4 and total hip
  - NHANES III total hip comparisons
  - Fracture risk based on WHO diagnostic classification
- Precision:
  - PA spine 1%
  - Hip 1.2%
- Radiation dose: less than 1.0 mRem in high-speed scan mode
- Dimensions: $72 \times 48 \times 49$ in ($182.8 \times 122.0 \times 124.5$ cm)
- Weight: 400 lb (181 kg)
- Recommended dedicated floor space: 7×7 ft (2.1×2.1 m)
- Operating environmental temperature: 60° to 104° F (15° to 40°C)
- Operating environmental relative humidity: up to 80%, noncondensing
- X-ray source: 100 kV, 1.3 mA
- X-ray filtration: Samarium
- X-ray beam geometry: Pencil-beam
- Detectors: two NaI scintillation detectors
- Scan path: Rectilinear
- Quality control: Automated with 77-step calibration standard and quality control phantom
- Operation: IBM compatible PC computer, HP DeskJet
- Accessories provided:
  - PA spine-positioning block
  - Hip sling with foot separator
  - 77-step calibration standard
  - Quality control phantom
- Options: Laptop computer

Excell™*plus*

- Manufacturer: Norland, a CooperSurgical Company, Ft. Atkinson, WI
- Technology: DXA
- Skeletal application(s):

Fig. 13-7. The Norland Excell™. A central pencil-beam dual energy X-ray absorptiometer. Photograph courtesy of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

PA spine
Proximal femur
Forearm
Lateral spine

- Scan time:
  PA spine less than 1.5 minutes
  Proximal femur less than 2 minutes
  Forearm less than 3 minutes
  Lateral spine less than 4 minutes
- Results:
  BMD (g/cm^2)
  BMC (g)
  Length (cm)
  Percent young reference and percent age-matched comparisons
  T-score and *z*-score
  sBMD (mg/cm^2) for L2–L4 and total hip
  NHANES III total hip comparisons
- Precision:
  PA spine 1%
  Hip 1.2%
  Forearm 0.8%
  Lateral spine 2.4%
- Radiation dose:
  PA spine, proximal femur, forearm less than 1 mrem
  Lateral spine less than 2 mrem

- Dimensions: 72 × 48 × 49 in (182.8 × 122.0 × 124.5 cm)
- Weight: 400 lb (181 kg)
- Recommended dedicated floor space: 7 × 7 ft (2.1 × 2.1 m)
- Operating environmental temperature: 60° to 104° F (15° to 40°C)
- Operating environmental relative humidity: up to 80%, noncondensing
- X-ray source: 100 kV, 1.3 mA
- X-ray filtration: samarium
- X-ray beam geometry: pencil-beam
- Detectors: Two NaI scintillation detectors
- Scan path: rectilinear
- Quality control: Automated with 77-step calibration standard and quality control phantom
- Operation: IBM compatible computer with Windows operating system, DeskJet printer, 15-in SVGA monitor
- Accessories provided:
  - PA spine-positioning block
  - Hip sling with foot separator for use in proximal femur studies
  - Lateral and forearm positioning aids
  - 77-step calibration standard
  - Quality control phantom
- Options: Software for research, small subject, or body composition; laptop computer; flat screen monitor; 17-in SVGA monitor

EXPERT®-XL

- Manufacturer: GE Medical Systems, Madison, WI
- Technology: DXA
- Skeletal regions studied:
  - PA spine
  - Lateral lumbar spine
  - Proximal femur
  - Forearm and hand
  - Total body
  - Orthopedic hip
  - Vertebral morphometry
- Scan times:
  - PA spine and proximal femur, 6 seconds
  - Forearm/hand 10 seconds
  - Lateral spine 24 seconds
  - Total body 160 seconds
  - Vertebral morphometry 38 seconds
- Results:
  - BMD (g/cm^2)
  - BMC (g)
  - Area (cm^2)
  - Percent young-adult and percent age-matched comparsions
  - *T*-score and *z*-score
  - Vertebral heights (mm) and vertebral height ratios

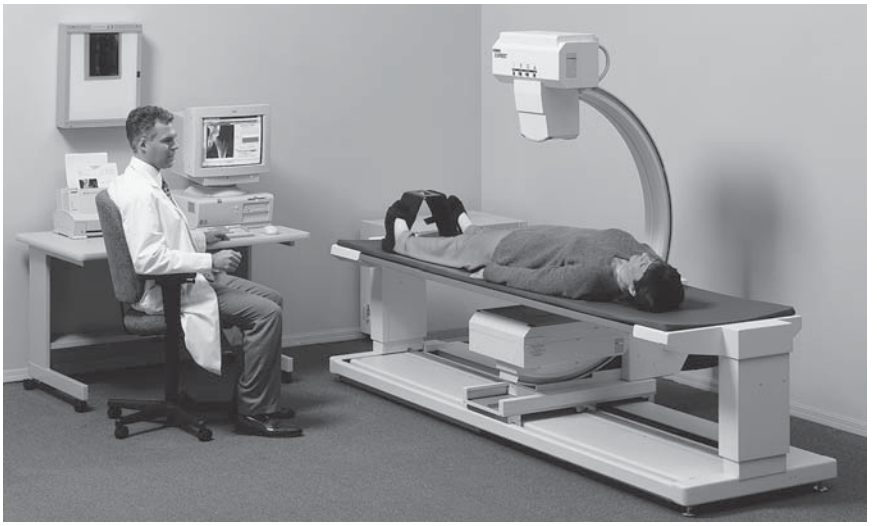

Fig. 13-8. The Lunar Expert®-XL. A central fan-array dual energy X-ray absorptiometer. Photograph courtesy of GE Medical Systems, Madison, WI.

- Precision: 1.0%
- Radiation dose:
  PA spine and proximal femur 27 mrem
  Forearm/hand 12 mrem
  Lateral spine 190 mrem
  Total body 5 mrem
  Morphometry 120 mrem
- Dimensions: 108 × 71 in (2.7 × 1.8 m). Motorized C-arm 140° rotation with 78 in (198 cm) longitudinal travel and 14 in (36 cm) transverse travel
- Weight: 750 lb (340.2 kg)
- Recommended dedicated floor space: 12 × 10 ft (3.7 × 3.1 m)
- Operating environmental temperature: 65° to 80° F (18° to 27°C)
- Operating environmental relative humidity: 30 to 75%, noncondensing
- X-ray source: 134 kV, 5 mA for PA spine, proximal femur, lateral spine, and morphometry
- X-ray beam geometry: Fan-beam
- Detectors: Dual energy solid state
- Scan path: Linear
- Image resolution: 0.5 mm
- Quality control: Internal hydroxyapatite; automated quality assurance program with spine phantom
- Operation: IBM compatible, Pentium®-based computer; Windows® environment; SVGA monitor; black and white laser printer; hand-held motor controller for C-arm rotation and table elevation
- Accessories provided: Spine phantom
- Options: Color printer; DICOM utilities

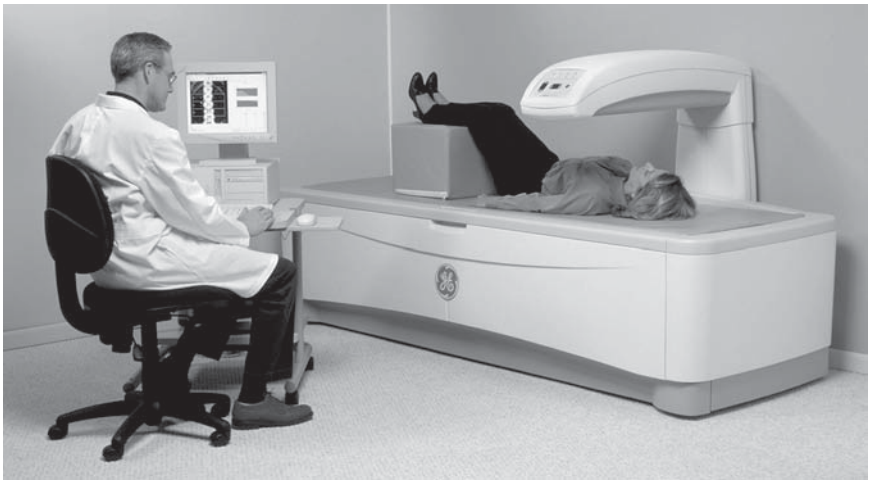

Fig. 13-9. The Lunar Prodigy™. A central fan-array dual energy X-ray absorptiometer. Photograph courtesy of GE Medical Systems, Madison, WI.

Prodigy™

- Manufacturer: GE Medical Systems, Madison, WI
- Technology: DXA
- Skeletal application(s):
  - PA spine
  - Proximal femur
  - DualFemur™
  - Customized regions of interest with metal removal
  - Total body and body composition
- Scan time:
  - PA spine and proximal femur 30 seconds
  - DualFemur™ 1 minute
  - Total body 5 minutes
- Results:
  - BMD (g/cm^2)
  - sBMD (mg/cm^2)
  - *T*-score and *z*-score
  - Fracture risk assessment based on WHO diagnostic classification
  - LUNAR® and NHANES III databases
- Precision:
  - PA spine and proximal femur 1%
  - DualFemur™ less than 1%
  - Total body less than 1%
- Radiation dose:
  - PA spine and proximal femur 3.7 mrem
  - Total body 0.037 mrem
- Dimensions: $103.5 \times 43.5 \times 50$ in ($263 \times 111 \times 127$ cm)

- Weight: 600 lb (272 kg)
- Recommended dedicated floor space: 9 × 7.5 ft (2.8 × 2.3 m)
- Scatter radiation: less than 0.3mR/hr (3 μSv/hr) at 39 in (1 m)
- Operating environmental temperature: 65° to 80° F (18° to 27°C)
- Operating environmental relative humidity: 20 to 80%, noncondensing
- X-ray source: 134 kV; 3.0 mA for PA spine, proximal femur, Lateral Vertebral Assessment (mA varies by skeletal site and scan mode)
- X-ray filtration: Constant potential cerium K-edge filter
- X-ray beam geometry: Narrow angle fan-beam
- Detectors: Cadium-zinc-telluride (CZT)
- Scan path: Rectilinear
- Quality control: Automatic test program with QA trending
- Operation: Windows NT®-based program on IBM-compatible Pentium® computer, printer
- Accessories provided:
  PA spine positioner
  DualFemur™ positioner
  Aluminum spine phantom
- Options: Pediatric, forearm, lateral spine and LateralView™software; encapsulated phantom

QDR® 4500 A

- Manufacturer: Hologic, Inc., Bedford, MA
- Technology: DXA
- Skeletal regions studied:
  PA spine
  Proximal femur
  Forearm
  Whole body
  Supine lateral lumbar spine
- Scan time (in the 60 Hz scan mode):
  PA lumbar spine and proximal femur 10 seconds
  Lateral spine 120 seconds
  Forearm 30 seconds
  Whole body 3 minutes
  Lateral imaging with MXA 7.5 s
- Results:
  BMD (g/cm^2)
  BMC (g)
  Area (cm^2)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  sBMD (mg/cm^2) for L2–L4 and total hip
  NHANES III total hip comparisons
- Precision: Less than 1%

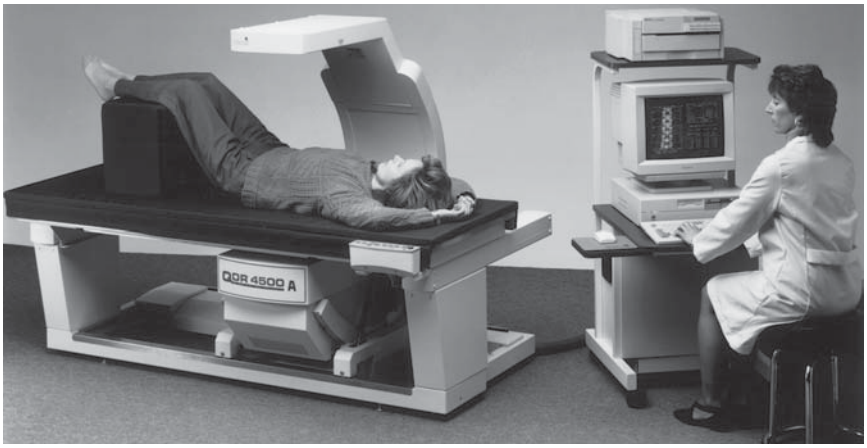

Fig. 13-10. The Hologic QDR® 4500 A. A central fan-array dual energy X-ray absorptiometer. Photo courtesy of Hologic, Inc., Bedford, MA.

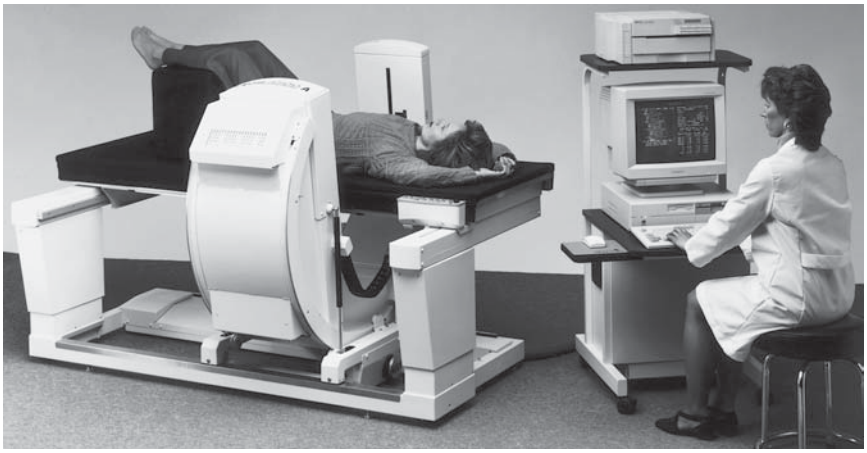

Fig. 13-11. The Hologic QDR® 4500 A. The gantry is rotated to perform supine lateral lumbar spine studies. Photograph courtesy of Hologic Inc., Bedford, MA.

- Radiation dose (in the 60 Hz scan mode):
  PA lumbar 7 mR
  Proximal femur 7 mR
  Lateral spine 35 mR
  Forearm 5 mR
  Whole body 1 mR
  Lateral imaging with MXA 7 mR
- Dimensions: 79.5 × 41 × 28 in (202 × 104 × 71 cm), 118.9 × 57 in (302 × 145 cm) with C-arm rotated and table extended
- Weight: 800 lb (364 kg)
- Recommended dedicated floor space: 8 × 10 ft (2.4 × 3.1 m)

- Scatter radiation: Less than 1.0 mR/hr (0.01 mSv/hr) measured at 6.6 ft (2.0 m) from the examination table for most scan modes
- Operating environmental temperature: 60° to 90° F (15° to 32°C)
- Operating environmental relative humidity: 20% to 80%
- X-ray source: Switched pulse, dual energy
- X-ray beam geometry: Fan-beam
- Detectors: Multi-element detector array
- Scan path: Linear
- Quality control: Self-calibrating with patented Hologic Automatic Internal Reference System and automated quality control program
- Operation: IBM-compatible Pentium computer with Windows operating system, 17-in monitor, HP LaserJet® B&W printer
- Accessories provided: Anthropomorphic spine phantom
- Options: Magneto optical disk storage; network configurations; body composition analysis software, MXA software, small animal software

QDR® 4500 C

- Manufacturer: Hologic, Inc., Bedford, MA
- Technology: DXA
- Skeletal application(s):
  PA spine
  Proximal femur
  Forearm
- Scan time (in the 60 Hz scan mode):
  PA lumbar spine and proximal femur 15 seconds
  Forearm 30 seconds
- Results:
  BMD (g/cm^2)
  BMC (g)
  Area (cm^2)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  sBMD (mg/cm^2) for L2–L4 and total hip
  NHANES III total hip comparisons
  Fracture risk and diagnostic classification based on WHO Criteria
- Precision: Less than 1%
- Radiation dose (in the 60 Hz scan mode):
  PA lumbar spine 5 mR
  Proximal femur 5 mR
  Forearm 10 mR
- Dimensions: 79.5 × 41 × 28 in (202 × 104 × 71 cm)
- Weight: 650 lb (296 kg)
- Recommended dedicated floor space: 8 × 8 ft (2.4 × 2.4 m)
- Scatter radiation: Less than 1.0 mR/hr (0.01 mSv/hr) measured at 6.6 ft (2 m) from the examination table for most scan modes

- Operating environmental temperature: 60° to 90° F (15° to 32°C)
- Operating environmental relative humidity: 20 to 80%, noncondensing
- X-ray source: Switched pulse, dual energy, 140 V peak
- X-ray beam geometry: fan-beam
- Detectors: Multi-element detector array
- Scan path: Linear
- Quality control: Self-calibrating with patented Hologic Automatic Internal Reference System and automated quality control program
- Operation: IBM-compatible Pentium computer with Windows operating system, 17-in monitor, HP DeskJet® printer
- Accessories provided: Anthropomorphic spine phantom
- Options: Magneto optical disk storage; network configuration; HP LaserJet® B&W printer

QDR® 4500 SL

- Manufacturer: Hologic, Inc., Bedford, MA
- Technology: DXA
- Skeletal application(s):
  PA spine
  Proximal femur
  Forearm
  Supine lateral lumbar spine
- Scan time (in the 60 Hz scan mode):
  PA lumbar spine and proximal femur 10 seconds
  Lateral spine 120 seconds
  Forearm 30 seconds
  Lateral imaging with MXA 7.5 seconds
- Results:
  BMD (g/cm^2)
  BMC (g)
  Area (cm^2)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  sBMD (mg/cm^2) for L2–l4 and total hip
  NHANES III total hip comparisons
- Precision: Less than 1%
- Radiation dose (in the 60 Hz scan mode):
  PA lumbar spine 7 mR
  Proximal femur 7 mR
  Lateral spine 35 mR
  Forearm 5 mR
  Lateral imaging with MXA 7 mR
- Dimensions: 79.5 × 41 × 28 in (202 × 104 × 71 cm), 79.5 × 57 in (202 × 145 cm) with C-arm rotated and table extended
- Weight: 800 lb (364 kg)
- Recommended dedicated floor space: 8 × 8 ft (2.4 × 2.4 m)

- Scatter radiation: Less than 1.0 mR/hr (0.01 mSv/hr) measured at 6.6 ft (2.0 m) from the examination table for most scan modes
- Operating environmental temperature: 60° to 90° F (15° to 32°C)
- Operating environmental relative humidity: 20 to 80%
- X-ray source: Switched pulse, dual energy
- X-ray beam geometry: fan-beam
- Detectors: Multi-element detector array
- Scan path: Linear
- Quality control: Self-calibrating with patented Hologic Automatic Internal Reference System and automated quality control program
- Operation: IBM-compatible Pentium computer with Windows operating system, 17-in monitor, HP DeskJet® printer
- Accessories provided: Anthropomorphic spine phantom
- Options: Magneto optical disk storage; network configurations; HP LaserJet® B&W printer; MXA software

QDR® 4500 W

- Manufacturer: Hologic, Inc., Bedford, MA
- Technology: DXA
- Skeletal regions studied:
  PA spine
  Proximal femur
  Forearm
  Whole body
- Scan time (in the 60 Hz scan mode):
  PA lumbar spine and proximal femur 15 seconds
  Forearm 30 seconds
  Whole body 6.8 minutes
- Results:
  BMD (g/cm^2)
  BMC (g)
  Area (cm^2)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  sBMD (mg/cm^2) for L2–L4 and total hip
  NHANES III total hip comparisons
- Precision: Less than 1%
- Radiation dose (in the 60 Hz scan mode):
  PA lumbar spine 5 mR
  Proximal femur 5 mR
  Forearm 10 mR
  Whole body 1.5 mR
- Dimensions: $79.5 \times 48 \times 28$ in ($202 \times 122 \times 71$ cm), $118.9 \times 59 \times 28$ in ($302 \times 150 \times 71$ cm) with table extended
- Weight: 680 lb (310 kg)
- Recommended dedicated floor space: 8×10 ft (2.4×3.1 m)

Fig. 13-12. The Norland XR-46™. A central pencil-beam dual energy X-ray absorptiometer. Photograph courtesy of Norland a CooperSurgical Company, Ft. Atkinson, WI.

- Scatter radiation: Less than 1.0 R/hr (0.01 mSv/hr) measured at 6.6 ft (2.0 m) from the examination table for most scan modes
- Operating environmental temperature: 60° to 90° F (15° to 32°C)
- Operating environmental relative humidity: 20 to 80%
- X-ray source: Switched pulse, dual energy
- X-ray beam geometry: Fan-beam
- Detectors: Multi-element detector array
- Scan path: Linear
- Quality control: Self-calibrating with patented Hologic Automatic Internal Reference System and automated quality control program
- Operation: IBM-compatible Pentium computer with Windows operating system, 17-in monitor, HP DeskJet® printer
- Accessories provided: Anthropomorphic spine phantom
- Options: Magneto optical disk storage; network configurations; HP LaserJet® B&W printer; body composition analysis software

XR-46™

- Manufacturer: Norland, a CooperSurgical Company, Ft. Atkinson, WI
- Technology: DXA
- Skeletal regions studied:
  PA spine
  Lateral spine
  Proximal Femur

  Forearm
  Whole body with soft tissue composition
- Scan time:
  PA spine less than 1.5 minutes
  Hip less than 2 minutes
  Forearm less than 3 minutes
  Lateral spine less than 4 minutes
  Whole body 5 minutes
- Results:
  BMD (g/cm^2)
  BMC (g)
  Percent young-reference and percent age-matched comparisons
  T-score and *z*-score
  sBMD (mg/cm^2) for L2–L4 and total hip based on NHANES III reference data
- Precision:
  PA spine 1%
  Hip 1.2%
  Forearm 0.8%
  Lateral Spine 2.4%
  Whole body BMD 1%
- Radiation dose:
  PA spine, hip, and forearm less than 1 mrem
  Lateral spine less than 5 mrem
  Whole body less than 0.1 mrem
- Dimensions: $103 \times 48 \times 51$ in ($261.6 \times 122.0 \times 129.5$ cm)
- Weight: 556.5 lb (252.4 kg)
- Recommended dedicated floor space: 10×7 ft (3.1×2.1 m)
- Operating environmental temperatures: 60° to 90° F (15° to 32°C)
- Operating environmental relative humidity: Up to 80%, noncondensing
- X-ray source: 100 kV, 1.3 mA
- X-ray filtration: Eight-level automated samarium
- X-ray beam geometry: Pencil-beam
- Detectors: Two NaI detectors
- Scan path: Rectilinear
- Quality control: Automatic with supplied calibration standard and quality control phantom
- Operation: IBM-compatible computer with HP color DeskJet printer. DOS program with Microsoft® Windows™ resident
- Accessories provided:
  77-step calibration standard
  Quality control phantom
  PA spine positioning block
  Hip sling with foot separator
  Lateral spine positioner
  Forearm positioner
- Options: Flat panel display; 17-in SVGA monitor; laptop configuration; research and small subject software

Fig. 13-13. The Schick accuDEXA™. A peripheral dual energy X-ray absorptiometer used to measured bone density in the phalanges. Photograph courtesy of Schick Technologies, Inc., Long Island City, NY.

PERIPHERAL X-RAY DENSITOMETERS

accuDEXA™

- Manufacturer: Schick Technologies, Inc., Long Island City, NY
- Technology: DXA
- Skeletal application(s): Middle phalanx of the long finger
- Scan time: Less than 1 minute
- Results:
  BMD (g/cm^2)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  Diagnostic classification based on WHO Criteria
- Precision: Less than 1%
- Radiation dose: 0.0003 μSv
- Dimensions: 14 × 15 × 14 in (35.56 × 38.1 × 35.56 cm)
- Weight: 66 lb (29.7 kg)
- Environmental operating temperature: 70° to 85° F (21° to 29°C)
- Environmental operating relative humidity: 20 to 80%
- X-ray source:
  Low energy 50 kVp, 0.5 mA
  High energy 70 kVp, 0.9 mA
- X-ray filtration (high energy only): zinc
- Scatter radiation: 6.1 mR/hr at 1 m
- Quality control: Automatic, no user intervention required.
- Operation: Data input with touch pad on the device, data output with printer supplied by user (list of compatible printers available from manufacturer)

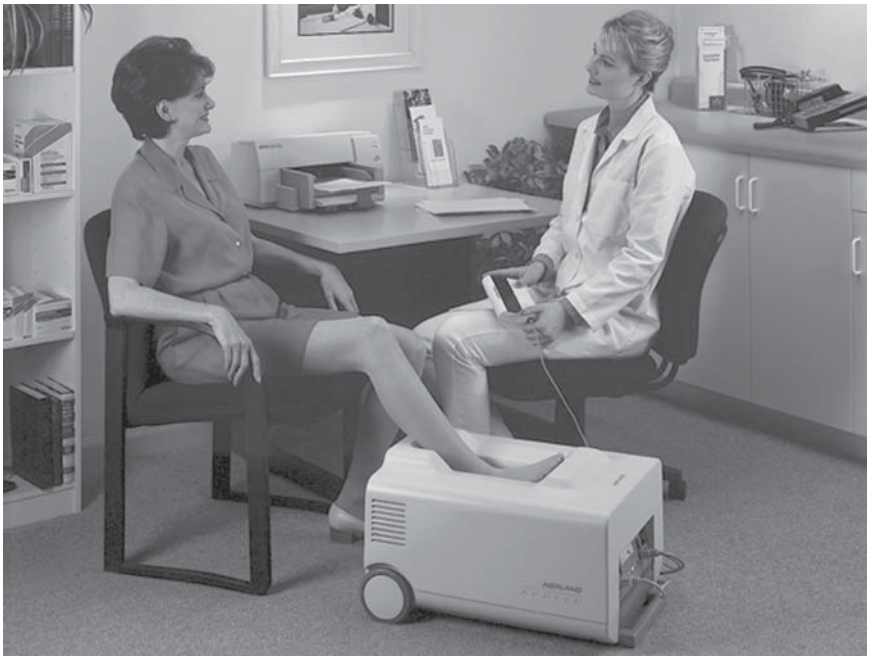

Fig. 13-14. The Norland Apollo™. A peripheral dual energy X-ray absorptiometer used to measured bone density in the calcaneus. Photograph courtesy of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

Apollo™

- Norland, a CooperSurgical Company, Ft. Atkinson, WI
- Technology: DXA
- Skeletal application(s): calcaneus
- Scan time: 15 seconds
- Results:
  BMD (g/cm^2)
  BMC (g)
  Area (cm^2)
  Percent young reference and percent age-matched comparisons
  T-score and *z*-score
  Fracture risk based on WHO diagnostic classification
- Precision: 1.8%
- Radiation dose: Less than 0.2 mrem
- Dimensions: 22.5 × 17.5 × 14 in (57.2 × 44.5 × 35.6 cm)
- Weight: 64 lb (29 kg)
- Operating environmental temperature: 50° to 90° F (10° to 32°C)
- Operating environmental relative humidity: 20 to 95%, noncondensing
- X-ray source: 60kV, less than 0.3 mA
- X-ray filtration: tin
- Detectors: Two solid state

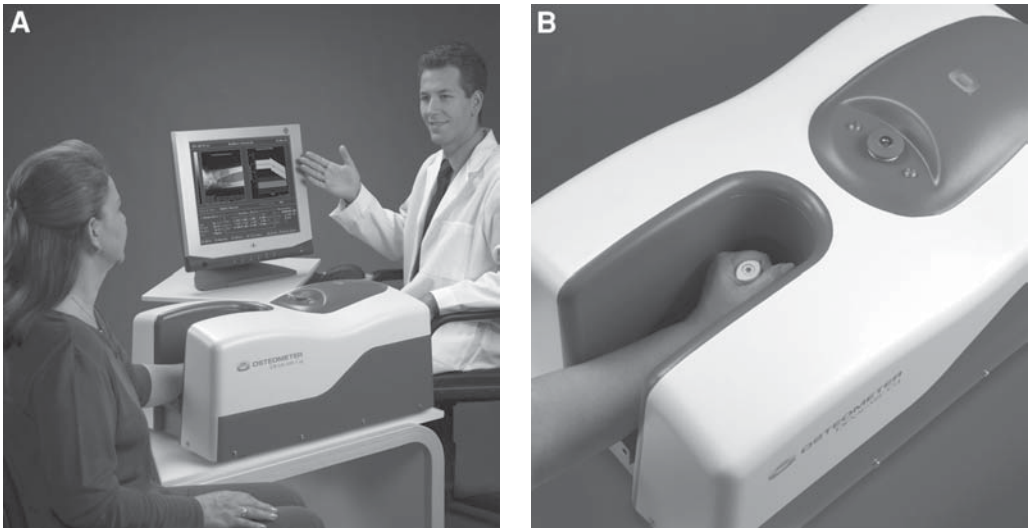

Fig. 13-15. (A) The Osteometer DexaCare® G4. A peripheral dual energy X-ray absorptiometer used to measure bone density in the forearm. **(B)** The forearm is placed into the well on the top of the machine. Photographs courtesy of Osteometer MediTech, Hawthorne, CA.

- Quality control: Automatic with internal phantoms requiring less than 5 minutes
- Operation: Hand-held console with fluorescent display. Unit on wheels with retractable handle. Built in floppy disc drive for data transfer. Built in parallel printer port for Canon BJC color printer or equivalent
- Options: Laptop configuration

DexaCare® G4

- Manufacturer: Osteometer MediTech, Inc., Hawthorne, CA
- Technology: DXA
- Skeletal application(s): Forearm
- Scan time: 2 minutes, distal forearm
- Results:
  BMD (g/cm^2)
  BMC (g), area (cm^2)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
- Precision: Less than 1%
- Radiation dose: 0.1 μSv per scan
- Dimensions: 12.5 × 26 × 15.5 in (32 × 66 × 40 cm)
- Weight: 49 lb (22 kg)
- Environmental operating temperature: 58° to 86° F (15° to 30°C)
- X-ray source: 55 kV, 300 μA
- X-ray filtration: K-edge filtration

Fig. 13-16. The Osteometer DTX-200 DexaCare®. A peripheral dual energy X-ray absorptiometer used to measure bone density in the forearm. Photograph courtesy of Osteometer MediTech, Hawthorne, CA.

- Detectors: Solid state
- Imaging resolution: 0.4 × 0.4 mm
- Scatter radiation: Less than 0.25 μSv/hr at 1 m
- Calibration system: Line-by-line internal reference calibration
- Operation: IBM-compatible computer, HP DeskJet 600C or equivalent printer, VGA display

DTX-200 DexaCare®

- Manufacturer: Osteometer MediTech, Inc., Hawthorne, CA
- Technology: DXA
- Skeletal application(s): Forearm
- Scan time: 4.5 minutes
- Results:
  BMD (g/cm^2)
  BMC (g), area (cm^2)

Fig. 13-17. The Osteometer DTX-200 DexaCare®. The forearm is placed into the well in the top of the machine. Photograph courtesy of Osteometer MediTech, Hawthorne, CA.

Percent young-adult and percent age-matched comparisons
T-score and *z*-score

- Precision: Less than 1%
- Radiation dose: 0.1 μSv per scan
- Dimensions: 32 × 24 × 12 in (80 × 62 × 30 cm)
- Weight: 114 lb (52 kg)
- Environmental operating temperature: 58° to 86° F (15° to 30°C)
- X-ray source: 55 kV, 300 μA
- X-ray filtration: tin, K-edge filtration
- Detectors: Solid state
- Imaging resolution: 0.4 × 0.4 mm
- Scatter radiation: < 0.25 μSv/hr at 1 m
- Quality Control: Automated with forearm phantom supplied by manufacturer
- Operation: IBM-compatible computer, HP DeskJet 600C or equivalent printer, VGA monitor, unit on wheels for easy mobility

pDEXA®

- Manufacturer: Norland, a CooperSurgical Company, Ft. Atkinson, WI
- Technology: DXA
- Skeletal application(s): Forearm
- Scan time: Less than 5 minutes

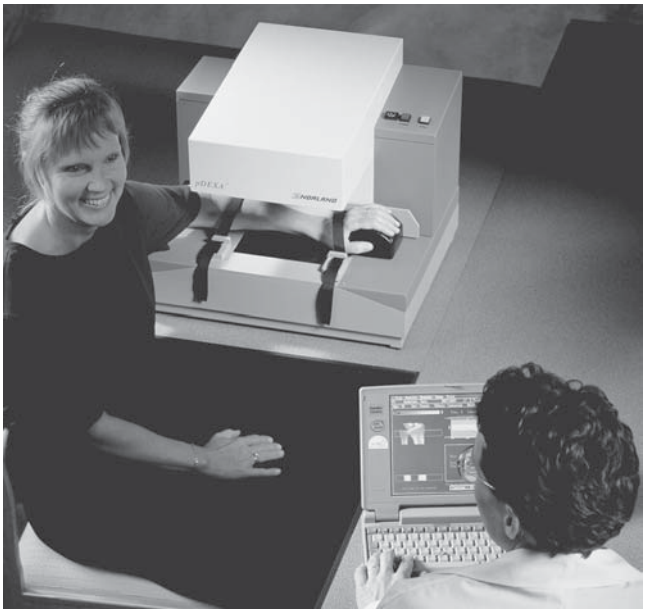

Fig. 13-18. The Norland pDEXA®. A peripheral dual energy X-ray absorptiometer used to measure bone density in the forearm. Photograph courtesy of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

- Results:
  BMD (g/cm^2)
  BMC (g)
  area (cm^2)
  Percent young-reference and percent age-matched comparisons
  T-score and *z*-score
- Precision: Less than 2.0%
- Radiation dose: Less than 1.5 mrem at high speed
- Dimensions: 20.5 × 17 × 16.7 in (52 × 43 × 42.5 cm)
- Weight: 59.4 lb (27 kg)
- Environmental operating temperature: 60° to 82° F (15° to 28°C)
- Environmental operating relative humidity: up to 80%, noncondensing
- X-ray source: 60 kV, less than 0.3 mA
- X-ray filtration: tin
- Detectors: Two solid state
- Quality control: Automatic with manufacturer supplied calibration standard and quality control phantom
- Operation: IBM-compatible laptop computer with Windows operating system, HP DeskJet printer and mouse.
- Options: IBM-compatible desktop computer with Windows operating system, 15-in SVGA monitor, 15-in flat-panel display, 17-in SVGA monitor, HP DeskJet

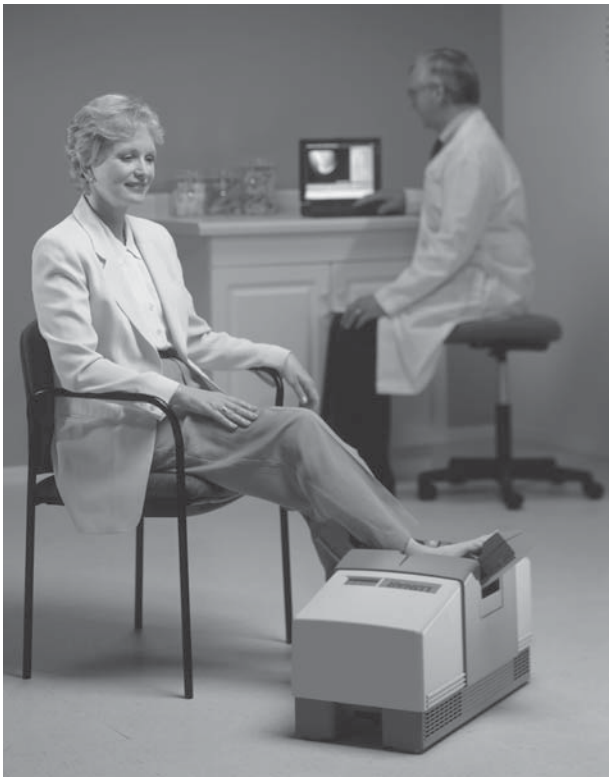

Fig. 13-19. The Lunar PIXI®. A peripheral dual energy X-ray absorptiometer shown here in the configuration used to measure bone density in the calcaneus. The device can be reconfigured and used to measure bone density in the forearm. Photograph courtesy of GE Medical Systems, Madison, WI.

PIXI® (Peripheral Instantaneous X-Ray Imager)

- Manufacturer: GE Medical Systems, Madison, WI
- Technology: DXA
- Skeletal application(s): calcaneus, forearm
- Scan time: 5 seconds
- Results:
  BMD (g/cm^2)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
- Precision: Less than 1.5%
- Radiation dose: 0.032 μSv
- Dimensions: $12 \times 25 \times 13$ in ($30 \times 63 \times 33$ cm)
- Weight: 66 lb (less than 30 kg)
- Environmental operating temperature: 64° to 81° F (18° to 27°C)
- X-ray source: Cone-beam geometry, 250 μA current

Fig. 13-20. The Stratec XCT 2000™. A peripheral quantitative computed tomography device used to measure bone density in the forearm. Photograph courtesy of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

- Image resolution: 0.2 × 0.2 mm
- Quality control: Aluminum os calcis and forearm phantoms supplied by the manufacturer
- Operation: Laptop computer, printer
- Options: Portable color printer, reusable hard shipping case, soft-sided portability case and cart

XCT 2000™

- Manufacturer: Stratec Medizintechnik, Pforzheim, Germany
- Distributor: Orthometrix, Inc., White Plains, NY
- Technology: QCT
- Skeletal application(s): Forearm
- Scan time: 80 seconds
- Results: BMD (mg/cm^3) for total bone and trabecular and cortical compartments
- Precision: ±3 mg/cm^3 for trabecular bone; ±9 mg/cm^3 for cortical bone
- Radiation dose: 0.03 mSv per scan
- Dimensions: 21.7 × 36.6 × 24.4 in (55 × 93 × 62 cm)
- Weight: Less than 100 lb (less than 45 kg)
- X-ray source: 55 to 60 kV, less than 0.3 mA
- Detectors: 12 semiconductor detectors with amplifiers
- Operation: Pentium computer, monitor, and color printer
- Options: Magneto opticals for data backup

Fig. 13-21. The Lunar Achilles+™. A peripheral quantitative ultrasound device used to measure the calcaneus, shown here in the closed position. Photograph courtesy of GE Medical Systems, Madison, WI.

ULTRASOUND BONE DENSITOMETERS

Achilles+™

- Manufacturer: GE Medical Systems, Madison, WI
- Technology:
  - Ultrasound
  - Transmitted through bone
  - Wet
- Skeletal application(s): Calcaneus
- Scan time: 1 minute
- Results:
  - SOS (m/s)
  - BUA (db/MHz)
  - Stiffness Index
  - Percent young-adult and percent age-matched comparisons
  - *T*-score and *z*-score
- Precision: 2% for Stiffness™ Index
- Dimensions: 20 × 13 × 24 in (51 × 33 × 61 cm)
- Weight: 44 lb (20 kg)
- Operating environmental temperature: 59° to 95° F (15° to 35°C)
- Operating environmental relative humidity: 20 to 80%
- Operation: Self-contained LCD touch screen, thermal printer, 50-measurement memory, built-in carrying handle

Fig. 13-22. The Lunar Achilles+™. A peripheral quantitative ultrasound device used to measure the calcaneus, shown here in use. Photograph courtesy of GE Medical Systems, Madison, WI.

- Accessories provided:
  Water-soluble ultrasonic gel
  Premeasured surfactant
- Options: Laptop computer, external printer

Achilles Express™

- Manufacturer: GE Medical Systems, Madison, WI
- Technology:
  Ultrasound
  Transmitted through bone
  Dry
- Skeletal application(s): Calcaneus
- Scan time: 1 minute
- Results:
  Stiffness Index
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
- Precision: 2%

Figure 13-23. The Lunar Achilles Express™. A peripheral quantitative ultrasound device used to measure the calcaneus. Photograph courtesy of GE Medical Systems, Madison, WI.

- Dimensions: 10 × 12 × 24 in (25 × 31 × 61 cm)
- Weight: 22 lb (10 kg)
- Operating environmental temperature: 59° to 95° F (15° to 35°C)
- Operating environmental relative humidity: 20 to 80%
- Operation: Self-contained LCD touch screen that swivels, thermal printer, 100-measurement memory; built-in carrying handle
- Accessories: Water-soluble ultrasonic gel

Achilles InSight™

- Manufacturer: GE Medical Systems, Madison, WI
- Technology:
  Ultrasound
  Transmitted through bone
  Dry
- Skeletal application(s): Calcaneus
- Scan time: 15 seconds
- Results:
  Stiffness Index
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
  WHO classification
  Heel image
  Reference graph

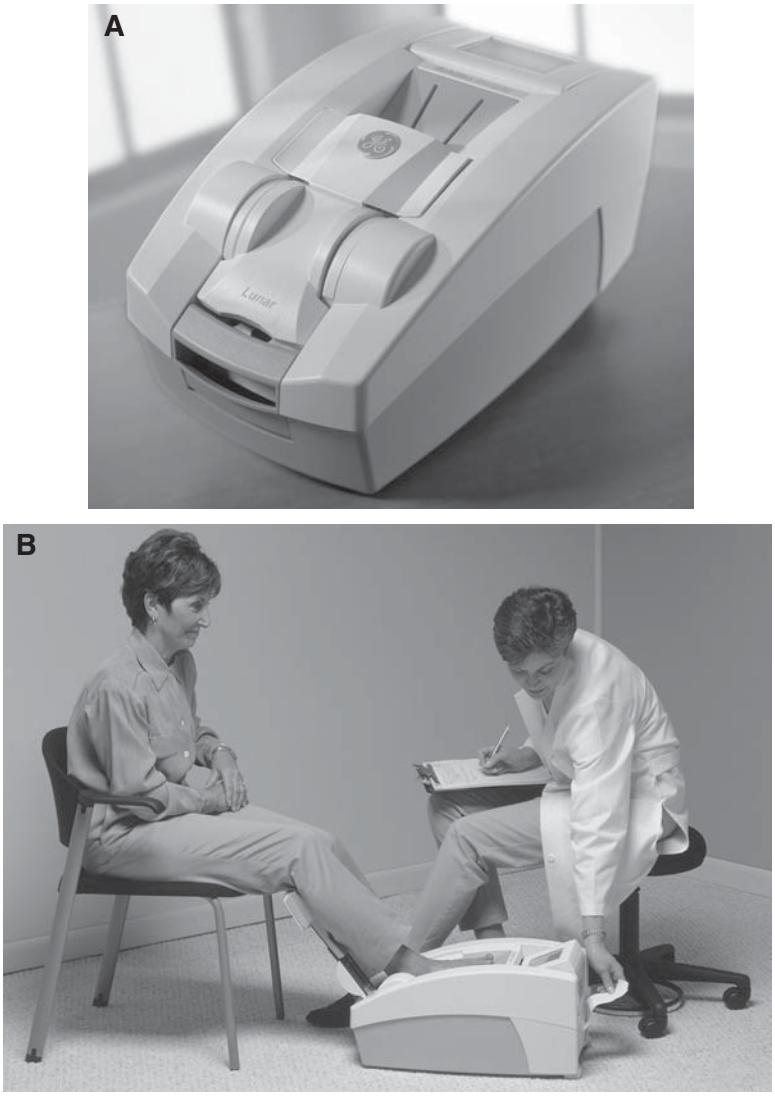

Fig. 13-24. (A) The Lunar InSight™. A peripheral quantitative ultrasound device used to measure the calcaneus. **(B)** The Lunar InSight™ shown in use. Photographs courtesy of GE Medical Systems, Madison, WI.

- Precision: Less than 2.0% CV
- Dimensions: $10 \times 12 \times 24$ in ($25 \times 31 \times 61$ cm)
- Weight: 22 lb (10 kg)
- Operating environmental temperature: 59° to 95° F (15° to 35°C)
- Operation: Self-contained LCD touch screen that swivels, thermal printer, 100-measurement memory; built-in carrying handle. No gel required.
- Options: External computer, external color printer, Windows® XP user interface; external PC software

Fig. 13-25. The Osteometer DTU-one Ultrasure®. A peripheral quantitative ultrasound device used to measure the calcaneus. Photograph courtesy of Osteometer MediTech, Hawthorne,CA.

Fig. 13-26. The Osteometer DTU-one Ultrasure®. A peripheral quantitative ultrasound device used to measure the calcaneus. Shown here in use. Photograph courtesy of Osteometer MediTech, Hawthorne, CA.

DTU-one UltraSure®

- Osteometer MediTech Inc., Hawthorne, CA
- Technology:
  Imaging ultrasound

Transmitted through bone
Wet

- Skeletal application(s): Calcaneus
- Scan time: 3 minutes
- Results:
  SOS (m/s)
  BUA (dB/MHz)
  Percent young-adult and percent age-matched comparisons
  T-score and *z*-score
- Precision:
  SOS 0.2%
  BUA 1.6%
- Dimensions: 21 × 11 × 17 in (53 × 28 × 44 cm)
- Weight: 64 lb (29 kg)
- Environmental operating temperature: 59° to 86° F (15° to 30°C)
- Image resolution: 0.6 mm
- Quality control: Automated with supplied phantom
- Operation: IBM-compatible Pentium computer with Windows NT™ operating system, SVGA 15-in monitor, printer
- Accessories provided: Phantom

McCue C.U.B.A.Clinical™ (Contact Ultrasound Bone Analyzer)

- Distributor: Norland, a CooperSurgical Company, Ft. Atkinson, WI
- Technology:
  Ultrasound
  Transmitted through bone
  Dry
- Skeletal application(s): Calcaneus
- Scan time: 1 minute
- Results:
  BUA in db/MHz
  Percent young-reference and percent age-matched comparisons
  T-score and *z*-score
- Precision: 1.3% for BUA
- Dimensions: 17.8 × 13.9 × 10.2 in (45.2 × 35.3 × 25.9 cm)
- Weight: 22 lb (10 kg)
- Environmental storage temperature: 23° to 122° F (-5° to 50°C)
- Environmental storage humidity: 10 to 95%
- Quality control: Internal phantom and external QA phantom
- Operation: IBM-compatible computer with a minimum of 10 MB free hard drive space, 486DX2 microprocessor at 66 MHz, 1.44 MB floppy disc drive, serial port, Windows 3.1 or higher (Windows NT not supported) and Microsoft® Windows™ supported printer (all computer equipment supplied by end user)

Fig. 13-27. The McCue C.U.B.A. Clinical™. A peripheral quantitative ultrasound device used to measure the calcaneus. Photograph courtesy of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

- Accessories provided:
  Padded carrying bag for C.U.B.A.
  Padded carrying bag for QA phantom, QA phantom
  Bottle of ultrasound gel
  Two anatomical foot inserts
  C.U.B.A. plus+ software
  Serial cable
  Power cable
  User's manual

Omnisense™ 7000S Ultrasound Bone Sonometer

- Manufacturer: Sunlight Medical, Israel
- Technology:
  Ultrasound
  Axially transmitted along bone
  Dry
- Skeletal application(s): Forearm (other regions pending FDA approval)
- Scan time: Approximately 1 minute
- Results:
  SOS (m/s),
  T-score and *z*-score
- Precision: 0.4% to 0.8% as the RMS CV, depending on the site

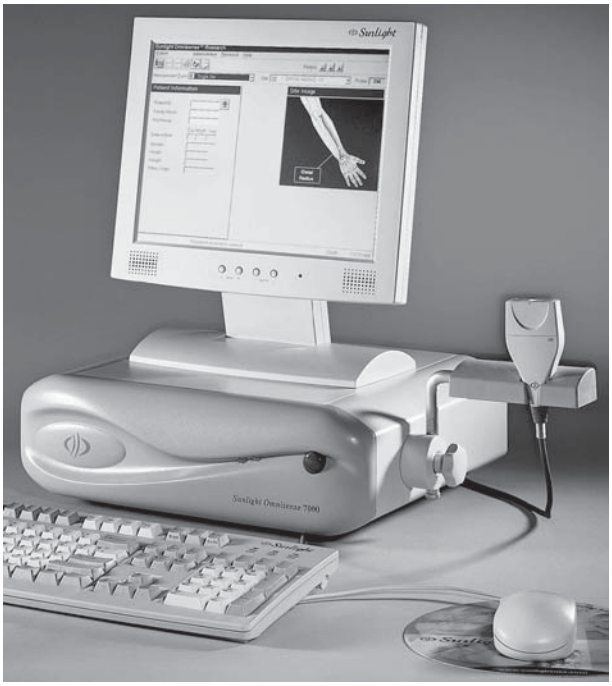

Fig. 13-28. The Sunlight Omnisense™ 7000S. A peripheral quantitative ultrasound device used to measure the radius. Photograph courtesy of Sunlight Medical Ltd., Rehovot, Israel.

Fig. 13-29. The Sunlight Omnisense™ 7000S. A peripheral quantitative ultrasound device used to measure the radius. Shown here in use. Photograph courtesy of Sunlight Medical Ltd., Rehovot, Israel.

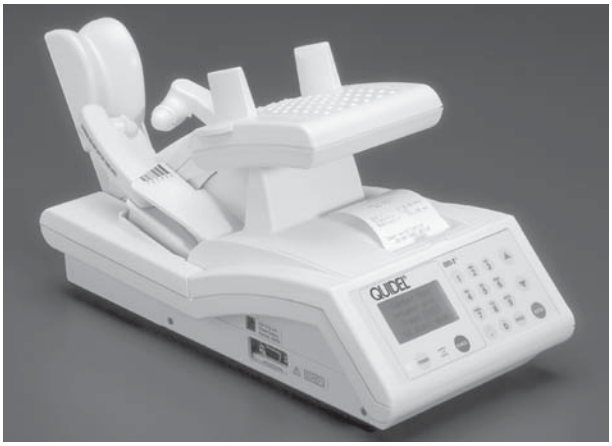

Fig. 13-30. The Quidel QUS™-2. A peripheral quantitative ultrasound device used to measure the calcaneus. Photograph courtesy of Quidel Corporation, Mountain View, CA.

- Main unit dimensions: 15.4 × 5.1 × 13 in (39 × 13 × 33 cm)
- Main unit weight: 15 lbs (7 kg)
- Operating environmental temperature: 50° to 95° F (10° to 35°C)
- Operating environmental relative humidity: 30 to 75%, noncondensing
- Quality control: Calibration free. Daily system verification with phantom required.
- Operation: IBM-compatible computer with Windows 95 interface, 14-in CRT monitor, mouse or trackball, printer
- Accessories provided:
  System quality verification phantom
  Aquasonic® Clear® Ultrasound Gel
- Options: Flat panel display

QUS-2® Calcaneal Ultrasonometer

- Manufacturer: Quidel Corp., San Diego, CA
- Technology:
  Ultrasound
  Transmitted through bone
  Dry
- Skeletal application(s): Calcaneus
- Scan time: Approximately 1 minute
- Results:
  BUA (dB/MHz)
  T-score
- Precision: 2.6%
- Dimensions: 7.5 × 16.0 × 9.0 in (19.1 × 40.6 × 22.9 cm)
- Weight: 7 lb (3.2 kg)
- Environmental operating temperature: 59° to 95° F (15° to 35°C)

- Environmental operating relative humidity: 30 to 75%, noncondensing
- Quality control: Automated with supplied test object
- Operation: Self-contained unit with messages displayed on LCD screen. Keyboard on unit allows data entry. Results printed by on-board printer. Foot size accommodated ranges from women's shoe size 5 to men's shoe size 12. Onboard storage capacity of approximately 8000 scan summary files. RS232 interface for download of scan data to a computer.
- Accessories provided:
  QUS-2 power supply
  Rechargeable battery
  AC cable
  Operator's manual
  Printer paper
  Aqueous gel
  Alcohol prep pads
  Test object
- Options: Carrying case

Sahara Clinical Bone Sonometer®

- Manufacturer: Hologic Inc., Bedford, MA
- Technology:
  Ultrasound
  Transmitted through bone
  Dry
- Skeletal application(s): Calcaneus
- Scan time: Less than 10 seconds
- Results:
  Estimated BMD (g/cm^2)
  QUI obtained from BUA and SOS
  T-score and *z*-score
- Precision:
  BMD 3% or 0.014 g/cm^2
  QUI 2.6% or 2.2
- Dimensions: $17 \times 14 \times 12$ in ($43 \times 36 \times 30$ cm)
- Weight: 22 lb (10 kg)
- Environmental operating temperature: 60° to 100° F (15° to 37.7°C)
- Environmental operating relative humidity: 20 to 80% noncondensing
- Quality control: Daily, with supplied quality control phantom
- Operation: Embedded microprocessor. Data and command input from touch pad on unit. Built-in strip printer.
- Accessories provided:
  Quality control phantom
  Sahara coupling gel
  Alcohol wipes
  Patient report forms
  Operator training video

Fig. 13-31. The Hologic Sahara Clinical Bone Sonometer®. A peripheral quantitative ultrasound device used to measure the calcaneus. Photograph courtesy of Hologic Inc., Bedford, MA.

Fig. 13-32. The Hologic Sahara Clinical Bone Sonometer®. A peripheral quantitative ultrasound device used to measure the calcaneus shown here in use. Photograph courtesy of Hologic Inc., Bedford, MA.

- Options
  - Carrying case
  - AC power cable
  - Spare Battery

I Appendix

Contacts for Bone Densitometry Manufacturers and Organizations of Interest

MANUFACTURERS

The products listed by manufacturer refer to the products discussed in Chapter 13 and do not necessarily represent the entire line of densitometers available from the manufacturer.

Alara Inc.

2545 Barrington Court
Hayward, CA 94545-1134
Tel.: 510-723-0110
Fax: 510-723-0111

Website: www.alara.com
Email: through website

Product: MetriScan™

CompuMed Inc.

5777 W. Century Blvd., Suite 1285
Los Angeles, CA 90045
Tel.: 310-258-5000
Tel. (Osteo-systems): 310-258-5027
Fax: 310-645-5880

Website: www.compumed.net
Website: www.osteogram.com
Email: osteo@compumed.net

Product: Automated Osteogram®

GE Medical Systems, Lunar

726 Heartland Trail
Madison, WI 53717-1915
Tel.: 608-828-2663
Fax: 608-826-7102

Toll free Tel.: 1-888-795-8627
Website: www.gemedicalsystems.com
Email: info@gemedicalsystems.com

Products: EXPERT®-XL, DPX-IQ™, DPX MD™, DPX MD+™, DPX- NT™, DPX Pro™, Prodigy™, Achilles+™, Achilles Express™, Achilles Insight™, PIXI®,

Hologic Inc.

35 Crosby Drive
Bedford, MA 01730-1401
Tel.: 781-999-7300
Fax: 781-280-0669

Toll free Tel.: 800-343-XRAY
Customer support Tel.: 800-321-HOLX
Website: www.hologic.com
Email: support@hologic.com

Products: QDR® 4500 A, QDR® 4500 C, QDR® 4500 SL, QDR® 4500 W, Delphi™, Discovery™, Sahara Clinical Bone Sonometer®

Image Analysis Inc.

1380 Burkesville Street
Columbia, KY 42728
Tel: 270-384-6400
Fax.: 270-384-6405

Toll free Tel.: 800-548-4849
Website: www.image-analysis.com
Email: info@image-analysis.com

Products: QCT-5000 DICOM

Norland, a CooperSurgical Company

W6340 Hackbarth Road
Fort Atkinson, WI 53538
Tel.: 920-563-9504
Fax: 920-563-8626

Toll free Tel.: 1-800-563-9504
Customer service tel.: 800-444-8456
Technical support
Tel.: 920-563-8456
Fax: 920-568-4216
Website: www.coopersurgical.com
Email: through website

Products: XR-46™, Excell™, Excell™ plus, Apollo™, pDEXA®, McCue C.U.B.A. Clinical™

Orthometrix Inc.

106 Corporate Park Drive, Suite 106
White Plains, NY 10604
Tel.: (914) 694-2285
Fax.: (914) 694-1464

Website: www.orthometrix.net
Email: info@orthometrix.net

Products: Distributor in North America of the Stratec XCT 2000

Osteometer MediTech Inc.

12515 Chadron Ave.
Hawthorne, CA 90250
Tel.: (310) 978-3073
Fax: (310) 676-0948

Toll free Tel.: 866-421-7762
Website: www.osteometer.com
Email: info@osteometer.com

Products: DTX-200 DexaCare®, DTU-one Ultrasure™, DexaCare®G4

Quidel Corporation

10165 McKellar Court
San Diego, CA 92121
Tel.: (408)-616-4301
Fax: (408)-616-4310

Toll free Tel.: (800)-524-6318 (USA only)
Website: www.quidel.com
Email: through website

Product: QUS-2®

Schick Technologies Inc.

31-00 47th Avenue
Long Island City, New York 11101
Tel.: 718-937-5765
Fax: 718-937-5962

Toll free Tel.: 1-888-818-4BMD
Product support
Toll-free Tel.: 888-4-SCHICK
Fax: 718-482-2030
Website: www.schicktech.com
Email: through website

Product: accuDEXA™

Sectra North America Inc.

4 Corporate Dr., Suite 197
Shelton, CT 06484
Tel.: 203-925-0899
Fax: 203-925-0906

Website: www.sectra.com

Products: Sectra Osteoporosis Package™ IDS5™ Workstation Clinical Application

Sectra Imtec AB

Teknikringen 20
SE-583 30 Linköping, Sweden
Tel.: 46 13 23 52 00
Fax.: 46 13 21 21 85

Website: www.sectra.com

Stratec Medizintechnik

Durlacher Strasse 35
D-75172 Pforzheim
Germany
Tel.: 49 7231 145420
Fax.: 49 7231 145422

Website: www.stratec-med.com
Email: info@stratec-med.com

Products: XCT™ 2000

Sunlight Medical Ltd.

100 Davidson Avenue, Suite 108
Somerset, NJ 08873
Tel.: (732) 560-8770
Fax.: (732) 560-9462

Toll free Tel.: 1-800-750-6011
Website: www.sunlightnet.com
Email: info@sunlightnet.com

Product: Omnisense™ 7000S

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ORGANIZATIONS OF INTEREST

American Society of Radiologic Technologists

15000 Central Avenue, S.E.
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Website: www.asrt.org

Foundation for Osteoporosis Education and Research

300 27th Street, Suite 103
Oakland, CA 94612
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International Society for Clinical Densitometry

342 North Main Street
West Hartford, CT 06117-2507
Tel.: 860-586-7563
Fax: 860-586-7550

Website: www.iscd.org
Email: info@iscd.org

National Osteoporosis Foundation

1232 22nd St., N.W.
Washington, DC 20037-1292
Tel.: 202-223-2226

Website: www.nof.org
Email: through web site

II Appendix

Conversion Formulas

PA SPINE CONVERSIONS BETWEEN CENTRAL DXA DEVICES *(1)*

$$\text{Hologic QDR-2000 Spine}_{BMD} = (0.906 \times \text{Lunar DPX-L Spine}_{BMD}) - 0.025$$
$$\text{Hologic QDR-2000 Spine}_{BMD} = (0.912 \times \text{Norland XR-26 Spine}_{BMD}) + 0.088$$
$$\text{Lunar DPX-L Spine}_{BMD} = (1.074 \times \text{Hologic QDR-2000 Spine}_{BMD}) + 0.054$$
$$\text{Lunar DPX-L Spine}_{BMD} = (0.995 \times \text{Norland XR-26 Spine}_{BMD}) + 0.135$$
$$\text{Norland XR-26 Spine}_{BMD} = (0.983 \times \text{Lunar DPX-L Spine}_{BMD}) - 0.112$$
$$\text{Norland XR-26 Spine}_{BMD} = (1.068 \times \text{Hologic QDR-2000 Spine}_{BMD}) - 0.070$$

FEMORAL NECK BMD CONVERSIONS BETWEEN CENTRAL DXA DEVICES *(1)*

$$\text{Hologic QDR-2000 Neck}_{BMD} = (0.836 \times \text{Lunar DPX-L Neck}_{BMD}) - 0.008$$
$$\text{Hologic QDR-2000 Neck}_{BMD} = (0.836 \times \text{Norland XR-26 Neck}_{BMD}) + 0.051$$
$$\text{Lunar DPX-L Neck}_{BMD} = (1.013 \times \text{Hologic QDR-2000 Neck}_{BMD}) + 0.142$$
$$\text{Lunar DPX-L Neck}_{BMD} = (0.945 \times \text{Norland XR-26 Neck}_{BMD}) + 0.115$$
$$\text{Norland XR-26 Neck}_{BMD} = (0.961 \times \text{Lunar DPX-L Neck}_{BMD}) - 0.037$$
$$\text{Norland XR-26 Neck}_{BMD} = (1.030 \times \text{Hologic QDR-2000 Neck}_{BMD}) + 0.058$$

STANDARDIZED BMD (sBMD) CALCULATIONS FOR PA SPINE FOR CENTRAL DXA DEVICES *(1)*

$$\text{sBMD}_{SPINE} = 1000\ (1.0761 \times \text{Norland XR-26 BMD}_{SPINE})$$
$$\text{sBMD}_{SPINE} = 1000\ (0.9522 \times \text{Lunar DPX-L BMD}_{SPINE})$$
$$\text{sBMD}_{SPINE} = 1000\ (1.0755 \times \text{Hologic QDR-2000 BMD}_{SPINE})$$

[1] Although specific models of the central DXA devices are noted in the equations, the formulas may be used to convert BMD measured on any model for a given manufacturer to the BMD for any model of the other manufacturer. It must be recognized, however, that the error in these conversions is too great too allow serial monitoring of BMD to be done using devices from different manufacturers.

sBMD CALCULATIONS FOR TOTAL HIP FOR CENTRAL DXA DEVICES *(2)*

$$sBMD_{TOTAL\ HIP} = 1000\ [(1.012 \times \text{Norland XR-26 } BMD_{TOTAL\ HIP}) + 0.006]$$
$$sBMD_{TOTAL\ HIP} = 1000\ [(0.979 \times \text{Lunar DPX-L } BMD_{TOTAL\ HIP}) - 0.031]$$
$$sBMD_{TOTAL\ HIP} = 1000\ [(1.008 \times \text{Hologic QDR-2000 } BMD_{TOTAL\ HIP}) + 0.006]$$

sBMD CALCULATIONS FOR HIP SUBREGIONS FOR CENTRAL DXA DEVICES *(3)*

$$SBMD_{FEMORAL\ NECK} = 1000\ [(1.087 \times \text{Hologic } BMD_{FEMORAL\ NECK}) + 0.019]$$
$$SBMD_{FEMORAL\ NECK} = 1000\ [(0.939 \times \text{Lunar } BMD_{FEMORAL\ NECK}) - 0.023]$$
$$SBMD_{FEMORAL\ NECK} = 1000\ [(0.985 \times \text{Norland } BMD_{FEMORAL\ NECK}) + 0.006]$$
$$sBMD_{TROCHANTER} = 1000\ [(1.105 \times \text{Hologic } BMD_{TROCHANTER}) - 0.017]$$
$$sBMD_{TROCHANTER} = 1000\ [(0.949 \times \text{Lunar } BMD_{TROCHANTER}) - 0.042]$$
$$sBMD_{TROCHANTER} = 1000\ [(0.961 \times \text{Norland } BMD_{TROCHANTER}) + 0.057]$$
$$sBMD_{WARD'S} = 1000\ [(0.940 \times \text{Hologic } BMD_{WARD'S}) + 0.101]$$
$$sBMD_{WARD'S} = 1000\ [(0.980 \times \text{Lunar } BMD_{WARD'S}) - 0.106]$$
$$sBMD_{WARD'S} = 1000\ [(1.091 \times \text{Norland } BMD_{WARD'S}) + 0.001]$$

BMD CALCULATIONS FOR THE ULTRADISTAL (su), MID (sm), AND PROXIMAL (sp) FOREARM FOR FOUR DXA DEVICES *(4)*

$$suBMD = (0.945 \times \text{PIXI BMD}) + 0.015$$
$$suBMD = (1.158 \times \text{Hologic Radius + Ulna Ultradistal BMD}) - 0.019$$
$$suBMD = (0.802 \times \text{Osteometer BMD}) + 0.071$$
$$suBMD = (1.027 \times \text{Norland Distal BMD}) + 0.084$$
$$smBMD = (1.011 \times \text{PIXI BMD}) + 0.033$$
$$smBMD = (0.894 \times \text{Hologic Radius + Ulna Mid BMD}) - 0.030$$
$$smBMD = (0.856 \times \text{Osteometer BMD}) + 0.094$$
$$smBMD = (1.106 \times \text{Norland Distal BMD}) + 0.105$$
$$spBMD = (1.091 \times \text{PIXI BMD}) + 0.119$$
$$spBMD = (0.861 \times \text{Hologic Radius + Ulna 1/3 BMD}) + 0.020$$
$$spBMD = (0.917 \times \text{Osteometer BMD}) + 0.188$$
$$spBMD = (0.596 \times \text{Norland Proximal BMD}) + 0.114$$

2 All equations are multiplied by 1000 to express the sBMD in mg/cm^2 instead of g/cm^2.

3 All equations are multiplied by 1000 to express the sBMD in mg/cm^2 instead of g/cm^2. The term total hip and total femur are interchangeable.

4 All equations are multiplied by 1000 to express the sBMD in mg/cm^2 instead of g/cm^2.

METRIC/ENGLISH CONVERSIONS FOR UNITS OF MEASURE

English to Metric	Metric to English
1 in = 2.54 cm	1 cm = 0.39 in
1 lb = 0.45 kg	1 kg = 2.20 lb
Degrees in F = (1.8 C°) + 32	Degrees in C = (F° – 32) × 0.555
1 rad = 100 Gy	1 Gy = 0.01 rad
1 rem = 100 Sv	1 Sv = 0.01 rem

MATHEMATICAL SYMBOLS AND DESIGNATIONS OF MULTIPLES

Symbol	Designation	Factor
G	giga-	10^{9}
M	mega-	10^{6}
k	kilo-	10^{3}
d	deci-	10^{-1}
c	centi-	10^{-2}
m	milli-	10^{-3}
μ	micro-	10^{-6}
n	nano-	10^{-9}
p	pico-	10^{-12}

REFERENCES

1. Genant HK, Grampp S, Gluer CC, et al. Universal standardization for dual X-ray absorptiometry: patient and phantom cross-calibration results. J Bone Miner Res 1994;9:1503–1514, with permission of the American Society for Bone and Mineral Research.
2. Hanson J. Standardization of femur BMD. J Bone Miner Res 1997;12:1316–1317.
3. Lu Y, Fuerst T, Hui S, Genant HK. Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle. Osteoporos Int 2001;12:438–444.
4. Shepherd JA, Cheng XG, Lu Y, et al. Universal standardization of forearm bone densitometry. J Bone Miner Res 2002;17:734–745, with permission of the American Society for Bone and Mineral Research.

III Appendix

Formulas and Tables Used in Serial Bone Density Measurements

FORMULAS *(1)*

1. To calculate precision as the RMS-SD:

$$SD_{RMS} = \sqrt{\frac{\sum_{i=1}^{m} \left(SD^2\right)}{m}}$$

2. To calculate precision as the RMS-CV:

$$CV_{RMS} = \sqrt{\frac{\sum_{i=1}^{m} \left(CV^2\right)}{m}}$$

3. To calculate the least significant change (LSC):

$$LSC = Z' \left(Pr\right) \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

4. To calculate the LSC for one measurement at baseline and follow-up at 95% confidence:

$$_{1x1}LSC^{95} = 1.96\left(Pr\right)\ 1.414 = 2.77\left(Pr\right)$$

5. To calculate the LSC for one measurement at baseline and follow-up at 80% confidence:

$$_{1x1}LSC^{80} = 1.28\left(Pr\right)\ 1.414 = 1.81\left(Pr\right)$$

6. To calculate the LSC for two measurements at baseline and follow-up at 95% confidence:

$$_{2x2}LSC^{95} = 1.96\left(Pr\right)\ 1 = 1.96\left(Pr\right)$$

7. To calculate the LSC for two measurements at baseline and follow-up at 80% confidence:

$$_{2x2}LSC^{80} = 1.28\left(Pr\right)\ 1 = 1.28\left(Pr\right)$$

[1] *See* Chapter 11 for detailed explanations of the formulas.

Combination of Number of Patients and Scans Per Patient for 30 Degrees of Freedom in a Precision Study

Number of Patients	*Number of Scans per Patient*
1	31
5	7
10	4
15	3
30	2

Z' Values for Various Levels of Statistical Confidence

Statistical Confidence Level	*Z' Value*
99%	2.58
95%	1.96
90%	1.65
85%	1.44
80%	1.28

The Interval Between BMD Measurements Required to Obtain the $_{1x1}LSC^{95}$ for Various Levels of Precision and Expected Rates of Change

		Interval Between BMD Measurements	
Precision as % CV	*Change (%)/Year*	*Months*	*Years*
0.5	1	16.7	1.39
	3	5.60	0.46
	5	3.30	0.28
1	1	33.2	2.77
	3	11.0	0.92
	5	6.70	0.55
1.5	1	50.0	4.16
	3	16.6	1.39
	5	10.0	0.83
2	1	66.5	5.54
	3	22.2	1.85
	5	13.3	1.11
2.5	1	83.2	6.93
	3	27.7	2.31
	5	16.6	1.39

Levels of Statistical Confidence (%) for Various Combinations of Precision and Change in BMD

Change in BMD (g/cm^2)	*Precision (g/cm^2)*									
	0.005	*0.010*	*0.015*	*0.020*	*0.025*	*0.030*	*0.035*	*0.040*	*0.045*	*0.050*
0.005	52	28	19	14	11	9	8	7	6	6
0.010	84	52	36	28	22	19	16	14	12	11
0.015	97	71	52	40	33	28	24	21	19	17
0.020	100	84	65	52	43	36	31	28	25	22
0.025	100	92	76	62	52	44	39	34	31	28
0.030	100	97	84	71	60	52	46	40	36	33
0.035	100	99	90	78	68	59	52	46	42	38
0.040	100	100	94	84	74	65	58	52	47	43
0.045	100	100	97	89	80	71	64	57	52	48
0.050	100	100	98	92	84	76	69	62	57	52
0.055	100	100	99	95	88	81	73	67	61	56
0.060	100	100	100	97	91	84	77	71	65	60
0.065	100	100	100	98	93	87	81	75	69	64
0.070	100	100	100	99	95	90	84	78	73	68
0.075	100	100	100	99	97	92	87	82	76	71
0.080	100	100	100	100	98	94	89	84	79	74
0.085	100	100	100	100	98	95	91	87	82	77
0.090	100	100	100	100	99	97	93	89	84	80
0.095	100	100	100	100	99	97	95	91	86	82
0.100	100	100	100	100	100	98	96	92	88	84

Note: Table created by and reproduced courtesy of Ken Faulkner, PhD

Confidence Intervals for the Measured Change in BMD for Different Values of Precision

	Precision, %CV				
Confidence Interval	*1*	*1.25*	*1.5*	*1.75*	*2.0*
99%	± 3.65	± 4.56	± 5.48	± 6.39	± 7.30
95%	± 2.77	± 3.46	± 4.16	± 4.85	± 5.54
90%	± 2.33	± 2.91	± 3.50	± 4.08	± 4.66
85%	± 2.04	± 2.55	± 3.06	± 3.57	± 4.08
80%	± 1.81	± 2.26	± 2.72	± 3.17	± 3.62

Note: All values are in %.

$_{1x1}LSC^{99}$ for Different Values of Precision Expressed as the %CV

Precision (%CV)	$_{1x1}LSC^{99}$ *(%)*
0.50	1.83
0.75	2.74
1.00	3.65
1.25	4.56
1.50	5.48
1.75	6.39
2.00	7.30
2.25	8.21
2.50	9.13
2.75	10.04
3.00	10.95
3.25	11.86
3.50	12.78

$_{1x1}LSC^{95}$ for Different Values of Precision Expressed as the %CV

Precision (%CV)	$_{1x1}LSC^{95}$ *(%)*
0.50	1.39
0.75	2.08
1.00	2.77
1.25	3.46
1.50	4.16
1.75	4.85
2.00	5.54
2.25	6.23
2.50	6.93
2.75	7.62
3.00	8.31
3.25	9.00
3.50	9.70

$_{1x1}LSC^{90}$ for Different Values of Precision Expressed as the %CV

Precision (%CV)	$_{1x1}LSC^{90}$ *(%)*
0.50	1.17
0.75	1.75
1.00	2.33
1.25	2.91
1.50	3.50
1.75	4.08
2.00	4.66
2.25	5.24
2.50	5.83
2.75	6.41
3.00	6.99
3.25	7.57
3.50	8.16

$_{1x1}LSC^{85}$ for Different Values of Precision Expressed as the %CV

Precision (%CV)	$_{1x1}LSC^{85}$ *(%)*
0.50	1.02
0.75	1.53
1.00	2.04
1.25	2.55
1.50	3.06
1.75	3.57
2.00	4.08
2.25	4.59
2.50	5.10
2.75	5.61
3.00	6.12
3.25	6.63
3.50	7.14

$_{1x1}LSC^{80}$ for Different Values of Precision Expressed as the %CV

Precision (%CV)	$_{1x1}LSC^{80}$ *(%)*
0.50	0.91
0.75	1.36
1.00	1.81
1.25	2.26
1.50	2.72
1.75	3.17
2.00	3.62
2.25	4.07
2.50	4.53
2.75	4.98
3.00	5.43
3.25	5.88
3.50	6.34

IV Appendix

World Health Organization Criteria for the Diagnosis of Osteoporosis Based on the Measurement of Bone Density (1)

Diagnosis	*Bone Density Criteria*	T-*Score Criteria*
Normal	Not more than 1 SD below the young-adult peak bone density	–1 or better
Osteopenia	More than 1 but less than 2.5 SD below the young-adult peak bone density	Between –1 and –2.5
Osteoporosis	2.5 SD or more below the young-adult peak bone density	–2.5 or poorer
Severe or established osteoporosis	2.5 SD or more below the young-adult peak bone density and a fracture	–2.5 or poorer + a fracture

Note: From ref. *1*.

REFERENCE

1. World Health Organization. (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group. *WHO Technical Report Series.* WHO, Geneva.

[1] The WHO Criteria were intended to be applied to measurements of bone density made in postmenopausal Caucasian women only. In the absence of other criteria, they are often applied to postmenopausal women of other races and to men of any race over the age of 50. They should not be applied to healthy premenopausal women of any race, however.

V Appendix

Recent Guidelines for Bone Density Testing

1998 NATIONAL OSTEOPOROSIS FOUNDATION GUIDELINES FOR BONE DENSITY TESTING IN POSTMENOPAUSAL WOMEN*

Bone density should be measured in the following populations:

1. All postmenopausal women age 65 and older.
2. All postmenopausal women under age 65 with one or more risk factors.
3. Postmenopausal women who present with fractures.
4. Women who have been on estrogen or hormone replacement therapy for prolonged periods of time.
5. Women who are considering therapy for osteoporosis if BMD testing would aid the decision.

(From National Osteoporosis Foundation. Physician's Guide to Prevention and Treatment of Osteoporosis. Excerpta Medica, Belle Meade NJ, 1999.)

*In 2003, the NOF reissued these guidelines for bone density, omitting items 4 and 5.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS 2001 MEDICAL GUIDELINES FOR THE PREVENTION AND MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS

BMD measurements should be performed in the following settings:

1. For risk assessment in perimenopausal or postmenopausal women who have risk factors for fractures and are willing to consider available interventions.
2. In women who have X-ray findings that suggest osteoporosis.
3. In women beginning or receiving long-term glucocorticoid therapy or other drugs associated with bone loss.
4. In all adult women with symptomatic hyperparathyroidism or other diseases or nutritional conditions associated with bone loss in whom evidence of bone loss would result in adjustment of management.
5. For establishing skeletal stability and monitoring therapeutic response in women receiving treatment for osteoporosis (baseline measurements should be made before intervention).
6. In all women 40 years old or older who have sustained a fracture.
7. In all women 65 years of age and older.
8. In younger postmenopausal women who have risk factors.

(From Osteoporosis Task Force. American Association of Clinical Endocrinologists 2001 medical guidelines for clinical practice for the prevention and management of postmenopausal osteoporosis. Endocr Pract 2001;7:293–312.)

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS GUIDELINES FOR BONE DENSITY MEASUREMENTS

Bone density measurements should be made in the following populations:

1. All postmenopausal women 65 years of age or older.
2. Postmenopausal women under 65 years of age who have one or more risk factors.
3. All postmenopausal women who have sustained a fracture.

Bone density measurements may be useful in the following groups:

1. Pre- or postmenopausal women with diseases or conditions associated with an increased risk of osteoporosis.

(From ACOG releases recommendations for bone density screening for osteoporosis. Washington, DC: American College of Obstetricians and Gynecologists, 2002. Accessed March 26, 2002, at: http://www.acog.org/from_home/publications/press_releases/nr02-28-02-1.htm)

POSITION STATEMENT ON MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS FROM THE NORTH AMERICAN MENOPAUSE SOCIETY

Bone mineral density should be measured in the following groups:

1. All women who are at least 65 years of age regardless of risk factors.
2. All postmenopausal women younger than 65 with one or more risk factors.
3. Premenopausal women with low trauma fractures or known secondary causes of bone loss.

(From Management of postmenopausal osteoporosis: position statement of The North American Menopause Society. Menopause 2002;9:84–101.)

US PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS FOR BONE DENSITY TESTING

Bone density should be measured in the following patients:

1. All postmenopausal women 65 years of age and older.
2. All postmenopausal women age 60 to 64 at high risk for osteoporosis.

(From US Preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. Ann Intern Med 2002;137:526–528.)

VI Appendix

Bone Mass Measurement Act of 1997 (1)

Medicare recipients are potentially eligible for reimbursement of bone mass measurements performed in the following circumstances:

- An estrogen-deficient woman at clinical risk for osteoporosis, based on medical history and other findings.
- An individual with vertebral abnormalities demonstrated by X-ray suggesting osteoporosis, osteopenia or fracture.
- An individual being monitored to assess efficacy of an FDA-approved drug therapy.
- An individual receiving or expected to receive corticosteroids of 7.5 mg or more of prednisone for more than 3 months.
- An individual with primary hyperparathyroidism.

FREQUENCY STANDARDS

At least 23 months must have passed since the month the last measurement was performed except in the following situations:

- For monitoring patients on long-term glucocorticoid therapy.
- For allowing a confirmatory baseline measurement to permit future monitoring if the initial test was performed with a technique that is different from the proposed monitoring method.

[1] From Federal Register 42 CFR Part 410; Vol 63, No. 121, June 24, 1998.

VII Appendix

CPT Codes for Bone Densitometry

Technique	*Skeletal Site*	*CPT Code*
DXA[a,d]	PA spine Lateral spine Pelvis Proximal femur	76075
DXA[b]	Body composition	0028T
DXA	Forearm Heel Phalanges	76076
SXA	Heel	G0130
QUS[c]	Heel	76977
RA	Hand	76078
DXR	Phalanges Forearm	76078
QCT[a]	PA spine Proximal femur	76070
QCT	Forearm Heel	76071
SPA	Forearm	78350
DPA[a,e]	PA Spine Proximal femur Total body	78351

[a] In the description of the code, the skeletal sites noted are characterized as axial sites, even though anatomically the proximal femur and pelvis are part of the appendicular skeleton.

[b] This is a temporary, category III code.

[c] The code for quantitative ultrasound indicates both the procedure and the interpretation.

[d] There is no specific code for a dual energy X-ray total body bone density study. However, the 76075 code describes a dual energy X-ray study of one or more sites such as the spine, pelvis, and proximal femur.

[e] This code is described as DPA, one or more sites. Therefore, total body bone density studies are not excluded by this code.

CPT™ codes are level I codes developed and maintained by the American Medical Association *(1)*. These are five-digit codes that are widely accepted for reporting services by healthcare providers. The modifier "-TC" is attached to the code to indicate billing for the technical component.

HCPCS codes *(2)*, pronounced "hick-picks," are level II codes that are developed and assigned by the Health Care Finance Administration (HCFA). They are intended to meet the needs of Medicare and Medicaid and allow coordination of government programs by providing a uniform reporting system of procedures. HCPCS codes begin with a letter and are followed by four digits. Category III codes are temporary codes assigned to new or emerging technologies. They allow data collection for the particular procedures. Category III codes consist of four digits followed by a letter. If a category III code is available for a procedure, it must be used. Procedures assigned a category III code may eventually receive a category I code. Category III codes are not assigned for longer than 5 years however.

REFERENCES

1. AMA. CPT™ 2003. Professional edition. Chicago, IL: AMA Press, 2002.
2. AMA. HCPCS 2000. Medicare's national Level II Codes. 12th edition. Dover DE: AMA Press, 1999.

State	Locality (Fee Schedule Area)	76075	76075-26 (professional component)	76075-TC (technical component)	76076	76076-26 (technical component)	76076-TC (technical component)
AL		$111.06	$14.38	$96.68	$34.44	$10.60	$23.84
AK		$147.59	$16.66	$130.93	$44.63	$12.31	$32.32
AR		$105.71	$13.85	$91.87	$32.73	$10.17	$22.57
AZ		$124.81	$15.09	$109.71	$38.25	$11.15	$27.10
CO		$124.78	$14.95	$109.83	$38.09	$11.02	$27.07
CA	Marin/Napa/Solano	$152.54	$16.24	$136.30	$45.47	$11.95	$33.52
(National	San Francisco	$176.30	$17.65	$158.65	$51.97	$12.98	$39.00
Heritage)	San Mateo	$173.21	$17.33	$155.88	$51.06	$12.74	$38.32
	Oakland/Berkeley	$151.39	$16.47	$134.92	$45.30	$12.12	$33.18
	Santa Clara	$167.38	$17.27	$150.11	$49.59	$12.69	$36.89
	Rest of State	$129.16	$15.32	$113.83	$39.32	$11.28	$28.03
CA	Ventura	$139.62	$15.93	$123.70	$42.18	$11.73	$30.46
(Trans Occi)	Los Angeles	$142.41	$16.35	$126.06	$43.12	$12.05	$31.07
	Anaheim/Santa Ana	$147.17	$16.32	$130.85	$44.27	$12.03	$32.24
	Rest of State	$129.16	$15.32	$113.83	$39.32	$11.28	$28.03
CT		$144.28	$16.36	$127.92	$43.59	$12.06	$31.53
DC		$145.07	$16.37	$128.70	$43.77	$12.07	$31.71
DE		$129.20	$15.45	$113.76	$39.38	$11.37	$28.01
FL	Fort Lauderdale	$133.40	$15.55	$117.85	$40.81	$11.56	$29.25
	Miami	$140.90	$16.13	$124.77	$43.12	$12.04	$31.08
	Rest of State	$121.90	$14.81	$107.09	$37.45	$10.96	$26.49
GA	Atlanta	$132.92	$15.48	$117.44	$40.37	$11.42	$28.96
	Rest of State	$114.09	$14.42	$99.67	$35.25	$10.65	$24.60

(continued)

State	Locality (Fee Schedule Area)	76075	76075-26 (professional component)	76075-TC (technical component)	76076	76076-26 (technical component)	76076-TC (technical component)
HI		$139.45	$15.60	$123.85	$42.00	$11.50	$30.50
ID		$110.39	$14.11	$96.28	$34.06	$10.38	$23.68
IL	East St. Louis	$121.93	$15.02	$106.91	$37.69	$11.16	$26.53
	Suburban Chicago	$138.10	$15.79	$122.32	$42.00	$11.71	$30.30
	Chicago	$141.49	$16.16	$125.32	$43.06	$12.00	$31.06
	Rest of State	$114.90	$14.43	$100.48	$35.52	$10.67	$24.85
IN		$115.06	$14.50	$100.56	$35.38	$10.66	$24.73
IA		$110.37	$14.12	$96.25	$34.08	$10.39	$23.69
KS		$113.38	$14.30	$99.08	$34.96	$10.53	$24.42
KY		$110.91	$14.30	$96.61	$34.39	$10.55	$23.84
LA	New Orleans	$122.14	$15.07	$107.07	$37.64	$11.15	$26.49
	Rest of State	$112.39	$14.36	$98.03	$34.85	$10.62	$24.23
MA	Metropolitan Boston	$152.36	$16.52	$135.83	$45.59	$12.16	$33.43
	Rest of State	$139.88	$15.75	$124.13	$42.16	$11.60	$30.56
MD	Baltimore/ Surrounding Counties	$130.66	$15.55	$115.11	$39.85	$11.47	$28.38
	Rest of State	$122.20	$14.84	$107.37	$37.39	$10.93	$26.45
ME	Southern Maine	$124.55	$14.85	$109.69	$37.93	$10.93	$27.00
	Rest of State	$114.52	$14.30	$100.22	$35.21	$10.53	$24.68
MI	Detroit	$140.80	$16.45	$124.35	$43.32	$12.30	$31.02
	Rest of State	$122.92	$15.13	$107.79	$37.95	$11.23	$26.72
MN		$120.74	$14.79	$105.95	$36.91	$10.87	$26.04
MS		$107.03	$14.01	$93.03	$33.27	$10.33	$22.94

(continued)

State	Locality (Fee Schedule Area)	76075	76075-26 (professional component)	76075-TC (technical component)	76076	76076-26 (technical component)	76076-TC (technical component)
MO	Metropolitan Kansas City	$122.09	$14.89	$107.20	$37.40	$10.97	$26.43
(Western)	Rest of State	$113.38	$14.30	$99.08	$34.96	$10.53	$24.42
(Eastern)	Rest of State	$105.67	$13.85	$91.82	$32.86	$10.21	$22.65
	Metropolitan St. Louis	$118.95	$14.84	$104.11	$36.61	$10.94	$25.67
MT		$110.98	$14.07	$96.91	$34.25	$10.37	$23.88
NC		$116.55	$14.46	$102.10	$35.76	$10.64	$25.13
NE		$109.46	$13.94	$95.51	$33.73	$10.25	$23.48
NH		$128.91	$15.11	$113.80	$39.17	$11.13	$28.04
NJ	Northern NJ	$147.88	$16.55	$131.32	$44.53	$12.19	$32.34
	Rest of State	$138.40	$15.91	$122.49	$41.90	$11.72	$30.18
NM		$114.83	$14.48	$100.35	$35.44	$24.76	$10.68
NV		$132.19	$15.49	$116.70	$40.28	$11.45	$28.83
NY	Manhattan	$170.10	$17.86	$152.23	$50.86	$13.23	$37.63
	NYC Suburbs/Long Island	$160.32	$17.29	$143.03	$48.27	$12.83	$35.43
	Poughkeepsie/ Northern NYC Suburbs	$136.59	$15.72	$120.87	$41.49	$11.63	$29.86
NY-GHI		$157.23	$17.06	$140.17	$47.37	$12.66	$34.72
NY-Western		$119.21	$14.87	$104.34	$36.67	$10.96	$25.71
ND		$111.04	$14.06	$96.98	$34.24	$10.35	$23.89
SD		$109.30	$13.80	$95.50	$33.61	$10.14	$23.47
OH		$120.15	$14.83	$105.32	$36.94	$10.95	$25.99
OK		$109.64	$14.16	$95.48	$33.88	$10.41	$23.47

(continued)

State	Locality (Fee Schedule Area)	76075	76075-26 (professional component)	76075-TC (technical component)	76076	76076-26 (technical component)	76076-TC (technical component)
OR	Portland	$129.00	$15.15	$113.85	$39.10	$11.13	$27.97
	Rest of State	$115.81	$14.31	$101.50	$35.46	$10.51	$24.95
PA	Metropolitan Philadelphia	$139.35	$15.97	$123.38	$42.33	$11.82	$30.51
	Rest of State	$117.51	$14.72	$102.79	$36.18	$10.85	$25.33
PR/Virgin Islands	Puerto Rico	$89.67	$12.50	$77.17	$28.13	$9.18	$18.96
	Virgin Islands	$128.87	$14.92	$113.95	$39.12	$11.01	$28.11
RI		$133.42	$15.60	$117.82	$40.54	$11.50	$29.04
SC		$111.90	$14.28	$97.62	$34.44	$10.48	$23.97
TN		$113.17	$14.39	$98.78	$34.90	$10.59	$24.31
TX	Brazoria	$126.02	$15.15	$110.87	$38.64	$11.22	$27.43
	Dallas	$133.61	$15.55	$118.06	$40.57	$11.46	$29.11
	Galveston	$124.98	$15.07	$109.91	$38.35	$11.16	$27.19
	Houston	$129.51	$15.57	$113.94	$39.70	$11.52	$28.18
	Beaumont	$116.30	$14.80	$101.50	$36.10	$10.96	$25.13
	Fort Worth	$124.08	$14.96	$109.12	$37.95	$11.04	$26.92
	Austin	$125.34	$14.98	$110.35	$38.25	$11.05	$27.20
	Rest of State	$112.84	$14.34	$98.50	$34.91	$10.59	$24.32
UT		$117.99	$14.58	$103.41	$36.19	$10.73	$25.46
VA		$116.96	$14.60	$102.36	$35.91	$10.73	$25.17
VT		$122.36	$14.69	$107.67	$37.28	$10.80	$26.48
WA	Seattle (King County)	$136.64	$15.58	$121.06	$41.29	$11.47	$29.81
	Rest of State	$122.25	$14.81	$107.44	$37.39	$10.91	$26.47
WI		$118.32	$14.69	$103.63	$36.42	$10.84	$25.57
WV		$111.79	$14.34	$97.45	$34.78	$10.63	$24.15
WY		$114.77	$14.43	$100.34	$35.44	$10.66	$24.78
National Average		$127.42	$15.18	$112.25	$38.88	$11.35	$27.53

IX Appendix

NHANES III Proximal Femur Reference Data (1)

NHANES III Femoral Neck BMD Data for Non-Hispanic White Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	409	0.858	0.120
30–39	518	0.825	0.120
40–49	444	0.791	0.125
50–59	450	0.737	0.121
60–69	454	0.681	0.119
70–79	556	0.619	0.110
80+	420	0.573	0.108

NHANES III Trochanter BMD Data for Non-Hispanic White Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	409	0.708	0.099
30–39	518	0.699	0.101
40–49	444	0.676	0.104
50–59	450	0.637	0.105
60–69	454	0.595	0.108
70–79	556	0.550	0.106
80+	420	0.509	0.108

NHANES III Total Femur BMD Data for Non-Hispanic White Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	409	0.942	0.122
30–39	518	0.931	0.129
40–49	444	0.907	0.135
50–59	450	0.863	0.138
60–69	454	0.797	0.139
70–79	556	0.728	0.128
80+	420	0.668	0.134

[1]Adapted with permission of the publisher from Looker AC, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 1998;8.468–489. ©Springer-Verlag.

Standardized NHANES III Total Femur BMD Data for Non-Hispanic White Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (mg/cm²)*	*SD (mg/cm²)*
20–29	409	955	123
30–39	518	945	130
40–49	444	920	136
50–59	450	876	139
60–69	454	809	140
70–79	556	740	129
80+	420	679	135

NHANES III Femoral Neck BMD Data for Non-Hispanic White Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	382	0.934	0.137
30–39	416	0.887	0.134
40–49	409	0.839	0.124
50–59	393	0.813	0.125
60–69	477	0.788	0.135
70–79	445	0.754	0.131
80+	408	0.698	0.140

NHANES III Trochanter BMD Data for Non-Hispanic White Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	382	0.778	0.118
30–39	416	0.762	0.112
40–49	409	0.737	0.107
50–59	393	0.740	0.120
60–69	477	0.736	0.129
70–79	445	0.711	0.127
80+	408	0.670	0.137

NHANES III Total Femur BMD Data for Non-Hispanic White Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	382	1.041	0.144
30–39	416	1.024	0.143
40–49	409	0.988	0.139
50–59	393	0.977	0.142
60–69	477	0.955	0.155
70–79	445	0.915	0.150
80+	408	0.846	0.159

NHANES III Standardized Total Femur BMD Data for Non-Hispanic White Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (mg/cm²)*	*SD (mg/cm²)*
20–29	382	1055	146
30–39	416	1038	144
40–49	409	1002	140
50–59	393	990	143
60–69	477	969	157
70–79	445	928	151
80+	408	859	161

NHANES III Femoral Neck BMD Data for Non-Hispanic Black Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	492	0.950	0.133
30–39	538	0.913	0.130
40–49	404	0.915	0.153
50–59	241	0.852	0.158
60–69	255	0.770	0.128
70–79	144	0.722	0.138
80+	55	0.632	0.115

NHANES III Trochanteric BMD Data for Non-Hispanic Black Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	492	0.753	0.113
30–39	538	0.733	0.114
40–49	404	0.752	0.127
50–59	241	0.700	0.130
60–69	255	0.646	0.117
70–79	144	0.613	0.117
80+	55	0.539	0.118

NHANES III Total Femur BMD Data for Non-Hispanic Black Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	492	1.026	0.134
30–39	538	1.003	0.140
40–49	404	1.020	0.159
50–59	241	0.959	0.173
60–69	255	0.877	0.153
70–79	144	0.825	0.153
80+	55	0.711	0.145

Standardized NHANES III Total Femur BMD Data for Non-Hispanic Black Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (mg/cm²)*	*SD (mg/cm²)*
20–29	492	1040	135
30–39	538	1017	142
40–49	404	1034	160
50–59	241	972	175
60–69	255	890	154
70–79	144	837	154
80+	55	723	146

NHANES III Femoral Neck BMD Data for Non-Hispanic Black Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	460	1.074	0.168
30–39	450	1.005	0.158
40–49	335	0.935	0.145
50–59	196	0.908	0.169
60–69	255	0.854	0.148
70–79	147	0.815	0.154
80+	49	0.769	0.189

NHANES III Trochanteric BMD Data for Non-Hispanic Black Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	460	0.871	0.141
30–39	450	0.823	0.135
40–49	335	0.789	0.126
50–59	196	0.789	0.138
60–69	255	0.763	0.132
70–79	147	0.724	0.143
80+	49	0.699	0.163

NHANES III Total Femur BMD Data for Non-Hispanic Black Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	460	1.174	0.169
30–39	450	1.126	0.165
40–49	335	1.079	0.160
50–59	196	1.058	0.183
60–69	255	1.013	0.166
70–79	147	0.970	0.171
80+	49	0.920	0.192

Standardized NHANES III Total Femur BMD Data for Non-Hispanic Black Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (mg/cm²)*	*SD (mg/cm²)*
20–29	460	1190	171
30–39	450	1141	166
40–49	335	1094	162
50–59	196	1072	185
60–69	255	1027	168
70–79	147	984	173
80+	49	933	194

NHANES III Femoral Neck BMD Data for Mexican-American Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	479	0.874	0.111
30–39	428	0.867	0.125
40–49	320	0.848	0.127
50–59	174	0.758	0.116
60–69	283	0.711	0.112
70–79	103	0.646	0.123
80+	40	0.556[a]	0.106

[a] Unreliable estimate

NHANES III Trochanteric BMD Data for Mexican-American Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	479	0.696	0.092
30–39	428	0.703	0.109
40–49	320	0.701	0.100
50–59	174	0.637	0.109
60–69	283	0.601	0.104
70–79	103	0.535	0.112
80+	40	0.450[a]	0.111

[a] Unreliable estimate

NHANES III Total Femur BMD Data for Mexican-American Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	479	0.950	0.113
30–39	428	0.961	0.137
40–49	320	0.960	0.132
50–59	174	0.877	0.138
60–69	283	0.819	0.124
70–79	103	0.732	0.146
80+	40	0.611[a]	0.150

[a] Unreliable estimate

NHANES III Standardized Total Femur BMD Data for Mexican-American Women as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (mg/cm²)*	*SD (mg/cm²)*
20–29	479	963	114
30–39	428	975	138
40–49	320	973	133
50–59	174	890	139
60–69	283	832	125
70–79	103	744	147
80+	40	622[a]	151

[a] Unreliable estimate

NHANES III Femoral Neck BMD Data for Mexican-American Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	623	0.982	0.137
30–39	429	0.922	0.127
40–49	354	0.870	0.121
50–59	156	0.857	0.130
60–69	298	0.827	0.123
70–79	124	0.798	0.135
80+	47	0.709	0.119

NHANES III Trochanteric BMD Data for Mexican-American Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	623	0.787	0.111
30–39	429	0.756	0.106
40–49	354	0.737	0.100
50–59	156	0.743	0.103
60–69	298	0.730	0.109
70–79	124	0.710	0.111
80+	47	0.639	0.120

NHANES III Total Femur BMD Data for Mexican-American Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (g/cm²)*	*SD (g/cm²)*
20–29	623	1.060	0.135
30–39	429	1.035	0.131
40–49	354	1.011	0.128
50–59	156	1.007	0.131
60–69	298	0.984	0.143
70–79	124	0.947	0.132
80+	47	0.854	0.127

NHANES III Standardized Total Femur BMD Data for Mexican-American Men as Acquired on the Hologic QDR-1000

Age	*N*	*Mean BMD (mg/cm^2)*	*SD (mg/cm^2)*
20–29	623	1074	136
30–39	429	1049	132
40–49	354	1025	129
50–59	156	1021	132
60–69	298	998	144
70–79	124	961	133
80+	47	867	128

X Appendix

Norland DXA Reference Data (1)

Norland DXA Caucasian Female PA Spine Reference Data

			BMD		
Region	*Young Reference*	*SD*	*Age 20*	*Age 50*	*Age 80*
L1	1.029	0.155	1.034	1.034	0.779
L2	1.097	0.163	1.094	1.094	0.824
L3	1.115	0.171	1.108	1.108	0.885
L4	1.082	0.169	1.063	1.063	0.893
L1–L4	1.086	0.159	1.074	1.074	0.851
L2–L4	1.102	0.162	1.087	1.087	0.869
Total Spine sBMD	1186	175	1170	1170	935

Active Date April 2000. All values are in g/cm^2 with the exception of the total spine sBMD which is in mg/cm^2.

Norland DXA Caucasian Female Proximal Femur Reference Data

			BMD		
Region	*Young Reference*	*SD*	*Age 20*	*Age 50*	*Age 80*
Femoral neck	0.987	0.117	0.981	0.873	0.655
Trochanter	0.787	0.109	0.775	0.699	0.599
Ward's	0.851	0.125	0.848	0.674	0.441

Active April 2000. All values are in g/cm^2.

Norland DXA Caucasian Female Total Hip sBMD Reference Data Based on NHANES III

	Young		*BMD*							
Region	*Reference*	*SD*	*Age 20*	*Age 25*	*Age 35*	*Age 45*	*Age 55*	*Age 65*	*Age 75*	*Age 85*
Total hip sBMD	956	123	956	956	944	920	876	809	740	679

Values are in mg/cm^2.

[1] Reproduced with permission of Norland, a CooperSurgical Company, Ft. Atkinson, WI.

Norland Caucasian Female Central DXA Forearm Reference Data

			BMD		
Region	*Young Reference*	*SD*	*Age 20*	*Age 50*	*Age 90*
Distal forearm	0.3567	0.05390	0.3567	0.3589	0.2279
Proximal forearm	0.8552	0.07484	0.8552	0.8731	0.5463
Proximal radius	0.8481	0.07472	0.8481	0.8575	0.5369

Active July 1998. Values are for the hydroxyapatite calibration. All values are in g/cm^2.

Norland DXA Caucasian Male PA Spine Reference Data

			BMD		
Region	*Young Reference*	*SD*	*Age 20*	*Age 50*	*Age 80*
L1	1.105	0.167	1.096	1.066	1.036
L2	1.171	0.186	1.158	1.127	1.097
L3	1.181	0.191	1.165	1.146	1.127
L4	1.134	0.199	1.126	1.126	1.126
L1–L4	1.148	0.176	1.130	1.119	1.107
L2–L4	1.164	0.184	1.146	1.133	1.121
Total spine sBMD	1253	198	1233	1219	1206

Active Date April 2000. All values are in g/cm^2 with the exception of the total spine sBMD which is in mg/cm^2.

Norland DXA Caucasian Male Proximal Femur Reference Data

			BMD		
Region	*Young Reference*	*SD*	*Age 20*	*Age 50*	*Age 80*
Femoral neck	1.108	0.125	1.111	0.940	0.770
Trochanter	0.933	0.113	0.925	0.838	0.751
Ward's	0.908	0.126	0.905	0.680	0.456
Total hip sBMD	1147	123	1150	1027	903

Active April 2000. All values are in g/cm^2 with the exception of the total hip sBMD which is in mg/cm^2. Total hip sBMD is based on Norland reference data.

Norland DXA Caucasian-Hispanic Female PA Spine Reference Data

			BMD		
Region	*Young Reference*	*SD*	*Age 20*	*Age 50*	*Age 80*
L1	1.054	0.152	1.041	1.041	0.775
L2	1.124	0.159	1.100	1.100	0.820
L3	1.133	0.167	1.112	1.112	0.882
L4	1.084	0.165	1.066	1.066	0.892
L1–L4	1.101	0.156	1.080	1.080	0.848
L2–L4	1.115	0.158	1.091	1.091	0.866
Total spine sBMD	1200	170	1174	1174	932

Active Date April 2000. All values are in g/cm^2 with the exception of the total spine sBMD, which is in mg/cm^2.

Norland DXA Caucasian-Hispanic Female Proximal Femur Reference Data

			BMD		
Region	*Young Reference*	*SD*	*Age 20*	*Age 50*	*Age 80*
Femoral neck	0.995	0.116	0.993	0.871	0.656
Trochanter	0.779	0.108	0.772	0.698	0.560
Ward's	0.846	0.124	0.849	0.674	0.442
Total hip sBMD	1022	118	1010	920	741

Active April 2000. All values are in g/cm^2 with the exception of the total hip sBMD, which is in mg/cm^2. Total hip sBMD is based on Norland reference data.

Norland DXA Caucasian-Hispanic Male PA Spine Reference Data

			BMD		
Region	*Young Reference*	*SD*	*Age 20*	*Age 50*	*Age 80*
L1	1.109	0.167	1.096	1.065	1.034
L2	1.176	0.187	1.160	1.125	1.089
L3	1.183	0.191	1.166	1.142	1.119
L4	1.138	0.199	1.122	1.122	1.122
L1–L4	1.152	0.176	1.130	1.118	1.106
L2–L4	1.168	0.185	1.147	1.130	1.113
Total spine sBMD	1257	199	1234	1216	1198

Active Date April 2000. All values are in g/cm^2 with the exception of the total spine sBMD, which is in mg/cm^2.

Norland DXA Caucasian-Hispanic Male Proximal Femur Reference Data

			BMD		
Region	*Young Reference*	*SD*	*Age 20*	*Age 50*	*Age 80*
Femoral neck	1.107	0.126	1.109	0.939	0.769
Trochanter	0.928	0.114	0.919	0.835	0.751
Ward's	0.900	0.128	0.898	0.678	0.457
Total hip sBMD	1146	124	1147	1025	903

Active April 2000. All values are in g/cm^2 with the exception of the total hip sBMD, which is in mg/cm^2. Total Hip sBMD is based on Norland reference data.

Norland DXA Hispanic Female PA Spine Reference Data

Region	*Young Reference*	*SD*
L1	1.088	0.126
L2	1.149	0.122
L3	1.144	0.126
L4	1.080	0.121
L1–L4	1.112	0.119
L2–L4	1.123	0.117
Total spine sBMD	1207	128

Active Date April 2000. All values are in g/cm^2 with the exception of the total spine sBMD, which is in mg/cm^2.

Norland DXA Hispanic Female Proximal Femur Reference Data

Region	*Young Reference*	*SD*
Femoral neck	0.982	0.111
Trochanter	0.740	0.103
Ward's	0.800	0.125
Total hip sBMD	1021	109

Active April 2000. All values are in g/cm^2 with the exception of the total hip sBMD, which is in mg/cm^2.

Norland DXA Asian Female PA Spine Reference Data

Region	*Young Reference*	*SD*
L1	1.005	0.129
L2	1.061	0.132
L3	1.090	0.130
L4	1.036	0.127
L1–L4	1.043	0.125
L2–L4	1.062	0.126
Total spine sBMD	1142	135

Active Date April 2000. All values are in g/cm^2 with the exception of the total spine sBMD, which is in mg/cm^2.

Norland DXA Asian Female Proximal Femur Reference Data

Region	*Young Reference*	*SD*
Femoral neck	0.866	0.113
Trochanter	0.697	0.108
Ward's	0.712	0.128
Total hip sBMD	929	117

Active April 2000. All values are in g/cm^2 with the exception of the total hip sBMD, which is in mg/cm^2.

Norland DXA Black Female PA Spine Reference Data

Region	*Young Reference*	*SD*
L1	1.206	0.140
L2	1.256	0.139
L3	1.259	0.136
L4	1.216	0.127
L1–L4	1.239	0.126
L2–L4	1.243	0.127
Total Spine sBMD	1338	137

Active Date April 2000. All values are in g/cm^2 with the exception of the total spine sBMD, which is in mg/cm^2.

Norland DXA Black Female Proximal Femur Reference Data

Region	*Young Reference*	*SD*
Femoral neck	1.046	0.140
Trochanter	0.797	0.125
Ward's	0.852	0.164
Total hip sBMD	1081	140

Active April 2000. All values are in g/cm^2 with the exception of the total hip sBMD, which is in mg/cm^2.

Norland DXA Black Male PA Spine Reference Data

Region	*Young Reference*	*SD*
L1	1.232	0.184
L2	1.291	0.204
L3	1.309	0.215
L4	1.279	0.201
L1–L4	1.271	0.191
L2–L4	1.293	0.202
Total spine sBMD	1391	218

Active Date April 2000. All values are in g/cm^2 with the exception of the total spine sBMD, which is in mg/cm^2.

Norland DXA Black Male Proximal Femur Reference Data

Region	*Young Reference*	*SD*
Femoral neck	1.161	0.205
Trochanter	0.933	0.181
Ward's	0.939	0.217
Total hip sBMD	1188	198

Active April 2000. All values are in g/cm^2 with the exception of the Total Hip sBMD which is in mg/cm^2.

XI Appendix

Hologic DXA Reference Data (1)

Hologic DXA PA Lumbar Spine L1-L4 Reference Data for Caucasian Females

Age	*BMD*	*SD*	*Age*	*BMD*	*SD*
0	0.336	0.035	30	1.047	0.110
1	0.399	0.040	35	1.041	0.110
4	0.512	0.053	40	1.024	0.110
7	0.607	0.070	45	0.999	0.110
10	0.677	0.085	50	0.967	0.110
13	0.838	0.099	60	0.892	0.110
16	1.010	0.110	70	0.815	0.110
18	1.015	0.110	80	0.752	0.110
20	1.019	0.110	85	0.731	0.110
25	1.040	0.110			

Active date 11/4/91. Peak BMD 1.047 g/cm^2. All BMD values are in g/cm^2.

Hologic DXA Supine Lateral Lumbar Spine L2-L4 Reference Data for Caucasian Women

Age	*BMD*	*SD*
20	0.820	0.084
25	0.813	0.084
30	0.803	0.084
35	0.789	0.084
40	0.770	0.084
45	0.746	0.084
50	0.716	0.084
55	0.680	0.084
60	0.636	0.084
65	0.584	0.084
70	0.523	0.084
75	0.453	0.084
80	0.373	0.084
85	0.283	0.084

Active date 7/27/92. Peak BMD 0.82 g/cm^2. All BMD values are in g/cm^2.

Hologic DXA Total Hip Caucasian Female Reference Data Based on NHANES

Age	*BMD*	*SD*
20	0.942	0.122
25	0.942	0.122
30	0.939	0.122
35	0.933	0.122
40	0.922	0.122
45	0.907	0.122
50	0.886	0.122
55	0.860	0.122
60	0.827	0.122
65	0.793	0.122
70	0.759	0.122
75	0.725	0.122
80	0.691	0.122
85	0.657	0.122

Active Date 2/1/97. Peak BMD 0.942 g/cm^2. BMD values are in g/cm^2.

[1] Reproduced courtesy of Hologic Inc., Bedford, MA.

Hologic DXA Femoral Neck Caucasian Female Reference Data Based on NHANES

Age	*BMD*	*SD*
20	0.849	0.111
25	0.849	0.111
35	0.831	0.111
45	0.803	0.111
55	0.732	0.111
65	0.682	0.111
75	0.618	0.111
85	0.569	0.111

Active Date 2/1/97. Peak BMD 0.849 g/cm^2. BMD values are in g/cm^2.

Hologic DXA Trochanteric Caucasian Female Reference Data Based on NHANES

Age	*BMD*	*SD*
20	0.703	0.101
25	0.703	0.101
35	0.703	0.101
45	0.681	0.101
55	0.635	0.101
65	0.594	0.101
75	0.546	0.101
85	0.504	0.101

Active Date 2/1/97. Peak BMD 0.703 g/cm^2. BMD values are in g/cm^2.

Hologic DXA Ultradistal Forearm Caucasian Female Reference Data

Age	*BMD*	*SD*
20	0.412	0.051
25	0.410	0.051
30	0.407	0.051
35	0.404	0.051
40	0.398	0.051
45	0.392	0.051
50	0.384	0.051
55	0.374	0.051
60	0.362	0.051
65	0.348	0.051
70	0.331	0.051
75	0.312	0.051
80	0.291	0.051
85	0.266	0.051

Active date 10/25/91. Peak BMD 0.412 g/cm^2. All values in g/cm^2.

Hologic DXA Mid Forearm Caucasian Female Reference Data

Age	*BMD*	*SD*
20	0.588	0.053
25	0.585	0.053
30	0.581	0.053
35	0.575	0.053
40	0.568	0.053
45	0.558	0.053
50	0.546	0.053
55	0.532	0.053
60	0.514	0.053
65	0.494	0.053
70	0.470	0.053
75	0.442	0.053
80	0.410	0.053
85	0.374	0.053

Active date 10/25/91. Peak BMD 0.588 g/cm^2. All values in g/cm^2.

Hologic DXA Inter-Trochanteric Caucasian Female Reference Data Based on NHANES

Age	*BMD*	*SD*
20	1.086	0.155
25	1.086	0.155
35	1.100	0.155
45	1.077	0.155
55	1.032	0.155
65	0.952	0.155
75	0.860	0.155
85	0.776	0.155

Active Date 2/1/97. Peak BMD 1.100 g/cm^2. BMD values are in g/cm^2.

Hologic DXA Ward's Caucasian Female Reference Data Based on NHANES

Age	*BMD*	*SD*
20	0.734	0.117
25	0.734	0.117
35	0.695	0.117
45	0.634	0.117
55	0.535	0.117
65	0.470	0.117
75	0.403	0.117
85	0.361	0.117

Active Date 2/1/97. Peak BMD 0.734 g/cm^2. BMD values are in g/cm^2.

Hologic DXA 1/3 Forearm Caucasian Female Reference Data

Age	*BMD*	*SD*
20	0.684	0.058
25	0.681	0.058
30	0.677	0.058
35	0.671	0.058
40	0.663	0.058
45	0.653	0.058
50	0.641	0.058
55	0.626	0.058
60	0.608	0.058
65	0.586	0.058
70	0.561	0.058
75	0.532	0.058
80	0.499	0.058
85	0.462	0.058

Active date 10/25/91. Peak BMD 0.684 g/cm^2. All values in g/cm^2.

Hologic DXA Total Forearm Caucasian Female Reference Data

Age	*BMD*	*SD*
20	0.564	0.051
25	0.561	0.051
30	0.557	0.051
35	0.552	0.051
40	0.546	0.051
45	0.537	0.051
50	0.526	0.051
55	0.513	0.051
60	0.497	0.051
65	0.478	0.051
70	0.456	0.051
75	0.430	0.051
80	0.401	0.051
85	0.368	0.051

Active date 10/25/91. Peak BMD 0.564 g/cm^2. All values in g/cm^2.

Hologic DXA Whole Body Bone Density Caucasian Female Reference Data

Age	*BMD*	*SD*
20	1.136	0.095
25	1.127	0.095
30	1.116	0.095
35	1.103	0.095
40	1.088	0.095
45	1.071	0.095
50	1.052	0.095
55	1.031	0.095
60	1.008	0.095
65	0.983	0.095
70	0.957	0.095
75	0.928	0.095
80	0.897	0.095
85	0.864	0.095

Active date 10/25/91. Peak BMD 1.136 g/cm^2. All values are in g/cm^2.

Hologic DXA PA Lumbar Spine L1-L4 Caucasian Male Reference Data

Age	*BMD*	*SD*	*Age*	*BMD*	*SD*
0	0.336	0.035	35	1.091	0.110
1	0.399	0.040	45	1.068	0.110
4	0.512	0.053	50	1.053	0.110
7	0.607	0.070	55	1.038	0.110
10	0.677	0.085	60	1.023	0.110
13	0.838	0.099	65	1.008	0.110
16	1.010	0.110	70	0.993	0.110
18	1.050	0.110	75	0.978	0.110
20	1.091	0.110	80	0.963	0.110
25	1.091	0.110	85	0.947	0.110

Active date 11/4/91. Peak BMD 1.091 g/cm^2. All values in g/cm^2.

Hologic DXA Total Hip Caucasian Male Reference Data Based on NHANES III

Age	*BMD*	*SD*
20	1.033	0.151
25	1.033	0.151
35	1.014	0.151
45	0.995	0.151
55	0.975	0.151
65	0.957	0.151
75	0.910	0.151
85	0.842	0.151

Active Date 2/1/97. Peak BMD 1.033 g/cm^2. BMD values are in g/cm^2.

Hologic DXA Femoral Neck Caucasian Male Reference Data Based on NHANES III

Age	*BMD*	*SD*
20	0.930	0.136
25	0.930	0.136
35	0.885	0.136
45	0.845	0.136
55	0.814	0.136
65	0.790	0.136
75	0.749	0.136
85	0.698	0.136

Active Date 2/1/97. Peak BMD 0.930 g/cm^2. BMD values are in g/cm^2.

Hologic DXA Intertrochanteric Caucasian Male Reference Data Based on NHANES III

Age	*BMD*	*SD*
20	1.195	0.181
25	1.195	0.181
35	1.188	0.181
45	1.171	0.181
55	1.149	0.181
65	1.117	0.181
75	1.058	0.181
85	0.974	0.181

Active Date 2/1/97. Peak BMD 1.195 g/cm^2. BMD values are in g/cm^2.

Hologic DXA Trochanter Caucasian Male Reference Data Based on NHANES III

Age	*BMD*	*SD*
20	0.777	0.126
25	0.777	0.126
35	0.754	0.126
45	0.743	0.126
55	0.738	0.126
65	0.739	0.126
75	0.705	0.126
85	0.667	0.126

Active Date 2/1/97. Peak BMD 0.777 g/cm^2. BMD values are in g/cm^2.

Hologic DXA Total Forearm Caucasian Male Reference Data

Age	*BMD*	*SD*
20	0.679	0.054
25	0.678	0.054
30	0.675	0.054
35	0.673	0.054
40	0.669	0.054
45	0.664	0.054
50	0.658	0.054
55	0.650	0.054
60	0.641	0.054
65	0.631	0.054
70	0.618	0.054
75	0.604	0.054
80	0.587	0.054
85	0.569	0.054

Active date 10/25/91. Peak BMD 0.679 g/cm^2. All values in g/cm^2.

Hologic DXA Ultradistal Forearm Caucasian Male Reference Data

Age	*BMD*	*SD*
20	0.509	0.056
25	0.506	0.056
30	0.503	0.056
35	0.498	0.056
40	0.493	0.056
45	0.488	0.056
50	0.481	0.056
55	0.474	0.056
60	0.467	0.056
65	0.458	0.056
70	0.449	0.056
75	0.440	0.056
80	0.429	0.056
85	0.418	0.056

Active date 10/25/91. Peak BMD 0.509 g/cm^2. All values in g/cm^2.

Hologic DXA Mid-Forearm Caucasian Male Reference Data

Age	*BMD*	*SD*
20	0.695	0.055
25	0.694	0.055
30	0.692	0.055
35	0.690	0.055
40	0.686	0.055
45	0.682	0.055
50	0.677	0.055
55	0.671	0.055
60	0.663	0.055
65	0.654	0.055
70	0.644	0.055
75	0.632	0.055
80	0.618	0.055
85	0.603	0.055

Active date 10/25/91. Peak BMD 0.695 g/cm^2. All values in g/cm^2.

Hologic DXA Ward's Caucasian Male Reference Data Based on NHANES III

Age	*BMD*	*SD*
20	0.785	0.141
25	0.785	0.141
35	0.712	0.141
45	0.637	0.141
55	0.579	0.141
65	0.541	0.141
75	0.487	0.141
85	0.440	0.141

Active Date 2/1/97. Peak BMD 0.785 g/cm^2. BMD values are in g/cm^2.

Hologic DXA PA Lumbar Spine L1-L4 Black Female Reference Data

Age	*BMD*	*SD*	*Age*	*BMD*	*SD*
0	0.369	0.035	30	1.150	0.110
1	0.438	0.040	35	1.143	0.110
4	0.562	0.053	40	1.124	0.110
7	0.666	0.070	45	1.097	0.110
10	0.743	0.085	50	1.062	0.110
13	0.920	0.099	60	0.979	0.110
16	1.109	0.110	70	0.895	0.110
18	1.114	0.110	80	0.826	0.110
20	1.119	0.110	85	0.803	0.110
25	1.142	0.110			

Active date 11/4/91. Peak BMD 1.150 g/cm^2. All values in g/cm^2.

Hologic DXA Total Hip
Black Female Reference Data
Based on NHANES

Age	*BMD*	*SD*
20	1.030	0.156
25	1.030	0.156
35	1.004	0.156
45	1.031	0.156
55	0.945	0.156
65	0.879	0.156
75	0.832	0.156
85	0.755	0.156

Active date 11/25/96. Peak BMD 1.031 g/cm^2. All values are in g/cm^2.

Hologic DXA Femoral Neck
Black Female Reference Data
Based on NHANES

Age	*BMD*	*SD*
20	0.951	0.142
25	0.951	0.142
35	0.913	0.142
45	0.925	0.142
55	0.839	0.142
65	0.769	0.142
75	0.728	0.142
85	0.670	0.142

Active date 11/25/96. Peak BMD 0.951 g/cm^2. All values are in g/cm^2.

Hologic DXA Ward's Area
Black Female Reference Data
Based on NHANES

Age	*BMD*	*SD*
20	0.834	0.147
25	0.834	0.147
35	0.762	0.147
45	0.746	0.147
55	0.613	0.147
65	0.545	0.147
75	0.496	0.147
85	0.444	0.147

Active date 11/25/96. Peak BMD is 0.834 g/cm^2. BMD values are in g/cm^2.

Hologic DXA Trochanteric
Black Female Reference Data
Based on NHANES III

Age	*BMD*	*SD*
20	0.760	0.123
25	0.760	0.123
35	0.734	0.123
45	0.761	0.123
55	0.691	0.123
65	0.646	0.123
75	0.620	0.123
85	0.572	0.123

Active date 11/25/96. Peak BMD 0.761 g/cm^2. BMD values are in g/cm^2.

Hologic DXA Intertrochanteric
Black Female Reference Data
Based on NHANES

Age	*BMD*	*SD*
20	1.203	0.190
25	1.203	0.190
35	1.187	0.190
45	1.220	0.190
55	1.128	0.190
65	1.042	0.190
75	0.988	0.190
85	0.891	0.190

Active date 11/25/96. Peak BMD 1.220 g/cm^2. All values are in g/cm^2.

Hologic DXA Total Hip
Black Male Reference Data
Based on NHANES

Age	*BMD*	*SD*
20	1.177	0.172
25	1.177	0.172
35	1.125	0.172
45	1.062	0.172
55	1.053	0.172
65	1.025	0.172
75	0.973	0.172
85	0.900	0.172

Active date 11/25/97. Peak BMD 1.033 g/cm^2. All values in g/cm^2.

Hologic DXA PA Lumbar Spine L1-L4 Black Male Reference Data

Age	*BMD*	*SD*	*Age*	*BMD*	*SD*
0	0.369	0.035	35	1.198	0.110
1	0.438	0.040	45	1.173	0.110
4	0.562	0.053	50	1.156	0.110
7	0.666	0.070	55	1.140	0.110
10	0.743	0.085	60	1.123	0.110
13	0.920	0.099	65	1.107	0.110
16	1.109	0.110	70	1.090	0.110
18	1.153	0.110	75	1.074	0.110
20	1.198	0.110	80	1.057	0.110
25	1.198	0.110	85	1.040	0.110

Active date 11/25/96. Peak BMD 1.198 g/cm^2. All values in g/cm^2.

Hologic DXA Femoral Neck Black Male Reference Data Based on NHANES

Age	*BMD*	*SD*
20	1.073	0.156
25	1.073	0.156
35	1.008	0.156
45	0.918	0.156
55	0.903	0.156
65	0.870	0.156
75	0.811	0.156
85	0.756	0.156

Active date 11/25/96. Peak BMD 1.073 g/cm^2. All values in g/cm^2.

Hologic DXA Ward's Black Male Reference Data Based on NHANES

Age	*BMD*	*SD*
20	0.926	0.173
25	0.926	0.173
35	0.824	0.173
45	0.708	0.173
55	0.661	0.173
65	0.620	0.173
75	0.554	0.173
85	0.501	0.173

Active date 11/25/96. Peak BMD 0.926 g/cm^2. All values in g/cm^2.

Hologic DXA Trochanteric Black Male Reference Data Based on NHANES

Age	*BMD*	*SD*
20	0.880	0.138
25	0.880	0.138
35	0.829	0.138
45	0.773	0.138
55	0.789	0.138
65	0.775	0.138
75	0.730	0.138
85	0.691	0.138

Active date 11/25/97. Peak BMD 0.880 g/cm^2. All values in g/cm^2.

Hologic DXA Intertrochanteric Black Male Reference Data Based on NHANES

Age	*BMD*	*SD*
20	1.361	0.206
25	1.361	0.206
35	1.322	0.206
45	1.258	0.206
55	1.232	0.206
65	1.198	0.206
75	1.143	0.206
85	1.052	0.206

Active date 11/25/96. Peak BMD 1.361 g/cm^2. All values in g/cm^2.

Hologic DXA PA Lumbar Spine L1-L4 Hispanic Male Reference Data

Age	*BMD*	*SD*
0	0.336	0.035
1	0.399	0.040
4	0.512	0.053
7	0.607	0.070
10	0.677	0.085
13	0.838	0.099
16	1.010	0.110
18	1.050	0.110
20	1.091	0.110
25	1.091	0.110
35	1.091	0.110
45	1.068	0.110
50	1.053	0.110
55	1.038	0.110
60	1.023	0.110
65	1.008	0.110
70	0.993	0.110
75	0.978	0.110
80	0.963	0.110
85	0.947	0.110

Active date 11/25/96. Peak BMD 1.091 g/cm^2. All values are in g/cm^2.

Hologic DXA PA Lumbar Spine L1-L4 Hispanic Female Reference Data

Age	*BMD*	*SD*
0	0.336	0.035
1	0.399	0.040
4	0.512	0.053
7	0.607	0.070
10	0.677	0.085
13	0.838	0.099
16	1.010	0.110
18	1.015	0.110
20	1.019	0.110
25	1.040	0.110
30	1.047	0.110
35	1.041	0.110
40	1.024	0.110
45	0.999	0.110
50	0.967	0.110
60	0.892	0.110
70	0.815	0.110
80	0.752	0.110
85	0.731	0.110

Active Date 11/25/96. Peak BMD 1.047 g/cm^2. BMD values are in g/cm^2.

XII Appendix

Lunar DXA Reference Data (1)

Lunar PA Lumbar Spine L2–L4 DXA Reference Data for Caucasian Women

Age	*BMD (g/cm²)*
20	1.200
25	1.200
30	1.200
35	1.200
40	1.200
45	1.200
50	1.153
55	1.105
60	1.058
65	1.010
70	0.970
75	0.960
80	0.950
85	0.940

Peak L2–L4 BMD is 1.200 g/cm². The SD is 0.12 g/cm².

Lunar PA Lumbar Spine L1–L4 DXA Reference Data for Caucasian Women

Age	*BMD (g/cm²)*
20	1.180
25	1.180
30	1.180
35	1.180
40	1.180
45	1.180
50	1.133
55	1.085
60	1.038
65	0.990
70	0.950
75	0.940
80	0.930
85	0.920

Peak L2–L4 BMD is 1.180 g/cm². The SD is 0.12 g/cm².

[1] Reproduced courtesy of GE Medical Systems, Madison, WI.

Lunar Femoral Neck DXA Reference Data for Caucasian Women

Age	*BMD (g/cm²)*
20	1.000
25	0.990
30	0.980
35	0.970
40	0.960
45	0.950
50	0.915
55	0.880
60	0.845
65	0.810
70	0.790
75	0.770
80	0.750
85	0.730

Peak femoral neck BMD is 0.980 g/cm². The SD is 0.12 g/cm².

Lunar Trochanteric DXA Reference Data for Caucasian Women

Age	*BMD (g/cm²)*
20	0.790
25	0.790
30	0.790
35	0.790
40	0.790
45	0.790
50	0.770
55	0.750
60	0.730
65	0.710
70	0.690
75	0.670
80	0.650
85	0.630

Peak trochanteric BMD is 0.790 g/cm². The SD is 0.11 g/cm².

Lunar Total Femur DXA Reference Data for Caucasian Women

Age	*BMD (g/cm²)*
20	1.010
25	1.005
30	1.000
35	0.995
40	0.990
45	0.985
50	0.955
55	0.925
60	0.895
65	0.865
70	0.838
75	0.810
80	0.783
85	0.755

Peak total femur BMD is 1.000 g/cm². The SD is 0.12 g/cm².

Lunar PA Lumbar Spine L2–L4 DXA Reference Data for Caucasian Men

Age	*BMD (g/cm²)*
20	1.240
25	1.240
30	1.240
35	1.240
40	1.240
45	1.230
50	1.219
55	1.209
60	1.198
65	1.188
70	1.177
75	1.167
80	1.156
85	1.146

Peak L2–L4 BMD is 1.240 g/cm². The SD is 0.12 g/cm².

Lunar PA Lumbar Spine L1–L4 DXA Reference Data for Caucasian Men

Age	*BMD (g/cm²)*
20	1.220
25	1.220
30	1.220
35	1.220
40	1.220
45	1.210
50	1.199
55	1.189
60	1.178
65	1.168
70	1.157
75	1.147
80	1.136
85	1.126

Peak L2–L4 BMD is 1.220 g/cm². The SD is 0.12 g/cm².

Lunar Femoral Neck DXA Reference Data for Caucasian Men

Age	*BMD (g/cm²)*
20	1.190
25	1.110
30	1.090
35	1.070
40	1.050
45	1.030
50	1.010
55	0.990
60	0.970
65	0.950
70	0.930
75	0.910
80	0.890
85	0.870

Peak femoral neck BMD is 1.090 g/cm². The SD is 0.13 g/cm².

Lunar Trochanteric DXA Reference Data for Caucasian Men

Age	*BMD (g/cm²)*
20	0.945
25	0.938
30	0.930
35	0.923
40	0.915
45	0.908
50	0.900
55	0.893
60	0.885
65	0.878
70	0.870
75	0.863
80	0.855
85	0.848

Peak trochanteric BMD is 0.930 g/cm². The SD is 0.11 g/cm².

Lunar Total Femur DXA Reference Data for Caucasian Men

Age	*BMD (g/cm²)*
20	1.120
25	1.105
30	1.090
35	1.075
40	1.060
45	1.045
50	1.033
55	1.020
60	1.008
65	0.995
70	0.980
75	0.965
80	0.950
85	0.935

Peak total femur BMD is 1.090 g/cm². The SD is 0.13 g/cm².

XIII Appendix

Densitometry Patient Questionnaire

Name: _____ Date: _____

Date of Birth: _____ Age: _____

Race: Caucasian Hispanic Black Asian Native American Other

Current weight: _____ Current height: _____

Height at age 20: _____

How would you rate your overall health? Excellent Good Fair Poor

Are you postmenopausal? Yes No

If yes, at what age did you become menopausal?

_____

Do you currently smoke? Yes No

Have any of your first-degree relatives had a fracture? Yes No

Did your mother ever break her hip? Yes No

Have you had a fracture as an adult? Yes No

If yes, which bones have you broken?

_____

_____

Do you have diabetes? Yes No

Do you have rheumatoid arthritis? Yes No

Do you have epilepsy? Yes No

Have you fallen in the last 12 months? Yes No

Have you ever had hyperthyroidism? Yes No

Have you ever had hyperparathyroidism? Yes No

Have you ever had sprue or celiac disease?	Yes	No
Do you have Crohn's Disease?	Yes	No
Do you have ulcerative colitis?	Yes	No
Have you ever had cancer?	Yes	No
Do you have problems with your balance?	Yes	No
Can you get up from a chair without using your arms?	Yes	No
Do you have uncorrected problems with your vision?	Yes	No
Have you ever had any part of your stomach removed surgically?	Yes	No
Have you ever had an intestinal bypass operation?	Yes	No
Do you take or have you ever taken any of the following:		
Hormone replacement or estrogen replacement therapy?	Yes	No
Corticosteroids, such as prednisone or cortisone?	Yes	No
Lithium?	Yes	No
Thyroid hormone?	Yes	No
Insulin?	Yes	No
Dilantin®?	Yes	No
Calcium supplements?	Yes	No
Multivitamins?	Yes	No
Lupron® (leuprolide) or Zoladex® (goserelin)?	Yes	No
Have you ever had a bone density test before?	Yes	No

If yes, when and where?

_____

_____

XIV Appendix

The CD-ROM Companion

There are 5 folders in the CD-ROM: the Patient Questionnaire, OST Paper, OST Electronic, Precision Calculator Companion and the CME Review Data Files. Put the CD-ROM into the CD-ROM drive of your computer. The CD is self-launching and will open automatically in your default web browser. If for some reason, the CD does not self-launch, the opening page can be accessed by double-clicking the STARTME.htm file. The simplest way to access all the folders and their contents is from the opening page. The folders may also be accessed through MY COMPUTER or through WINDOWS EXPLORER. To view the Patient Questionnaire, Microsoft Word must be installed on your computer. The OST .pdf files require Adobe Acrobat Reader for viewing. The Precision Calculator Companion requires Microsoft Excel. The OST Electronic calculator and the CME Review are stand-alone programs. Microsoft Word, Microsoft Excel, and Adobe Acrobat may also be used to open their respective programs directly.

OST PAPER

The OST Paper folder contains 2 Adobe Acrobat .pdf files. OSTAsian.pdf is a printable version of the OST nomogram for Asian women. The cut points on this nomogram are for the identification of Asian women who are at low, medium, or high risk of having an osteoporotic femoral neck bone density. Women who fall into the medium and high-risk categories should be referred for a bone density test. OSTCaucasian.pdf is a printable version of the OST nomogram for Caucasian women. The cut points on this nomogram are for the identification of Caucasian women who are at low, medium, or high risk of having an osteoporotic femoral neck bone density. Women who fall into the medium and high-risk categories should be referred for a bone density test. These printable versions of the OST nomogram can be used in waiting rooms or at health events.

OST ELECTRONIC

To use OST Electronic, enter the woman's age and weight and then click on CALCULATE (Mac users should use osteo_risk MAC). The software will automatically place the woman in the appropriate risk category on the OST nomogram. This page can be printed if you wish. For the next patient, simply click on START OVER. This is an

electronic version of the OST nomogram for Caucasian women. The cut points on this nomogram are for the identification of Caucasian women who are at low, medium, or high risk of having an osteoporotic femoral neck bone density. Women who fall into the medium and high-risk categories should be referred for a bone density test. This software can be used in waiting rooms or at health events.

THE PRECISION CALCULATOR COMPANION

There is only one Microsoft Excel workbook file in this folder. There are 2 spreadsheets within the workbook. The first spreadsheet is the Precision Calculator Companion. Instructions are given on the spreadsheet. This spreadsheet will allow you to calculate precision as the RMS-SD and RMS-%CV for a group of 15 patients studied 3 times each. The spreadsheet will also calculate the $_{1x1}LSC^{95}$ for this level of precision.

The second spreadsheet is the Statistical Confidence Calculator. The instructions for its use are included on the spreadsheet. This spreadsheet will allow you to calculate the absolute and percent change from baseline for two studies as well as the level of statistical confidence for that change and any precision value.

Each spreadsheet can be printed once the calculations are completed. The instructions will not be visible on the printout. The spreadsheets are locked but not password protected. This was done to prevent inadvertent erasure of the formulas. As long as the spreadsheets are not deliberately unlocked, it is not possible to erase the formulas embedded in the spreadsheets.

THE PATIENT QUESTIONNAIRE

There is only 1 file in the Patient Questionnaire folder: Patient Questionnaire.doc. The questionnaire is not protected in any way and can be altered to suit your individual practice needs.

THE CME REVIEW FOR *BONE DENSITOMETRY IN CLINICAL PRACTICE: APPLICATION AND INTERPRETATION, SECOND EDITION*

To begin the review, click on the link from the CD Companion launch page or double-click CMEReview.htm. Follow the on-screen instructions. This is a 100 multiple-choice question review. Each question has only 1 right answer. Select the answer you believe to be correct and then click SUBMIT. You will immediately be told if the answer is correct or incorrect. If incorrect, close the dialog box, return to the question and make another selection. Keep trying until you get the correct answer. You must click on SUBMIT for the answer to be recorded by the program. After obtaining the correct answer, close the dialog box as before and go to the next question. You may stop the review at any time and resume at a later date. (Users will be required to have cookies enabled for their browser in order for results to be saved.) After answering all 100 questions correctly, you may complete and print the Review Completion Certificate. Identifying data must be entered on the certificate prior to printing. Completion of the requested identifying information and course evaluation on the certificate is required for processing of CME credit. Successful completion of the Review will result in the

awarding of 30 hours of Category 1 continuing medical education credit. The certificate and processing fee of $150.00 should be sent to:

Foundation for Osteoporosis Education and Research
300 27th Street, Suite 103
Oakland, CA 94612

Funds must be in US dollars. Checks should be made out to FORE.

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