Clinical Use of *Bone Densitometry*

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Osteoporosis is a silent disease in that bone loss almost always occurs without any outward signs or symptoms, until the bones are weakened to the point of fracture. Once a fracture has occurred, the ability to restore bone strength is limited.

The key to preventing osteoporosis is to maximize peak bone mass, minimize age-related bone loss, and maintain bone strength. However, susceptibility to osteoporosis does not depend solely on development of an optimal peak bone mass. Even a well-invested "calcium bank account" can be put into deficit by excessive and frequent withdrawals.

Recent developments in medical imaging have allowed non-invasive assessment of bone mass through the use of several different bone densitometry devices.

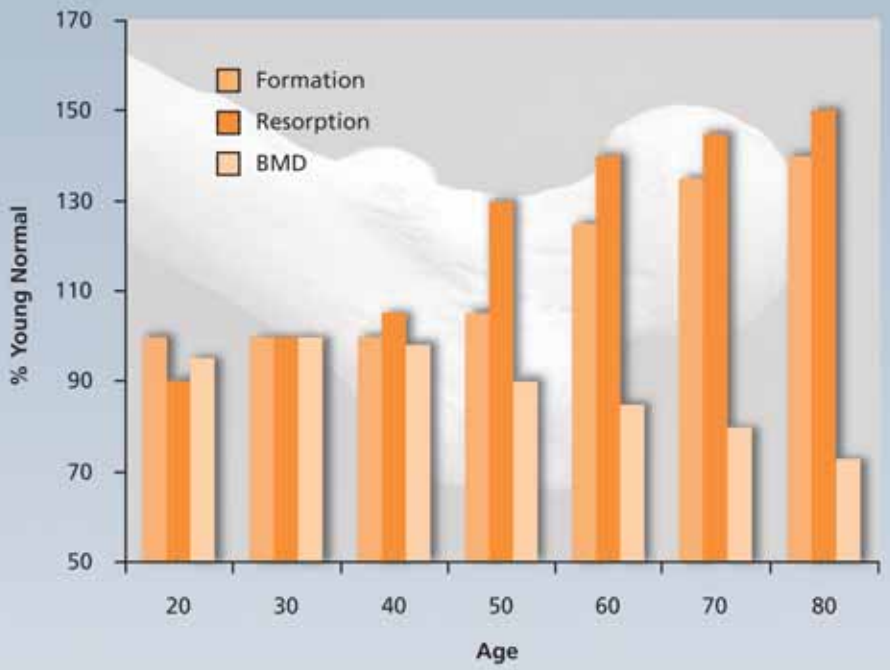


Figure 1: Expected changes in bone formation, bone resorption, and bone mineral density (BMD) in women. Note the increase in bone resorption at the time of menopause (age 50), resulting in an increased loss of bone density.

The rate of bone loss after skeletal maturity depends upon many factors. Bone tissue is in a constant state of renewal. This process, called remodeling, consists of new bone formation as well as the removal of old bone. The latter process is called resorption or bone loss. Cells known as osteoblasts are responsible for bone formation while cells known as osteoclasts are responsible for bone resorption or bone loss. Ideally, osteoclasts remove old bone, leaving small pits that are then refilled by the osteoblasts.

When we are young, the process of bone formation outpaces that of bone resorption, resulting in a net increase of bone density and bone growth. By age 25 to 35 years, the two processes balance and peak bone mass is attained (Figure 1).

After skeletal maturity bone mass stabilizes for a period, then osteoclastic activity begins to exceed that of the osteoblastic activity, such that the pits formed are not completely refilled in the rebuilding phase. The result is that not all the bone resorbed by the osteoclast is replaced by new bone. At the individual cellular level, the net loss of bone may be very small, but over time the accumulated losses can be significant.

For women, the difference between bone formation and resorption is enhanced by a decline in estrogen levels at the time of the menopause. If the formation-resorption difference is large enough and there is a low peak bone mass, osteoporosis can develop.

Identification and treatment of osteoporosis requires accurate knowledge of bone density and other risk factors related to the future risk for fracture. Recent developments in medical imaging have allowed noninvasive assessment of bone mass through the use of several different bone densitometry devices. Many studies have shown a strong relationship between bone density at virtually any skeletal site and the subsequent risk for fractures of the spine, hip, and forearm.[1] The exact strength of this relationship depends on the type of fracture and the skeletal site measured.

In most cases, the relationship between bone density and fracture by analogy is as strong or stronger than the relationship between lipid levels and coronary heart disease.[2]

Almost all of the available data relating bone density to fracture risk has been obtained from elderly, primarily Caucasian women. From these studies it has been determined that direct measurements of the hip are the most sensitive predictors of hip fracture.[3] Heel measurements have also been shown to be excellent for predicting hip fracture.[4-6]

For the prediction of spine fractures, data have shown spine, heel, forearm, and hand measurements to be relatively comparable for assessing risk in the elderly.[7]

It is believed that degenerative bone change influences spinal measurements in the elderly, by "falsely" elevating BMD measurement and underestimating fracture risk. Thus spinal measurements may be a more sensitive measure of vertebral fracture risk in younger populations, but this remains to be determined.

To assess overall fracture risk, spine, hip, and forearm BMD measurements appear to be relatively comparable in their predictive ability in elderly Caucasian women.[8]

Many different types of densitometers are available to measure bone mass. These devices fall into one of two categories depending on which skeletal sites they can be used to measure. Central densitometers are the current clinical gold standard, capable of measuring BMD in the central skeleton, i.e., at the lumbar spine and proximal femur. Central densitometry techniques include dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT). Peripheral densitometers are limited to measuring the peripheral skeleton; i.e., the distal appendicular skeleton.

Typical measurement sites for peripheral densitometers are the forearm, heel, and hand. Techniques include peripheral DXA (pDXA) and quantitative ultrasound (QUS). These devices are smaller, portable and less expensive than central densitometers, but they are less versatile as well. While peripheral densitometers are limited to measuring one or two skeletal sites in the body, central densitometers are capable of measuring virtually any skeletal site, either in the central or peripheral skeleton.

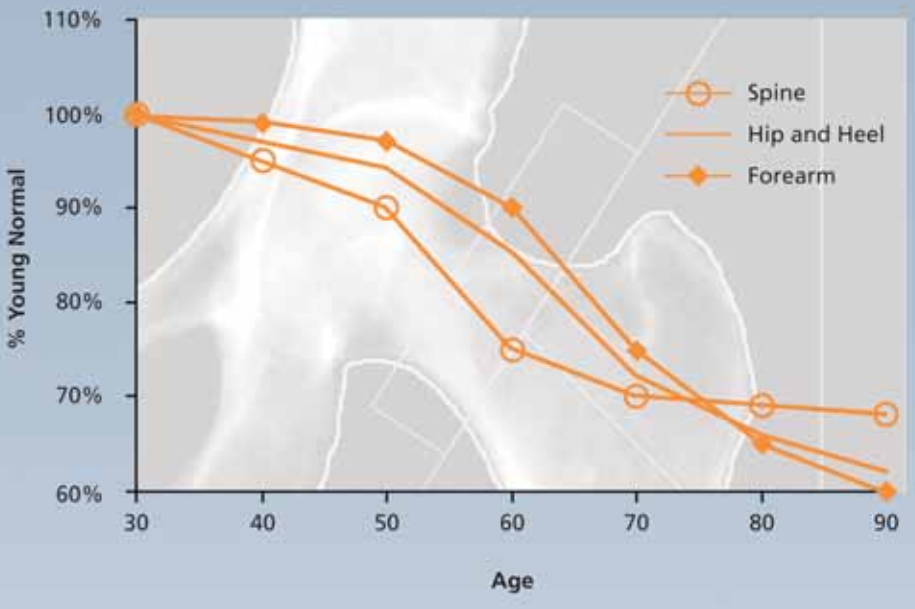


Figure 2: Anticipated age-related bone mineral density (BMD) changes in women at for different skeletal sites. Note accelerated bone loss around the time of menopause (age 50-52), particularly at the spine.

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) systems can measure the BMD of the lumbar spine, proximal femur, forearm, and, in many cases, the total body. They use a dual energy X-ray tube mounted inside a measurement table coupled with an X-ray detector mounted above the table. The X-ray tube and detector move across the area to be scanned, measuring each point at two X-ray energies.

The use of two X-ray energies allows the system to differentiate between bone and surrounding soft tissue to produce a measurement of just the bone density. More advanced DXA scanners use fan beam geometry and multiple X-ray detectors to decrease scan times. Recent advancements have provided improved image quality, allowing better visualization of the scan region as well as the ability to detect vertebral fractures.

Quantitative computed tomography

Quantitative computed tomography (QCT) is used clinically to measure the bone density of the spine, though methods have been developed for measuring the hip.[9-11] It has the advantage of measuring the center of the vertebral body, which is a more sensitive site for detecting bone mineral changes than most other skeletal sites. QCT can be performed on most commercial CT systems with the use of a bone mineral standard for calibration of the CT scanner.

Several different types of calibration systems are commercially available from CT manufacturers and other vendors. When properly performed, the radiation dose from QCT is no more than with a mammogram. Perhaps the largest disadvantage of QCT is access. Most CT systems are located in hospitals and imaging centers with limited time available for QCT bone measurements.

Peripheral DXA

Peripheral DXA (pDXA) systems use similar technology to central DXA devices but in a more compact format. Their smaller size results in reduced space requirements and facilitates portability.

Currently, pDXA devices are available for measuring the forearm, hand, and heel. Many have integrated computers, while some require a separate computer system to store the measurement data.

In general, these pDXA systems tend to be easy to use and are less sensitive to positioning errors than central DXA systems. They are extremely accurate and precise.

Method	Utility	Versatility	Ease	Availability	Cost	Radiation Dose
DXA	+++	+++	++	++	++	++
QCT	++	+	+	+	+++	++
pDXA	++	+	+++	++	+	+
QUS	++	+	+++	++	+	none

+++ = most, ++ = moderate, + = least

Figure 3: Each bone mass measurement technique has different advantages and disadvantages. There are differences in the skeletal sites that can be measured, clinical utility, radiation dose, availability, cost, and ease of use. The table above summarizes these factors based on the available research data and clinical experience.

However, their inability to measure the more clinically important skeletal sites at the spine and proximal femur limits their utility. When properly used, pDXA technologies can be used to increase accessibility to osteoporosis screening when access to central densitometry is limited.

Quantitative ultrasound

Ultrasound has been used for many years to investigate the mechanical properties of various engineering materials. It offers the theoretical advantage of measuring material properties other than density, though this has yet to be proved conclusively for bone.

Recently, several commercial ultrasound devices have been introduced for investigating bone status, primarily of the heel. This technique is termed quantitative ultrasound (QUS) to distinguish it from the more commonly known imaging ultrasound devices. QUS offers the advantages of small size, relatively quick and simple measurements, and no need for ionizing radiation. However, QUS is limited for technical reasons to measuring bones that have minimal and uniform soft tissue covering. Thus QUS is best used on peripheral bones, such as the heel, forearm, and fingers.

QUS has been shown by several researchers to be predictive of hip fracture, but in a different way than X-ray based bone density. This has fueled the interest in QUS as a measure of bone quality as well as density. Comparisons with X-ray techniques indicate that QUS is measuring a combination of bone density and some unknown "qualitative" property of the bone.

Some experts have speculated that QUS results may assess bone structure, such as trabecular size and spacing. If this is true, a QUS measurement would be valuable in combination with DXA or QCT bone density to get a better measure of bone status. The compact size and non-radiation based qualities of QUS make it an attractive choice for screening programs.

Comparison of techniques

From the above discussion, it is clear that each bone mass measurement technique has different advantages and disadvantages.[12] There are differences in the skeletal sites that can be measured, clinical utility, radiation dose, availability, cost, and ease of use. Figure 3 summarizes these factors based on the available research data and clinical experience.

Each bone mass measurement technique has different advantages and disadvantages.

While all available techniques have clinical utility, differences in the other categories, particularly versatility (due to the ability to measure multiple skeletal sites, including the spine and hip), favor DXA over the other methods. As a result, DXA has become the densitometry technique of choice for bone density in many clinical departments.

While other methods are still used in some clinics, there is an ongoing shift to DXA as the clinical standard. DXA has the primary disadvantage of higher cost because commercial units are typically more expensive than pDXA or QUS devices. Because of the advantages of low cost and portability, pDXA and QUS are often used for screening programs or in clinics where central densitometry cannot be accommodated.

Comparisons with normative data

For BMD measurements to be clinically useful, they must be compared to established normative ranges. All BMD device manufacturers provide normative databases for this purpose. These databases are derived from measurements of large groups of men or women of different ages and races. Comparisons are expressed either as a percentage of the expected normal value or as the number of standard deviations from the expected normal value.

The T-score is the most important comparison. The T-score is the number of standard deviations (SDs) that the measured BMD differs from the gender matched young normal (age 25-30 years) value.

For the diagnosis of osteoporosis, the World Health Organization (WHO) has defined the following criteria for the assessment of osteoporosis based on the T-score:[13-16]

Normal: A BMD less than 1 SD below young normal levels (T-score $<$-1.0).

Osteopenia (low bone mass): A BMD between 1 and 2.5 SDs below young normal levels (T-score between -1.0 and $<$-2.5).

Osteoporosis: A BMD more than 2.5 SDs below young normal levels (T-score $<$-2.5).

Severe osteoporosis: A BMD more than 2.5 SDs below young normal levels (T-score $<$-2.5) and the presence of one or more fragility fractures.

The WHO definitions were intended to be used for determining the percentage of a country's population with osteoporosis. They were not intended to be used for the diagnosis of osteoporosis in individuals. They are nevertheless commonly used for this purpose in clinical practice.

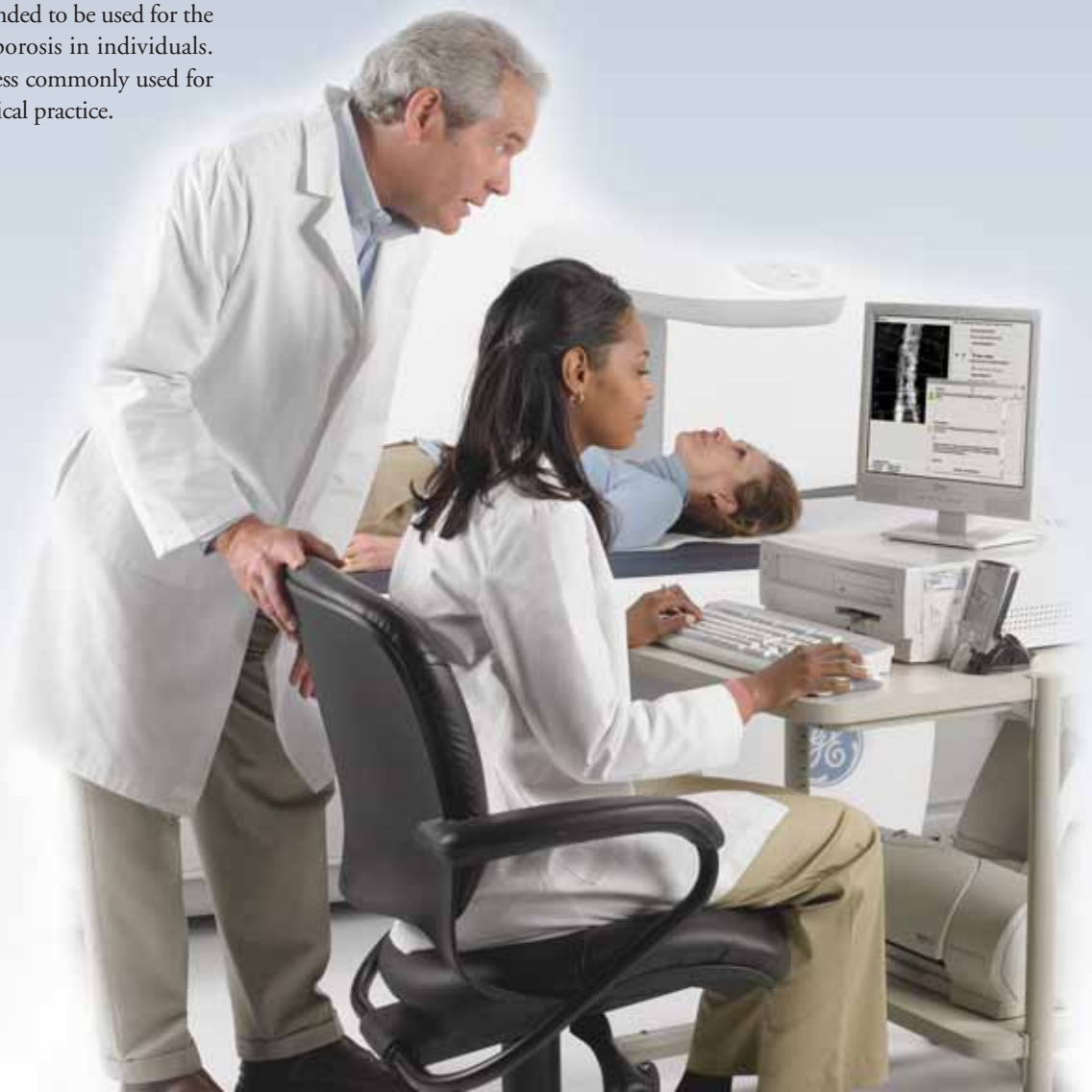
Who should receive a BMD test?

In 1998, the National Osteoporosis Foundation (NOF) in the United States, in collaboration with 10 other professional societies, created a set of guidelines for the use and interpretation of BMD measurements.[17] They recommend BMD measurements for postmenopausal Caucasian women who:

- Are under the age of 65 and have one or more additional risk factors for osteoporosis (in addition to being white, post menopausal and female).
- Are aged 65 and older regardless of additional risk factors.
- Have suffered a fragility fracture to confirm the diagnosis and determine disease severity.
- Are considering therapy for osteoporosis, if BMD testing would facilitate the decision.
- Have been on hormone replacement therapy (e.g. thyroid or corticosteroid) for prolonged periods.

At present, the NOF recommendations are limited to Caucasian women because only limited data are available for other populations. Many physicians are applying these guidelines to postmenopausal women of other races as well. In addition to the NOF recommendations, other high-risk populations should be considered for measurement. The most evident risk population includes both men and women presenting with a fragility fracture or who are taking corticosteroids.

Patients taking 7.5 mg/day of prednisone or its equivalent for more than three months should receive a BMD test and be



considered for antiresportive therapy to reduce bone loss associated with corticosteroid therapy. In addition, men with risk factors such as alcoholism, hypogonadism or radiographic evidence of bone loss, as well as men and women taking any other drugs known to influence bone density, should be considered for BMD testing.

Who should be treated?

Based on the bone density result, the NOF has recommended treatment for postmenopausal Caucasian women with:

1. BMD T-scores below -2.0 in the absence of osteoporosis risk factors, or

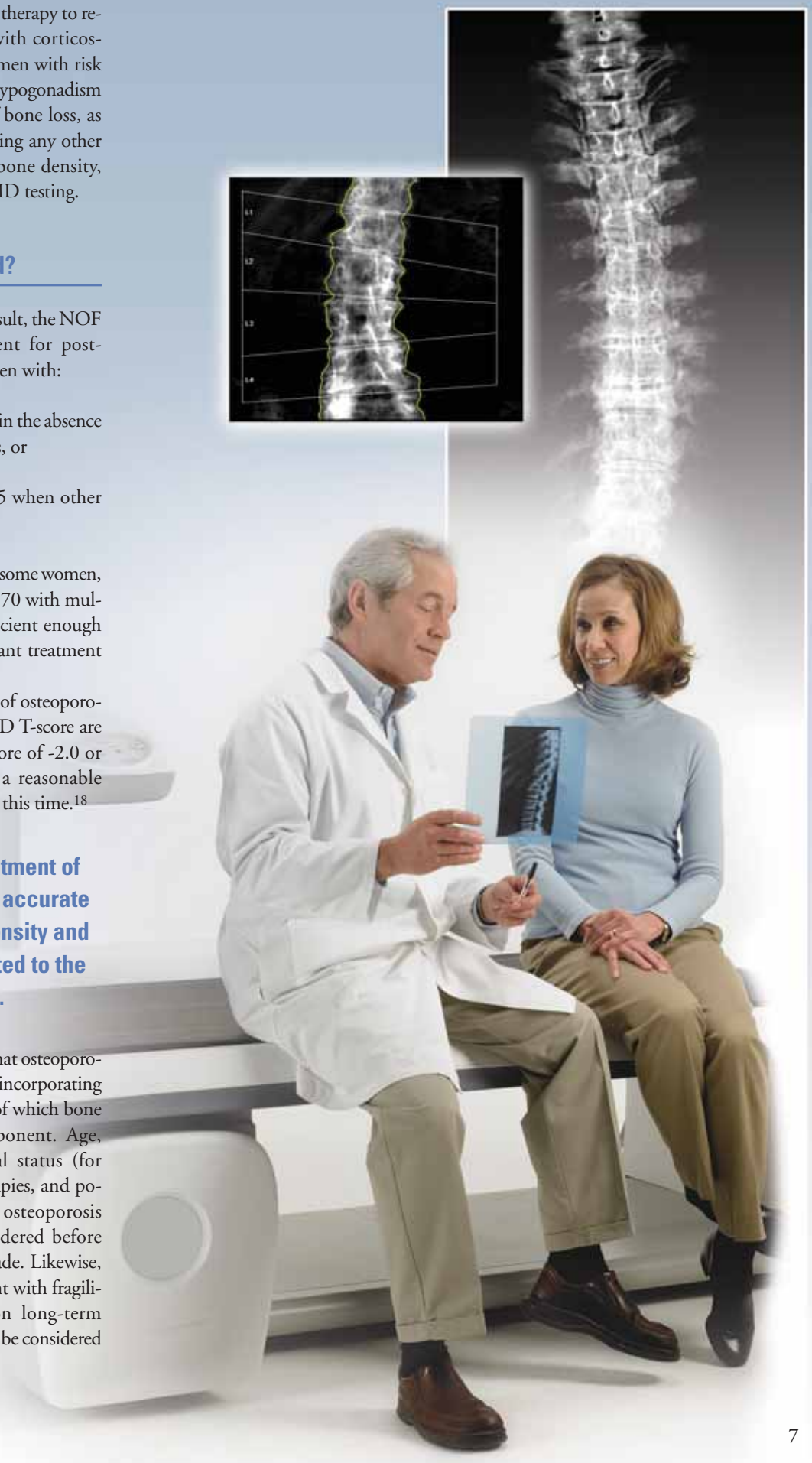
2. BMD T-scores below -1.5 when other risk factors are present.[17]

The NOF acknowledges that some women, such as those over the age of 70 with multiple risk factors, are at sufficient enough risk for osteoporosis to warrant treatment without BMD testing.

Guidelines for treatment of osteoporosis in men based on the BMD T-score are less well-defined, but a T-score of -2.0 or less has been proposed as a reasonable threshold for intervention at this time.[18]

Identification and treatment of osteoporosis requires accurate knowledge of bone density and other risk factors related to the future risk for fracture.

It is important to recognize that osteoporosis is a multifactorial disease incorporating many different risk factors, of which bone density is a primary component. Age, family history, menopausal status (for women), concomitant therapies, and potential secondary causes of osteoporosis must all be carefully considered before therapeutic decisions are made. Likewise, men and women who present with fragility fractures or who are on long-term corticosteroid therapy should be considered for treatment.



These guidelines are targeted for use with central densitometry measurements (e.g. DXA). When applied to peripheral measurements, particularly in those under 65 years of age, skeletal discordance can cause significant variation in T-scores between skeletal sites. Due to differences in skeletal aging and normative data at the different skeletal sites (Figure 2), variations of +1.0 or -1.0 or more on the T-score can be expected.

Usually it is the central skeleton that will show the first signs of age-related bone loss, so it is recommended to make treatment decisions based on the lowest T-scores at the spine or hip. In patients with low peripheral T-scores, referral for a spine/hip measurement should be considered. ww

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In February 2006, Kenneth G. Faulkner, PhD, rejoined Synarc as vice president of business development. Dr Faulkner is a co-founder of Synarc, the world's largest dedicated provider of centralized imaging and molecular marker services for clinical trials. In his new role, he will be responsible for leading Synarc's strategic alliances and expansion into new therapeutic areas.

For the past five years, Dr Faulkner has been the chief scientist for GE Healthcare in the Lunar Bone Densitometry division located in Madison, Wisc. Prior to joining GE Healthcare, he directed the osteoporosis service for Synarc until 2001.

Dr Faulkner received his PhD from the Biomedical Engineering Program at the University of California, Berkeley and San Francisco and was a faculty member of the Department of Radiology at the University of California, San Francisco, until 1992. At that time, he moved to Portland, Ore, where he directed the bone densitometry central laboratory at the Oregon Osteoporosis Center, which joined Synarc in 1998.

Dr Faulkner has published more than 75 papers related to bone densitometry, focused on the use of bone densitometry for the prevention and treatment of osteoporosis.