REVIEW
ΑΝΑΣΚΟΠΗΣΗ

# Diagnostic methods in osteoporosis

**The diagnosis and treatment of osteoporosis continue to present one of the great challenges to US health care providers. The rising costs associated with osteoporotic fractures in an aging population are increasingly difficult to deal with, while at the same time costs incurred in attempts at prevention may also seem prohibitive to those agencies which must bear them. Radiologic imaging provides the best means of both diagnosing fracture risk ard tracking the progress of therapeutic intervention. There are many monitoring options available to the clinician whose task it is to treat osteoporosis. Single and dual photon absorptiometry have largely given way to dual-energy X-ray absorptiometry which represents the most widely used means of measuring bone density. Ultrasound technology is improving and may make significant inroads in this area. Technological problems still remain to be resolved in bone density ultrasonography.**

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2000, 17(2):146–151

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Απεικονιστικές μέθοδοι στη διάγνωση της οστεοπόρωσης

*Περίληψη στο τέλος του άρθρου*

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Osteoporosis continues to be one of the great medical challenges affecting approximately 25 million of the estimated 40–50 million menopausal women alive in the USA at the present time and being responsible for over 1.5 million fractures per year.[1] While the consequences of this condition continue to plague the services with extremely high costs, nevertheless great strides have been made in both the diagnosis and the therapy of the disease. The health care expenditures in the US due to osteoporotic fractures in 1995 were estimated at approximately 13.8 billion dollars.[2] Approximately 300,000 people per year incur hip fractures with a female-to-male ratio of 2:1. Fractures of the hip cause more disability than other fractures with a 12–20% increase in mortality from related complications.[3,4] The number of hip fractures is expected to double or triple within the next quarter century[5] and over half of US women over the age of 65 will suffer osteoporotic fractures. The understanding of osteoporosis has benefitted from a renewed emphasis on the menopause in general.

Osteoporosis results from loss of bony tissue leading to diminished structural integrity and a greater susceptibility to fractures. Bone buildup reaches its peak around the mid-20s and maintains a plateau until the mid-30s. Bony tissue loss commences for both men and women at around age 35. The loss rates are always greater for women but remain more or less parallel for both sexes until the onset of menopause when true sexual dimorphism is characteristic. Around this time, in the absence of any medical intervention, female bone loss accelerates at a rate which far outpaces male bone loss and the osteopenic condition begins to take root. Increased activation of bone remodeling sites and a 20% increase in bone resorption attend the onset of menopause. This is referred to as type 1 or menopausal osteoporosis. Bone loss occurs mainly in trabecular (cancellous) bone which

is found in the vertebral bodies and in the metaphyses of long bones. Type II, or age-related osteoporosis shows less gender difference, and the bone loss involves mainly cortical bone. Type I osteoporosis lasts from age 50 to age 70 or 75 after which type II follows. The earliest consequences of type I osteoporosis are the vertebral fractures which are sustained by women shortly after the onset of the menopause, as well as the nearly 10: female to male ratio in wrist fracture incidence. A final type of osteoporosis, unrelated to type I or II, is secondary osteoporosis which may result from certain medical conditions or the use of specific drugs. Bone loss here occurs equally in men and women who typically present with vertebral or hip fracture (tabl. 1).

Concerns about both the medical and the financial consequences of osteoporosis and osteoporotic fractures, have led to an intense effort to better understand the disease. In the last 25 years important progress has been made in both the diagnosis and the treatment of osteoporosis. These efforts have led to actual reductions in fracture incidence although the real potential for benefit in this area has only been partially realized.

Part of the problem revolves around the costs involved in both the therapy and the monitoring of therapy in menopausal women. Diagnostic radiology stands at the center of a controversy which derives in a large part from fiscal considerations. In order to increase the number of women benefitting from hormone replacement therapy it is essential that the process is as rational as possible but also as cost effective as possible. While there is no doubt about the impressive progress made in the safety and efficacy of confirming the presence of osteoporosis and in monitoring the effectiveness of therapy, there is a lack of consensus on how to proceed in applying the diagnostic modalities which are available. This is to say which menopausal patients should be offered bone mineral density (BMD) or other analogous studies and how often?

**Table 1.** Medical conditions associated with osteoporosis.

| | |
|---|---|
| *Endocrine* | *Other* |
| Hypogonadism | Rheumatoid arthritis |
| Diabetes mellitus | Osteogenesis imperfecta |
| Hyperparathyroidism | Immobilization |
| Anorexia nervosa | Ehlers-Danlos syndrome |
| Hyperthyroidism/thyrotoxicosis | Marfan syndrome |
| Cushing's syndrome/ hypercortisolism | Homocystinuria |
| | Gaucher's disease |
| Acromegaly | *Pharmacologic agents* |
| *Hematologic* | Aluminum antacids |
| Leukemia | Anticonvulsants |
| Lymphoma | Cyclosporine |
| Multiple myeloma | Glucocorticoids |
| Hemolytic anemias | Cisplatin |
| Mastocytosis | Methotrexate |
| Waldenström's macroglobulinemia | Isoniazid |
| | Lithium |
| *Gastrointestinal-nutritional* | Loop diuretics |
| Inflammatory bowel disease | Thyroid hormone excess |
| Postgastrectomy | GnRH analogs |
| Hepatic insufficiency | Heparin |
| Primary biliary cirrhosis | Tetracycline |
| Malnutrition/malabsorption syndromes | Medroxyprogesterone acetate |
| Alcoholism | |
| Hypovitaminosis D | |

A great many techniques are available in the area of radiologic detection of osteopenia and osteoporosis. These include:

1. *Conventional X-ray.* This method has been largely abandoned and generally plays a role only in the occasional case in which an unsuspected significant loss of bone density may be detected in the course of another, unrelated investigation. Bone mass loss in the area of 20–50% is necessary before osteopenia is detectable by traditional X-ray methods. Even in the face of a 2–3% annual loss, too many years would have to pass before simple X-ray can be an effective diagnostic tool and therefore too many potential beneficial years of therapy would be lost.[1–6] Recently, the refinement of radiographic absorptiometry (RA) has made the analysis of a conventional image possible. Computerized processing and the use of an aluminum density standard on the film has allowed for the correction of variability of film quality and for an assessment of bone density status which is comparable in precision to results obtained with the newer, more sophisticated techniques. Currently, RA is proving to be a simple, low-cost, low-risk, technique for determination of BMD and for use as a screening tool for osteoporosis. Improvement and further investigation of RA will possibly increase its utility in diagnosing and monitoring osteoporosis.[7–10]

2. *Single-photon absorptiometry (SPA).* This is one of the older methods still in use but it remains a reliable, relatively inexpensive and relatively precise method. SPA also involves very low radiation exposure. Many SPA units were originally in use in private offices and their use is not generally thought to be in decline. SPA measures the bone mineral content of the radius, ulna or calcaneus. While density measurements in these areas correlate well with those of the spine, spinal loss occurs much earlier and spinal compression fractures may already have occurred in patients with still normal peripheral measurements.[1] SPA has been shown to compare favorably

with dual-energy X-ray absorptiometry (DEXA) in women with established osteoporosis.[11] SPA employs an iodine-125 ($^{125}$I) or americium ($^{241}$Am) source which makes its use harder to defend in light of advances made with devices employing an X-ray tube. SPA cannot distinguish cortical bone (radius, ulna) from trabecular bone and it cannot be used to measure bone mass at the hip or spine.[1]

3. *Dual photon absorptiometry (DPA).* DPA employs a gadolinium-153 source ($^{153}$Gd) which emits photons at two different energy levels thereby permitting better discumination between bone and soft tissue. It has largely replaced SPA as a standard procedure but has itself been displaced by the development of dual energy X-ray absorptiometry. DPA is relatively accurate with low radiation exposure. It is particularly useful for the lumbar spine and the femoral intertrochanteric locations, two areas quite susceptible to fractures. Pre-existing fracture sites and soft tissue calcifications are liable to confound the results. DPA is relatively time consuming compared to some other methods.[1,5,12,13] Lateral DPA, a technique which measures the BMD of vertebral bodies $L_2$–$L_4$ on a lateral projection, has been developed and this may be useful for detecting bone loss in early postmenopausal women.[14]

4. *Quantitative computed tomography (QCT).* The refinements of QCT allow for the separate assessment of trabecular and cortical densities within the same bone. QCT employs a single or dual X-ray energy source and uses a calibrated standard. In contradistinction to DPA, QCT is relatively unaffected by the presence of soft tissue calcifications and other artifacts. It may be preferable to dual energy X-ray absorptiometry (DEXA) for lateral spinal BMD measurement.[15] It has certain distinct clinical disadvantages however, such as greater radiation exposure and higher cost. Another disadvantage is that the mean values have to be created from the normal local population who need to be examined for the data base.[16] Specially designed QCT devices, which are only available commercially have been applied to the distal radius and ulna, and have the advantages of accurate measurement, low radiation dose and lower cost.

5. *Dual-energy X-ray absorptiometry (DEXA).* DEXA has largely replaced DPA as the preferred routine method for BMD measurement. It is similar to DPA in the technique of transmission scanning but the radionuclide source is replaced by an X-ray tube.[17] DEXA is more precise than DPA, with better image resolution and comparable diagnostic sensitivity.[18,19] It has the further advantage of a much shortened examination time of two minutes compared with 20–40 minutes needed for DPA.[20] It is of particular advantage for the lumbar spine and proximal femur areas and exposes patients to relatively low levels of radiation.[21] DEXA is perhaps the best absorptiometric tool of those currently available and it has become the "gold standard" for bone densitometry but there are several pitfalls with DEXA measurements.[22] The results of testing for defining both the actual status of bone density and providing a valid fracture prognosis for individual patients, must be evaluated with respect to recent World Health Organization (WHO) guidelines. WHO defines low bone density as existing when measurements range between 1 and 2.5 SD below the reference mean. Bone density below 2.5 SD is compatible with osteoporosis.[7] It has, however, been shown that even a 1 SD decrease in BMD may be associated with a 1.5–3 times increase in the relative risk of fracture.[17]

6. *Ultrasonography.* The ultrasound (US) technique has not yet gained widespread use in this field and, to some extent, is still at an experimental stage. Quantitative ultrasound (QUS) is an alternative method recently introduced to evaluate skeletal integrity at easily accessible peripheral sites and currently it is performed on the calcaneus, patella, tibia, finger and forearm.[23–25] Information regarding the material and structural properties of the bone can be obtained by estimating and counting the differences between the sound wave transmitted into a bone and the wave emerging after interaction with the bone. The velocity at which the wave travels through the skin and bone, known as the speed of sound (SOS) or US transmission velocity (UTV), and the broadband US attenuation (BUA), which is the frequency range for the transmission of US, are the basic measurements through which the outcome is expressed.[24,26]

SOS is related to the material properties of bone, such as elasticity, and BUA is related to bone structure.[27] Since QUS application is still relatively new in the areas of bone quality and fracture risk assessment, controversy exists in regard to the exact bone properties which are related to the US measurements of BUA and SOS in humans. *In vivo* studies have reported the ability of US to differentiate between subjects with fractures and those without fractures, and also to predict to a certain the extent risk of fractures. However, QUS has been shown to be inaccurate in identifying low BMD in the hip and spine in early postmenopausal women when compared to DEXA.[27]

It is still unclear whether US can replace DEXA in widespread clinical use. The absence of ionizing radiation, the rapidity of examination, and cost savings allow for the potential widespread use of QUS in managing osteo-

porosis. It may be best suited as a screening tool for osteoporosis but further research is needed in order to (a) correlate US measurement of various peripheral sites (tibia, calcaneus) with hip or vertebral fractures, (b) determine the use of the same or different criteria for diagnosing osteoporosis when using US rationalize measurement or standard bone densitometry, (c) acceptance of QUS values for clinical diagnosis of osteoporosis. There is a further need to determine the relationship between US attenuation and velocity on the one hand and structural information (skeletal density, architecture) on the other. Because the estimated odds ratios for osteoporotic fractures vary between ultrasonographic systems, comparison of results between studies may not be valid.[28]

With such a variety of methods, many choices may be open to the clinician as to methodologic preferences. Normally, however, these choices are left to the radiologist. The literature does not indicate total accord regarding many important questions such as at which sites and how these measurements should be made. Some authors, for instance, are in disagreement as to whether posteroanterior measurements are preferable to lateral measurements of the spine.[29,30] Some recommend total body DEXA as being helpful but this is rarely offered as a routine. Calcaneus measurement may still be carried out by SPA but it is generally not considered a useful adjunct to other measurements.[31,32] Measurement at any site may be equally predictive for most fractures but hip BMD measurement is the best predictor of hip fracture.[33] As stated above, a great deal of controversy exists in the area of bone loss diagnosis via bone densitometry. Selection of patients is vital under present financial conditions as there is a general consensus among practitioners that universal screening of all menopausal women is not economically feasible. A subcommittee of the Scientific Advisory Board of the National Osteoporosis Foundation,[34] supported by the published evidence,[12,35] has provided guidelines for patient selection, although even with these it will not be possible to screen all women at risk. An argument can be raised that, in the best of possible circumstances, all menopausal women would have baseline screening for bone density status and subsequent periodic testing to monitor changes in that status or to monitor the effects of therapy. This conclusion is supported by the fact that the majority of BMD loss in spinal osteoporosis occurs before the first appearance of fracture.[36] It is further supported by the fact that risk factor lists and patient history are generally poor predictors of fracture incidence.[37,38]

Recommended Clinical Uses of Bone-Mass Measurements[34] (Johnston CC Jr et al):

1. In estrogen deficient women with significant reduction of bone mass, in order to facilitate decisions regarding hormone replacement therapy.
2. In patients in whom X-ray examination has revealed evidence of significant bone loss or spinal deformity, in order to aid in decisions regarding further evaluation and therapy.
3. In monitoring of patients on long-term glucocorticoid therapy, to aid in potential adjustment of therapy.
4. In patients with asymptomatic primary hyperparathyroidism to identify those at risk for severe skeletal disease.

A particular subgroup which would seem to be well targeted for routine screening and monitoring would be the so-called "fast bone losers" (a subgroup of postmenopausal women who lose bone at an accelerated rate[39]) whose loss exceeds 3.5% per year.[40] The National Osteoporosis Foundation[12] has an expanded list of potential indications for bone mass measurement, shown in table 2. Even these recommendations may be difficult to implement in the face of resistance to routine testing. Cost variance may be confusing to the clinician who may wonder about the wide variability in pricing and its connection to the quality or usefulness of the report (tabl. 3).

**Table 2.** Indications for BMD measurements.

| |
|---|
| I. Screening for fracture risk |
| A. Unselective (mass screening) |
| B. Selected screening |
| – Patient concerns |
| – Risk factors |
| – Before starting treatment for other reasons |
| II. Diagnosing osteoporosis in patients with vertebral changes |
| III. Monitoring |
| A. Non-responders to therapy |
| B. Identifying "fast losers" |
| IV. Evaluating high-risk patients |
| A. Medications |
| – Steroids |
| – Anticonvulsants |
| – Thyroid medications |
| B. Endocrine and metabolic disorders |
| – Amenorrhea and amenorrhea/galactorrhea |
| – Hyperparathyroidism |
| – Anorexia |
| – Alcohol abuse |
| C. Skeletal factors |
| – History of multiple fracture |
| – Long-term immobilization |

Adapted from the National Osteoporosis Foundation[12]

**Table 3.** Varying costs of BMD measurements in Houston, Texas (January 1998).

| Institute | Type | Site | Costs ($) | | |
|---|---|---|---|---|---|
| | | | Exam | Interpretation | Total |
| Hospital A+ | DXA | Hip/spine | | | 300 |
| Hospital B+ | DXA | Hip-spine | 135 | 108 | 243 |
| Hospital C+ | DXA | Hip-spine | 137 | 202 | 339 |
| Hospital D+ | DXA | Hip-spine | 184 | 82 | 266 |
| Hospital E+ | DXA | Hip-spine | 200 | 30 | 230 |
| Hospital F* | QCT | Spine | | | 225 |
| Hospital G* | DXA | Hip/spine | | | 145 |

+=Not for profit
*=Private for profit

It is now widely accepted that diagnostic and therapy tracking potentials are associated with the available radiologic modalities. This is particularly important in light of the many therapeutic advances recently achieved in the field of osteoporosis. Indeed, it could be stated that more progress has been made in the understanding and treatment of this condition than in any other area related to the menopause. This would include major steps forward in all areas of diagnosis. Not only has much been achieved in the radiologic methodologies described above, but in addition significant progress has been made in biochemical testing for osteoporosis. Adding to this the most recent therapeutic breakthroughs provides an impressive picture of a disease with the potential to yield significantly to a concerted medical effort. Improvements in both the quality and duration of life would follow, along with a significant reduction in health care costs to the country.

However, caution should be exercised in ordering routine bone densiotometry. While not denying the advantages of BMD measurement, it would probably be prudent for the majority of measurements to be made in larger academic, diagnostic or research centers. It may be that chemical monitoring may eventually prove both more effective and cost efficient. This would throw the average clinician back to a reliance on history and risk factor considerations with their known shortcomings. Nevertheless, the average practitioner tends to become involved in the practice of random testing in a variety of centers, on different machnes, and of different skeletal sites, which cannot be very productive. The experimental findings and therapeutic conclusions emanating from the larger centers are far more likely to continue the advances already achieved in the USA.

## ΠΕΡΙΛΗΨΗ


### Απεικονιστικές μέθοδοι στη διάγνωση της οστεοπόρωσης

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Η διάγνωση και η θεραπεία της οστεοπόρωσης συνεχίζουν να αποτελούν μεγάλη πρόκληση για το ιατρικό, νοσηλευτικό και παραϊατρικό προσωπικό. Τα υψηλά έξοδα που σχετίζονται με τα οστεοπορωτικά κατάγματα, καθώς και τα έξοδα που δημιουργούνται στην προσπάθεια πρόληψης αυτών, δείχνουν να είναι απρόσιτα για εκείνους που θα πρέπει να τα αντιμετωπίσουν. Η ακτινολογική απεικόνιση αντιπροσωπεύει τον καλύτερο τρόπο, τόσο στην εκτίμηση του κινδύνου για δημιουργία κατάγματος, όσο και στην επιλογή της κατάλληλης θεραπευτικής παρέμβασης. Υπάρχουν αρκετές επιλογές στη διάθεση του ιατρού που θα κληθεί να διαγνώσει και να θεραπεύσει την οστεοπόρωση. Η μονοενεργειακή απορροφησιομετρία και η απορροφησιομετρία με φωτόνια δύο ενεργειών έχουν αντικατασταθεί από την απορροφησιομετρία με ακτίνες Χ δύο ενεργειών, που αντιπροσωπεύει το συχνότερα χρησιμοποιούμενο μέσο για τη μέτρηση της οστικής πυκνότητας. Η μέθοδος των υπερήχων συνεχώς εξελίσσεται και αναμένονται σημαντικές εξελίξεις όσον αφορά τεχνικά προβλήματα στη μέτρηση της οστικής πυκνότητας με υπερήχους.


**Λέξεις ευρετηρίου**: Απεικονιστικές τεχνικές, Διάγνωση, Εμμηνόπαυση, Οστεοπόρωση

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