EDITORIAL

Estimating the Risk of Osteoporosis

Generalized osteoporosis has many causes and different clinical presentations, all characterized by a loss of bone tissue to a level below that required for mechanical support of every day activities, resulting in nontraumatic fractures. Bone turnover may range from accelerated to severely reduced. Though the entire skeleton is ultimately affected, at early stages, skeletal sites with predominantly trabecular bone appear most vulnerable to bone loss. Clinically, osteoporosis is usually asymptomatic until fractures occur. The most frequent form is involutional osteoporosis. Suggested subclassifications are Type I (postmenopausal), Type II (senile) and Type III (associated with increased parathyroid function) (*1*).

By definition, established involutional osteoporosis requires the presence of insufficiency fractures on radiographs, and the exclusion of secondary causes of osteoporosis by biochemical and radiographic examinations. Therapeutic intervention can prevent accelerated bone loss, but replacement of bone once lost is generally not achievable. Therefore, the ability to diagnose osteoporosis prior to the occurrence of fracture has been in the forefront of osteoporosis research. This has not yet been achieved in the strictest sense. Instead, the strategy is to diagnose women with a high risk for skeletal fracture at the time of menopause by measuring bone mass, and, more recently, the rate of bone turnover. Both measurements provide different information. At a given time, bone mass is the result of peak bone mass achieved: a lifelong process of bone remodeling resulting in a net loss with advancing age and of possible exposure to one or more of the many osteoporosis risk factors. Bone turnover measurements, on the other hand, reflect bone turnover at the time of examination. Both low bone mass and high bone turnover are associated with increased fracture risk. Decisions on therapy designed to prevent future fractures are based on these measurements (*2*). Accelerated bone loss at low levels of bone mass requires the most aggressive therapy.

In vivo measurements of bone mass (or density) are performed by dual-energy x-ray absorptiometry (DXA) at selected skeletal sites, usually lumbar spine or proximal femur, less often the radius or calcaneus. Bone strength is closely correlated with its bone mineral density (BMD, g/cm^2). Overall, 75%–85% of the variance in the strength of bone tissue is accounted for by changes in BMD; the remainder is due to qualitative changes in bone composition and bone structure (trabecular thinning, cortical porosis). In recent years, prospective studies have shown that BMD can predict fracture risk, with an approximate doubling of risk for hip fracture for each standard deviation decline in bone mass (*3–12*). Assessing fracture risk on the basis of bone mass provides the opportunity to initiate preventive intervention before fracture has occurred. Bone mass measurements are not disease-specific. For example, osteoporosis and osteomalacia are indistinguishable.

Bone turnover can be estimated qualitatively by histomorphometry on iliac crest biopsy specimen. However, this procedure is invasive, the interpretation is complex and the skeletal sample may not uniformly reflect the entire skeleton. Studies of calcium kinetics are cumbersome, time-consuming and restricted to research. Repeated measurements of bone mass by DXA give useful estimates of bone loss in percent/year if measurements are conducted over 2–3 yr. This is unsuitable for management decisions at the time of diagnosis but useful for follow-up. Bone turnover can also be assessed by measuring chemical products associated with specific bone cell function or by measuring components of bone matrix released into blood or urine (Table 1). These biochemical markers of bone turnover are more readily available for clinical practice than the complex procedures. There are good markers for bone formation (osteocalcin, alk. phosphatase). However, for bone resorption (the major abnormality in osteoporosis), the presently available biochemical marker (hydroxyproline) is rather nonspecific. Newer markers of bone resorption such as pyridinoline crosslinks in the urine are promising to fill this gap in the near future. Clinical relevance of biochemical markers has been established by correlation with histomorphometry, studies of calcium kinetics and investigations of the cellular origin of the marker, their metabolism and excretion.

Bone remodeling during life follows predictable patterns which have been documented by histomorphometry, calcium kinetic studies and biochemical marker studies (*13–15*). In established involutional osteoporosis, patients may present with either high, normal or low bone turnover (*16,17*). High turnover (active osteoporosis) is more often seen in the early onset of menopause (Type I osteoporosis) and in elderly people with elevated PTH levels and hip fracture (Type III osteoporosis). Normal turnover (inactive osteoporosis) may represent a patient with low bone mass prior to menopause with normal estrogen-dependent bone loss during menopause. Low bone turnover (burnt out osteoporosis) is most frequently found in the elderly with Type II osteoporosis. A combination of a single measurement of serum osteocalcin, urinary hydroxyproline and D-Pyr can predict the rate of bone loss ($r = 0.77$) as estimated by DXA over 2 yr (*14*). Hansen et al. have shown that women who are identified as fast losers at the

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TABLE 1
Biochemical Markers of Bone Turnover

Bone turnover	Marker	Source	Remarks
Bone formation	Alkaline phosphatase (bone-liver-kidney isoform)	Serum	1. Direct promoter of mineralization via release of inorganic P into matrix. 2. Indirect stimulator of hydroxy apatite crystal formation.
	Osteocalcin (gla-protein)	Serum	Noncollagen protein of bone matrix produced by osteoblasts; 10%–25% escapes into the circulation.
	Carboxy terminal propeptide of Type I procollagen	Serum	Cleaved from procollagen prior to fibril formation. Amount proportional to bone matrix synthesis.
Bone resorption	Hydroxyproline	Urine	Product of collagen breakdown, about 30% of total is from bone collagen break down. Low specificity.
	Serum tartrate resistant acid phosphatase	Serum	Bone isoenzyme, specific marker of osteoblastic activity and bone resorption.
	Hydroxylysine glycosides	Urine	Reflects bone matrix breakdown.
	Pyridinoline crosslinks hydroxylysyl-p (Pyr) lysyl-p (D-Pyr)	Urine	Collagen crosslink metabolites, reflect the amount of bone collagen resorption.

time of menopause lose bone at an accelerated rate over 12 yr (*18*), which suggests that the accelerated loss is not just an accentuated short-term menopausal bone loss.

Quantification of skeletal uptake of ^{99m}Tc-labeled diphosphonates has also been evaluated to assess bone turnover. Many different technical approaches have been described over the years (Table 2). The complex uptake mechanism of the radiopharmaceutical has so far defied an explanation of what specific phase of bone turnover is actually measured. Known contributing factors to ^{99m}Tc-diphosphonate uptake are blood flow, capillary permeability, local acid-base relationship, quality of mineralizable bone, bone turnover, hormones, vitamins and renal function. Increased diphosphonate uptake and typical scintigrams have been described in a number of metabolic bone diseases (*19–21*). However, in the diagnosis or management of idiopathic osteoporosis, the information provided is less reliable than assessment by standard radiographs (*22*). A "washed-out" pattern has been described on scintigrams and has been related to "end stage" disease with a low bone mass and low bone turnover. Sy (*21*) observed these features in 72% of his patients with osteoporosis, Fogelman (*22*) in a smaller number. In all series, a few patients demonstrate increased skeletal uptake. These patients have been thought to have high rates of bone turnover, extensive bone involvement, or other etiologic factors that contribute to bone loss. In a study of 53 postmenopausal osteoporotic women, the mean value of ^{99m}Tc-MDP whole-body retention was higher ($p < 0.01$) than it was in 24 age- and sex-matched normal controls, as was osteocalcin and urinary hydroxyproline (*17*).

Clinical usefulness of diphosphonate uptake has never been demonstrated for osteoporosis work-up and management, and interest in this technique justifiably declined when assay procedures for biochemical markers became available. The latter procedures are comparatively inexpensive, more readily available to the endocrinologist, of better known specificity and more applicable to screening menopausal women.

In this issue of the *Journal*, Israel et al. (*30*) introduce another technique to measure ^{99m}Tc-diphosphonate uptake, which makes use of bone scans. The authors, however, do not supply convincing evidence that regional skeletal uptake of ^{99m}Tc-diphosphonate is more specific than total-body uptake or biochemical markers to identify fast bone losers, nor that increased diphosphonate uptake in the hip corresponds with local or general-

TABLE 2
Proposed Methods for Quantitative Evaluation of ^{99m}Tc-Diphosphonate Uptake in Bone

- Visual inspection of bone scintigrams (*20,22*)
- Ratio measurements with use of bone scintigrams
  - Comparison with presumably normal bone
  - Comparison of bone and soft tissue
  - Comparison with a simultaneously imaged phantom (*23*)
- Regional blood flow and clearance measurements (*24,25*)
  - Early vascular phase
  - Early uptake phase
  - Above with correction for glomerular filtration rate
- Whole-body retention at 24 hr (*26,27*)
  - Whole-body counter
  - Gamma camera
  - Thyroid-uptake probe (*28*)
  - 24-hr urine collection
- SPECT
  - Skull uptake (*29*)

Modified from Mazess RB, Wahner HW (Reference 19).

ized fast bone turnover. Diphosphonate uptake as a measure of markedly altered skeletal metabolism in focal bone lesions has been evaluated in the past to quantitate extension of metastasis (tumor burden to bone) and treatment response, for example in Paget's disease (*31–34*). In this latter application, diphosphonate uptake could conceivably have clinical applications other than osteoporosis because measurements of biochemical markers and bone mass are of limited use in focal disease.

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