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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

T Scores and Osteoporosis



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INTRODUCTION

In 1994, a working group of the World Health Organization (WHO) put forth an operational definition of osteoporosis based on bone mineral density.¹ The purpose of the WHO definition was to develop a framework to allow collection of epidemiological data in order to convince government and public health authorities that osteoporosis was a serious health problem. The WHO classification compares an individual's bone mineral density (BMD) with the young normal mean value and expresses the difference as a standard deviation score (e.g., "0" is equal to the young adult mean value, +1 is one standard deviation above the young adult mean, -1 is one standard deviation below, etc.). This unit of measure has since come to be known as the T score. The WHO definition of osteoporosis is shown in Table 1.

The T score is calculated using the following formula:

$$\frac{\text{Patient's BMD} - \text{Young Normal Mean}}{1 \text{ Standard Deviation of Young Normal}}$$

Table 1. World Health Organization (WHO) criteria for diagnosing osteoporosis using bone density measurements. Units are standard deviations below (minus sign) the young adult mean value.

	T score
Normal	Not more than -1.0 SD below the young adult mean
Osteopenia	Between -1.0 and -2.5 below the young adult mean
Osteoporosis	More than -2.5 below the young adult mean
Severe or established osteoporosis	More than -2.5 below the young adult mean with a fracture

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For example, if a patient has a BMD of 0.700 g/cm², the young normal mean is 1.000 g/cm², and the young normal standard deviation is 0.100 g/cm², then this patient's T score would be [(0.700 minus 1.000) divided by 0.100] or (-0.300 divided by 0.100) or -3.0.

Why was the T score concept developed?

T scores are used in self-defense. If there were only a single device for measuring bone density, and only a single skeletal site that was measured, absolute bone mineral density (BMD) numbers, in g/cm², would be used. Few if any clinicians are able to remember ideal or threshold cut-point values for the spine, femoral neck, total hip, etc., for a single machine, much less values from machines that are calibrated differently. Theoretically, the T score provides a way of using a single set of numbers for all devices and all skeletal sites.

Why not Z scores instead of T scores?

Z score is a standard statistical concept. Applied to BMD, Z score compares an individual with age-matched norms. While useful in determining how an individual's BMD compares with what is expected, use

FROM THE EDITOR

David F. Archer, M.D.

This issue of *Menopausal Medicine* focuses on diagnosis, monitoring, and treatment of low bone density with three outstanding articles.

Nelson B. Watts, M.D., explains the origins and interpretation of the T score in assessing bone mineral density with dual energy X-ray absorptiometry. The validity of the World Health Organization criteria for osteoporosis is contrasted with the risk of fragility fracture. A reasoned appeal is made to not use the term "osteopenia" since it is too broad for clinical interventions and requires correlation with clinical findings. Dr. Watts raises a question on using T-score or T score. *Menopausal Medicine* has opted for T score after consideration of the well-known G force.

Michael Kleerekoper, M.D., returns to *Menopausal Medicine* to enlighten us on the value of serum markers for bone turnover. DEXA technology can give us a static determination of bone density, but bone markers provide a more dynamic and readily available index of bone turnover. This allows the physician to monitor the results of a therapeutic intervention at a shorter interval rather than waiting one year or longer for the DEXA results. The figures of bone remodeling reflect the current state of knowledge in the field.

Socorro J. Vargas, M.D., and Edward G. Lufkin, M.D., provide us with information on the first commercially available medication for the stimulation of osteoblasts. Teriparatide is a fragment of the endogenous parathyroid hormone, which has been found to improve bone density and reduce fracture risk in osteoporotic men and women. The clinical utility of this preparation for older individuals is significant and represents the commercialization of a basic physiologic observation, that parathyroid hormone can be anabolic.

Menopausal Medicine

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of Z scores in an older population would result in the prevalence of osteoporosis remaining constant over time (i.e., giving the impression that an 80-year-old with a normal Z score is really "normal" in terms of bone health).

Why was -2.5 selected as the cut-point?

The WHO working group selected a T score of below -2.5 to define osteoporosis because "such a cutoff value identifies approximately 30% of postmenopausal women as having osteoporosis using measurements made at the spine, hip, or forearm. This is approximately equivalent to a lifetime risk of fracture at these sites. When measurements are made at the hip alone, then the prevalence is about one in five white women, comparable to the lifetime risk of a single osteoporotic fracture, such as a hip fracture." Figure 1 shows the prevalence of osteoporosis based on the WHO criteria and the lifetime risk of fractures.

APPLICATION OF THE WHO CLASSIFICATION

When does the WHO classification work well?

Although it was not intended that the WHO classification be applied to individual patients, it works well to define "normal" (T -1.0 and above) and "osteoporosis" (T -2.5 and below). Several large studies have shown a high risk of fracture in patients who have T scores of -2.5 and below and a significant reduction in fracture risk with treatment, making this threshold an "evidence based" criterion for the diagnosis of osteoporosis and for the initiation of treatment.

LIMITATIONS OF THE WHO CLASSIFICATION

What are the limitations of the WHO classification?

Fracture risk is continuous; there is no magic "fracture threshold." Marshall and colleagues performed a meta-analysis of 11 prospective cohort studies involving 90,000 person-years of observation and more than 2000 fractures. BMD was measured at a

variety of skeletal sites (distal radius, proximal radius, calcaneus, PA spine, femoral neck). BMD at baseline was correlated with fractures that occurred during the prospective observation period. The correla-

tion was remarkably consistent; that is, for each standard deviation decrease in BMD, regardless of the skeletal site measured, the risk of any osteoporotic fracture increased approximately 50% (the prediction of hip fracture is better for hip BMD measurement than for other sites). Thus, any system that sets an arbitrary cut point will inevitably "misclassify" some patients. Nevertheless, it helps clinicians to think categorically (i.e., "normal" vs. "osteoporosis").

Although it is sometimes useful to think categorically when dealing with a continuous variable, the category of "osteopenia" creates problems in at least two ways. First, many subjects who are in the upper part of this borderline range are perfectly normal. Applying a medical label such as "osteopenia" to a healthy young person can create considerable anxiety that may last lifelong. Second, subjects who are in the lower part of this range are almost as likely to fracture as patients on the lower side of the arbitrary cut point (perhaps more likely to fracture, depending on other risk factors for fracture). I try to avoid using the term "osteopenia" in patient care, and prefer to say that people in this category have "low bone mass," a nonjudgmental term that forces the clinician to think. Apparently healthy patients in the upper part of this range should usually be reassured then monitored perhaps every five years or so. Patients in the lower part of the range should at least be monitored more frequently, and may even be candidates for intervention, depending on how low their BMD is and the presence of other risk factors.²

Often ignored is the WHO category of "severe" or "established" osteoporosis, meant to apply to patients who have already fractured. Although a fragility fracture, particularly a vertebral fracture, is a strong predictor of future fracture, this is true whether the T score is -2.6 or -2.4 . In fact, there is an apparent contradiction: most patients who have fragility fractures have T scores above -2.5 ! Patients without fractures but with T scores of -2.5 or below are clearly at high risk of fracture; however, that is a

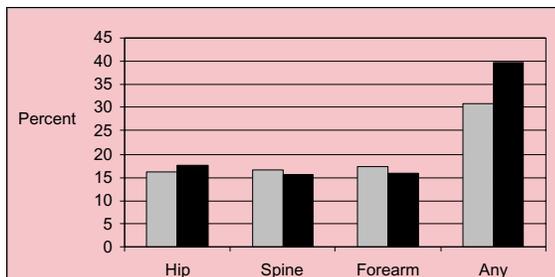


Figure 1: In postmenopausal Caucasian women, the prevalence of osteoporosis based on BMD testing at specific sites (T score -2.5 or below) is shown as gray bars, and the lifetime risk of fracture for specific sites is shown as black bars. Adapted from (11;11;12)

small percent of the population. Although the fracture rate is lower in the group with "low bone mass," there are so many more subjects with "low bone mass" than with "osteoporosis" (using the WHO classifica-

tion) that the absolute number of fractures is greater in the group with low bone mass. It is possible that some clinicians would not diagnose osteoporosis in a patient with a fragility fracture but with a T score above -2.5 ! I am not in favor of adding a category of “severe osteopenia” for patients with borderline low bone mass and fragility fractures; in my view, these patients have osteoporosis. In fact, a patient with low bone mass and fragility fracture is much more likely to fracture in the future than a patient with WHO-defined osteoporosis but without a fragility fracture.³

T SCORE DISCREPANCIES

There are also problems with using the WHO cut-points for measurements made at different skeletal sites. When the WHO working group selected -2.5 as the cut point to define osteoporosis, they considered measurements only at the hip (femoral neck), PAspine, and forearm. Other skeletal sites, such as the calcaneus, finger, hand, etc., are now being measured. Different technologies are used to measure the same sites. This calls into question whether or not a cut point of -2.5 has the same implications at all skeletal sites and for all devices. Is the prevalence of low bone mass similar? Is the risk of fracture similar?

A study by Greenspan et al.⁴ (Figure 2) showed a similar and appropriate prevalence of osteoporosis ($\sim 20\%$ - 30%) based on measurements made at the AP spine, total hip, and forearm, but a much higher prevalence ($\sim 65\%$ - 75%) for measurements made at Ward’s region of the hip or at the lateral spine. Clearly, using a cut-point of -2.5 or below at Ward’s region or the lateral spine (or quantitative computed tomography [QCT] for that matter) results in an over-diagnosis of osteoporosis. On the other extreme, quantitative ultrasonometry of the calcaneus identifies only about 5% of a postmenopausal Caucasian population at -2.5 or below, resulting in the under-diagnosis of osteoporosis.⁵

Possible explanations for these discrepancies include artifacts (such as degenerative change, fractures, etc., commonly seen in the spine) that will elevate BMD values, differences in means and standard deviations for the normative databases, technical variations, and regional differences in the rates and times of bone loss. “Normal populations” are different for different devices (and even for different sites using the same device), with different mean

and standard deviation values as a result of different inclusion and exclusion criteria and different statistical modeling. This means that a patient can have the same site measured on two different devices and have significantly different T scores. Normative data may change, as happened when one manufacturer replaced their own database with that of the National Health and Nutrition Examination Survey (NHANES).⁶ T scores at the femoral neck “improved” by about 0.7 T score “units” for the same BMD. For this reason, absolute BMD (in g/cm^2), not T scores, should be used to monitor patients over time.

peak bone mass (T score of 0 at all sites) at age 30 and loses 30% of their bone mass over time, would go to a T score of -1.5 at the heel, -2.0 at the hip, -3.0 at the spine, and -5.0 at the forearm! This variability in SD (i.e., more bone loss needed to change 1 T score “unit” at the heel than at the forearm) explains much of the discrepancies between devices and sites shown in Figure 2.

Some skeletal sites are more predictive of fracture than others.⁷ The predictive value of BMD per SD unit is different at different sites. Figure 3 shows the relative risk of hip fracture based on BMD measurement using measurements with different predictive power. It is apparent that hip BMD is the most predictive site for hip fracture, especially for patients with low BMD.

POSSIBLE SOLUTIONS

T score discrepancies

It is clear that the same T score does not have the same implication in terms of either prevalence or fracture risk at different sites and for different devices. The T score concept is flawed as the basis for diagnostic equivalence. A new paradigm is needed. At least one group has been working on this since 1998, but not specific recommendations have been published.

Possible solutions to the problem of a cut-point for a variety of devices and sites include adjusting BMD results to provide equal prevalence of low bone mass⁸ or adjusting BMD results to provide equal fracture risk. An adjustment based on equal prevalence is deceptively simple. Although it would be relatively easy to come up with a cut point that defined the appropriate percentage of the population, the risk of fracture for these groups would vary quite widely. The alternative, to adjust BMD results to provide equal fracture risk, is more appealing, but also more difficult to

implement. It is necessary to decide which type of fracture to consider (hip, spine, any?), what time horizon (one-year, five-year, 10-year, lifetime?), and what population (younger women, older women, men?).

One group has suggested using the five-year hip fracture risk of Caucasian women age 65 and over and using femoral neck BMD as the “gold standard” to anchor the fracture risk for other devices to a T score of -2.5 at the femoral neck.⁹ The practical effects of this “T score equivalents” approach are shown in Table 3. The “T score equivalents” approach still leaves discrepancies in the prevalence of osteoporosis.

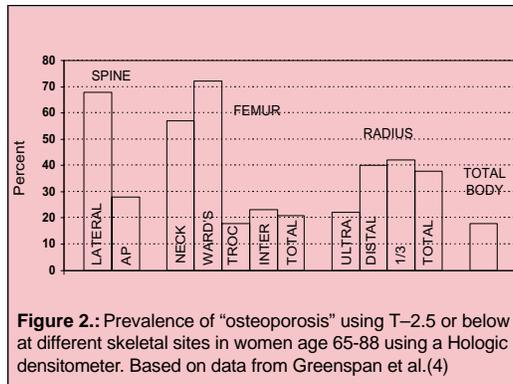


Figure 2.: Prevalence of “osteoporosis” using $T \leq -2.5$ or below at different skeletal sites in women age 65-88 using a Hologic densitometer. Based on data from Greenspan et al. (4)

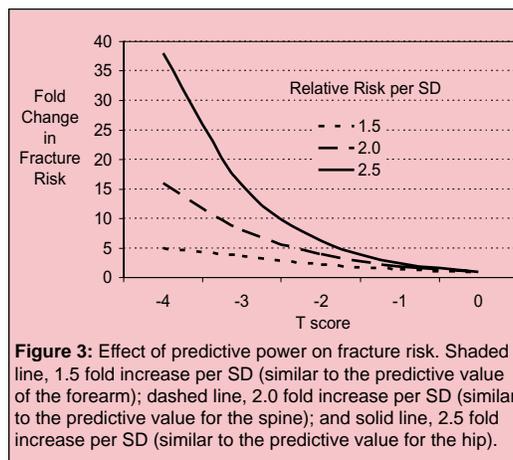


Figure 3: Effect of predictive power on fracture risk. Shaded line, 1.5 fold increase per SD (similar to the predictive value of the forearm); dashed line, 2.0 fold increase per SD (similar to the predictive value for the spine); and solid line, 2.5 fold increase per SD (similar to the predictive value for the hip).

Standard deviations (SD, expressed as a percent of the young-adult mean) differ considerably between skeletal sites, as shown in Table 2. Thus, someone who has a normal

Table 2: Difference in standard deviations (SD) in BMD at different skeletal sites, and the effect of this difference on T scores in an individual who is 30% below the young normal mean BMD at all these sites.

	SD*	T score**
Forearm	$\sim 6\%$	-5
Spine	$\sim 10\%$	-3
Hip (femoral neck)	$\sim 15\%$	-2
Calcaneus (ultrasound)	$\sim 20\%$	-1.5

*SD expressed as percent of young normal mean
**T score as a result of 30% bone loss

So what should we be doing now?

It is perfectly acceptable to continue using T scores based on measurements of the PA spine and proximal femur (excluding Ward's region) to define "normal" and "osteoporosis" in postmenopausal Caucasian women who have not yet fractured. The term "osteopenia" should be eliminated in the context of BMD testing, and replaced with "low bone mass." Patients with low bone mass and fragility fractures have osteoporosis, and should be treated. Apparently healthy subjects in the upper range of "low bone mass" should be reassured and monitored periodically; those in the lower range deserve consideration of pharmacologic intervention.

The WHO criteria should not be applied to sites other than the PA spine, proximal femur, or forearm. Absolute BMD rather than T scores should be used for monitoring BMD over time.

T SCORE TRIVIA

Why is it called a "T" score?

Although the Z score exists in standard statistics, the T score does not. Where did the term come from? And why is it called a "T" score, and not a "B" score (for bone) or "O" score (for osteoporosis)? After some investigation, I learned that Robert Neer, a clinician and researcher at Harvard and the Massachusetts General Hospital, coined the term. I contacted him and received the following response:

Yes, I first suggested the term T score.

This occurred during an afternoon conversation in my bone density lab with Tom Kelly.

At that time, my lab had for many years reported forearm BMD results to physicians as an absolute number, along with the mean and SD for young adults. Although our Lunar single photon forearm densitometer printed BMD results as a percentage of young normals (i.e., "90% of young normals"), my lab never transmitted that print-out to physicians because the wording suggested that such a

patient's BMD was at the 90th percentile for young normals, whereas in truth such a BMD was about 1 SD below the mean for young normals, near the 65th percentile. In my own practice I calculated in my head a Z score for the comparison with young normals, based on my knowledge that for young normals, 1.0 SD was about 10% of the mean BMD. Tom and I

felt a need to help other physicians make the same comparison and understand its separateness from the comparison with age-matched adults.

All labs in our hospital use 95% confidence limits to define a "normal range," and when comparing BMD results to age-matched normals, we calculated a standard deviation score (i.e., "the result is 2.2 SD below the mean for this age and sex"). Some labs were then already using the term Z score to denote this comparison with age-matched individuals, and physicians were generally familiar with the term Z score as shorthand for a standard deviation score. I decided that we needed to use Z score for the comparison with age-matched controls, and devised an analogous term for the comparison with young adults. I suggested "T score" because a hospital physician had recently asked me to convert SD scores to percentiles on our reports, and I was then trying to decide whether I should use Student's t-distribution or Gauss's Z-distribution for this conversion. I also suggested "T" to amuse Tom, whose name begins with T.

Tom Kelly was a major participant in the initial evaluation of DXA, as a technician in my lab, where Hologic put their fourth instrument. Tom subsequently moved to Hologic; Hologic immortalized the term T score by including it, and Z score, on their print-outs!¹⁰

Should it be "T score" or "T-score"? Does it need a hyphen?

I first tried a literature search using PubMed and Ovid, but, with both search engines, retrieved the same number of citations using "T score" and "T-score." I then examined abstracts and full text articles. I found 29 journals that used T-score (with a hyphen), 25 that used T score (without a hyphen), and four used it both ways. A few used lower case "t," which may have been an artifact of entering the text into Web-accessible format. Journals that consistently use T-score (with

a hyphen) include the *Annals of Internal Medicine*, *Osteoporosis International*, and *Journal of Clinical Densitometry*. Those that consistently use T score (without a hyphen) include the *New England Journal of Medicine*, *JAMA*, *Archives of Internal Medicine*, *American Journal of Medicine*, *British Medical Journal*, *Lancet*, and *Bone*. I conclude that T score can be used with or without the hyphen, and look forward to finding out how this is handled by *Menopausal Medicine*.

What is missing in the WHO classification?

Missing in the WHO classification is how to classify someone whose T score is -1.0 or -2.5. The WHO classification says that normal is "not more than -1.0 SD below the young adult mean," osteopenia is "between -1.0 and -2.5 below the young adult mean," and osteoporosis is "more than -2.5 below the young adult mean." That means that T scores of -1.0 and -2.5 are not included in the WHO criteria. The ISCD suggests that -1.0 and above be considered normal, and -2.5 and below be considered "osteoporosis."

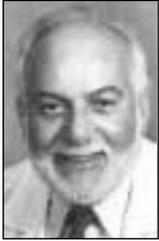
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Table 3. The effects on prevalence of "osteoporosis" of adjusting cut-points for different devices to the five-year hip fracture risk associated with a Tscore of -2.5 at the femoral neck for women age 70. From data presented by Black et al.⁹ BMD is the bone mineral density at which 5-year hip fracture risk is equivalent for these sites and devices. Tscore is the Tscore for each device calculated in the standard manner (femoral neck was selected at the standard, so by design is -2.5). Prevalence is the percentage of a population of Caucasian women, age 70, that would be designated as having osteoporosis using a cut-point at the designated BMD level (Tscore "equivalent" to -2.5 at the femoral neck).

Site	BMD (g/cm ²)	T score	Prevalence
Femoral neck	0.577	-2.5	24.5%
Radius (DXA)	0.383	-3.6	5.0%
Heel (ultrasound)	0.331	-1.9	13.3%

Use of Bone Markers in the Management of Women with Low Bone Density



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BONE REMODELING

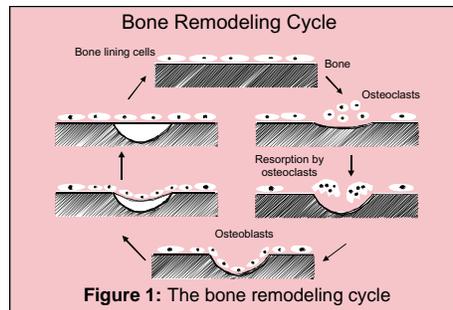
Bone is a structural tissue and, in common with all structural materials, is subject to fatigue damage. If allowed to accumulate without repair, this damage propagates and results in fracture. The ability to self-repair this fatigue damage is unique to the skeleton and limits the risk of fatigue fracture. The process of self-repair is bone remodeling with removal of older bone (resorption) and replacement with new bone (formation).

Resorption and formation are coupled and bone remodeling always begins with resorption, which takes place only on skeletal surfaces and in healthy individuals proceeds for approximately 10 days during which a 50 μ deep resorption cavity is formed. The presence of a resorption cavity on a skeletal surface such as a trabeculum of cancellous bone acts a site where stress is concentrated and the skeleton is weakened, albeit transiently.

The cells responsible for resorption are osteoclasts. During the resorption phase of bone remodeling, osteoblast precursors are recruited and mature, and bone formation begins when the resorption cavity is complete. Bone formation is much slower than resorption and takes place over approximately 90 days in healthy individuals. Formation begins with deposition of bone matrix, 90% of which is type I collagen, from the bottom of the resorption cavity toward the original trabecular surface. This is followed by mineralization of this matrix with hydroxyapatite, again from the bottom of the cavity toward the original surface (Figure 1). During growth, bone remodeling is accelerated and formation exceeds resorption resulting in net accumulation of bone. Remodeling is greatest during early infancy, increases again during the pubertal growth spurt, and returns to basal levels during the third decade.

For the next decade or two, resorption and formation are in balance with no net loss or gain of bone. After age 50, approximately, and for unidentified reasons, resorption slightly exceeds formation at each remodeling cycle resulting in net negative bone balance – “age-related” bone loss which is universal in humans.

Many circumstances can accelerate the bone remodeling process in adults. With each cycle resulting in a net negative balance anything that accelerates the rate of remodeling also accelerates bone loss. Menopause is just one such circumstance but since it occurs in all women who live long enough, it is the most prevalent cause of accelerated bone loss. This, together with a lower peak bone mass (than men) is why osteoporosis is most prevalent in post-menopausal women. Two independent lines of evidence point to increased rates of bone remodeling as an independent predictor of risk of fracture^{1,2} and, as detailed below, information about both bone density and bone remodeling provide additive information about risk of fracture.³



BIOCHEMICAL MARKERS OF BONE REMODELING MARKERS OF RESORPTION

The markers of bone resorption are breakdown products of bone. Both bone mineral, mainly calcium, and bone matrix, mainly type I collagen, are broken down and released into the circulation. The fasting urine calcium: creatinine ratio is increased

on average in patients documented by other means to have rates of bone remodeling post-menopause, but this test is too non-specific and insensitive to be of much clinical value in individual patients. Type I collagen consists of two $\infty 1$ and one $\infty 2$ molecules in a triple helix arrangement. At the amino- and carboxy-terminal ends of the triple helix is a straight portion of the molecule known as telopeptides. The telopeptide of one molecule of collagen is linked to the helical portion of an adjacent molecule by the pyridinium cross-links deoxypyridinoline (DPD) which is more specific for type I collagen and pyridinoline (PYD) which is the more abundant cross-link but less specific for type I collagen of bone (Figure 2). Levels of the amino-terminal telopeptide (NTX), carboxy-terminal telopeptide (CTX), DPD, and PYD are all increased in the circulation during resorption and rapidly filtered by the kidney where they can be measured in the urine. Until recently, assays were only available for urine measurements, giving rise to problems with both specimen collection and laboratory analysis. Most recently, sensitive serum assays for NTX and CTX have become available^{5,6}, even on automated platforms in larger reference laboratories.⁷ This has dramatically reduced assay problems and resolved some of the specimen collection issues. However, there is considerable diurnal variation of the entire bone remodeling process so that the specimen least affected by issues of food intake and diurnal variation remains the early morning fasting blood sample.

Markers of bone formation

Bone specific alkaline phosphatase (BSAP, BAP) and osteocalcin (OCN) are secretory products of the osteoblast that can be readily measured in serum as markers of bone formation. As serum assays they do not have the problems that plague urine based assays and there is very minimal diurnal variation in blood levels. However there are important shortcomings for both markers. BSAP can be measured by either immunoradiometric assay or enzyme immunoassay, but each assay has approximately 15% cross-reactivity with hepatic alkaline phosphatase. In practice this cross-reactivity poses little problem particularly when serial measurements are made.

OCN poses more problems for pathophysiologic and analytic reasons. OCN is secreted by the osteoblast but is also incorporated into the bone matrix from which it is released during bone resorption. OCN should more properly be termed a marker of bone turnover than a specific marker

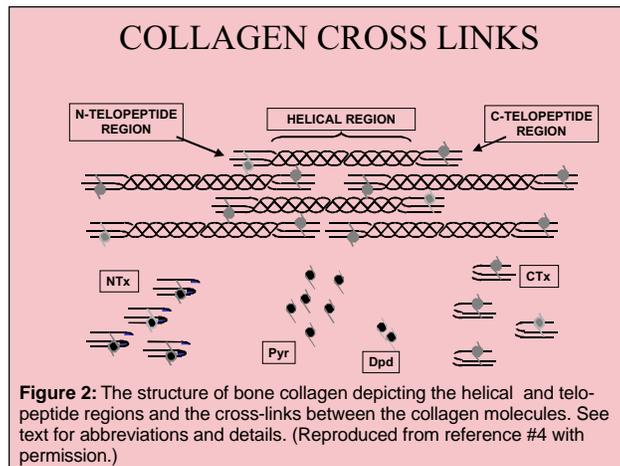


Figure 2: The structure of bone collagen depicting the helical and telopeptide regions and the cross-links between the collagen molecules. See text for abbreviations and details. (Reproduced from reference #4 with permission.)

of bone formation and this might offer an advantage to OCN measurements. Against this there are numerous assays available for OCN, OCN fragments, and varying degrees of carboxylation of OCN. The literature on bone remodeling has used these assays almost interchangeably, resulting in observations that are sometimes difficult to interpret. In clinical practice, provided the physician has assurance that the same assay is used for all his/her patients and that serial measurements are also performed using the same assay, OCN can provide information about bone remodeling that is as reliable as the other markers of resorption and formation.

Since resorption and formation are coupled and loss or gain of bone is a function of the balance between the two processes, it would be ideal to use a marker of resorption and formation and a formula that permits an estimate of the balance. Regrettably, while several models have been proposed, none really has found a role in day-to-day clinical practice.

**Clinical utility of the markers:
Selecting patients for therapy**

For patients who have not yet sustained their first fragility fracture, the short-term two to three years) risk of sustaining a clinically relevant fracture is quite low, even when the bone mineral density (BMD) is already below a T score of -2.5. In general the younger the patient, the higher the BMD, the lower the short-term risk of fracture, and vice versa. At the menopause, if the BMD T score is between -1.0 and -2.5 (low bone mass or osteopenia) the short-term goal is to prevent bone loss, not prevent fracture. A four-year prospective study completed in Europe demonstrated that early postmenopausal women in whom the value for any of the markers of resorption or formation was still within the reference interval for premenopausal women, bone loss was <1% over the four years. These women would probably derive little benefit from anti-resorptive therapies aimed at preventing bone loss. In those women in whom one or more of the markers were above the premenopausal reference interval, the rate of bone loss was 2% or faster (Figure 3).⁸ Anti-resorptive therapy would be most effective in this group, particularly those in whom BMD was also at the lower end of the spectrum. Additional data indicate that biochemical markers can be useful in predicting rates of loss in older women as well.⁹

The phase of accelerated bone loss at the menopause is short-lived (five to seven years) before reverting to the slower rate of age-related bone loss.¹⁰ There is a suggestion that the rate of loss accelerates somewhat after age 75¹¹ and that this can be evaluated biochemically,¹² but these data are less secure.¹³ As has been noted in the introduction the rate of bone remodeling is an independent predictor of short-term fracture risk in older (> 70) women and biochemical markers of bone remodeling can predict hip fracture risk almost as well as can hip BMD measurement in some epidemiologic studies. The information from the two sources (BMD and marker) is additive.¹⁴ If a decision about the need for therapy is not clear-cut on the basis of history, physical examination, and BMD, measurement of one or more markers can provide additional decision-making information. Using markers to

make yes/no therapeutic decisions is not as helpful or necessary in most cases in older women as this approach might be at the menopause.

SELECTING THERAPY FOR PATIENTS

Each of the current FDA approved therapies for the prevention of bone loss and the treatment of osteoporosis acts by inhibiting some aspect of bone resorption and is thus anti-resorptive. Knowledge of the rate of bone remodeling does not allow a clinician to select between these therapies for individual patient care.

Synthetic human parathyroid hormone (hPTH 1-34), when administered intermittently as a daily subcutaneous injection, represents a new class of drug, formation-stimulation therapy,¹⁵ and is likely to be FDA-approved before the end of 2002. When that happens, markers of bone remodeling will

likely play a more important role in therapeutic decision-making. Theoretically, but not yet demonstrated in clinical trials, anti-resorptive therapy would be the starting treatment of choice in patients with increased rates of remodeling, while hPTH 1-34 would be the starting treatment of choice when remodeling rates are not elevated. The markers would also likely play a role in deciding combinations of an anti-resorptive and a formation stimulation agent whether given concurrently or sequentially.

Monitoring patients on therapy

The goal of anti-resorptive therapy is to halt bone loss and permit refilling of any resorption cavities present when therapy is initiated. This will result in either stability or slight increase in BMD and reduction in fracture risk. Change in BMD is slow, particularly if therapy only slows bone loss and does not significantly increase bone mass, and the recommended interval between measurements is two years. In all of the controlled clinical trials where biochemical markers have been monitored, a significant (group) reduction in markers of resorption can be seen as early as after four to six weeks of therapy,¹⁶⁻¹⁹ reaching a nadir by six months, remaining at this lower level as long as therapy is continued, and remaining low for as long as one year after discontinuation of bisphosphonate therapy. Pre-treatment values are seen within a very short period after discontinuing other therapies. Several studies have demonstrated that the

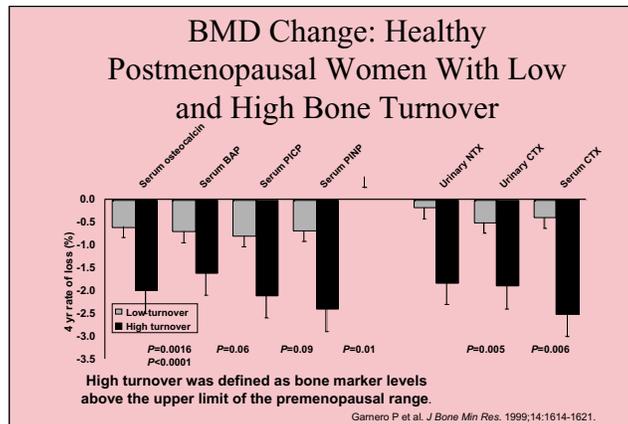


Figure 3: Over a four-year period, early postmenopausal women in whom baseline marker values were elevated (i.e. above the reference interval for healthy premenopausal women) lost significantly more bone than women in whom baseline marker values were normal. BAP= bone specific alkaline phosphatase; P1CP= Carboxy-terminal pro-peptide of type 1 collagen; P1NP = Amino-terminal pro-peptide of type 1 collagen. These are markers of bone formation. Urinary and serum CTX and urinary NTX are markers of bone resorption. (Reproduced from reference # 8 with permission).

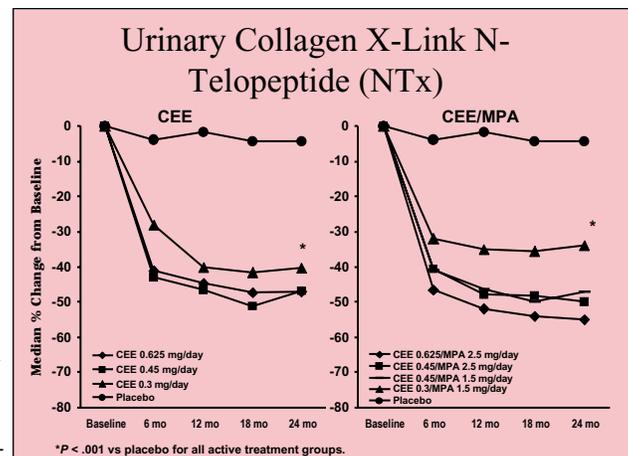


Figure 4: Therapy with conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA) results in a significant and substantial decrease in urine NTx excretion which has reached a nadir by six months of therapy. There is no change in NTx in patients receiving placebo. (Reproduced from reference # 20 with permission)

reduction in marker on therapy is a reasonable predictor that BMD will either remain stable or increase (Figure 4).²⁰ Reductions in markers of formation lag behind the changes in resorption markers but they too reach a nadir by six months. Patients and clinicians may appreciate having this indication of effectiveness within weeks or months of initiating therapy rather waiting two years. One recent report indicated that the six-month change in markers is a better predictor of anti-fracture effectiveness than even the two-year change in BMD (Figure 5).²²

When monitoring individual patients on therapy, if a pre-treatment value has been obtained the aim should be a 50% reduction from the pre-treatment value. If a baseline value was not indicated prior to therapy, the goal should be to maintain the biochemical marker value in the bottom half of the pre-menopausal reference interval.

Less is known about the use of markers in monitoring patients receiving formation stimulation therapy. Since the gains in BMD are expected to be larger than those seen with anti-resorptive therapy the interval between serial measurements should be shorter and there would be less need for monitoring with biochemical markers. The initial change documented in the clinical trials with hPTH 1-34 has been an increase in formation markers.²²

CLINICAL APPLICATION OF BIOCHEMICAL MARKERS OF BONE REMODELING

Markers cannot and should not be used to establish a diagnosis of osteoporosis or used on their own to make therapeutic decisions. In the early postmenopausal years, the markers can be successfully used to predict short-term (four years or less) bone loss. In conjunction with BMD measurement this information can aid the clinician in deciding which patient might best benefit from specific intervention. In those patients with low bone mass but not osteoporosis, a normal value for markers would suggest that intervention is not yet necessary as bone loss can be expected to be slow. Conversely, an elevated marker value would indicate that bone loss would be more rapid and those with the lowest (non-osteoporotic BMD values) are likely to benefit from intervention. Once therapy has been initiated with an anti-resorptive drug, the short-term (three to six months) goal should be to have the marker value within the bottom half of the pre-menopausal reference interval. This goal is applicable to any patient being treated with

an anti-resorptive drug, independent of how the initial decision to begin therapy was established. Clinicians should become familiar with one of the several available markers, and preferably a serum marker, preferably one readily available through their usual laboratory facility. There is little indication for serial marker measurements once goal has been achieved. If the therapeutic goal is not achieved, one should check that the therapy is being taken as prescribed. If it is, a repeat evaluation for secondary causes of bone loss should be undertaken.

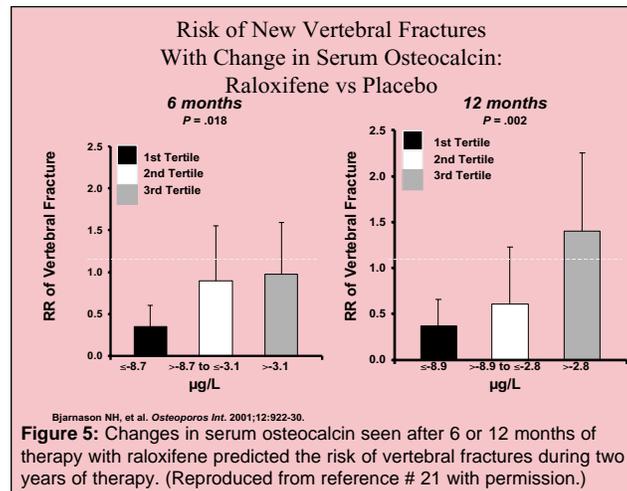


Figure 5: Changes in serum osteocalcin seen after 6 or 12 months of therapy with raloxifene predicted the risk of vertebral fractures during two years of therapy. (Reproduced from reference # 21 with permission.)

SUMMARY

The availability of serum based assays for markers of bone resorption has substantially improved the application of these tests to individualize patient care. In the early menopause, the markers can help decide which woman is most likely to benefit from specific skeletal therapy. In older patients who are more likely to already be on several medications for diverse medical conditions, biochemical markers are an important adjunct to BMD in assessing hip fracture risk and can be used to make intervention decisions.

When formation stimulation therapies for osteoporosis become available, it is likely that markers will help the clinician decide the more appropriate form of therapy for the individual patient. When therapy is an anti-resorptive drug, there are decided advantages to monitoring the effectiveness of therapy with biochemical markers. This may not be the case with formation stimulation therapy.

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Teriparatide [PTH(1-34)] as a Treatment Option for Osteoporosis



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INTRODUCTION

Osteoporosis is a silent progressive disease characterized by compromised bone strength and increased susceptibility to fracture. It manifests initially as a fracture that occurs with minimal trauma and may involve any bone in the body, although fractures of the spine, wrist, hip, and ribs occur commonly. Fractures associated with osteoporosis have substantial physical, psychosocial, and economic consequences and have become an increasing public health threat as the population ages.¹

Bone remodeling is a continuous lifelong process of removing old bone and replacing it with new bone. In a normal young adult, the amount of bone formed equals the amount of bone resorbed. However, with increasing age, inefficiency of this process leads to bone loss. The amount of adult bone is determined by peak bone mass attained in early adulthood minus bone loss associated with aging and other factors such as

lifestyle. However, once osteoporosis is established, pharmacologic agents are necessary for treatment.

CURRENT ANTIRESORPTIVE THERAPIES

It is generally agreed that osteoporosis develops when bone resorption exceeds the capacity of osteoblasts to replace previously removed bone. Current treatments for osteoporosis have focused on reducing bone resorption. The antiresorptive therapies approved for the prevention and/or treatment of osteoporosis include a selective estrogen receptor modulator (SERM), raloxifene; the bisphosphonates, alendronate and risedronate; calcitonin; and estrogen or hormone replacement therapy (ERT/HRT). These agents suppress bone remodeling and reduce the number of active remodeling sites at any given time. Consequently, there are fewer resorption cavities to concentrate the effect of mechanical loads and act as points of least resistance. Furthermore, by slowing the rate at which bone is remodeled, more time is allowed for existing bone to mineralize and bone mineral density increases.² While these drugs slow bone loss and stabilize, but not increase, bone mass, fracture risk is reduced but not eliminated, and missing bone structure is not restored (Table 1).

An optimal drug treatment for osteoporosis would directly stimulate bone formation, increase bone mass, restore architecture, and improve strength. Once-daily subcutaneous administration of the biologically active amino-terminal portion of human parathyroid hormone [hPTH(1-34), generic name: teriparatide] has been shown to stimulate new bone formation, increase bone mass, and to significantly reduce the incidence of both vertebral and nonvertebral fractures (Table 1).³ Teriparatide is currently being reviewed by the U.S. Federal Drug Administration and will be the first clinically useful bone anabolic agent for the treatment of osteoporosis. Clinical trials are also underway to evaluate the therapeutic potential of the full-length 84-amino acid PTH peptide [4], as well as fragments and analogs of PTH and PTHrP(PTH-related protein),⁵⁻⁷ and

agents that stimulate endogenous PTH release.⁸ However, there are no published results on fracture-prevention efficacy of those compounds.

In the remainder of this paper, we shall focus on recently published clinical trial results concerning teriparatide as treatment for osteoporosis in postmenopausal women and in men.

PTH AS A BONE ANABOLIC AGENT

The primary physiologic function of endogenous 84-amino-acid PTH is to regulate extracellular calcium concentration within a narrow range by mobilizing calcium from the skeleton, reducing renal calcium loss, and increasing intestinal calcium absorption. Endogenous PTH is also a primary regulator of plasma phosphate concentration and renal phosphate excretion. Teriparatide and the 34 N-terminal amino acids of PTH bind to cell-surface receptors with comparable affinity and have similar actions on bone and kidney.⁹

Traditionally, PTH has been viewed as catabolic to bone because the classic disorder of PTH excess, severe primary hyperparathyroidism, is associated with excessive osteoclastic activity and bone loss. However, widely reproduced studies in a variety of species clearly show that PTH may have striking anabolic effects on bone. The bone anabolic effect of parathyroid extract was first reported by Fuller Albright in 1929³⁸ and confirmed by Hans Selye in 1932.³⁹ Interest in these seminal observations was revived in the 1970s with technological developments leading to the purification and sequencing of human PTH. In the past 25 years, the anabolic activity of PTH has been confirmed and further defined in animal and clinical trials [for comprehensive reviews, see references 10-13]. Although the exact molecular and cellular events responsible for the skeletal anabolic action of PTH remain to be elucidated, it is clear that the paradoxical effects of teriparatide on the skeleton depend upon the pattern of systemic exposure. Once-daily subcutaneous injection stimulates new bone formation on trabecular and cortical bone surfaces by preferential stimulation of

osteoblasts over osteoclasts. By contrast, continuous exposure to high levels of endogenous PTH, as found in hyperparathyroidism, may be harmful to the skeleton because osteoclast-mediated resorption exceeds bone formation.

Table 1: Approaches to the Treatment of Osteoporosis Based on Mechanism of Action

Antiresorptive agents	Teriparatide
<ul style="list-style-type: none"> • Reduce osteoclastic bone resorption • Suppress bone remodeling • Decrease prevalence of resorption cavities that act as "stress risers" • Promote matrix mineralization • Allay bone loss • Reduces fracture risk 	<ul style="list-style-type: none"> • Increases bone mass by stimulating bone formation on cortical and trabecular surfaces • Increases bone remodeling • Restores skeletal microarchitecture • Improves biomechanical strength • Reduces fracture risk

Clinical Trials in Postmenopausal Women with Osteoporosis

In humans, the anabolic effects of teriparatide are manifested as increases in skeletal mass and markers of bone formation and resorption, and reduction in incidence of vertebral and nonvertebral fractures. Several small, randomized and controlled clinical trials have demonstrated the anabolic effect of PTH alone or in combination with estrogen¹⁴⁻¹⁶ or cyclically with or without sequential calcitonin¹⁷ in postmenopausal women with osteoporosis. In all studies, synthetic teriparatide markedly increased bone mass at various skeletal sites, particularly the lumbar spine, when given for two to three

years in doses ranging from 400-800 U/day. In a study of 52 postmenopausal women with osteoporosis receiving concurrent estrogen, Cosman and colleagues reported a reduction in the occurrence of vertebral fractures by 75% to 100%.¹⁵

The Fracture Prevention Trial was a randomized, double-blind, placebo-controlled, multinational trial in 1637 postmenopausal women having osteoporosis and prior vertebral fractures.³ Neer and colleagues evaluated the effect of once-daily subcutaneous self-injections of 20 or 40 mcg/day recombinant teriparatide versus placebo on the incidence of vertebral and nonvertebral nontraumatic fractures.¹⁸ Spinal radiographs at

baseline and end of study were evaluated using a semiquantitative scoring method. Mild, moderate and severe vertebral fractures were defined by decreases in vertebral height of >20, >25 and >40%, respectively. Bone mineral density (BMD) at the lumbar spine, hip, and other skeletal sites was measured by dual energy x-ray absorptiometry (DXA). All patients received supplemental calcium 1000 mg/day and vitamin D 400-1200 IU/day. The baseline characteristics were similar among study groups (Table 2). The planned duration of the study was three years. The study sponsor voluntarily stopped the trial when a concurrently running carcinogenicity study revealed that rats

Table 2: Summary of Baseline Characteristics and Study Endpoints in the Teriparatide Fracture Prevention Trial in Postmenopausal women with Osteoporosis*

	Placebo	Teriparatide	
	N=544	20mcg/d N=541	40mcg/d N=552
Baseline Characteristics			
Age (yrs)	69 ± 7	70 ± 7	70 ± 7
Years postmenopausal	21 ± 9	21 ± 9	22 ± 8
Lumbar spine T score	-2.6	-2.6	-2.6
Vertebral Fractures			
1	28%	31%	32%
≥ 2	62%	60%	58%
≥ 1 New Vertebral Fractures +			
No. of women (%)	64(14)	22(5)	19(4)
Relative Risk Reduction		65% ^a	69% ^a
Absolute Risk Reduction		9%	10%
≥ 1 Moderate or Severe Vertebral Fractures+			
No. of women (%)	42(9)	4(<1)	9(2)
Relative Risk Reduction		90% ^a	78% ^a
Absolute Risk Reduction		9%	7%
New Nonvertebral Fragility Fractures			
No. of women (%)	30(5)	14(3)	14(2)
Relative Risk Reduction		53% ^b	54% ^b
Absolute Risk Reduction		3%	3%
Mean % Change in BMD^c			
Lumbar spine	1.1 ± 5.5	9.7 ± 7.4 ^b	13.7 ± 9.7 ^b
Femoral Neck	-0.7 ± 5.4	2.8 ± 5.7 ^b	5.1 ± 6.7 ^b
Total Hip	-1.0 ± 4.3	2.6 ± 4.9 ^b	3.6 ± 5.4 ^b
Ultradistal Radius	-1.6 ± 8.3	-0.1 ± 7.2	-1.5 ± 8.4
Distal 1/3 Radius	-1.3 ± 3.3	-2.1 ± 4.2	-3.2 ± 4.5 ^b
Total Body Bone Mineral Content	-0.7 ± 5.6	1.9 ± 5.6 ^b	2.8 ± 5.5 ^b

Values are the mean ± standard deviation

^a p<0.05 vs. placebo; ^bp<0.001 vs. placebo

^c Intent-to-treat analysis, last observation carried forward

* Adapted from Neer, et al., *New Engl J Med.* 2001;344:1434-1441.

treated with near-lifetime teriparatide injections developed a dose-dependent increase in the incidence of bone proliferative lesions, including osteosarcoma.¹⁹ Since the study was discontinued early, the actual duration of treatment did not exceed two years (median of 19 months).

The incidence of one or more new vertebral fractures was reduced from 14% in the placebo group to 5% and 4% in the teriparatide 20 and 40 mcg groups, respectively. Teriparatide 20 and 40 mcg reduced the absolute risk by 9% and 10%, respectively, and the relative risk by 65% and 69%, respectively. For moderate or severe vertebral fractures, teriparatide 20 and 40 mcg reduced the absolute risk by 9% and 7%, respectively, and the relative risk by 90 and 78%, respectively (Table 2). Moderate and severe vertebral deformities are clinically important since they cause substantial pain, disability, or loss of height.²⁰

Teriparatide 20 or 40 mcg once daily reduced the occurrence of nonvertebral fragility fractures by 53% and 54%, respectively (Table 2). Fragility fractures were defined as fractures occurring with minimal trauma, for example, falling from no more than a standing height. Although the numbers of nonvertebral fractures at specific skeletal sites were too low to estimate incidence of each type of fracture, the incidence of fractures at almost all skeletal sites was numerically lower in the patients receiving teriparatide compared to placebo. In a Kaplan-Meier analysis, the cumulative percentage of women who sustained new nonvertebral fragility fractures also was lower in the teriparatide-treated groups. The protective effects of teriparatide against nonvertebral fractures became evident after nine to 12 months of treatment. The effect was progressive during treatment and reached statistical significance at the end of study.³

Teriparatide 20 and 40 mcg/day substantially increased lumbar spine BMD by 9.7% and 13.7%, respectively (Table 2). Statistically significant increases were seen as early as three months and continued to increase throughout the treatment period. Statistically significant dose-dependent increases in BMD compared to placebo were also found at nonvertebral sites, except at the radius (Table 2). Although the density of the ultradistal radius did not differ among treatment groups, women receiving 40 mcg teriparatide had decreased BMD at the distal 1/3 radius. Zanchetta and colleagues examined this finding in greater depth in a subset of patients using peripheral quantitative computed tomography (pQCT). The teriparatide-treated women showed features of improved cross-sectional geometry and biomechanical

strength compared to placebo.²¹ The numerically lower incidence of wrist fractures in the teriparatide-treated groups compared to placebo, together with these improvements in cross-sectional geometry on pQCT, suggest that the changes in BMD observed on DXA do not indicate an adverse effect of teriparatide on cortical bone. These findings, plus the increase in total body bone mineral content in the teriparatide-treated women refute the concern that gains in trabecular bone might be made at the expense of cortical bone.²² Although increases in BMD were greater in the 40 mcg than the 20 mcg group,

“People who are at high risk for fracture include those with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy...”

there were no differences between the two doses in fracture risk reduction.³ The skeletal response to teriparatide was independent of age, initial vertebral BMD, and number of fractures at the beginning of the study.²³

CLINICAL TRIALS

Clinical Trials in Men with Osteoporosis

In an 18-month placebo-controlled trial in 23 men with idiopathic osteoporosis, Kurland and colleagues reported that daily subcutaneous injections of 400 IU synthetic teriparatide increased lumbar spine and femoral neck BMD by 13.5% and 2.9%, respectively, compared to no change in the control group. Too few fractures occurred to assess fracture risk reduction.²⁴

In a large randomized, double-blind, placebo-controlled multinational trial, the efficacy of recombinant teriparatide was

investigated in 437 men with primary or hypogonadal osteoporosis.²⁵ Orwoll and colleagues evaluated the effect of subcutaneous self-injections of placebo vs. 20 or 40 mcg teriparatide once-daily on changes in BMD at the lumbar spine and other skeletal sites. All patients received supplemental calcium 1000 mg/day and vitamin D 400-1200 IU/day. The planned duration of the study was two years, but the unexpected finding of osteosarcomas in rats given near-lifetime teriparatide injections led to its early termination.¹⁹ The actual duration of treatment did not exceed 14 months (median of 11 months).

At the end of the study, teriparatide had significantly increased lumbar spine and femoral neck BMD by 5.9% and 1.5%, respectively. Statistically significant increases in lumbar spine BMD were seen at three months and continued throughout the treatment period. BMD responses to teriparatide were similar regardless of age, gonadal status, and baseline BMD.²⁵ After stopping therapy, 81% of the men volunteered for an 18-month observation study to determine the incidence of vertebral fractures. During the 30-month period, including 18 months of no treatment, combined doses of teriparatide reduced the incidence of new vertebral fractures by 50% and moderate or severe vertebral fractures by 83%.²⁶

Clinical Trials in Drug-induced Bone Loss

Finkelstein and colleagues examined the effect of 40 mcg (500 U) synthetic teriparatide on bone loss in 40 premenopausal women with estrogen deficiency induced by the gonadotropin-releasing hormone agonist nafarelin for treatment of endometriosis and uterine leiomyomas. After 12 months of treatment, teriparatide increased lumbar spine BMD and prevented bone loss from the proximal femur and total body.²⁷

Glucocorticoid use is the most common cause of secondary osteoporosis and current data suggest that the primary effect of glucocorticoids on bone is inhibition of osteoblastic bone formation. An anabolic agent to directly stimulate bone formation would seem to be ideal to treat this condition. Lane and colleagues examined the effect of 40 mcg (400 U) synthetic teriparatide in 51 postmenopausal women with osteoporosis receiving glucocorticoids (> 5mg/day prednisone or equivalent) and estrogen.²⁸ After 12 months of treatment, teriparatide was stopped while estrogen was continued for another year. Lumbar spine BMD increased significantly by 11.8% at 12 months and was maintained at 11.9% above baseline 12 months after stopping teriparatide. The changes in total hip and femoral neck BMD were not significant at 12 months but

increased to 4.7% and 5.2% at 24 months, respectively.²⁸ At this time, no studies have established the extent of fracture risk reduction by teriparatide in patients having osteoporosis secondary to glucocorticoid use.

Effects of Teriparatide on Trabecular (Cancellous) and Cortical Bone Structure

Changes in BMD resulting from treatment with antiresorptive drugs account for only a fraction of fracture risk reduction.²⁹ Improvements in bone microarchitecture, which may not directly translate to changes in BMD, appear to play an important role in fracture risk reduction. Histomorphometric assessment of the effects of teriparatide is limited to a few studies employing iliac crest bone biopsies. In the first clinical trial with teriparatide, Reeve and colleagues found that synthetic teriparatide significantly increased trabecular bone volume.³⁰ Dempster and colleagues performed two- and three-dimensional (2D and 3D, respectively) morphometric analysis of bone structure in paired biopsy specimens from eight postmenopausal women treated with 400 U/day synthetic teriparatide and estrogen for 36 months and from eight men treated with 400 U/day synthetic teriparatide for 18 months.³¹ Teriparatide increased cortical width, maintained cancellous bone area, and did not increase cortical porosity. Microcomputed tomography (microCT) revealed an increase in connectivity density, a 3D measure of trabecular connectivity. They further demonstrated that teriparatide directly stimulates bone formation without prior resorption on cancellous and endocortical surfaces.³²

Jiang and colleagues examined the effects of teriparatide on bone microstructure of paired iliac crest biopsies from a subset of women enrolled in the Fracture Prevention Trial described above.³³ Teriparatide increased cancellous bone volume and connectivity, shifted the trabeculae towards a more plate-like structure, and increased the thickness of cortical bone without increasing cortical porosity.

The positive effects of teriparatide on human trabecular and cortical bone structure are consistent with findings in nonhuman primates, data that have been reviewed previously.¹¹ Bone of cynomolgus monkeys treated for 18 months with recombinant teriparatide had improvements in trabecular microarchitecture, increased bone mass and biomechanical strength, resulting from new bone formation in both trabecular and cortical bone.

Rat Osteosarcoma

As is common practice in the development of therapeutic agents intended for chronic use, teriparatide was tested in a standard

two-year carcinogenicity rat bioassay. Weanling (six-week-old) Fischer 344 rats received injections of vehicle or teriparatide at daily doses of 5, 30, or 75 mcg/kg body weight, resulting in systemic exposures of three to 60 times higher than the systemic exposure observed in humans following a subcutaneous dose of 20 mcg, based on an area under the curve (AUC) comparison. Injections were given for 2 years, nearly the expected lifespan of the rats. There was an unexpected finding of dose-related bone proliferative lesions, including osteosarcoma. Osteosarcomas were observed in all active treatment groups, but their incidence was dose-related, approaching 50% at the highest dose.¹⁹ The background rate of osteosarcoma in Fischer 344 rats is estimated to be 0.1-0.5%. Additional information regarding the rat osteosarcoma finding has been published.^{3,34}

Osteosarcoma has not been observed in any of the one-to three-year clinical trials enrolling over 2,500 patients or in primates treated with teriparatide. In conditions of chronically stimulated osteoblastic activity, such as in naturally occurring primary and secondary hyperparathyroidism, there is no increase in the incidence of osteosarcoma. A systematic search of the national cancer registry in Sweden was performed over a period of 40 years, identifying 12,644 patients with either a parathyroid adenoma or hyperplasia representing a cumulative 114,000 patient-years of observation. There was no case where the diagnosis of hyperparathyroidism or osteosarcoma occurred in the same patient.^{3, 34}

A second two-year study in Fischer 344 rats showed that dose and duration of treatment are important factors in the development of bone neoplasms.³⁵

Safety

In the large phase III trials^{3,25} adverse events associated with teriparatide generally were mild and did not require discontinuation of therapy. The most common adverse effects associated with treatment included dizziness and leg cramps with the 20 mcg dose, and nausea and headache with the 40 mcg dose. Small increases in serum calcium, usually within the normal range, were occasionally observed four to six hours post-injection, but serum calcium returned to baseline levels within 24 hours. There were no increases in conditions traditionally associated with hyperparathyroidism, such as cardiovascular disease, hypertension, peptic ulcer disease, renal insufficiency or urolithiasis. Small increases in serum uric acid were observed but these did not result in any clinical sequelae. Circulating antibodies to teri-

paratide were detected in 3% to 8% of women but these antibodies had no effects on serum calcium and BMD responses to treatment. Concomitant administration of a variety of pharmacologic agents did not result in any clinically significant drug interactions.

Therapy for Osteoporosis

In clinical trials, monotherapy with teriparatide was effective and well tolerated in postmenopausal women and in men with osteoporosis. Patients for whom teriparatide is most likely to be indicated are men or postmenopausal women with osteoporosis who are at high risk for fractures, and with characteristics similar to those who participated in the pivotal trials. People who are at high risk for fracture include those with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy, based upon their physician's assessment.

Questions have been posed regarding how to maximize and maintain the benefits of anabolic therapies. Because the mechanism of action of teriparatide differs completely from that of antiresorptive agents, the idea of combination therapy has been considered an attractive notion. Relatively little is known about the effects of sequential or combined treatment regimens using PTH and antiresorptive drugs. Concomitant therapy with estrogen^{14, 15, 16, 28} did not seem to blunt the anabolic effects of teriparatide in postmenopausal women. However, there is no evidence that the combination produces a greater effect on bone mass than teriparatide alone, or that any combination of drugs enhances fracture risk reduction. An NIH-sponsored trial (PaTH) in 240 postmenopausal women is underway to evaluate effects of PTH(1-84) alone and in combination with alendronate on BMD, but this trial is too small to determine relative clinical benefits.⁴

The use of teriparatide with antiresorptive maintenance has also been reported. Lane and colleagues examined a cohort of postmenopausal women with glucocorticoid-induced osteoporosis given non-recombinant teriparatide and estrogen for one year and were followed for another year on estrogen alone.²⁸ As previously described above, the increase in BMD at the lumbar spine was maintained, while hip BMD that was unchanged at 1 year increased further during continued estrogen administration in the year after teriparatide was discontinued. Cosman and colleagues reported that the gains in BMD remained stable during continued estrogen replacement one year after teriparatide was discontinued.¹⁵ Rittmaster and

colleagues reported that after a one-year course of PTH(1-84) in postmenopausal women with osteoporosis, treatment with alendronate further increased lumbar spine BMD.³⁶ There is no evidence that pretreatment with antiresorptives produces an effect greater than that achieved with PTH alone. However, data published by Lindsay and Cosman,^{14, 15} Roe and colleagues,¹⁶ and Lane and colleagues²⁸ show that pretreatment with estrogen did not appear to blunt the anabolic effects of teriparatide. We must emphasize that the relationship between small increments of BMD and fracture risk reduction is weak, and it is not possible at this time to advocate use of teriparatide or any other osteoporosis drugs in combination. Clearly, properly designed studies are needed.

After conclusion of the recombinant teriparatide Fracture Prevention Trial described above, 77% or 1,262 women participated in an observational study to determine the effects of withdrawal of teriparatide treatment on vertebral fracture occurrence.³⁷ Fifty-four percent of the women received other approved osteoporosis treatments, based on treating physician's

judgment, at some time during the 18-month post-treatment observation period. Because the use of treatments was balanced across groups, analyses were performed without adjusting for antiresorptive use. After the 19-month active treatment period, the absolute risk reduction for new vertebral fracture was 9% and 10%, respectively, for teriparatide 20 and 40 mcg, and over the total period of 37 months (19 months active treatment plus 18 months observation), the absolute risk reduction was 13% for each teriparatide group. For moderate or severe incident vertebral fractures, the absolute risk reduction was 8.5% and 7.3%, respectively, for teriparatide 20 and 40 mcg, and over the total 37-month period, the absolute risk reduction was 11% for both teriparatide groups.³⁷ These data provide evidence of durable effects of teriparatide on fracture risk reduction and suggest that antiresorptive treatment may be useful in maintaining the increases in bone mass achieved with teriparatide.

CONCLUSION

The skeletal anabolic effect of PTH has been known for over 70 years. In all recent

studies, PTH and related peptides have increased bone mass and biomechanical strength, restored bone architecture, and in the Fracture Prevention Trial,³ reduced fracture risk. In clinical trials, monotherapy with teriparatide was effective and well tolerated in postmenopausal women and in men with osteoporosis. The availability of the bone-formation agent teriparatide would represent an advancement in the treatment of postmenopausal women with osteoporosis and high risk of fracture.

REFERENCES

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