



**EDUCATIONAL OBJECTIVE:** Readers will gain a better appreciation of the limitations of bone densitometry in clinical practice

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# Bone density vs bone quality: What's a clinician to do?

## ■ ABSTRACT

Studies of the epidemiology of osteoporosis and of drug treatments for it have challenged the concept that denser bone means stronger bone. Bone strength or resistance to fracture is not easily measured by routine densitometry, being a function of both density and quality.

## ■ KEY POINTS

Bone quality is a composite of properties that make bone resist fracture, such as its microarchitecture, accumulated microscopic damage, the quality of collagen, mineral crystal size, and bone turnover.

The T score was derived from a population of white women in their mid to late 60s and older; in other populations, low T scores do not necessarily reflect the disease state—osteoporosis—with its inherent decreased strength and propensity to fracture.

In assessing the risk of fractures, clinicians should consider not only the bone mineral density but also clinical risk factors.

Markers of bone turnover are elevated in some cases of primary osteoporosis and return to normal levels with antiresorptive therapy but not with anabolic therapy.

**M**OST CLINICIANS WERE TAUGHT directly or indirectly that bone density is the gauge for assessing bone strength and the response to antiosteoporotic treatment. In recent years, however, the concept of bone strength has moved beyond density alone and has expanded to include a number of characteristics of bone that collectively are called *quality*.

This paper describes how the notion of quality has emerged and some of the clinical scenarios in which quality applies. It discusses several observations in the clinical literature that challenge our understanding of bone density and strength and provides the practitioner a better understanding of densitometry in clinical practice.

## ■ WHAT IS BONE QUALITY?

Bone quality is not precisely defined. It is described operationally as an amalgamation of all the factors that determine how well the skeleton can resist fracturing, such as microarchitecture, accumulated microscopic damage, the quality of collagen, the size of mineral crystals, and the rate of bone turnover. The term became popular in the early 1990s, when paradoxes in the treatment of osteoporosis challenged the generally accepted orthodoxy that bone density itself was the best way to assess strength of bone.

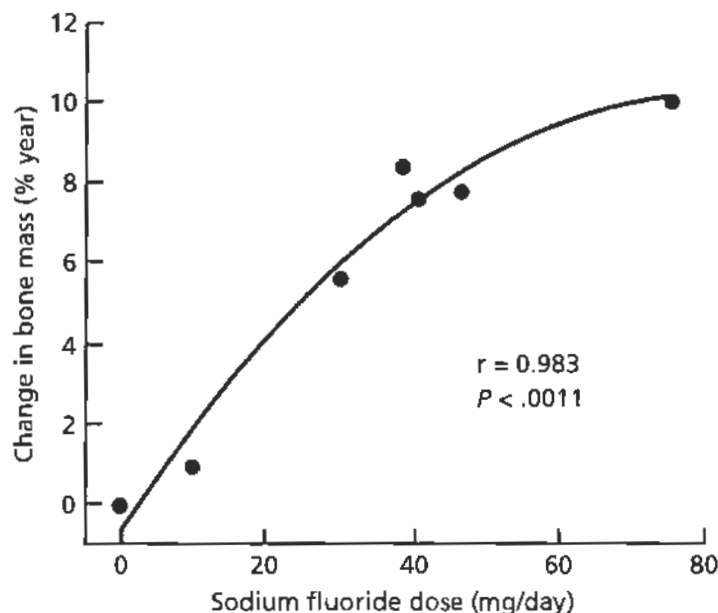
## ■ FROM BONE MASS TO T SCORES TO BONE QUALITY

Today's practitioners appreciate the importance of the T score in diagnosing osteoporosis. It was not always this way, since the early attempts to use bone densitometry focused on

\*The author has disclosed that he has received honoraria from the Eli Lilly, Merck, and Novartis companies for teaching and speaking.

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### Fluoride looks good as a treatment if we look only at density



**FIGURE 1.** Although the dose-response curve indicates that sodium fluoride increases bone mass, this drug actually increases the fracture rate because it makes bone more brittle.

KLEERKOPER M, BALENA R. FLUORIDES AND OSTEOPOROSIS. ANNU REV NUTR 1991; 11:309-324  
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a specific cutoff of bone mass as a risk for fracture and not the statistical T scores or Z scores that we know.<sup>1-3</sup>

The T score concept was originally developed to assess the probability of fragility fractures in postmenopausal white women in their mid to late 60s and older.<sup>4</sup> It has been useful because the disease prevalence is high in this age group. The T score as originally used was a surrogate marker for the histologic changes in aged bone that render it weak and susceptible to fractures from low loading forces: the lower the score, the worse the fracture risk. It followed intuitively that a low T score clinched the diagnosis of primary osteoporosis.

But the T score has its problems when used outside this intended population. Practitioners have assumed that all patients with abnormally low scores have primary osteoporosis. However, this number alone is insuff-

icient to accurately make such a diagnosis in patients outside the demographic group in which it was developed, because the low disease prevalence in younger groups makes the score less accurate as a predictive tool. Moreover, reevaluation of data from pivotal clinical trials has brought into question our long-held idea that increases in bone density parallel increases in bone strength and reduction in fractures, and that therapeutic improvement in bone density is the mark of success. Bone strength or resistance to fracture is more complex than density alone. Into this arena enters the concept of bone quality, which attempts to explain the following observations.

#### ■ DENSER BONE IS NOT ALWAYS STRONGER

The first inkling of the discrepancy between density and strength arose with the use of sodium fluoride to treat osteoporosis. Although sodium fluoride produced large increases in bone mass (and therefore in density) (FIGURE 1), the strength of the bone did not parallel this change.<sup>5,6</sup> In fact, fluoride made bone more brittle, because it changed the quality of the mineral and rendered it more susceptible to fracturing. High serum fluoride levels increased the vertebral fracture rate despite higher bone density.<sup>6</sup>

#### ■ NOT ALL LOW BONE MINERAL DENSITY IS OSTEOPOROSIS

The following case describes a clinical scenario in which a patient has low bone density but does not have osteoporosis.

#### A young healthy woman with low bone density

A 35-year-old healthy woman who has jogged recreationally for decades is evaluated for possible treatment of osteoporosis. She started to feel back pain after doing heavy work in her garden. Spinal radiographs did not show a reason for her pain, but her physician, concerned about osteopenia, sent her for dual-energy x-ray absorptiometry. Her spinal T scores and Z scores were 2.5 standard deviations below the mean.

Should she start pharmacologic therapy?

### Young bone is stronger than older bone

This case shows the other end of the spectrum from the fluoride story. Here, a young healthy person inappropriately underwent a density scan, which led to confusion about how to interpret the results.

As stated above, T scores are not appropriate for young patients—the Z score is used instead. In this case, the low value implied deficiency of bone mass compared with age-matched norms. However, in this patient with no clinical risk factors for fracture, a low T score meant that her bone density was low, but not that she had osteoporosis.

Several factors could account for her low bone density. It could be genetic, if her family is small in stature, or she could be at the extreme end of the distribution curve for normal individuals. Runners tend to be slight in build, and so may have lighter bones. Furthermore, for women, excessive running could lead to lower estrogen activity and therefore lower bone mineral density.

Drug treatment is not warranted for this patient, but standard therapy with exercise, vitamin D, and adequate elemental calcium from the diet or supplements is reasonable.

Two decades ago, in one of the first indications that something besides bone density was critical to strength, a landmark study showed that fracture rates are dramatically different across similar levels of bone mass or T scores depending on a person's age (FIGURE 2).<sup>7</sup> Many subsequent observations also brought into question how important density is.<sup>8,9</sup>

Thus, the notion of quality entered the clinical arena. Young bone and older bone are qualitatively different in strength, even with similar bone density. This difference was later found to be related to significant qualitative changes within the microscopic architecture of the bone, the collagen, the mineral, and the physiologic activity of the skeletal cells—elements that the T score does not reflect.

Hence, young bone is stronger than older bone across all levels of bone mass or T scores. Its quality is better.

### ■ CHANGES IN DENSITY ACCOUNT FOR ONLY PART OF THE DECREASE IN RISK

Clinical studies showed that the drugs approved

### At any T score, young bone is stronger than older bone

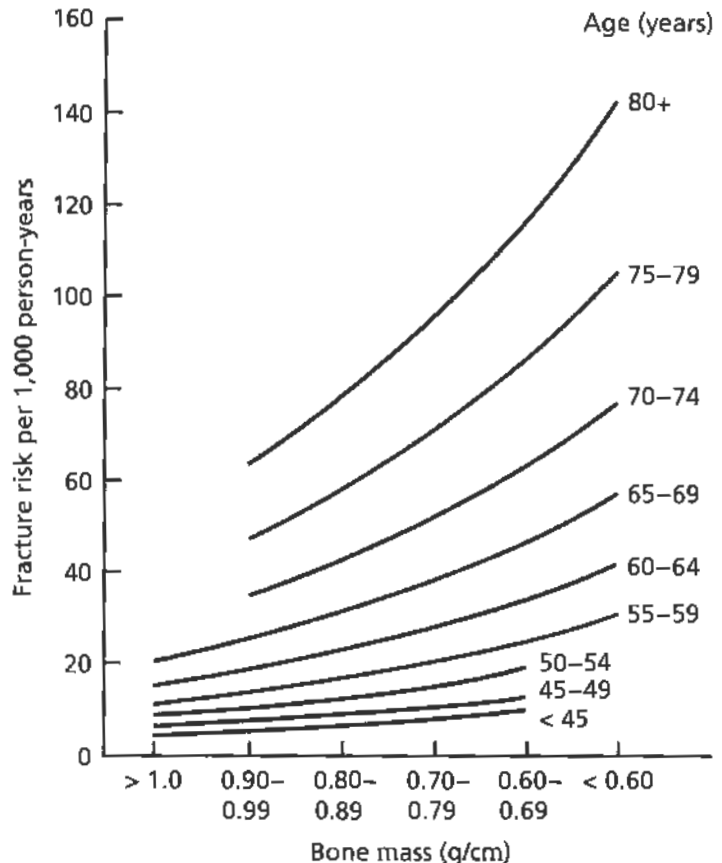


FIGURE 2. Estimated incidence of fracture as a function of age and bone mass in 521 white women followed for an average of 6.5 years.

HUIJSL, SLEMENDA CW, JOHNSTON CC JR. AGE AND BONE MASS AS PREDICTORS OF FRACTURE IN A PROSPECTIVE STUDY. J CLIN INVEST 1988; 81:1804-1809.

for treating osteoporosis prevented fractures better than we would expect from their effects on bone density. The increases in density ranged from about half a percent with vitamin D to over 10% with high doses of teriparatide (Forteo), while the decreases in the risk of vertebral fractures ranged from 23% to 69% (TABLE 1).<sup>10,11</sup> Cummings et al,<sup>12</sup> reviewing data from the Fracture Intervention Trial,<sup>13</sup> estimated that the change in bone density with alendronate (Fosamax) 5 mg explained only 16% (95% confidence interval 11%–27%) of the reduction in spinal fracture risk. With raloxifene (Evista), only 4% of the reduction in vertebral fracture risk is ascribable to the changes in density—96% is unexplained.<sup>14</sup>

**TABLE 1**

**Small increases in bone density, large decreases in fracture risk**

DRUG	% INCREASE IN SPINAL DENSITY	% DECREASE IN NEW FRACTURES
Vitamin D	0.4	37
Calcium	1.7	23
Raloxifene (Evista)	2.5	40
Calcitonin (Miacalcin)	3.7	54
Risedronate (Actonel)	4.5	36
Alendronate (Fosamax)	6.1	48
Teriparatide (Forteo) 20 µg	9.7	65
Teriparatide 40 µg	13.7	69

ADAPTED FROM GUYATT GH, ET AL. SUMMARY OF META-ANALYSIS OF THERAPIES FOR POSTMENOPAUSAL OSTEOPOROSIS AND THE RELATIONSHIP BETWEEN BONE DENSITY AND FRACTURES. *ENDOCRINOL METAB CLIN NORTH AM* 2002; 31: 659-679 AND DATA FROM NEER RM, ARNALD CD, ZANCHETTA JR, ET AL. EFFECT OF PARATHYROID HORMONE (1-34) ON FRACTURES AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS. *N ENGL J MED* 2001; 344: 1434-1441. WITH PERMISSION FROM ELSEVIER, WWW.ELSEVIER.COM.

**■ BONES BECOME STRONGER BEFORE THEY BECOME DENSER**

**Bone strength is more complex than density alone**

In a number of clinical trials, antiresorptive drugs of various classes started to reduce the risk of fractures before the increases in bone density reached their maximum. Raloxifene significantly reduces the incidence of fractures within 6 to 12 months of starting treatment, whereas the maximal increase in spinal bone density of 2% to 3% is seen at 3 years.<sup>15</sup> This type of information further supported the discordance of density and bone strength and underscored the concept that drug therapy affects other factors in bone physiology.

One of these other factors is skeletal turnover, which is assessed by measuring the levels of enzymes or collagen fragments released by osteoblasts or osteoclasts in the blood or urine. These substances are markers of bone metabolism. They do not establish the diagnosis of specific diseases, but their concentrations are higher in high-bone-turnover states such as in some cases of primary osteoporosis. The topic has been reviewed in detail by Singer and Eyre ([www.ccjm.org/content/75/10/739](http://www.ccjm.org/content/75/10/739)).<sup>16</sup>

Antiresorptive therapy decreases the levels of these markers to normal within weeks

of starting therapy. This prompt response is believed to be the reason that fracture risk reduction is seen so early. This effect of therapy represents a reduction in high osteoclastic activity and, secondarily, preservation of the microarchitecture. Meanwhile, osteoblastic activity adds bone to these less-active osteoclastic sites. If the amount is sufficient, bone densitometry may detect it.

**■ LACK OF CHANGE IN DENSITY DOES NOT NECESSARILY MEAN LACK OF RESPONSE**

The lack of change in bone density in patients taking bisphosphonates does not necessarily mean a lack of response. The following clinical scenario exemplifies this paradox.

**A middle-aged woman on bisphosphonate therapy**

A 68-year-old woman is seen because she seems to be having a poor response to oral bisphosphonate therapy, which was started 3 years ago after she had two vertebral fractures. Her bone density has not changed during this time, but the levels of her bone turnover markers have decreased and remain normal.

Should she start another type of therapy?

**Bone turnover markers indicate a response**

Studies show that patients with osteoporosis can be stratified into those at low or high risk of fractures on the basis of the activity of bone turnover markers. The risk of fractures is two times higher in people who have high levels of these markers than in those with normal levels, and can rise to four to five times as high in people who have both high marker levels and low bone density.<sup>17</sup>

All antiresorptive treatments lower the levels of these markers to the normal range and keep them low. In the patient described above, her normal levels of bone turnover markers after treatment indicate a good therapeutic response. The treatment should be continued.

**■ WHAT'S A CLINICIAN TO DO?**

These cases illustrate some important questions that often arise in the treatment of patients.

How should the risk of fractures be assessed? Bone densitometry is a better marker of fracture risk than of bone strength because it cannot detect the important qualitative elements of strength. The higher prevalence of osteoporosis in the older population gives the T score cutoff of 2.5 standard deviations below the mean a greater predictive power to diagnose osteoporosis than it does in a younger population with a lower disease prevalence. In younger patients, this cutoff at best represents low bone density and is not diagnostic of osteoporosis unless it is present with other risk factors for fracture.

Newer tools for assessing fracture risk are now entering clinical practice. Estimates of absolute fracture risk are being used,<sup>18-20</sup> and a fracture risk assessment tool is being implemented worldwide.<sup>21-23</sup> Developed by the World Health Organization and called FRAX, it is based on the bone mineral density of the femoral neck combined with other factors: the patient's age, sex, weight, and height, whether the patient has a personal or family history of fracture, and whether the patient smokes, uses glucocorticoids, has rheumatoid arthritis, has secondary osteoporosis, or consumes alcohol in excess. It is available online ([www.shef.ac.uk/FRAX/tool.jsp](http://www.shef.ac.uk/FRAX/tool.jsp)) and gives an estimate of the 10-year risk of fracture.

How should response to therapy be assessed? In clinical practice, patients who show no changes in bone density may still be responding to therapy, and the response can be detected by the levels of bone turnover markers. Patients using antiresorptive drugs have normal levels of these markers, decreased from a higher baseline value. Patients using anabolic agents show higher levels of these bone markers, indicating enhanced bone building. So therapeutic efficacy is seen as stable or increased bone density coupled with decreased and normal turnover markers with antiresorptive drug use and increased turn-

over markers with anabolic drug use.

When fractures occur in patients on therapy, however, it becomes difficult to assess good or poor drug response. Patients who have a fracture within the first year of therapy are best left on the treatment, since this may not generate the full response. Patients who start having fractures years into therapy, however, may be experiencing secondary forms of osteoporosis superimposed on the original primary disease.<sup>24</sup> Vitamin D deficiency, hyperparathyroidism, and celiac disease are common problems. Or, perhaps, patients may not be adherent to therapy.<sup>25-27</sup> Poor compliance, inappropriate use of medications (especially the bisphosphonate drugs), or even problems of malabsorption of oral medication may be a consideration. The intravenous forms of bisphosphonate drugs warrant consideration in this scenario.<sup>28-30</sup>

In the future, we may have better tests of bone quality. One such test, called finite element analysis, uses computer modeling and three-dimensional imaging. It has been used for years by engineers designing and testing the strength of bridges, airplanes, and other structures and is now being evaluated as a way to estimate bone strength.

In summary, bone physiology and bone strength are very complex issues that have recently attained new and important nuances. The original use of bone densitometry was to assess the risk of fragility fractures and, secondarily, to diagnose primary osteoporosis in the population of patients for which it was originally developed. While the bone densitometry score does bear some relationship to bone strength, it is not a sufficient surrogate marker in many cases. Hence, clinicians need to judiciously use these testing procedures in combination with a number of clinical factors to diagnose osteoporosis and assess the response to therapy. ■

**T scores are not appropriate for young patients—the Z score is used instead**

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# CLINICAL USE OF TERIPARATIDE IN THE REAL WORLD: INITIAL INSIGHTS

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## ABSTRACT

**Objective:** To summarize expert opinion regarding clinical application of the recently introduced anabolic agent teriparatide [human parathyroid hormone (1-34)] in treatment of postmenopausal osteoporosis in women, and osteoporosis in men.

**Summary:** The anabolic agent teriparatide was approved for clinical use by the Food and Drug Administration (FDA) on November 26, 2002. Since the launch of teriparatide, many more questions about clinical use of this exciting agent have emerged than there are answers provided by clinical trials or FDA-approved product labeling. A group of clinicians with a broad range of experience in research and clinical applications of teriparatide met recently to address practical issues related to its use. This manuscript is a compendium of the consensus opinions of the authors that attempts to provide practical answers to many real-world questions being asked about teriparatide therapy since its approval by the FDA. (*EndocrPract*, 2004;10:139-148)

### Abbreviations:

**BMD** = bone mineral density; **BSAP** = bone-specific alkaline phosphatase; **DXA** = dual energy x-ray absorptiometry; **FDA** = United States Food and Drug

**Administration LS** = least significant **PTH** = ; **C** change;

parathyroid hormone

## INTRODUCTION

The United States Food and Drug Administration (FDA) approved the recombinant form of teriparatide [human parathyroid hormone (1-34)]; (Forteo, Eli Lilly

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and Company, Indianapolis, IN, USA)] for clinical use on November 26, 2002. Product labeling regarding use of teriparatide can be viewed in the package insert of this new therapy for osteoporosis. Indications, contraindications, and guidance for monitoring teriparatide therapy are summarized in Tables 1 through 4. These recommendations are based on data from a pivotal clinical trial and additional smaller studies in men and postmenopausal women (1-2).

As would be expected with the initial use of any therapeutic agent, questions concerning use of teriparatide have arisen since its approval. In an attempt to provide early answers to these questions, clinicians with wideranging experience with investigational and clinical use of teriparatide met in a workshop setting to discuss common questions and formulate advice regarding how best to use this new agent. Admittedly, the resulting recommendations more often reflect individual opinion and perspective than evidence-based conclusions.

Undoubtedly, as experience with teriparatide becomes more extensive and more data are brought to bear on the issues discussed in this paper, ideas about teriparatide therapy will change. We feel, however, that there is a pressing current need to identify and answer common questions about teriparatide, and we offer our views in the hope that they may help clinicians manage their patients better using this promising new therapeutic agent.

This report is based upon the following 6 key goals identified during our meeting:

1. Develop a framework for identifying patients who should and should not be considered for teriparatide therapy
2. Recommend a core set of baseline tests that should be considered before initiating teriparatide therapy
3. Recommend approaches to monitoring patients receiving teriparatide
4. Consider the influence of previous or concurrent antiresorptive therapy on teriparatide use
5. Consider ways in which bone density can be maintained after teriparatide is discontinued
6. Discuss "real-world" issues in teriparatide therapy, including adverse events, utilization, and reimbursement

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These questions make up the framework for the following statements, which reflect the consensus of the group.

**CONSENSUS STATEMENTS**

**Who Should be Considered for Teriparatide Therapy?**

Consistent with FDA guidelines, we agree that teriparatide treatment should be reserved for patients with osteoporosis who are at "high-risk" for fracture. Guidelines for identifying such patients are summarized in Table 1. Certainly, patients who have sustained one fragility fracture are at high risk for having another (3-5). Second, patients with T-scores below -3.0 at the lumbar spine, hip, or forearm could be at high risk, especially if they are over 70 years of age and/or have other well-defined risks for fracture.

Patients who sustain fractures while on antiresorptive regimens or are losing bone mass (i.e., exceeding the least significant change [LSC] of serial measurements) should be considered candidates for teriparatide therapy, even though these two concerns cannot be equated with treatment failure. Incidentally, clinicians performing dual x-ray absorptiometry (DXA) must know how to determine LSC values before accurate interpretations of serial BMD (bone mineral density) changes can be made (6,7). Also, while the definition of "nonresponse" to therapy may be controversial, patients who lose significant BMD should be considered non-responders or noncompliant patients.

Likewise, patients may continue to sustain fractures while on effective antiresorptive therapy. This circumstance is not necessarily due to therapeutic failure, as no existing therapeutic agent completely abolishes fracture

approximately 50% of cases, so a substantial percentage of all individuals on appropriate therapy will sustain further fractures (8-14). Thus, a fracture event in the presence of seemingly appropriate antiresorptive therapy does not necessarily indicate treatment failure, but does raise significant concerns. In these patients, an aggressive search for secondary causes of bone loss should be undertaken, and poor treatment compliance with the antiresorptive regimen must be considered (15). Without evidence that adding to or changing teriparatide therapy will prevent further fractures beyond the reduced risk achieved by antiresorptive therapy, teriparatide is nevertheless a reasonable option.

Teriparatide may also be indicated for patients who have had a reasonable response to therapy with antiresorptive agents (i.e., improvement in BMD with no fragility fractures) but who still have remarkably low T-scores. Low T-scores are of particular concern in patients on long-term antiresorptive therapy in whom improvements become less dramatic over time. This view recognizes an opposing one: namely that such patients may be doing about as well as can be expected, so converting to teriparatide therapy may not bring additional clinical improvements. Inertia on the part of the physician with regard to changes in course is, therefore, understandable. We nevertheless feel that in some patients with advanced age, prevalent vertebral fractures, or low BMD level, the persistent high risk of additional fractures justifies teriparatide therapy (16-19) (Table 1).

While it is recognized that fracture incidence increases as the number of risk factors for fracture increase, it is not as clear that the benefit of fracture reduction with osteoporotic therapy improves as the

**Table 1**  
**Indications for Teriparatide Administration**

- High-risk patients (those with prevalent vertebral fractures, T-score of -3.0 or lower, or increased age [women and men 70 years of age or older])
- Patients losing BMD on currently available osteoporosis-specific pharmacological agents without an identifiable secondary cause
- Patients sustaining fractures without an identifiable secondary cause while on currently available osteoporosis-specific pharmacological agents
- Patients with glucocorticoid-induced osteoporosis (off-label indication)
- Patients who cannot tolerate an oral bisphosphonate or in whom administration of an oral bisphosphonate may not be safe (scleroderma esophagus, achalasia, etc)

BMD = bone mineral density.

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may not be a function of baseline patient fracture risk, though these findings may be somewhat biased, as most osteoporosis-treatment clinical trials have involved higher-risk patients. Nevertheless, clinicians intuitively consider additional therapies for patients perceived to be at persistently high-risk for additional fracture.

Teriparatide therapy may also be appropriate for patients who ordinarily would be candidates for oral bisphosphonate or raloxifene therapy, but for whom there are contraindications or issues of intolerance. Patients who, for example, have gastrointestinal intolerance to a bisphosphonate, or who have lower extremity venous disease or a thromboembolic event that precludes raloxifene or estrogen therapy, may be appropriate candidates for teriparatide therapy, assuming that they are at high-risk as defined above. An alternative to teriparatide therapy in these instances might be the off-label use of the intravenous bisphosphonates pamidronate or zoledronate. Use of these parenteral bisphosphonates is associated with increases in bone density and reductions in bone turnover, though data associating these surrogate markers of treatment efficacy with fracture reduction are not currently available.

Glucocorticoid-induced osteoporosis is a particularly noteworthy disorder for which teriparatide might be considered. Although both alendronate and risedronate are registered for treatment of glucocorticoid osteoporosis (22-24), FDA approval of teriparatide does not specifically name glucocorticoid-induced osteoporosis as an indication for therapy. The terminology "high-risk" would, however, certainly include some patients receiving glucocorticoids. Individuals who are to receive prolonged, high-dose glucocorticoid therapy, and who would therefore be at high risk would be, in our view, candidates for teriparatide therapy. This view does not necessarily include premenopausal women on glucocorticoids, in whom the risks of teriparatide therapy are unknown. Although no fracture data are available regarding postmenopausal women with glucocorticoid-induced osteoporosis treated with teriparatide, observed changes in bone density, bone markers, and recent data on changes in bone geometry suggest that teriparatide may well lead to fracture reduction in these individuals (25-27).

Is teriparatide necessarily *the* drug of choice for patients with osteoporosis at high risk for fracture? Bisphosphonates are also highly efficacious in such individuals. In fact, the major clinical trials with alendronate and risedronate and raloxifene enrolled patients at high risk for fracture. These pivotal clinical trials clearly show that antiresorptive agents reduce incident vertebral fracture in high risk patients (7-13). Bisphosphonates also reduce the incidence of nonvertebral fractures, including hip fracture. In patients with recent vertebral fracture, in whom the risk for a subsequent vertebral or hip fracture is high if left untreated, risedronate has been shown in prospective trials to reduce vertebral fracture risk within one year of therapy (28). In

post-hoc analyses, alendronate and raloxifene also reduced clinical vertebral fractures (29-30). Thus, there is evidence of rapid reduction in fracture events with use of the antiresorptive agents. In the case of teriparatide, the study design (x-rays prior to treatment and 18 months after treatment was started) does not allow one to draw similar conclusions about a "rapid" therapeutic effect of this agent (1). In fact, the time course of non-vertebral fracture events suggests that teriparatide may not significantly reduce fractures until after approximately 1 year of therapy. On the other hand, preclinical data support rapid effects of teriparatide on bone geometry, bone microarchitecture, and increased bone strength, even though the remodeling space increases with early teriparatide use (31-37). Impressive effects of teriparatide on the elements of bone strength such as trabecular connectivity and cortical width (38-39) may be expected to promote early fracture reduction as well, especially at the lumbar spine.

One can quite reasonably wonder about the rationale for using teriparatide, which is much more expensive than the bisphosphonates, in treatment of patients at high risk for osteoporotic fracture, in whom both teriparatide and the bisphosphonates may lead to fracture risk reduction of similar magnitude, as appears to be the case based on existing data. While bisphosphonates maintain microarchitecture that may contribute to improvements in bone strength (40,42), we note that additional parameters of bone quality are affected by teriparatide (39). If one has the option to use a therapeutic agent that may restore or reconstruct skeletal microstructure and favorably influence geometrical parameters of bone therefore, it is attractive to use it.

#### **Who Should Not be Considered for Teriparatide Therapy?**

Certainly, individuals who do not have advanced osteoporosis at high risk for fracture should not be considered for teriparatide therapy. This agent is not recommended for preventive therapy, or in patients whose T-scores or other assessments do not reflect advanced osteoporotic disease. Patients with known contraindication to teriparatide use should, of course, not receive this drug (Table 2). A potentially unclear contraindication to its use is "prior skeletal irradiation." This FDA term is specific for therapeutic irradiation, not diagnostic irradiation. Teriparatide is, further, not to be considered for prevention of early postmenopausal bone loss, a group of patients who may have small reductions in BMD and are at low absolute fracture risk. Finally, cost considerations are important. If insurance coverage is not available and the patient cannot afford the expense of this agent, one should advise another therapeutic approach.

#### **What Baseline Tests Should be Obtained Prior to Starting Teriparatide?**

Clinical tests that we recommend prior to initiating therapy with teriparatide are listed in Table 3. We strongly advise that patients undergo serum calcium determination prior to starting teriparatide therapy, primarily because it is contraindicated in patients with hypercalcemia. Baseline renal function tests and creatinine clearance determinations are also useful. A routine 24-hour urine calcium determination does not appear necessary, as urinary calcium excretion did not change significantly during the pivotal clinical trial (1). In patients with history of nephrolithiasis, however, 24-hour urinary calcium determination should be made, possibly in concert with other tests, to explore the etiology of the kidney stones.

Because serum uric acid levels rise slightly during teriparatide treatment, a baseline uric acid level would be helpful, particularly in patients with histories of hyperuricemia or gout. Baseline bone density should obviously be obtained, even in patients with overt skeletal features of osteoporosis or who have sustained fragility fractures. Our group also felt that since teriparatide has a major effect on markers of bone turnover, baseline evaluation of these markers might be useful. Patients should therefore undergo baseline evaluation of the bone formation marker bone-specific alkaline phosphatase (BSAP) or osteocalcin, and a bone resorption marker [collagen-cross links: N- or C-telopeptide (NTX or CTX) or pyridinoline (DPD)] (43-44). The total alkaline phosphatase level could be ordered first, since it is less expensive than the BSAP, and if this value is elevated, the BSAP can be ordered to identify the tissue source of the total alkaline phosphatase. Since teriparatide is contraindicated in patients with unexplained elevations of BSAP, an alkaline phosphatase level should be determined at baseline both for initial assessment purposes and for possible monitoring over time. If the BSAP level is elevated, a search for the etiology of the increased BSAP is indicated (Paget's disease, metastatic disease to bone,

hyperparathyroidism, osteomalacia, etc), as teriparatide would be contraindicated in such cases.

We also recommend that baseline 25 hydroxyvitamin D (25 OHD) and parathyroid hormone (PTH) levels be obtained before initiating teriparatide therapy. Vitamin D insufficiency is relatively common, and can be associated with elevated PTH levels. The normal range for 25-OHD, the storage form of vitamin D, should be above the now accepted lower limit of the normal physiological range (20 ng/ml), not the laboratory reference range (9 ng/ml) (45). The need for measuring PTH before starting therapy is in part because PTH elevation could reflect an occult vitamin D deficiency. Another reason is that a new phenotype of primary hyperparathyroidism is now recognized, in which serum calcium levels are normal but PTH levels are elevated. These patients do not have any obvious cause for secondary hyperparathyroidism, and in fact, may represent the earliest manifestation of primary hyperparathyroidism (46). It would seem unwise to begin teriparatide therapy in patients with even the earliest manifestations of primary hyperparathyroidism. Our group felt that a PTH level above the normal range in a normocalcemic patient with no other identifiable cause of secondary hyperparathyroidism contraindicates use of teriparatide. Clinical tests that we recommend prior to initiating therapy with teriparatide are listed in Table 3.

#### How Should Patients be Monitored While on Teriparatide?

Essential monitoring tests for patients treated with teriparatide are described in Table 4. Patients experience impressive early increases in vertebral BMD while on teriparatide therapy, according to evaluation by dual energy x-ray absorptiometry (DXA) technology (1). Increases in BMD associated with use of antiresorptive therapies are linked to fracture reduction, although the relationship between the magnitude of increase in BMD

**Table 2**  
**Contraindications to the Use of Teriparatide\***

- 
- Hypercalcemia
  - Paget's disease
  - Unexplained elevation of BSAP
  - Osteogenic sarcoma
  - Unfused epiphysis
  - Previous irradiation to the skeleton
  - Pregnancy or breast-feeding
  - Bone cancer or metastatic cancer to bone
  - Allergic reaction to PTH or to ingredients in the vehicle
- 

\*Teriparatide prescribing information.

BMD = bone mineral density; BSAP = bone-specific alkaline phosphatase; PTH = parathyroid hormone.

and the magnitude of fracture reduction is not proportional (47-50). Yet, serial BMD determinations are helpful in monitoring teriparatide therapy, and patient awareness of improvements in BMD may improve compliance (51).

In accordance with the Bone Mass Measurement Act, a regulation that applies only to the Medicare population, bone mass measurement may be permitted 1 year after initiation of an FDA-approved therapy. With teriparatide, changes in bone density in the lumbar spine are so rapid and of such a large magnitude that it is likely significant changes exceeding the LSC will be seen after 1 year of therapy. As to whether guidelines for use of BMD for monitoring results of antiresorptive agents (i.e., monitoring every 23 months after the first year of therapy) will be applicable to teriparatide is not clear. Clinicians will be influenced by these guidelines dictating reimbursement for the test, but will also recognize that there are situations in which one is justified in obtaining a bone mass measurement earlier than this relatively long 23-month waiting period.

Expected large changes in BMD apply primarily to the lumbar spine after teriparatide therapy. The hip typically shows more sluggish, less dramatic change in BMD, as is seen during therapy with antiresorptive agents as well. The distal third of the radius does not demonstrate significant increases in BMD after teriparatide therapy as measured by DXA though bone strength does appear to improve in the forearm, as the cross sectional area of the radius increases during teriparatide therapy (39). It is well known that areal changes in bone without any changes, or even a decline, in areal BMD can be associated with improvements in bone strength. On a biomechanical basis, therefore, even without any change in areal BMD, teriparatide appears efficacious at the forearm. Measurement of true bone density, as assessed by instruments such as quantitative computed tomography that measure bone mass in  $g/cm^3$ , may more completely

**Table 3**  
**Suggested Clinical Tests Prior to Initiating Teriparatide Therapy**

BMD by DXA (spine and hip)	
▲	Total serum calcium
▲	Total serum alkaline phosphatase
▲	25-hydroxyvitamin D
▲	Parathyroid hormone
▲	Creatinine clearance

BMD = bone mineral density; DXA = dual energy x-ray absorptiometry.

assess the global effects of teriparatide on bone mass (52-53). Teriparatide affects markers of bone turnover in ways opposite to changes seen after antiresorptive therapy. While antiresorptive

agents reduce levels of bone turnover markers (54-57), teriparatide increases them (58). Another difference is that significant changes in levels of bone turnover markers are associated treatment with teriparatide (e.g., up to 3 times higher than baseline measurements) in contrast to the antiresorptive agents. It would appear then that bone formation markers may be useful indicators of the efficacy of teriparatide treatment. This expectation contrasts with those in the case of antiresorptive agents, in which reductions in bone turnover, although substantial, are often not great enough in individual patients to meet the criteria of significance (i.e., the LSC).

While reductions in bone resorption and bone formation marker levels are correlated with reductions in both new vertebral and non-vertebral fracture risk during treatment with the two FDA-approved bisphosphonates, the relationship between the increase in formation markers and reduction in fracture risk has not been studied regarding teriparatide therapy. It is reasonable, nevertheless, to expect that such a relationship exists. The increase in BSAP or osteocalcin seen as early as 1 to 3 months after initiation of teriparatide therapy has the potential to provide useful, early feedback about the effectiveness of teriparatide in a given patient.

Another point of interest regarding bone resorption markers during teriparatide therapy is that the increase in these markers does not appear to be sustained. After 12 to 18 months of teriparatide treatment, rates of bone formation and levels of bone resorption markers tend to decline to or toward baseline measurements, though more data is needed regarding the kinetic processes involved in these changes. The eventual fall in bone marker levels with continued use of teriparatide may signal a waning of the anabolic effect on bone density, though in some clinical trials BMD continued to increase (59). This

eventual decline in bone marker levels may not, therefore, signal the termination of other salutary effects of the drug on other bone qualities. Certainly, available fracture data suggest that teriparatide has effects that extend well beyond dynamic changes in bone markers (60).

What safety endpoints are reasonable to monitor with regard to teriparatide? Existing clinical trials with teriparatide indicate no major risk of hypercalcemia at the FDA-approved dosage of 20  $\mu$ g daily. Nevertheless, we feel that it is prudent to obtain a serum calcium level 1 month after starting teriparatide therapy, with blood samples obtained within 16 hours after the last dose of teriparatide. Other monitoring parameters are optional, as there is no evidence that patients develop hypercalciuria or abnormalities in liver or renal function. In patients with elevated serum uric acid levels or in whom these levels are in the upper range of normal, it seems useful to remeasure serum uric acid levels within a month of initiating teriparatide therapy.

#### Should Antiresorptive Agents be Continued or Stopped When Teriparatide Therapy is Begun?

Many patients who may be candidates for teriparatide are currently on antiresorptive agents. In patients previously treated with estrogen, teriparatide appears to be associated with prompt, significant increases in bone density (61). This observation has also been noted in patients with glucocorticoid-induced osteoporosis who have previously been treated with estrogen (27,62). In an observational study by Ettinger et al, among patients treated with a 28-month course of raloxifene (another modest antiresorptive agent), subsequent effects of teriparatide do not appear slowed (63). In the same study, patients previously treated with alendronate for 28 months were monitored after being switched to teriparatide treatment. Among these patients, bone density did not change appreciably at the lumbar spine during the first six months of teriparatide treatment, though a slight decline in bone density was noted at the hip during this period. Over the following 12-month period, however, at both the lumbar spine and hip, bone

density rose at a rate comparable to that observed in previous raloxifene users (63). At the end of the 18-month observation period, however, gains in bone density among the previous alendronate users were substantially lower than those noted among previous raloxifene users. These observations raise the possibility that the use of a potent antiresorptive agent like alendronate may be associated with a sluggish initial response to teriparatide with respect to BMD. No data exist regarding this question in individuals previously treated with risedronate.

These observations led to the differing opinions that either teriparatide should not be used in patients previously treated with alendronate for any substantial period of time, or that the bisphosphonate agent should be discontinued and teriparatide treatment "held" for a 6- to 12-month period to allow bone turnover to increase. The latter view holds that the greater the inhibition of bone resorption, the longer it will take for teriparatide to improve bone density. However, other factors must be considered as well, such as the duration of suppressive action of the bisphosphonate on bone turnover. There are, however, no current data available regarding the influence of previous bisphosphonate use on other parameters of teriparatide efficacy such as bone geometry, bone microarchitecture, and fracture rate.

How should the clinician regard this vexing issue? Since there is no evidence that previous estrogen or raloxifene therapy impairs subsequent effects of teriparatide, one could continue these agents when beginning therapy with teriparatide. With alendronate, however, one may want to discontinue therapy when teriparatide is initiated, as alendronate's effects are so long lasting that there does not appear to be any rationale for waiting a period of time before beginning teriparatide. No comparable data are available for risedronate with regard to this question. One might speculate, however, that previous risedronate use may not impair subsequent effects of teriparatide on BMD to the same extent as alendronate because risedronate does not reduce bone turnover to the extent alendronate does. Risedronate may, further, be released from the bone surface after

**Table 4**  
**Monitoring of Patients on Teriparatide Therapy**

- 
- ▲ Spine and total hip BMD by DXA 12 months after initiation of treatment
  - ▲ Avoid forearm BMD measurement by DXA (see text)
  - ▲ Possibly quantitative computerized tomography of the wrist (developmental)
  - ▲ Biochemical markers of bone formation at baseline and 3-6 months after beginning teriparatide, such as bone-specific alkaline phosphatase or serum osteocalcin
- 

**BMD** = bone mineral density; **DXA** = dual energy x-ray absorptiometry.



discontinuation more quickly in the case of alendronate (64,65).

#### **Combining Antiresorptive and Anabolic Therapy**

The recent PaTH study provides interesting information regarding the question of combining antiresorptive and anabolic therapy (66). This study tested PTH (1-84) alone and in combination with alendronate compared to alendronate alone in 238 postmenopausal women with osteoporosis. Patients had not previously been treated with antiresorptive therapy. Using quantitative computed tomography, these investigators demonstrated no advantage to combination therapy compared to PTH alone. DXA analysis revealed greater increases in total hip BMD with combination therapy in this investigation, and a greater increase in total body BMD was noted with combination therapy in a related study by Finkelstein et al (67). In some respects and at some sites, the presence of alendronate seemed to retard the effects of PTH. Again, these studies provide no data regarding the effect of these agents on fracture rates or bone microarchitecture. At this point, therefore, there may not be any advantage gained by combination therapy with PTH and alendronate, though available data are very preliminary.

#### **How Can Teriparatide's Effects on BMD be Sustained After Teriparatide Discontinuation?**

The use of a relatively short-term anabolic therapy (18-24 months) raises the obvious question of what to do after teriparatide treatment is discontinued. Studies involving estrogen treatment have shown that bone mass is maintained when estrogen therapy is continued after teriparatide therapy has been stopped (62,68). Yet, these studies by Lindsay, Cosman, and Lane did not include an experimental arm in which antiresorptive therapy was discontinued, so do not evaluate what happens to BMD after discontinuation of teriparatide in the absence of ongoing antiresorptive therapy. Data from large existing clinical trials in women and men suggest that bone loss begins rapidly among patients not immediately placed on antiresorptive therapy after teriparatide discontinuation (2,68). In contrast, preliminary data from these trials suggest that BMD is maintained in patients begun on antiresorptive therapy immediately after teriparatide is discontinued. Finally, in the phase II clinical trial evaluating the effect of rhPTH (184) in postmenopausal women over 12 months, additional improvement was noted in spine BMD as measured by DXA when alendronate was added after PTH was discontinued (69,70).

Generalizability of conclusions reached in the above studies is limited case, however, because of lack of prospective study design and, in some instances, small patient populations. There are, further, no data available regarding microarchitectural or geometric changes after teriparatide is discontinued with or without sustained

antiresorptive treatment. In an analysis of fracture incidence after teriparatide discontinuation, data from the pivotal clinical trial does not allow determination of whether bisphosphonate use was important after teriparatide therapy with regard to the prolonged fracture protection experienced by these patients, though the number of observed fracture events was small (60). Again, the post-hoc observational nature of these requires confirmation in future studies using a more rigorous experimental design. Until better evidence is available, it seems wise take measures to prevent a decline in BMD after teriparatide therapy is terminated. An antiresorptive agent, in our opinion, should therefore be used regularly after teriparatide is discontinued.

#### **"Real-World" Issues in Teriparatide Treatment:**

**Adverse Events, Utilization and Reimbursement** In our experience, teriparatide is well tolerated. Patients quickly learn to self-administer teriparatide by subcutaneous injection. The "pen" injector with disposable 31-gauge needles offers almost painless injection, and a nurse-educator or other knowledgeable health care professional optimizes the patient education process. A few patients have developed hypercalcemia 2 weeks after teriparatide treatment was begun. Teriparatide was discontinued in these instances, and serum calcium levels returned to normal in 2 days each case. When oral calcium intake was subsequently reduced by 500 mg/day, hypercalcemia did not recur once teriparatide therapy was restarted in these patients. In most cases, patients' original calcium intake could be resumed without hypercalcemia appearing again. Allergic wheals have been observed at the teriparatide injection site on occasion. In one case, a patient who developed severe large wheals at the injection site was successfully "desensitized" to teriparatide under treatment by an allergist. Severe headache has led to discontinuation of teriparatide therapy in one patient; in another, severe headaches were avoided when the patient drank 12 ounces of water at the time of teriparatide administration. Two patients have sustained transient heart palpitations, and one patient had to discontinue teriparatide treatment because of reproducible severe vertigo that came on 8 hours after teriparatide administration. Two patients suffered incapacitating leg cramps relieved by drinking a sports rehydration drink soon after teriparatide administration. These adverse events are rare relative to the number of patients we have collectively treated with teriparatide over the past 6 months. It is our opinion, therefore, that the vast majority of patients tolerate teriparatide without significant adverse effects.

The FDA approved the recombinant form of teriparatide with a "black box warning" because rat toxicity studies revealed the development of osteosarcoma when high doses of teriparatide were administered for prolonged periods of time. It is important for the physician to discuss results of these preclinical studies with patients

and to point out that comparable tumors have not been noted among monkeys given teriparatide in a comparable manner. It is also noteworthy that in disorders of chronic PTH excess (primary and secondary hyperparathyroidism, and parathyroid carcinoma), the number of reports of osteosarcoma is extremely small (71), with the occasional report well below the incidence rate one might expect based on coincidence.

Prior skeletal irradiation is a known contraindication to teriparatide use. The teriparatide FDA label states that the drug should not be taken "if you have had radiation therapy involving your bones." The intention of the FDA in this instance was to exclude therapeutic radiation, not diagnostic skeletal irradiation, radioiodine treatment, electron beam radiation, or some forms of brachytherapy such as installation of radioactive pellets or rods into body cavities. In the latter cases the radiation therapy physician should be asked whether the patient receiving brachytherapy sustained a radiation dose sufficient to expose adjacent bone.

#### Concluding Comments

The introduction of teriparatide marks an exciting new advance in our field, as a safe, effective anabolic agent that improves bone density, bone microarchitecture, and bone size is now available. Patients at high risk will clearly benefit from treatment with this new agent. In this article we have discussed a number of important issues that have emerged with the approval of teriparatide. As we gain more experience with teriparatide and as more information becomes available regarding how to use it, we should be able to address many of these questions more thoroughly in the near future. Other questions still remain to be raised and await greater understanding. A representative sample of some outstanding questions related to use of teriparatide is listed below.

- Does teriparatide reduce fracture rates to a greater degree than is currently achieved by antiresorptive regimens alone?
- Can patients achieve equal clinical benefits with shorter duration or intermittent administration of teriparatide therapy?
- Can patients achieve greater clinical benefits with longer duration of teriparatide use?
- Could patients benefit by retreatment after a first course of teriparatide (i.e., a "cyclical" teriparatide regimen)?
- The past, present, and future use of antiresorptive therapy needs further clarification in the context of teriparatide use.
- Does teriparatide reduce the incidence of hip fracture?
- Does teriparatide enhance fracture healing?
- How can one practically measure the efficacy of teriparatide with indices beyond the use of bone density and bone markers?

- In addition to glucocorticoid-induced osteoporosis, what other secondary causes of osteoporosis could conceivably be treated with teriparatide?

Although there remains much to be learned about this anabolic agent, it is clear that its availability offers clinicians new avenues of opportunity in the treatment of women and men with osteoporosis.

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