

ANGELO LICATA, MD, PhD*

Director, Center for Space Medicine; Consultant, Departments of Biomedical Engineering and Endocrinology, Diabetes, and Metabolism, Metabolic Bone Center, Cleveland Clinic; Editor-in-Chief, *Clinical Reviews in Bone and Mineral Metabolism*; Editor-In-Chief, National Osteoporosis Foundation *Osteoporosis Clinical Updates*

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.

MOST 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.

doi:10.3949/ccjm.76a.08041

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

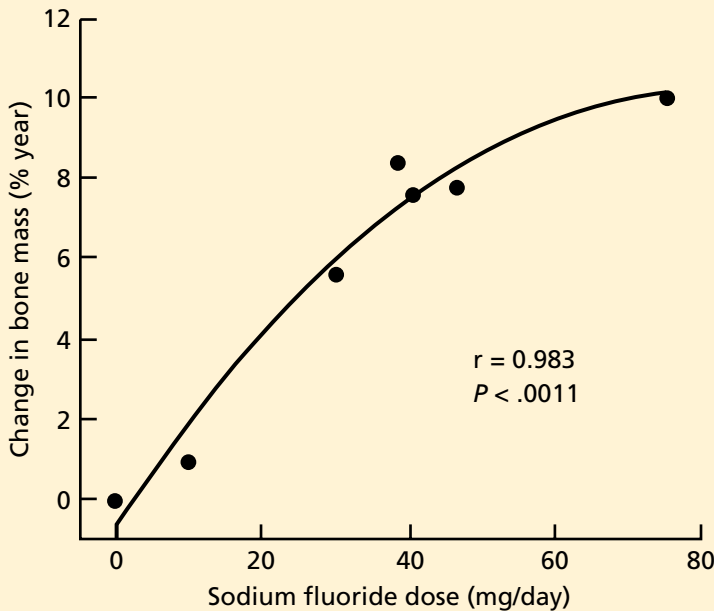


FIGURE 1. Although the dose-response curve indicates that sodium fluoride increases bone mass, this drug actually increases the fracture rate because it makes bone more brittle.

KLEEREKOPER M, BALENA R. FLUORIDES AND OSTEOPOROSIS. ANNU REV NUTR 1991; 11:309-324 REPRINTED WITH PERMISSION © 1991 FROM ANNUAL REVIEWS, WWW.ANNUALREVIEWS.ORG

a specific cutoff of bone mass as a risk for fracture and not the statistical T scores or Z scores that we know.¹⁻³

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.⁴ 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 insuf-

ficient 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.^{5,6} 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.⁶

■ 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 hallmark 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).⁷ Many subsequent observations also brought into question how important density is.^{8,9}

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

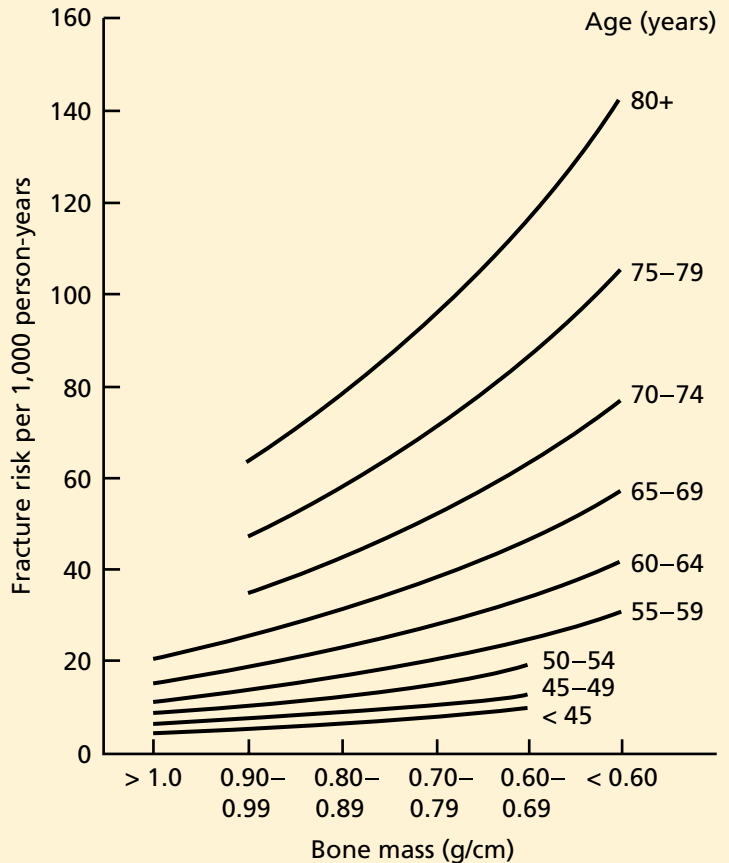


FIGURE 2. Estimated incidence of fracture as a function of age and bone mass in 521 white women followed for an average of 6.5 years.

HUI SL, 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).^{10,11} Cummings et al,¹² reviewing data from the Fracture Intervention Trial,¹³ 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.¹⁴

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, ARNAUD 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.¹⁵ 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).¹⁶

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.¹⁷

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,^{18–20} and a fracture risk assessment tool is being implemented worldwide.^{21–23} 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) 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.²⁴ Vitamin D deficiency, hyperparathyroidism, and celiac disease are common problems. Or, perhaps, patients may not be adherent to therapy.^{25–27} 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.^{28–30}

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

REFERENCES

1. Parfitt AM. Interpretation of bone densitometry measurements: disadvantages of a percentage scale and a discussion of some alternatives. *J Bone Miner Res* 1990; 5:537–540.
2. Webber CE. Uncertainties in bone mineral density T-scores. *Clin Invest Med* 1998; 21:88–93.
3. Blake GM, Fogelman I. Interpretation of bone densitometry studies. *Semin Nucl Med* 1997; 27:248–260.
4. Miller PD. Guidelines for the diagnosis of osteoporosis: T-scores vs fractures. *Rev Endocr Metab Disord* 2006; 7:75–89.
5. Kleerekoper M, Balena R. Fluorides and osteoporosis. *Annu Rev Nutr* 1991; 11:309–324.
6. Riggs BL, Hodgson SF, O'Fallon WM, et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med* 1990; 322:802–809.
7. Hui SL, Slemenda CW, Johnston CC Jr. Age and bone mass as predictors of fracture in a prospective study. *J Clin Invest* 1988; 81:1804–1809.
8. Seeman E, Delmas PD. Bone quality—the material and structural basis of bone strength and fragility. *N Engl J Med* 2006; 354:2250–2261.

9. **Seeman E.** Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? *Bone* 2007; 41:308–317.
10. **Guyatt GH, Cranney A, Griffith L, et al.** Summary of meta-analyses of therapies for postmenopausal osteoporosis and the relationship between bone density and fractures. *Endocrinol Metab Clin North Am* 2002; 31:659–679.
11. **Neer RM, Arnaud 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.
12. **Cummings SR, Karpf DB, Harris F, et al.** Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med* 2002; 112:281–289.
13. **Black DM, Cummings SR, Karpf DB, et al.** Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996; 348:1535–1541.
14. **Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD.** Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. *J Bone Miner Res* 2002; 17:1–10.
15. **Qu Y, Wong M, Thiebaud D, Stock JL.** The effect of raloxifene therapy on the risk of new clinical vertebral fractures at three and six months: a secondary analysis of the MORE trial. *Curr Med Res Opin* 2005; 21:1955–1959.
16. **Singer FR, Eyre DR.** Using biochemical markers of bone turnover in clinical practice. *Cleve Clin J Med* 2008; 75:739–750.
17. **Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD.** Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. *J Bone Miner Res* 2000; 15:1526–1536.
18. **Siminoski K, Leslie WD, Frame H, et al.** Recommendations for bone mineral density reporting in Canada: a shift to absolute fracture risk assessment. *J Clin Densitom* 2007; 10:120–123.
19. **Czerwinski E, Badurski JE, Marciniowska-Suchowierska E, Osielec J.** Current understanding of osteoporosis according to the position of the World Health Organization (WHO) and International Osteoporosis Foundation. *Ortop Traumatol Rehabil* 2007; 9:337–356.
20. **Siris ES, Brenneman SK, Barrett-Connor E, et al.** The effect of age and bone mineral density on the absolute, excess, and relative risk of fracture in postmenopausal women aged 50-99: results from the National Osteoporosis Risk Assessment (NORA). *Osteoporos Int* 2006; 17:565–574.
21. **Borgstrom F, Kanis JA.** Health economics of osteoporosis. *Best Pract Res Clin Endocrinol Metab* 2008; 22:885–900.
22. **Honig S.** Treatment strategies for patients with low bone mass: the younger postmenopausal female. *Bull NYU Hosp Jt Dis* 2008; 66:240–243.
23. **Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E.** FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008; 19:385–397.
24. **Painter SE, Kleerekoper M, Camacho PM.** Secondary osteoporosis: a review of the recent evidence. *Endocr Pract* 2006; 12:436–445.
25. **Lau E, Papaioannou A, Dolovich L, et al.** Patients' adherence to osteoporosis therapy: exploring the perceptions of postmenopausal women. *Can Fam Physician* 2008; 54:394–402.
26. **Zambon A, Baio G, Mazzaglia G, Merlino L, Corrao G.** Discontinuity and failures of therapy with bisphosphonates: joint assessment of predictors with multi-state models. *Pharmacoepidemiol Drug Saf* 2008; 17:260–269.
27. **Ringe JD, Christodoulakos GE, Mellstrom D, et al.** Patient compliance with alendronate, risedronate and raloxifene for the treatment of osteoporosis in postmenopausal women. *Curr Med Res Opin* 2007; 23:2677–2687.
28. **Eisman JA, Civitelli R, Adami S, et al.** Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. *J Rheumatol* 2008; 35:488–497.
29. **Lewiecki EM, Babbitt AM, Piziak VK, Ozturk ZE, Bone HG.** Adherence to and gastrointestinal tolerability of monthly oral or quarterly intravenous ibandronate therapy in women with previous intolerance to oral bisphosphonates: a 12-month, open-label, prospective evaluation. *Clin Ther* 2008; 30:605–621.
30. **Lewiecki EM.** Intravenous zoledronic acid for the treatment of osteoporosis. *Curr Osteoporos Rep* 2008; 6:17–23.

ADDRESS: Angelo Licata, MD, PhD, Department of Endocrinology, A53, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail licataa@ccf.org.