



How can we tell who will fracture? Beyond bone mineral density to the new world of fracture risk assessment

Dr. Susan E. Brown, PhD

Bone density testing: falling short of expectations

More than 25 years ago, I first consulted with several of the individuals who developed the bone density testing machines. The hope was clear — if we could measure bone density, we would be able to predict who will experience an osteoporotic fracture. The concept was quite simplistic; it assumed that the most important fracture-determining factor was low bone density. Over the last few decades, bone density testing has become widespread; yet the hope of a simple, straight predictor of fracture has faded.

Today, nearly three decades later, we realize that you cannot predict who will fracture from measurements of bone density alone. In fact, recent large studies show that a large percentage of people who do fracture do not have osteoporotic bone density, but actually have only osteopenia or even normal bone density. Furthermore, many people with an osteoporotic bone density never fracture.

Most fractures occur in those who do not have osteoporotic bone density

As early as the mid 1980's, thoughtful osteoporosis researchers noted that hip fractures could not simply be attributed to low bone mass. As Steven Cummings wrote in 1985, "Patients with hip fractures do not appear to be distinctly more osteoporotic than persons of similar age. Therefore, factors besides bone mass, such as a tendency to fall, may be important determinants of which elderly persons will have fractures; thus, measurements of bone mass might not be a reliable way to identify those at greatest risk of hip fracture."¹


Over the last two decades numerous clinical trials have borne out the truth of Dr. Cummings's early observation. For example, the U.S. Study of Osteoporotic Fractures (SOF) looked at 8,065 women 65 and older, following them for hip fracture incidence over a five year period. Within these five years, 243 hip fractures occurred, 54% of which were in women who did not have an osteoporotic bone density at the start of follow-up.² Further reports from this same Study of Osteoporotic Fractures database found that only 10% to 44% of osteoporotic fractures occurred in those with an osteoporotic bone density. As these authors summarize, "Finding effective prevention strategies for fractures in older women will require additional interventions beside [sic] preventions for bone loss, such as prevention of falls and other fracture risk factors."³

The same has been found true in other large studies of osteoporotic fractures, such as the 149,524-women U.S. NORA study. Over a one-year period in this large group of women (mean age 64.5), 2,259 new fractures were self-reported, including 393 hip fractures. Of those who fractured, a full 82% had a non-osteoporotic bone density (greater than -2.5 SD T score) and a full 67% had a T score greater than -2.0. In total, 6.4% of all women

¹ Cummings, SR. 1985. Are patients with hip fractures more osteoporotic? *Am J Med*, 78:487-494.

² Wainwright, SA. 2005. Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab*, 90(5):2787-2793.

³ Stone, KL, Seeley, DG, Lui, LY, et al. 2003. BMD at multiple sites and risk of fracture of multiple types: Long-term results from the study of osteoporotic fractures. *J Bone Miner Res*, 18(11):1947-1954.


Susan E. Brown, PhD
Center for Better Bones
605 Franklin Park Drive
East Syracuse, NY 13057
www.betterbones.com



had an osteoporotic bone density. Although fracture rates were highest in this “osteoporotic bone mineral density” group, these women experienced only 18% of all osteoporotic fractures and 26% of all hip fractures.⁴

All in all, many factors are as important or even more important indicators of fracture risk than is bone mineral density. For example, fracture after age 40, parental history of hip fracture, low body weight, a high rate of bone resorption, deficiencies of vitamins D and K, use of steroid medications, and several other factors are stronger fracture predictors than bone mineral density.⁵

The new fracture assessment tools: multiple risk factor assessment with and without bone density measurements

So a new question arises. How can we tell who will experience an osteoporotic fracture? We now realize that the answer lies not in any single factor like bone density, but rather in assessment of multiple risk factors. What we are already beginning to see is a series of assessment tools that allow individuals and health practitioners to sort out who is likely to fracture according to a series of important variables, not just according to bone mineral density. Further, we see that the operative risk factors may vary somewhat by populations studied.

New fracture risk assessment tools: post-menopausal women One of the best known early fracture assessment tools is the “The Fracture Index.” This index was developed using data from the large US Study of Osteoporotic Fractures (SOF). In the SOF, a total of 7,782 US women aged 65 and older were studied over five years.⁶

In the SOF, measurements over time were made of bone density and other variables which were thought to reflect upon bone strength. These variables were compared with actual fracture incidence allowing for the development of a fracture risk screening and assessment tool. With this large data base, researchers identified a seven-variable model which allowed them to make a fairly accurate prediction of the five-year risk of suffering an osteoporotic fracture for any individual.

So what were the factors and variables that seem to determine if one will fracture or not? According to the SOF research, the seven most important factors were found to be:

1. age
2. bone mineral density T-score
3. fracture after age 50
4. maternal hip fracture after age 50
5. weight less than or equal to 125 pounds (57 kg)

⁴ Siris, ES, Chen, YT, Abbott, TA, et al. 2004. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med*, 164:1108-1112; Siris, ES, Brenneman, SK, Barrett-Connor, E, et al. 2006. 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*, 17:565-574.

⁵ Heaney, RP. 2000. *Osteoporos Int*, 11(suppl 2):S43-S46; Brown, SE. 2008. Vitamin D and fracture reduction: An evaluation of the existing research. *Altern Med Rev*, 13(1):21-33; Vergnaud, P, Garnero, P, Meunier, PJ, et al. 1997. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: The EPIDOS study. *J Clin Endocrinol Metab*, 82:719-24; Kanis, JA, Borgstrom, F, De Laet, C, et al. 2005. Assessment of fracture risk. *Osteoporos Int*, 16(6):581-9.

⁶ Black, DM, Steinbuch, M, Palermo, L, et al. 2001. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporos Int*, 12(7):519-28.



6. smoking status
7. use of arms to stand up from chair

According to researchers, this simple seven-factor assessment was shown to be predictive of hip fracture, as well as other non-vertebral fractures. It is also interesting that this risk assessment was shown to be predictive of fracture likelihood with or without the incorporation of one's bone density into the assessment. Subjects with the greatest number of risk factors, even without accounting for bone mineral density, had a 14-fold increase risk of fracture as compared to those with the lowest number of risk factors.

In a similar fashion, the large Women's Health Initiative (WHI) study used its data to develop another five-year fracture risk assessment tool. This 7.6-year trial studied 93,676 women of various ethnic backgrounds, ages 50 to 79 at entry. They found that each year some 1.6% of all women suffered a hip fracture. From their analysis they developed a risk assessment tool identifying 11 key risk factors (not including bone density) to predict who would fracture a hip over the next five years. This model, based on these key risk factors, was found to be of similar predictive value as the more expensive bone density tests.⁷

The 11 key risk factors uncovered from the Women's Health Initiative (WHI) were:

1. age
2. self-reported health
3. weight
4. height
5. race/ethnicity
6. self-reported physical activity
7. history of fracture after age 54
8. parental hip fracture
9. current smoking
10. current corticosteroid use
11. treated diabetes

New fracture risk assessment tools: identifying osteopenic women at risk for fracture More than half of all low-trauma osteoporotic fractures among women occur in those who do not have an "osteoporotic" bone density; rather, they occur in women with an osteopenic bone density or, even in some cases, a normal bone density. Obviously in these cases we must look beyond bone density in our attempt to assess who is likely to fracture.

Data from the large US National Osteoporosis Risk Assessment (NORA) attempted to identify those osteopenic women at short-term risk for fracture. In the NORA study, 57,421 post-menopausal women ages 50-99 were identified as having osteopenia. That means they had a bone mineral density from -1.0 to -2.5 SD T-score. In this study, bone density was measured at the heel, forearm, or hand. These women had bone density lower than that of young women, but they did not have an "osteoporotic" bone density (-2.5 SD T-score or more). Of

⁷ Robbins, J, Aragaki, AK, Kooperberg, C, et al. 2007. Factors associated with 5-year risk of hip fracture in postmenopausal women. *JAMA*, 298(20): 2389-98.



the osteopenic women studied, 130 reported a new fracture within one year of the bone density measurement (Miller et al. 2004).⁸

Four risk factors were found to be the most important for identifying those at highest risk of short-term fracture. These were:

1. Previous fracture
2. Bone density T score of -1.8 or less
3. Self-rated poor health status
4. Poor mobility

Women with a previous fracture had a one-year fracture risk of 4.1%, followed by women with T-scores of -1.8 or less, or with poor health status. Nearly 2% of the women with poor mobility came to fracture within the year. About 1% of the osteopenic women not identified as being at risk experienced a fracture within the year. This 1% per year fracture incidence is the same as that found among women with normal bone density.

Other interesting findings of this study showed that being younger did not seem to protect the early post-menopausal women.

- Younger women, aged 50 to 59, that shared a similar risk profile to that of women aged 60 to 69 had a similar 1-year risk of fracture (1.6% as compared to 1.7%).
- Younger women aged 50 to 59 who were identified to be at increased risk had an absolute fracture risk of 2.6%. This was similar to that of the entire at-risk population of all ages (50 to 99 yrs).
- Younger women aged 50 to 59 with a history of previous fracture after age 45 had a 4.5% fracture risk. This is similar to the risk for women with an osteoporotic bone density.

New fracture risk assessment tools: the World Health Organization (WHO) master assessment The World Health Association (WHO) has over the years analyzed various large population-based studies to develop a fracture risk assessment tool based on clinical factors. This assessment tool is designed to be useful both with and without bone density measurements and indeed, this is important, as much of the world does not have access to bone density measurements.⁹ Completed in March 2008, the WHO Fracture Risk Assessment Tool identifies 10 factors found to increase fracture risk independent of bone mineral density. (See <http://www.shef.ac.uk/FRAX>.) The independent risk factors are:

- Age
- Sex
- Weight and height
- Previous fractures
- Parental hip fracture history

⁸ Miller, PD, Barlas, S, Breneman, SK, et al. 2004. An approach to identifying osteopenic women at increased short-term risk of fracture. *Arch Intern Med*, 164:1113-20.

⁹ Kanis, JA, Borgstrom, F, De Laet, C, et al. 2005. Assessment of fracture risk. *Osteoporos Int*, 16(6):581-9; Kanis, JA, Oden, A, Johnell, O, et al. 2007. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int*, 18(8):1033-46.



- Smoking status
- Glucocorticoid use
- Rheumatoid arthritis
- Secondary disorders linked to osteoporosis, such as type 1 diabetes
- Whether a person drinks three or more alcoholic beverages per day

WHO Fracture Risk Assessment

At age 40, a US Caucasian woman weighing 135 lbs at 5'8" with none of the WHO risk factors has a 2.3% risk of experiencing a major osteoporotic fracture within ten years. The same woman with five of the WHO risk factors has a 15% risk of experiencing a major osteoporotic fracture. At age 65, the same woman with none of the WHO risk factors has a 14% chance of experiencing a major osteoporotic fracture within ten years. This same woman at 65 with five of the WHO risk factors has a 55% risk of experiencing a major osteoporotic fracture. At age 80, this woman with none of the WHO risk factors has a 28% chance of experiencing a major osteoporotic fracture within ten years. This same 80-year old woman with five of the WHO risk factors has a 71% risk of experiencing a major osteoporotic fracture.

Age	Weight & Height	Number of Additional "WHO" Risk Factors	Risk % for a Major Osteoporotic Fracture within 10 Years
40	135 lbs. / 5'8"	0	2.3%
40	135 lbs. / 5'8"	5	15%
65	135 lbs. / 5'8"	0	14%
65	135 lbs. / 5'8"	5	55%
80	135 lbs. / 5'8"	0	28%
80	135 lbs. / 5'8"	5	71%

You may want to take this risk assessment yourself. It can be done with or without a bone density measurement. The link is: <http://www.shef.ac.uk/FRAX>

Does fracture risk vary by ethnicity?

This is a fascinating question which we have just begun to ask. I am confident the answer will be yes, risk does vary by ethnicity. Even with the little bit of existing research we have on the topic, we know that bone mineral density in African-American women does not carry with it the same risk of fracture as it does among Caucasian women. African-American women have about 30% fewer fractures at any given bone mineral density than Caucasian women.¹⁰ We also know that overall, Asians experience many fewer fractures than do Caucasians, yet their bone density is significantly lower.

The future of fracture risk assessment

As director of The Better Bones Foundation, I know that multi-variable risk assessments are indeed the tools of the future. I am not sure, however, whether the seven-variable model set forth by the US Study of Osteoporotic Fractures, the 11-factor model from the Women's Health Initiative, or even the new WHO assessment will end

¹⁰ Cauley, JA, Lui, LY, Ensrud, KE, Zmuda, JM, et al. 2005. Bone mineral density and the risk of incident nonspinal fractures in black and white women. *JAMA*, 293(17):2102-2108.



up being the best risk assessment tool. Yet a few things we do know for sure. One is that bone strength is determined by many factors, not just bone density; and many factors contribute to bone weakness. Further, every day we come to understand more about important new fracture risk factors which are yet to be incorporated in the risk assessment tools.

New risk factors: what the future might hold

As new questions are asked and new research unfolds, we are confident that many more new risk factors will be found to be more important than bone mineral density. The new important fracture risk factors I would like to review here are the following:

- High rates of bone protein matrix breakdown (high bone resorption rates)
- Low serum levels of vitamin D
- Low serum levels of vitamin K
- Use of various additional medications

New risk factor: high rates of bone protein matrix breakdown

Bone can be visualized as a living protein sponge matrix upon which are imbedded mineral crystals. As bone is lost, this living protein matrix breaks down and is excreted in the urine. The more bone protein fragments found in the urine, the higher the rate of bone breakdown. This is known as the rate of bone resorption. High bone resorption generally indicates a high rate of bone loss. Urine tests which measure bone resorption include the NTx, CTx, and the free deoxypryidinoline urine tests. These urine indices of skeletal turnover are as useful, or nearly as useful, as bone density in predicting fractures. They are fracture risks independent of bone density. Further, the combination of high bone resorption and low bone density is especially predictive of increased fracture risk.¹¹

New risk factor: low serum levels of vitamin D

Only recently have we begun to understand the overwhelming importance of vitamin D in fracture prevention. While it is beyond the scope of this paper, suffice it here to report that the vast majority of hip fractures occur in vitamin D deficient people. Among those who experience an osteoporotic fracture, vitamin D deficiency is the rule, not the exception. For example, a Minnesota hospital study of 82 minimal-trauma fracture patients ages 52–97 found that 97% of the fractures were hip fractures and that all but two of the patients had deficient vitamin D status (less than 30 ng/mL).¹² In a large British study, vitamin D deficiency was found in 95% of hip fracture patients.¹³ Further supporting this, 78% of hip fracture

¹¹ Johnell, O, Oden, A, DeLaet, C, et al. 2002. Biochemical indices of bone turnover and the assessment of fracture probability. *Osteoporos Int*, 13:523-26.

¹² Simonelli, C, Weiss, TW, Morancey, J, et al. 2005. Prevalence of vitamin D inadequacy in a minimal trauma fracture population. *Curr Med Res Opin*, 21:1069-1074.

¹³ Gallacher, SJ, McQuillan, C, Harkness, M, et al. 2005. Prevalence of vitamin D inadequacy in Scottish adults with non-vertebral fragility fractures. *Curr Med Res Opin*, 21:1355-1361.



patients in a Boston study were vitamin D deficient.¹⁴ Findings such as these have led some researchers to ask if vitamin D level is not the best predictor of fracture risk.¹⁵

New risk factor: low serum levels of vitamin K

While only limited research attention has been given to the vitamin K–fracture link, the powerful role of this nutrient in fracture prevention is obvious. European researchers have shown that the marker of vitamin K insufficiency (undercarboxylated osteocalcin) strongly predicts fracture. Those with the greatest signs of vitamin K insufficiency were found to have twice the risk of hip fracture, independent of bone density. Further, a combination of low vitamin K status and low bone density increased one’s risk of hip fracture by more than five-and-a-half-fold.¹⁶

New risk factor: use of additional various medications

It has long been known that the use of corticosteroids like prednisone greatly increase one’s risk of fracture. Now researchers are beginning to uncover links between other medications and fracture risk. For example, a recent British study found that those using higher doses of acid blockers (proton pump inhibitors) for more than a year had a 250% increased risk of hip fracture than non-users.¹⁷ Anti-depressants are another example of medications that increase fracture risk. Recently the large CAMOS 5-year Canadian osteoporosis study found that use of anti-depressants known as serotonin reuptake inhibitors (SSRIs) was associated with increased fracture risk. Individuals using these medications, such as Prozac, Zoloft, and Paxel, for five years or more had twice the risk of osteoporotic fracture than those not using these drugs. Further, hip bone density was 4% lower and spinal bone density 2.4% lower in those who used anti-depressants as compared to non-users.¹⁸

In conclusion

While it is interesting to look at large studies and try to sort out the characteristics of folks at high risk for fracture, it is important to keep in mind that we can only predict relative fracture risk. We cannot foretell who will fracture. As research continues, more fracture risk factors will be uncovered and a relative weighting of their importance outlined. In the meantime, the known cluster of bone-weakening factors now include **advancing age, low body weight, inadequacies of vitamins D and K, parental hip fracture, personal low-trauma fracture, selected medications, fragility and poor mobility, poor health in general, high bone resorption, and low bone density.**

¹⁴ Glowacki, J, Kolatkar NS, Harris MB, LeBoff MS. 2006. Importance of vitamin D in the design of hospital hip fracture care pathways. ASBMR Meeting, Abstract T46.

¹⁵ Malavolta, N, Pratelli L, Frigato M, et al. 2005. The relationship of vitamin D status to bone mineral density in an Italian population of postmenopausal women. *Osteoporos Int*, 16:1691-1697.

¹⁶ Vergnaud, P, Garnero, P, Meunier, PJ, et al. 1997. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: The EPIDOS study. *J Clin Endocrinol Metab*, 82:719-24.

¹⁷ Yang, YX, Lewis, JD, Epstein, S, Metz, DC. 2006. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*, 296(24):2947-2953.

¹⁸ Richards, JB, Papaioannou, A, Adachi, JD, et al. 2007. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med*, 167:188-194.



Susan E. Brown, PhD
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605 Franklin Park Drive
East Syracuse, NY 13057
www.betterbones.com