

Bone Strength and Surrogate Markers: The First, Second, and Third Fiddle*

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Ever since the publication of the United States fluoride clinical trial data showing that the studied dose of fluoride therapy in postmenopausal osteoporosis (PMO) induced a linear increase in spinal bone mineral density (BMD) but without a reduction in fracture risk,⁽¹⁾ registration for all subsequent therapies for the treatment of PMO required evidence for fracture risk reduction as the primary endpoint—the first fiddle.⁽²⁾ The previous preemptive role that this surrogate marker (pharmacologically-induced increase in BMD) had held as the indicator for improvement in bone strength now became the second fiddle. In a symphony orchestra the second fiddle plays a less robust role to the first fiddle—changes in BMD became the less robust endpoint for risk reduction and it now became the second fiddle for registration of therapies for the treatment of PMO.

Nevertheless, despite fracture reduction required for primary registration, the subsequent registration of the intermittent dosing formulations of bisphosphonate therapies for the treatment of PMO, with the exception of annual intravenous (IV) zoledronic acid, were approved, not on the basis of any fracture data, but on the demonstration that the weekly or monthly oral, or quarterly IV bisphosphonates showed a non-inferior increase in lumbar spine BMD as the fracture-proven daily formulation.^(3–5) For these studies, the second fiddle regained the first fiddle's chair. Annual zoledronic acid registration for PMO still required fracture data for primary registration, because there had not been a previous dosing formulation studied with a placebo group in a fracture trial with this bisphosphonate.⁽⁶⁾

In the years 2000 and 2002 there appeared two meta-analyses from similar datasets, examining the relationship between osteoporosis drug-induced increases in spine BMD and fracture risk reduction that came to dissimilar conclusions: the first, that the relationship between increases in BMD and risk reduction was linear; the second, that it was not.^(7,8)

Since these meta-analyses were published, there have been analyses examining either the validity or the magnitude of this relationship,^(9,10) and others comparing osteoporosis therapies that increase BMD between bisphosphonates but without fracture data.^(11,12) Some of the differences among published conclusions may be related to real differences between or

among agents, differences in compliance, or differences in study design or study analysis.^(13–22) The uncertainty between the importance of the first fiddle versus the second fiddle, understandably, has led the U.S. Food and Drug Administration (FDA) to still require evidence for fracture risk reduction over 3 years as compared to placebo for registration of treatments for PMO—a prohibitively expensive, and perhaps unethical, place for patients, clinical investigators, and industry research and development to be put at this time. The search for the replacement of the first fiddle and an accurate surrogate marker of bone strength has been intense, with promising data suggesting that perhaps a more perfect surrogate marker can be found.⁽²³⁾ Promising data suggest that a more trustworthy surrogate marker of bone strength, such as finite element analysis (FEA), could substitute for fracture endpoints.^(24,25) In addition, the FDA requires, in all registration trials, evidence of normal bone histomorphometry, because one of the reasons that higher doses of fluoride-induced increases in BMD may not be associated with risk reduction is the abnormal, “woven” bone and increased osteoid seen on bone histomorphometry.⁽²⁶⁾

It seems more evident that if BMD measurement performed by dual-energy X-ray absorptiometry (DXA) declines beyond the in vivo least significant change (LSC) as compared to patients whose BMD remains stable or increases, a fracture benefit is minimized.^(27,28) Thus, in clinical practice, serial BMD measurements performed by DXA at 2-year intervals in the osteoporotic population on therapy remains the practitioners first fiddle.^(22,27–29) Biochemical markers of bone turnover (BTM) that also reflect the pharmacological response(s) to osteoporosis therapies to reduce fracture risk, at least in groups of patients, are certainly in the orchestra and may take an increasingly important role in monitoring: perhaps, now, the third fiddle.^(30–33) For individual patient management, there must be improvements in the BTM assay standardization, harmonization, and reference population databases before they become a trusted third fiddle.^(34–36)

In this issue of the *JBMR*, Jacques and colleagues⁽³⁷⁾ report that, once again, there appears to be a robust relationship between the increase in total hip BMD as measured by DXA and the reduction in fracture risk with annual (5 mg) IV zoledronic acid. The authors also found that the third fiddle retained its

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importance. The magnitude of decline in the BTM in this large clinical trial independently contributed to a large antifracture effect. Has an increase in BMD been moved back to the first fiddle position? Similar conclusions have also been reported in the denosumab PMO registration trial.⁽³⁸⁾ In the denosumab registration trial there was also a robust relationship observed between the increase in total hip BMD as measured by DXA with the administration of the registered doses of denosumab for PMO (60 mg every 6 months [Q6MOS]) and fracture risk reduction. Jacques and colleagues, the authors of the zoledronic acid trial reported in this issue, suggest that “previous” studies comparing the magnitude of the change in BMD to the magnitude of risk reduction may have underestimated the magnitude of the BMD effect on bone strength, “due to the better compliance” with an intravenous preparation.⁽³⁷⁾ In the denosumab trial some of these same authors suggest that the stronger relationship between increases in BMD and risk reduction with denosumab may be due to the unique “mechanism of action of denosumab.”⁽³⁸⁾ Perhaps it is simpler than these hypotheses; eg, changes in BMD by DXA do count for a large proportion of the improvement in bone strength and might have to become, once again, the first fiddle.

Another reason why these two potent antiresorptive agents registered for the treatment of PMO have such robust fracture benefit may have to do with that other surrogate marker—the third fiddle. Both of these FDA-registered agents seem to have the greatest effect on reducing bone remodeling (turnover), and there is evidence that fracture risk reduction with antiresorptive agents is independently associated with reduction in bone turnover—an effect seen even after adjusting for the component of fracture risk reduction due to increases in BMD.^(19,22,30–31,35) Bone microarchitectural data suggests that bone strength is impaired by the effect of higher bone turnover on remodeling space (“stress-risers” and/or geometry of the trabecular plates or cortical porosity) which may influence bone strength beyond bone density.^(39–43)

What can we take away from these important data? First, potent antiresorptive agents do reduce global (vertebral, nonvertebral, and hip) fracture risk, in large part, by increasing BMD as measured by DXA. Monitoring appropriate patients at appropriate intervals with serial BMD by DXA remains the best clinical tool for managing higher-risk patients.^(22,27,44) Second, that even though in these studies the relationship between drug-induced increases in BMD and fracture risk reduction is robust, increases in BMD still do not explain all of the fracture benefit; and, that in clinical practice, wider use of BTM to compliment BMD in assessing pharmacological response to treatment may be appropriate in specific populations—the third fiddle.^(31,32) Third, that a loss of BMD as assessed by DXA is not acceptable, and that perhaps the best clinical measurement of “treatment failure” is a loss of BMD in compliant patients on therapy.^(22,27–29) Finally, whereas for primary FDA registration of treatments for osteoporosis, increase in BMD is currently still the second fiddle and fracture reduction the first fiddle, there must evolve a new first fiddle, which substitutes surrogates for fracture reduction for registration, because newer agents will have a more difficult task of becoming registered if the current first fiddle cannot be rearranged. The costs of fracture trials are prohibitive. I might

submit that a rearrangement may be in order for registration of antiresorptive agents—first fiddle: increases in BMD; second fiddle: changes in BTM; and third fiddle: increases in bone strength using newer surrogate markers. Thus, although we must have three fiddles in the modern orchestra, their order may need to be rearranged.

The article by Jacques and colleagues⁽³⁷⁾ reinforces the position of the second fiddle—increases in BMD by DXA to assess zoledronic acid-induced increases in bone strength—and takes us back to 2000 when this strong relationship was first described.⁽⁷⁾ Although in osteoporosis increases in pharmacologically-induced BMD will continue to be an important surrogate marker for changes in bone strength, the changes can only be trustworthy when done within the context of DXA facilities knowing their in vivo LSC (least significant change); eg, DXA-precision studies performed in patients, not just on phantoms.^(45–47) Finally, incorporating BTM as a complimentary clinical tool to aid in management decisions for the treatment of osteoporosis may become more valuable in the future. In the end, the orchestra will retain three fiddles and the harmony will be heard by all who listen.



References

1. Riggs BL, Hodgson SF, O'Fallon WM, Chao EY, Wahner HW, Muhs JM, Cedel SL, Melton LJ 3rd. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med.* 1990;322(12):802–9.
2. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet.* 1996; 348:1535–41.
3. Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, Kiel D, Felsenberg D, Recker RR, Tonino RP, Roux C, Pinchera A, Foldes AJ, Greenspan SL, Levine MA, Emkey R, Santora AC, Kaur A, Thompson DE, Yates J, Orloff JJ. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Aging (Milano).* 2000;12:1–12.
4. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, Li Z, Balske A, Lindsay R. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. *Calcif Tissue Int.* 2002;71:103–11.
5. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, Reginster JY, Zaidi M, Felsenberg D, Hughes C, Mairon N, Masanaukaite D, Reid DM, Delmas PD, Recker R. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. *J Rheumatol.* 2008;35:488–97.
6. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu HL, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR. Once yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med.* 2007;356(18): 1809–22.
7. Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. *J Clin Endocrinol Metab.* 2000;85:1–6.
8. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, Black DM. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med.* 2002;112:281–9.

9. Delmas PD, Li Z, Cooper C. Relationship between changes in bone mineral density and fracture risk reduction with antiresorptive drugs: some issues with meta-analyses. *J Bone Miner Res.* 2004;19:330–7.
10. Delmas PD, Seeman E. Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with antiresorptive therapy. *Bone.* 2004;34:599–604.
11. Rosen CJ, Hochberg M, Bonnicksen S, McClung MR, Miller PD, Broy S, Kagan R, Chen E, Petruschke RA, Thompson DE, de Papp AE. Fosamax-Actonel Comparator Trial Investigators. Treatment with once-weekly alendronate 70 mg compared to once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized, double-blind study. *J Bone Miner Res.* 2005;20:141–51.
12. Miller PD, Epstein S, Sedarati F, Reginster JY. Once monthly oral ibandronate compared with weekly alendronate: results from the head-to-head MOTION study. *Curr Med Res Opin.* 2008;24:207–13.
13. Li Z, Meredith MP, Hoseyni MS. A method to assess the proportion of treatment effect explained by a surrogate endpoint. *Stat Med.* 2001;20:3175–88.
14. Shih J, Bauer DC, Orloff J, Capizzi T, Thompson D, Oppenheimer L, Ross PD. Proportion of fracture risk reduction explained by BMD changes using Freedman analysis depends on choice of predictors. *Osteoporos Int.* 2002;13(Suppl):S38–9.
15. 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.
16. Miller PD, Delmas PD, Huss H, Patel KM, Schimmer RC, Adami S, Recker RR. Increases in hip and spine bone mineral density are predictive for vertebral anti-fracture efficacy with ibandronate. *Calcif Tissue Int.* 2010;87(4):305–13.
17. Chen P, Miller PD, Delmas PD, Misurski DA, Krege JH. Change in lumbar spine bone mineral density and vertebral fracture risk reduction in teriparatide-treated postmenopausal women with osteoporosis. *J Bone Miner Res.* 2006;21:1785–90.
18. Watts NB, Miller PD, Kohlmeier LA, Sebba A, Chen P, Wong M, Krohn K. Vertebral fracture risk is reduced in women who lose femoral neck BMD with teriparatide treatment. *J Bone Miner Res.* 2009;24(6):1125–31.
19. Hochberg M, Greenspan S, Wasnich R, Miller PD, Thompson D, Ross P. Changes in bone density and turnover explain the reductions in incidence of non-vertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab.* 2002;87:1586–92.
20. Watts NB, Geusens P, Barton IP, Felsenberg D. Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. *J Bone Miner Res.* 2005;20:2097–104.
21. Miller PD. Non-vertebral fracture risk reduction with oral bisphosphonates: challenges with interpreting clinical trial data. *Curr Med Res Opin.* 2008;24:107–19.
22. Bonnicksen SL, Lee Shulman L. Monitoring osteoporosis therapy: bone mineral density, bone turnover markers, or both?. *Am J Med.* 2006;119(4A):25–31.
23. Griffith JF, Engelke K, Genant HK. Looking beyond bone mineral density: Imaging assessment of bone quality. *Ann N Y Acad Sci.* 2010;1192:45–56. Review.
24. Amin S, Kopperdhal DL, Melton LJ 3rd, Achenbach SJ, Thorneau TM, Riggs BL, Keaveny TM, Khosla S. Association of hip strength estimates by finite-element analysis with fractures in women and men. *J Bone Miner Res.* 2011;26(7):1593–600.
25. Keaveny TM. Biomechanical computed tomography—noninvasive bone strength analysis using clinical computed tomography scans. *Ann NY Acad Sci.* 2010;1192:57–65.
26. Lundy MW, Stauffer M, Wergedal JE, Baylink DJ, Featherstone JD, Hodgson SF, Riggs BL. Histomorphometric analysis of iliac crest biopsies in placebo treated vs fluoride treated subjects. *Osteoporos Int.* 1995;5(2):115–29.
27. Lewiecki EM, Watts NB. Assessing response to osteoporosis therapy. *Osteoporos Int.* 2008;19(10):1363–8.
28. Watts NB, Lewiecki EM, Bonnicksen SL, Laster AJ, Binkley N, Blank RD, Geusens PP, Miller PD, Petak SM, Recker RR, Saag KG, Schousboe J, Siris ES, Bilezikian JP. Clinical value of monitoring BMD in patients treated with bisphosphonates for osteoporosis. *J Bone Miner Res.* 2009;24(10):1643–6.
29. Miller PD, Zapalowski C, Kulak CAM, Bilezikian JP. Bone densitometry: the best way to detect osteoporosis and to monitor therapy. *J Clin Endocrinol Metab.* 1999;84:1867–71.
30. Hernandez CJ. How can bone turnover modify bone strength independent of bone mass?. *Bone.* 2008;42:1014–20.
31. Civitelli R, Armamento-Villareal R, Napoli N. Bone turnover markers: understanding their value in clinical trials and clinical practice. *Osteoporos Int.* 2009;20:843–51.
32. Eastell R, Hannon RA. Biomarkers of bone health and osteoporosis risk. *Proc Nutr Soc.* 2008;67:157–62.
33. McCloskey EV, Vasikaran S, Cooper C. FRAX[®] Position Development Conference Members. Official Positions for FRAX[®] clinical regarding biochemical markers from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX[®]. *J Clin Densitom.* 2011;14(3):220–2.
34. Schafer AL, Vittinghoff E, Ramachandran R, Mahmoudi N, Bauer DC. Laboratory reproducibility of biochemical markers of bone turnover in clinical practice. *Osteoporos Int.* 2010;21:439–45.
35. Vasikaran S, Eastell R, Bruyère O, Foldes AJ, Garner P, Griesmacher A, McClung MR, Morris HA, Silverman S, Trenti T, Wahl DA, Cooper C, Kanis JA; for the IOF-IFCC Bone Marker Standard Working Group. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int.* 2011;22:391–420.
36. Bauer DC, Leary E, Silverman S, Lane N, Payette M, Krege J, Libanati C, Miller PD, Durham S, Myers G, Vesper HE, Randall S, Lee D, Lindsay R. National Bone Health Alliance Bone Marker Turnover Project: Current practices and the need for U.S. harmonization, standardization and common reference ranges. *Osteoporosis Int.* 2012; in press.
37. Jacques RM, Boonen S, Cosman F, Reid IR, Bauer DC, Black DM, Eastell R. Relationship of changes in total hip bone mineral density to vertebral and non-vertebral fracture risk in women with postmenopausal osteoporosis treated with once-yearly zoledronic acid 5 mg: the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res.* 2012; XX:XXX-XXX.
38. Austin M, Yang YC, Vittinghoff E, Adami S, Boonen S, Bauer DC, Bianchi G, Bolognese MA, Christiansen C, Eastell R, Grauer A, Hawkins F, Kendler DL, Oliveri B, McClung MR, Reid IR, Siris ES, Zanchetta J, Zerbin CA, Libanati C, Cummings SR; FREEDOM Trial. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Miner Res.* 2012;27(3):687–93.
39. Cohen A, Dempster DW, Recker RR, Stein EM, Lappe JM, Zhou H, Wirth AJ, van Lenthe GH, Kohler T, Zwahlen A, Müller R, Rosen CJ, Cremers S, Nickolas TL, McMahon DJ, Rogers H, Staron RB, LeMaster J, Shane E. Abnormal bone microarchitecture and evidence of osteoblast dysfunction in premenopausal women with idiopathic osteoporosis. *J Clin Endocrinol Metab.* 2011;96(10):3095–105.
40. Siegmund T, Allen MR, Burr DB. Can deterministic mechanical size effects contribute to fracture and microdamage accumulation in trabecular bone?. *J Theor Biol.* 2010;265(2):202–10.
41. Eswaran SK, Bevil G, Nagarathnam P, Allen MR, Burr DB, Keaveny TM. Effects of suppression of bone turnover on cortical and trabecular load sharing in the canine vertebral body. *J Biomech.* 2009; 11; 42(4):517–23.

42. Borah B, Dufresne TE, Ritman EL, Jorgensen SM, Liu S, Chmielewski PA, Phipps RJ, Zhou X, Sibonga JD, Turner RT. Long-term risedronate treatment normalizes mineralization and continues to preserve trabecular architecture: sequential triple biopsy studies with micro-computed tomography. *Bone*. 2006;39(2):345–52.
43. Christiansen BA, Kopperdahl DL, Kiel DP, Keaveny TM, Bouxsein ML. Mechanical contributions of the cortical and trabecular compartments contribute to differences in age-related changes in vertebral body strength in men and women assessed by QCT-based finite element analysis. *J Bone Miner Res*. 2011;26(5):974–83. DOI: 10.1002/jbmr.287.
44. Lewiecki EM, Laster AJ, Miller PD, Bilezikian JP. More bone testing is needed, not less. *J Bone Miner Res*. 2012;27(4):739–42.
45. Bonnick SL, Johnston CC Jr, Kleerekoper M, Lindsay R, Miller P, Sherwood L, Siris E. Importance of precision in bone density measurements. *J Clin Densitom*. 2001;4(2):105–10.
46. Leslie WD, Moayyeri A; Manitoba Bone Density Program. Minimum sample size requirements for bone density precision assessment produce inconsistency in clinical monitoring. *Osteoporos Int*. 2006;17(11):1673–80.
47. Lewiecki EM, Binkley N, Petak SM. DXA quality matters. *J Clin Densitom*. 2006;9(4):388–92.