COMMENTARY

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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.

Disclosures

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