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Contribution of bone mineral density and bone markers to the estimation of fracture risk and to the fracture risk reduction with antiresorptive agents

Forward

Bone mineral density (BMD) and markers of bone turnover are widely used in clinical research as well as in clinical practice to identify patients at risk for osteoporosis-related fractures and to monitor therapeutic responses. Since the primary goal of osteoporosis treatment is not to increase BMD or to alter the rate of bone turnover but to prevent fractures, and fractures are relatively rare events, it is critical that BMD and markers of bone turnover reliably identify patients at risk for fracture and reliably predict the desirable treatment effect.

In this issue of the Journal two timely review papers examine the contribution of BMD and bone markers to the risk of fractures. While Garnero and Delmas provide an extensive review on the relation of BMD and bone markers to fracture risk in an observational setting, Li et al. focus on statistical validation of BMD as a surrogate endpoint, primarily in a setting of a clinical trial.

Garnero and Delmas point out that although the level of BMD has been shown to be a strong and independent predictor of fracture risk in postmenopausal women, about half of patients with incident fractures have BMD value above the operating diagnostic threshold for osteoporosis (T-score $\geq$ -2.5). Thus, there is a significant overlap in BMD levels between those with and without osteoporosis-related fractures. Several recent prospective studies have demonstrated that an increased bone resorption evaluated by biochemical markers is strongly associated with increased risk of fractures independently of BMD. When both low BMD and a level of bone resorption marker above the normal range for healthy premenopausal women are combined, the risk of fracture increases further supporting independent contributions of BMD and high bone turnover to fracture risk. Although the mechanism by which high rate of bone turnover increases the risk of fractures is not completely understood, a recent work by Borah and colleagues showed a significant deterioration in trabecular microarchitecture only in those postmenopausal osteoporotic women who had rates of bone turnover in the upper half of the distribution[1]. Importantly, treatment with an antiresorptive agent, risedronate, prevented this deterioration supporting the deleterious effect of high bone turnover on bone architecture.

Garnero and Delmas discuss recent advances in bone matrix biochemistry, such as post-translational modifications in type I collagen, that may have an effect on material properties of bone and thus bone strength. The urine ratio between native and isomerized type I collagen may play a role in determining the mechanical competence of cortical bone, independently of BMD. The ratio of reducible and non-reducible collagen cross-links may also reflect material properties of bone and thus be used as one of the markers of bone quality.

Li et al. review the requirements for statistical validation of a surrogate endpoint in general and BMD in particular. The review indicates that although BMD is strongly correlated with fracture risk, there is limited evidence to support BMD as a reliable substitute for fracture endpoint. A valid surrogate endpoint has to capture and predict a significant portion of the treatment effect. Studies with antiresorptive agents such as alendronate, risedronate and raloxifene indicate that increases in BMD explain only a small portion of the fracture risk reduction observed with these agents. Less then 30% of the treatment effect is explained by increases in BMD. It is important to apply the appropriate statistical methodology to explain treatment effects. For example, analyses based on individual patient data indicate that a limited proportion of the anti-fracture efficacy with antiresorptive agents is explained by BMD increases. Analyses employing meta-regression based on summary statistics, however, could over- or underestimate the proportion of the treatment effect explained by BMD.

If BMD increases contribute only a small portion to the treatment effect, what are the other factors that could help to explain the treatment effect? In a recent work, Eastell et al. using individual patient data have shown that reduction in markers of bone resorption (N-telopeptide and C-telopeptide of type I collagen) at 3-6 months accounted for more than one-half of risedronate's effect in reducing vertebral and non-vertebral fractures after 3 years of treatment relative to placebo[2].

Therefore, a substantial portion of the treatment effect is not captured by either BMD or bone markers indicating that more research is needed to identify new and better surrogate markers that could fully capture and predict the antifracture effects of therapeutic agents.

Based on the current knowledge of the role of BMD and markers of bone turnover in osteoporosis treatment, what recommendations could we give to a practicing physician? First, BMD is still the best single tool to identify patients at risk for fractures. Markers of bone turnover could complement BMD in the assessment of fracture risk in borderline situations. The

primary role of markers of bone turnover is in monitoring therapeutic responses, especially during the first 3-6 months of treatment.

References

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