Monitoring Osteoporosis Therapy

Osteoporosis is a prevalent condition that may exist in a silent form, in which increased fracture risk can be detected by measurement of bone mineral density (BMD), or as a symptomatic condition after a fragility fracture has occurred. In October 2004, the Surgeon General of the United States published a lengthy report on osteoporosis (1), which is a must-read for healthcare professionals interested in this disease.

The chapter “Assessing the Risk of Bone Disease and Fracture” discusses many aspects of bone mass measurement, but relegates biochemical markers of bone turnover to the subsection “Looking to the Future: Potential Complements to BMD” (1). In a sense, this designation is appropriate because these markers currently have no “diagnostic” value, whereas the WHO has designated a BMD >2.5 SD below the mean for healthy adults younger than 50 years as diagnostic for osteoporosis even in the absence of a bone fracture.

Considerable evidence exists, however, that biochemical marker data alone can be used to assess fracture risk in older persons and are additive to BMD data with respect to fracture risk prediction. In reality, neither clinical tool is optimal for this purpose. Two recent studies in older populations have pointed out that among individuals who have sustained a fragility fracture, before the fracture only 40%–45% would have been diagnosed with osteoporosis based on densitometric criteria (2, 3).

Prospective studies in both younger (early postmenopause) and older populations have demonstrated that increased concentrations of biochemical markers of bone remodeling are related to the short-term rate of bone loss (5 years or less) (4–6). In combination with BMD, these markers should help in identification of patients who do not yet have osteoporosis on the basis of BMD but are nonetheless candidates for therapy to prevent bone loss.

Many predictors of risk of an adverse clinical outcome, whether determined from patient history, physical examination, or diagnostic procedures, are extremely useful when applied to populations, but their application to individual patients is an inexact science. For individual patient care, these predictors have been most helpful when used to monitor changes in response to therapy. Unless a therapy has been demonstrated prospectively to reduce the likelihood of fragility fractures, however, it cannot receive regulatory approval for treatment of osteoporosis. In all trials, the effect of therapy on BMD has been significantly greater in the active therapy arm than in the placebo arm. Unfortunately, in many patients it may take up to 2 years before any increase in BMD is apparent, and in a substantial minority there is no detectable increase. A relationship between increased BMD and antifracture effectiveness has been extremely difficult to demonstrate.

Biochemical markers of bone remodeling appear to be superior in many ways to BMD for monitoring response to osteoporosis therapy. Changes in biochemical markers can be seen months earlier than any change in BMD. With compliance being a big issue among the elderly, biochemical markers may provide a good way for physicians to monitor patient compliance with prescribed therapy. In addition, there is growing evidence that baseline measurements, and even more so, measurements of temporal changes in markers, are better predictors of antifracture effectiveness than measurements of either baseline BMD or changes in BMD (7–10).

In this issue of Clinical Chemistry, Välimäki and Tahtelä (11) report the results of direct comparison of 2 independent markers of bone remodeling and comparison of the utility of these 2 markers for monitoring 2 bisphosphonates, risedronate and alendronate, which are widely used for treatment of osteoporosis. Twenty women received placebo, 26 risedronate (5 mg/day orally), and 23 alendronate (70 mg orally once weekly). All study participants also received calcium (1000 mg/day orally). Those with low serum 25-hydroxyvitamin D also received vitamin D (400 IU/day). The amino-terminal propeptide of type I procollagen (P1NP) was studied as a marker of bone formation, and tartrate-resistant acid phosphatase isoform 5b (TRACP5b) was used as a marker of bone resorption. During 12 months of therapy, both markers were unchanged in the placebo arm, whereas in the treatment arms both markers decreased significantly, and both markers were significantly more reduced in the alendronate arm than the risedronate arm. At 1 month there were more responders (change greater than the least significant change) identified with TRACP5b than with P1NP, but thereafter the number of responders was greater with P1NP than TRACP5b. At each time point there were more responders to alendronate than risedronate. BMD data were not reported.

Välimäki and Tahtelä (11) conclude that “measurement of PINP instead of TRACP5b is indicated for monitoring treatment with less efficacious suppressants of bone turnover.” How valid and/or useful is that conclusion based on the data provided? There is clear evidence that bisphosphonates are more potent at inhibiting bone resorption than either calcitonin or raloxifene. Similarly, alendronate and risedronate, the 2 drugs used in this study, are more potent than the earlier bisphosphonate, etidronate. However, there is less evidence that these newer bisphosphonates are more potent at inhibiting resorption than is estrogen. The greater inhibition of resorption observed in this and other studies using alendronate rather than risedronate does not appear to have much, if any, clinical significance with respect to preservation or increase in BMD or protection from fractures.

The important message in the report by Välimäki and Tahtelä (11) is not which marker is better in specific circumstances. Instead, the clear message from this and several other sources is that biochemical markers of bone turnover/remodeling are very effective tools for monitoring the effectiveness of antiresorptive therapy in individual patients as well as in groups of patients. In individual

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patients, the earliest indication of effective inhibition of resorption is provided by these markers, and in groups of patients, changes in the markers appear to be superior to changes in BMD for predicting antifracture effectiveness.

One downside of this otherwise excellent study, particularly for readers in the United States, is that neither P1NP nor TRACP5b is commercially available. It will be important to document that the amino-terminal peptide of collagen cross-links (NTX), pyridinoline (PYD), or deoxypyridinoline (DPD) perform as well when subjected to such rigorous study. Such a study should directly compare the relative utility of serum samples, early-morning voided urine samples, and 24-h urine samples. Such a controlled clinical trial could be difficult to design and complete, but is essential before clinicians caring for patients with or at risk for osteoporosis will be convinced that biochemical markers of bone turnover must become an integral part of their clinical practice.

References


Michael Kleerekoper¹
Pauline Camacho*²

¹ Wayne State University
Detroit, MI
² Loyola University Health System
Maywood, IL

* Address correspondence to this author at: Loyola University Health System, 2160 S. First Avenue, Bldg 54, Maywood, IL 60153. Fax 708-216-5936; e-mail pcamach@lumc.edu.

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