Editorials

Controversies in Family Medicine

Should Bone Turnover Markers Be Used Routinely to Monitor Oral Bisphosphonate Osteoporosis Therapy?

Yes: Measuring Adherence and Effectiveness of Therapy Benefits Patients

Krupa B. Doshi, MD, Mayo Clinic, Scottsdale, Arizona

Leila Zeinab Khan, MD, Cleveland Clinic Foundation, Cleveland, Ohio

The skeleton undergoes a continuous remodeling process. Bone turnover markers, a group of proteins and peptides released during bone remodeling, provide a snapshot of this dynamic biochemical change. The use of these markers in clinical practice is not well appreciated, partly because the results vary widely if the test is not appropriately performed; physicians then erroneously conclude that these markers lack clinical utility. Bone turnover markers are not meant to be used for diagnosis of osteoporosis, but they reliably show a significant decline with appropriate use of oral antiresorptive drugs. Several trials have shown an association between the decrease in bone turnover markers after initiation of oral bisphosphonate therapy and long-term antifracture effectiveness.[1-4]

The osteoporosis landscape has changed significantly over the past decade. Although more treatment options are available, fewer patients are being treated, and the negative effects of osteoporosis and preventable fragility fractures are rising at an alarming rate in the United States and worldwide.[5] This discordance between guidelines and real-world practice is termed the osteoporosis treatment gap and is considered such a major concern that multiple global health organizations have issued calls to tackle this crisis.[6] Bone turnover markers are a convenient tool to monitor osteoporosis treatment and improve the treatment gap.

Early discontinuation of oral bisphosphonate treatment is a widespread problem; in a recent systematic review, 39% to 70% of individuals were still taking oral bisphosphonate therapy at six months, and only 18% to 75% continued use one year after initiation.[7] The reasons for bisphosphonate discontinuation may include cost, adverse effects, inconvenience, and lack of visible benefit. There is no practical way to assess bisphosphonate adherence and effectiveness using bone density testing, but bone turnover markers can quickly provide this information.

Oral bisphosphonate therapy first lowers bone resorption markers (e.g., C-terminal telopeptide of type I collagen, N-terminal telopeptide of type I collagen), followed by bone formation markers (e.g., procollagen I intact N-terminal propeptide).[8] These changes can be detected as early as one to three months after starting bisphosphonate treatment. The markers can be measured in a laboratory and checked more often than dual energy x-ray absorptiometry. Many studies have found a positive association between suppression of bone turnover markers and fracture reduction.[1-3] As a result, patients and physicians can be confident that bisphosphonate therapy is effective when the marker remains suppressed over serial measurements.

Patients are far more likely to adhere to long-term therapy when they "see" that treatment is working well for them.[4] Failure of a marker to be suppressed while a patient is taking oral bisphosphonate therapy should prompt physicians to identify the barrier to nonadherence.

Monitoring bone turnover markers may be useful when considering a bisphosphonate drug holiday.[9,10] Some experts believe that a highly suppressed bone turnover marker (as compared with baseline value before treatment) indicates continued antiresorptive effect and, theoretically, continued antifracture benefit.[11] Although the data are insufficient to support this use of bone turnover markers, monitoring for rising markers could provide useful individualized feedback about the loss of therapeutic effect and could prompt physicians to reevaluate a patient's fracture risk.[11]

Use of bone turnover markers requires understanding the controllable and uncontrollable sources of their variability.[8] Obtaining serial samples in a fasting state at the same time of day, preferably in the same laboratory, reduces variability. Efforts are underway to standardize and harmonize commercially available assays so that they can be compared

This is one in a series of pro/con editorials discussing controversial issues in family medicine.

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across different systems.[12] Some assays are currently available on automated platforms, which may reduce cost and variability.[12]

The International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine are working on benchmarking contemporary reference standards.[12,13] Newer clinical practice recommendations from multiple national and international societies propose adopting bone turnover markers for monitoring adherence and effectiveness of oral bisphosphonate therapy.[13-15] Measurement of bone turnover markers is approved by Medicare, and Current Procedural Terminology (CPT) codes have been assigned to these tests. Although third-party payors have denied payment for these tests in the past, payment refusals are becoming less common.

Because of projected growth in the older population, the World Health Organization has issued a call to action for primary care physicians to lead efforts in osteoporosis fracture prevention.[16] Indeed, as quarterbacks in their patients' care, primary care physicians are uniquely positioned to identify and treat these individuals.[17] Using bone turnover markers as a tool to ascertain adherence to, and effectiveness of, oral bisphosphonate antiresorptive therapy is a practical strategy that can take us another step toward closing the osteoporosis treatment gap.

Address correspondence to Krupa B. Doshi, MD, at Doshi.Krupa@mayo.edu. Reprints are not available from the authors.

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