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Making best use of bone turnover markers to monitor oral bisphosphonate therapy

WE NOW HAVE MORE AGENTS than ever before to treat osteoporosis, including newer anabolic drugs such as teriparatide, abaloparatide, and romosozumab that increase bone formation and are extremely effective at preventing fractures. But the oral bisphosphonates remain the most widely prescribed antifracture drugs and continue to pose clinical challenges such as measuring therapeutic efficacy and ensuring patient adherence.

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Poor gastrointestinal absorption, potential gastrointestinal and musculoskeletal adverse effects, irregular dosing regimens, and patient fear of rare but serious complications of therapy such as atypical femoral fracture and osteonecrosis of the jaw—all have a potential negative impact on patient adherence to therapy.

In this issue of the *Cleveland Clinic Journal of Medicine*, Ashcherkin and colleagues¹ review how bone turnover markers (BTMs) can be used to monitor oral bisphosphonate treatment efficacy and patient adherence. However, the clinical applications of bone turnover markers (BTMs) can extend beyond these roles: BTMs can be utilized to determine when to start or end a bisphosphonate “holiday,” and they can also measure treatment response.

■ WHAT ARE BONE RESORPTION AND BONE FORMATION MARKERS?

As discussed by Ashcherkin and colleagues,¹ BTMs are byproducts of bone remodeling released into the

bloodstream. The phrase “bone turnover” encapsulates markers of bone resorption and markers of bone formation. Markers of bone resorption are breakdown products resulting from osteoclastic activity in the bone that are released in the bloodstream; likewise, markers of bone formation are byproducts of osteoblastic activity in bone that are released when bone is formed.²

Markers of both bone formation and bone resorption can be used clinically, and many clinicians, myself included, use markers of bone formation such as procollagen type 1 to assess a patient’s response to an anabolic agent such as teriparatide, abaloparatide, or romosozumab. However, I would like to focus my comments here on bone resorption.

■ CURRENT RECOMMENDATIONS

Markers of bone resorption include collagen breakdown products C-terminal telopeptide of type I collagen (CTX) and N-terminal telopeptide of type I collagen (NTX), noncollagen proteins, osteoclastic enzymes, and osteocyte activity markers.² The International Osteoporosis Foundation has proposed that the serum CTX level be used as a reference marker of bone resorption and that procollagen type 1 be used as a reference for bone formation.² CTX and NTX are released in the bloodstream and can be measured in serum or urine, though some may argue that measuring serum levels of BTMs is preferable.³ However, the important point here is for the clinician to choose a specific BTM and become familiar with the properties of that test. In other words, one must be familiar with the proper way of collecting the sample, the least significant change, and the advantages and limitations of that particular test.

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■ THE VALUE OF MARKERS OF BONE RESORPTION

In healthy bone, there should be a balance between resorption and formation. Markers of bone resorption are elevated in situations where there is greater bone resorption than bone formation, such as in postmenopausal osteoporosis, although, as Ashcherkin and colleagues point out,¹ an elevated marker of resorption is hardly specific for postmenopausal osteoporosis and can be seen in a variety of disease states. The value of these byproducts of osteoclastic activity lies in the observation that bone turnover decreases in response to treatment with antiresorptive agents such as bisphosphonates. The relatively rapid decrease in markers of bone resorption (within days of intravenous or injection therapy, and within weeks to months of initiating oral therapy) lies in stark contrast to the slower, less dramatic changes observed on bone density scans.⁴⁻⁶ In addition to providing information on bone resorption or formation, BTMs are useful in that they can be measured more frequently than bone density scans can be obtained, therefore providing the clinician with more real-time data to aid decision-making.⁴

■ CLINICAL USE OF MARKERS OF BONE RESORPTION

BTMs cannot be used to diagnose osteoporosis or predict fracture risk. However, they can and should be used to assess patient adherence and biologic response to oral bisphosphonate therapy, as emphasized by Ashcherkin and colleagues. It should be understood that a baseline BTM level must first be obtained as a point of comparison, otherwise posttreatment measurements are meaningless.

Although an area of some debate, an approximately 30% to 55% decrease in a marker of bone resorption 3 to 6 months after starting antiresorptive therapy would generally indicate an adequate therapeutic response.⁷ In a patient on alendronate therapy, a follow-up BTM level that has not decreased as anticipated would therefore indicate either poor absorption or poor adherence. That particular patient may benefit from a switch to an intravenous bisphosphonate such as zoledronic acid.

However, markers of bone turnover have additional useful clinical applications. In my clinical practice, I obtain a baseline urine NTX level for all patients with osteoporosis before starting oral or intravenous

bisphosphonate therapy. I use follow-up NTX levels to assess response to therapy and make management decisions based on the results. In patients who are on a bisphosphonate holiday, I obtain a repeat NTX level to help determine the need to restart therapy, as an increase in NTX would prompt me to reconsider restarting bisphosphonate therapy.

Whenever the BTM level and the bone density scan are not congruent, I make decisions based on the bone density scan, as this measurement represents the gold standard in bone density ascertainment and osteoporosis care. If a patient clinically has osteoporosis based on bone density scan or fracture history, a lower-than-expected baseline BTM would never dissuade me from treatment. Likewise, if a patient's bone density has increased in response to antiresorptive therapy while the BTM has not decreased as expected, I would certainly not judge that treatment as less than successful based on one BTM test. However, in the face of a stable bone density scan, a rising NTX in a patient who is otherwise clinically stable based on bone density scan and fracture history would indicate that it is time to restart therapy.

One criticism leveled at the use of BTMs in this manner is that we do not yet have sufficient randomized controlled trial data to support this specific use clinically. However, BTMs have been investigated in numerous pharmacodynamic trials, which have demonstrated a significant decline in markers of resorption days to weeks after initiation of antiresorptive therapy.⁸⁻¹⁰ Additional data beyond a bone density scan are often needed to make treatment decisions, particularly if a bone density scan cannot be covered by insurance, and measuring BTMs can fill this role adequately. Without the use of BTMs we would otherwise be operating in a clinical vacuum in many instances. As do many others in this field, I maintain that it is better to have at least some data from BTMs to guide management decisions than to have no data whatsoever. Although additional data would be helpful in guiding further use, standardization, and interpretation of these tests, we currently have enough clinical experience to enable the reasonable use of BTMs in clinical osteoporosis management. ■

■ DISCLOSURE

The author reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

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