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EDITORIAL

The impact of bone turnover marker on medication adherence and the health economics-related consequences

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1. Introduction

Osteoporosis is a metabolic bone disorder characterized by an imbalance in bone turnover, resulting in reduced bone mineral density (BMD) and increased risk of fragility fractures. Anti-osteoporosis medications (AOM) have been shown to be effective in fracture risk reduction [1]; however, as a chronic disease, non-adherence to pharmacological treatment in osteoporosis is a well-recognized problem [2]. Oral bisphosphonates as the first-line treatment for osteoporosis are poorly adhered as reported in extensive studies. One review summarized persistence and adherence data from 89 observational studies published up to April 2018, reporting that the mean persistence of oral bisphosphonates for 6 months, 1 year, and 2 years ranged from 34.8% to 71.3%, 17.7% to 74.8%, and 12.9% to 72.0%, respectively [3]. Apart from oral bisphosphonates, medication adherence of other AOM such as denosumab and teriparatide is also suboptimal [4]. This problem significantly jeopardizes the treatment efficacy (worsening health outcomes) and cost-effectiveness of drug therapy [5]. Therefore, identifying reliable methods to monitor medication adherence is imperative to tackle this problem. In clinical practice, the dual-energy X-ray absorptiometry (DXA)-based BMD measurement is commonly used to monitor the treatment response as it is a major determinant of bone mass and can be used to predict fractures [6]; however, a clinically meaningful change in BMD takes at least two years after initiation of treatment [7,8]. Moreover, non-adherence most frequently occurs shortly after treatment initiation [9]; this strongly supports that a more sensitive marker demonstrating earlier response would be preferable. Recently, the International Osteoporosis Foundation (IOF) and the European Calcified Tissue Society (ECTS) have convened a working group and recommended to use bone turnover markers (BTMs), namely procollagen type I N-terminal propeptide (PINP) and collagen type I C-terminal telopeptide (CTX), to monitor the adherence of oral bisphosphonates in patients with osteoporosis [10]. There is no universal standard to adjudicate a clinically meaningful change in BTMs, and the recommendation published by the International Federation of Clinical Chemistry (IFCC) and the IOF is commonly used [8]. Specifically, this involves measuring whether the decrease in bone turnover markers 3 months after commencing is beyond the least significant change (LSC). Observing a decrease in BTM above the threshold might reinforce patients that the therapy is already effective after 3 months; on the other hand, it may help to early detect ineffectiveness, due to lack of adherence or other reasons. The advantages of using BTMs to monitor treatment response in clinical setting are multifaceted. First, BTMs are less expensive and widely available. Measuring BTM indicates higher sustainability compared to DXA scan, given the sample can be taken locally at the doctor's office or at the local laboratory. Second, their rapid responsiveness makes a decrease in marker values to be seen within weeks of initiating treatment [7], which can be used as an intervention to improve osteoporosis medication adherence and persistence [11]. Third, it is suggested that the BTM can be used as a surrogate marker of fracture risk independently from BMD [8,12,13]. Several studies suggest that the larger the decrease in turnover markers with anti-resorptive agents, the greater the reduction in fracture risk [14].

2. The clinical and economic impact of bone turnover marker

With the endorsement by several scientific committees, BTMs are increasingly used in clinical practice recently. Increasing number of studies have supported the use of BTMs as a tool to ascertain therapy response and medication adherence, and to assess the fracture risk. In addition, the potential health-economic benefits of using BTMs were also explored.

2.1. The potential value of bone turnover marker on medication adherence

Although the clinical utility of BTMs is increasing, we found the real-world evidence of the effect of BTM monitoring on medication adherence is quite limited. The potential value of BTMs on medication adherence was reported in terms of the

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change in BTM supplies reassurance to the clinician and can be used to encourage the patient. For example, Delmas et al. [15] showed that feedback of a positive BTM response (>30% reduction) was associated with a decreased rate of discontinuation of oral risedronate therapy [hazard ratio (HR) = 0.71, 95% confidence interval (CI) 0.53–0.95]. However, feedback of a negative BTM response led to an increased rate of discontinuation (HR = 2.22, 95% CI 1.27–3.89). This association was confirmed by another study [9], suggesting a trend for increased adherence compared with usual care in subjects with a positive response to raloxifene therapy using BTMs, and monitoring resulted in a 25% increase in persistence compared to non-monitoring. In addition, the PINP and Osteoporosis in Sheffield Evaluation (the POSE study) [16] indicated that patients in BTM monitoring group more often initiated oral treatment (77.4% vs 49.1%; $p < 0.001$) (treatment initiation is an important part of medication adherence as defined in ABC taxonomy by a European research group [17]) and were more likely to switch to parenteral therapies ($p = 0.005$) such as zoledronic acid to maximize the treatment efficacy compared to no-monitoring group. However, different results were revealed by Silverman et al. [18], reporting the provision of BTM results is not an effective way to enhance early compliance and persistence with drug therapy. The primary reason women complied with a bisphosphonate prescription was their concern about their risk for osteoporosis, while the women felt that BTM results were helpful to them.

Given medication adherence is a complex issue with various determinants, reasons for non-adherence differ greatly from patient to patient. While monitoring BTM as an intervention continues to pose challenges in altering the phenomenon, it can be used by clinicians to timely identify the treatment ineffectiveness, to explore potential reasons (mainly due to the lack of adherence), and to assist treatment decisions. It can be also used as an effective feedback tool as endorsed by several clinical practice guidelines [19–21] to facilitate communication between clinicians and patients, namely the BTM results can be translated to understandable medical information to help patients understand the effectiveness of treatment, to investigate patient preferences regarding treatment, and to further optimize medication adherence and osteoporosis management (shared decision making). While the use of BTM for monitoring osteoporosis treatment has been predominantly discussed in relation to oral bisphosphonate treatment, where non-adherence issues relate to a number of factors, BTM might also prove useful in monitoring adherence to parenteral medications such as teriparatide and romosozumab, both given subcutaneously and for monitoring change of treatment from subcutaneous denosumab to other treatments.

2.2. The impact of bone turnover marker on health economics-related aspects

In addition to the revealed clinical benefits of BTMs on medication adherence, the impact of BTMs on fracture risk was also reported. The study of Lane et al. [22] indicated that the BTM monitoring was associated with 13% lower odds of fracture versus those unmonitored. This association is potentially due to clinician's decision to change therapies reducing fracture risk based on insufficient treatment response detected by BTM. In turn, the improvement in medication adherence and the reduction in fracture risk result from BTM monitoring could potentially lead to economic benefits. From the patient's perspective, BTM monitoring for effective medication management can avoid unnecessary personal healthcare expenses due to treatment ineffectiveness, switch to effective treatment timely, motivate them to well adhere to therapy, and reduce fracture risk and economic burden in the long-term.

One UK study [16] explored both clinical and economic values of using one BTM (PINP) and suggested that patients in the BTM monitoring group had a greater increase in total hip BMD (+2.74% vs + 0.42%; p value = 0.003) and fewer new fractures compared to unmonitored patients. Although the BTM monitoring strategy is associated with additional costs (£28.28), it also results in additional QALYs gained (0.0041) as a greater proportion of patients started an anti-fracture treatment in the PINP monitoring arm, suggesting PINP monitoring has the potential to be cost-effective in a UK National Health Service (NHS) setting. Given the current evidence is limited to reveal an overall cost-effectiveness of using BTMs in osteoporosis management, it could be interesting to further evaluate the health-economic value of BTMs in future studies.

3. Conclusion

The use of BTMs as an effective tool to ascertain treatment response and aid treatment decisions demonstrates immense potential to improve clinical outcomes. There remains limited empirical evidence regarding their direct impact on medication adherence and healthcare costs in spite of the positive association revealed in several studies. As BTMs are a simpler and more effective way (compared to DXA) in light of the aging population and the lack of health care professionals to handle the labor-intensive DXA scanners, the clinical application of BTMs should be highlighted, and relevant analyses would become ever more vital for ascertaining true clinical- and cost-effectiveness of BTMs through longitudinal studies.

4. Expert opinion

BTM testing offers potential advantages versus traditional BMD testing, as the latter requires an interval of more than two years to capture treatment response. Bone turnover, by contrast, changes early and can be assessed within 3 months of starting treatment, which makes BTM an effective tool to be used in clinical practice. Research on the impact of BTMs in osteoporosis management reveals key findings and potential values; a notable strength is the effective integration of BTMs for early treatment ineffectiveness and medication non-adherence detection. This integration has demonstrated direct influence on treatment decision and patients' outcomes (however, the BTMs are not the sole determinant of treatment adherence, and the treatment decision should be made in conjunction with

other clinical indicators) and further on healthcare and societal costs. BTM could potentially lead to cost-saving when the resulted decrease in costs (due to increased medication adherence and prevented fracture events) could counterbalance the costs of BTM. In addition, in the context of shared decision making, BTMs can be used as a decision aid to help patients understand how medication works, and a positive message (based on BTM results) that highlights a good bone turnover marker response could motivate an improvement in medication adherence. Besides, the reported potential of BTMs in predicting serious adverse event might be a signal to discontinue current treatment, and switch to effective treatment timely, which would be helpful to avoid unnecessary healthcare expenses [12,13]. Given the limited evidence now, it may be interesting to further evaluate the impact of BTMs on medication adherence in a real-life setting, considering also the cost-effectiveness balance. While the current recommendation by the IOF and IFCC is to measure CTX and PINP in plasma, it is also interesting for future studies to compare different kinds of BTMs given their differences in testing methods and conditions, such as bone formation and bone resorption BTMs, though plasma should be the preferred sample material due to ease of collection as compared to urine. The importance of research on BTM is also highlighted in a recent study [23] as a research priority to support medicine optimization in osteoporosis. The wider availability of reliable, cost-effective, sensitive, and specific assays for BTMs would complement or even replace the follow-up DXA after 2 years and optimize osteoporosis management with the extensive support of real-world evidence in predicting clinical outcomes such as rate of fractures.

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Declaration of interest

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Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author (Nannan Li).

Author contributions

All authors contributed to the following: conceptualization of the study design, extracted data, analyzed data, and drafted the manuscript.

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