Insight into the potential of bone turnover biomarkers: integration in the management of osteoporosis and chronic kidney disease-associated osteoporosis

Pauline Brouwers[a], *Antoine Bouquegneau*[b] *and Etienne Cavalier*[a]

Purpose of review
Disturbances in mineral and bone metabolism occurring in osteoporosis and chronic kidney disease-associated osteoporosis place patients at high risk of fracture making these conditions a major public health concern. Due to the limited use of bone histomorphometry in clinical practice, the gold standard for assessing bone turnover, extensive efforts have been made to identify bone turnover markers (BTMs) as noninvasive surrogates. Since the identification of certain commonly used markers several decades ago, considerable experience has been acquired regarding their clinical utility in such bone disorders.

Recent findings
Mounting evidence suggested that BTMs represent a simple, low-risk, rapid and convenient way to obtain data on the skeletal health and that they may be useful in guiding therapeutic choices and monitoring the response to treatment.

Summary
BTMs could provide clinicians with useful information, independent from, and often complementary to bone mineral density (BMD) measurements. They have proven valuable for monitoring the effectiveness of osteoporosis therapy, as well as promising for discriminating low and high turnover states. Improved performance is observed when BTMs are combined, which may be useful for selecting treatments for chronic kidney disease-bone mineral disorders (CKD-MBD).

Keywords
bone fractures, bone turnover markers, chronic kidney disease-mineral and bone disorder, osteoporosis

INTRODUCTION

In adult skeleton, bone is continually remodeled and its dynamic metabolism is characterized by two opposite activities occurring at different rates throughout the entire life: bone resorption and bone formation. Osteoclasts (resorption cells originating from hematopoietic stem cells) participate in the catabolism of bone matrix constituents through enzymatic degradation. Osteoblasts (osteoid producing cells originating from mesenchymal stem cells) secrete bone matrix proteins forming the organic matrix (or osteoid) which then mineralizes to form the bone. Osteocytes (differentiating from osteoblasts) are the major component in mature adult bone tissue and play a central biological role in bone turnover as well as a source of circulating factors crucial in calcium and phosphate homeostasis [1▪▪,2,3].

The histomorphometric analysis of a tetracycline double-labeled bone biopsy is the gold standard for the evaluation of bone turnover. Nonetheless, the procedure is invasive and specific skills are required for both sampling and result analysis, which entails expenses and necessitates specialized histopathological expertise [4]. Due to the limitations associated with this analysis, extensive efforts were made to

[a]Department of Clinical Chemistry, University of Liege and [b]Department of Nephrology, Dialysis and Transplantation, CHU de Liege, Liege, Belgium

Correspondence to Prof. Etienne Cavalier, Department of Clinical Chemistry, University of Liège, CHU de Liège, Domaine du Sart-Tilman, 4000 Liège, Belgium. Tel: +32 4 3238822;
e-mail: Etienne.cavalier@chuliege.be

Curr Opin Endocrinol Diabetes Obes 2024, 31:000–000
DOI:10.1097/MED.0000000000000869

KEY POINTS

- Measurements of bone turnover markers could be a valuable tool for monitoring treatment response in postmenopausal women, as their variations may reflect bone changes faster than bone mineral density measurements, providing useful insights into treatment efficacy and patient compliance.
- Bone turnover markers may be measured after bisphosphonate withdrawal to assess the likelihood of bone mineral density loss and provide an indication for treatment resumption.
- The diagnostic performance of nonkidney cleared bone turnover markers has been found promising to discriminate high and low turnover bone diseases, making them valuable tools in the management of chronic kidney disease-associated osteoporosis.

identify bone turnover markers as a noninvasive assessment of remodeling process activity. This remodeling process follows an orderly sequence, starting with a period of bone resorption followed by a period of bone formation. Enzymatic degradation initiated by osteoclasts involves the release of tartrate-resistant acid phosphatase 5b (TRACP-5b), an enzyme that reflects the number of active osteoclasts and has been suggested to play a role in their migration. Catalysis of the demineralized collagen matrix by proteases (e.g., cathepsin K) releases fragments such as β isomerized C-terminal telopeptide of type I collagen (β-CTX-I). Both TRACP-5b and β-CTX-I enter the circulation allowing their measurement as biochemical markers of bone resorption. The period of bone resorption is then followed by the synthesis of the bone matrix mediated by the osteoblasts that releases proteins [e.g., osteocalcin (OC)] or cleaved fragments of collagen as pro-collagen I N-terminal propeptide (PINP). Mineralization process in which hydroxyapatite is deposited between the collagen fibrils is promoted by bone-specific alkaline phosphatase (BALP). Therefore, osteocalcin (OC), PINP and BALP can be designated as bone formation biomarkers [1▪▪,3].

The term bone turnover marker (BTM) can encompass the biomarkers listed above that assess the remodeling rate through bone cell number and/or activity as well as the circulating factors exercising a tight control over bone turnover [e.g., parathyroid hormone (PTH), sclerostin]. Several diseases are characterized by abnormal BTMs levels such as Paget's disease, rickets, osteomalacia, osteoporosis, chronic kidney disease-mineral and bone disorder (CKD-MBD), multiple myeloma, metastatic bone diseases, hypoparathyroidism, primary and secondary hyperparathyroidism (sHPT) [5]. Even though the accuracy with which BTMs reflect metabolic bone disease activity varies for each marker and pathology, BTMs could still provide useful information, independent from, and often complementary to bone mineral density (BMD) measurements in the management of such bone disorders [6].

Nowadays, BTMs are extensively employed in both research and clinical practice. Many of the commonly used markers were developed over two decades ago. Since then, considerable experience has been acquired regarding the sources of variability of these markers and their clinical utility. In fact, a wide range of variables may affect BTMs concentrations in biological fluids and actual commercial assays suffer from a lack of standardization. The biological variability as well as preanalytical and analytical considerations are already well described in other publications and are outside the scope of this article [6,7]. The aim of this short review is to present current data regarding the application of BTMs in the setting of osteoporosis and CKD-associated osteoporosis. Emerging biomarkers from the epigenetic and metabolomic fields will then be discussed as future perspectives in the evaluation of bone disorders.

USE OF BONE TURNOVER MARKERS IN OSTEOPOROSIS

Osteoporosis is a chronic disease defined as a skeletal disorder characterized by low bone mass and abnormal microarchitecture leading to the risk of bone fragility and fracture (National Institutes of Health Consensus Development Panel on Osteoporosis) [8]. According to the World Health Organization (WHO) definition, a BMD lying 2.5 standard deviations (SD) or more below the average value for young healthy women also defines osteoporosis [9]. With the aging population and longer life expectancy, the incidence of osteoporosis is escalating worldwide. Osteoporosis-related fractures and associated morbi-mortality have a significant social and economic impact making osteoporosis a major public health concern [10,11]. The burden of fragility fractures on healthcare systems was recently reviewed and estimated to be €169.8 billion in Europe [12]. However, the disease remains underdiagnosed and insufficiently treated. Despite the availability of medications reducing fracture risk, most patients who could benefit from treatment do not receive it. In a recent real-world study, Diffenderfer *et al.* [11] found that only 16.8% of patients at high risk of fracture and who are eligible for treatment actually receive medication. Among this group, only 21.2% received an appropriate risk-based treatment.

Use in the diagnosis of osteoporosis and fracture prediction

Regarding their clinical utility in the diagnosis of postmenopausal osteoporosis and the prediction of bone loss and fractures in individuals, BTMs have limited value [1▪▪,13,14]. In absence of fracture, the diagnosis of osteoporosis relies on a BMD T-score below −2.5 at the hip or spine or the presence of a fragility fracture. However, most patients with postmenopausal osteoporosis have PINP values in the upper portion of the reference range and the presence of a very high BTM value (more than one standard deviation above the upper reference limit) could suggest the need to investigate for a secondary cause for osteoporosis [6,7,14].

BTMs do not play a role in the identification of patients at high fracture risk and are currently not included in commonly used fracture risk calculators such as Fracture Risk Assessment Tools (FRAX) [6,7,15]. The FRAX, recommended by the World Health Organization (WHO), is a computer-based algorithm that calculates the probability of a major osteoporotic fracture (PMOF) and the probability of hip fracture (PHF) over the next 10 years [15]. This assessment tool, used worldwide and adapted to each population, is suitable for patients with at least one clinical risk factor for fracture, particularly those with no history of fracture but with reduced bone mass [16]. However, in the absence of a BMD measurement, a 10-year PMOF exceeding 20% can be used as the threshold for initiating treatment [15]. A recent study from the collaborative project of the International Osteoporosis Foundation (IOF) in China evaluated the relationship between FRAX, BMD and BTMs in fracture risk assessment. It emerged that FRAX values mainly showed a negative correlation with lumber and femoral neck BMD and a positive correlation with β-CTX-I. In addition, the authors found an inverse relationship between PHF and OC. Nevertheless, they did not detect any impact of BTMs regardless of BMD that could allow the determination of a potential association between BTMs and fracture risk [16]. Ivaska *et al.* [10] showed that β-CTX-I and TRACP-5b are predictive of short-term fracture in an elderly female population, whereas BTMs appear to be less valuable than other accumulated risk factors in the long term or after age 80. However, stronger evidence is still needed to determine their interaction with other risk factors and thus their contribution in risk assessment [14,17]. Hence, BTMs are not currently used as an independent tool without concomitant assessment of BMD, albeit they may have promising application prospects for fracture prediction [10,16].

Use in osteoporosis therapy monitoring

Categorizing patients according to their pretreatment bone turnover status (high or low) based on their baseline BTMs measurements could theoretically provide clinicians with useful information to select the most appropriate pharmacological treatment (antiresorptive therapies for patients with increased BTMs and anabolic therapies for patients with low bone turnover) [14]. The Copenhagen BTM study investigated the ability of baseline levels of β-CTX-I and PINP to predict the response of osteoporosis patients to antiresorptive treatment based on the change in BMD. The authors have shown an association between high pretreatments levels of β-CTX-I and/or PINP and greater increases in BMD, reflecting the effectiveness of bisphosphonate therapy. However, this real-world study could not provide evidence that baseline BTMs can predict antifracture efficacy of osteoporosis therapies [18]. Therefore, BTMs are not currently part of the selection process for pharmacological treatment [6].

The clinically silent nature of the osteoporotic disease combined with the need for long-term treatment to maintain the efficacy of therapy without tangible results that are perceptible to the patient, can lead to nonadherence, which can significantly hinder the effectiveness of treatment [6,7,14]. Moreover, the slow detection of BMD change by dual-energy X-ray absorptiometry (DXA) after initiation of antiresorptive therapy – repeat measurement is not indicated before 1–3 years – have highlighted the need for surrogate markers to assess treatment efficacy and patient adherence [19▪]. BTMs are a simple, low-risk, rapid and convenient way to obtain data on total skeleton physiology and to evaluate compliance [20]. Therefore, a panel of experts convened by the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommended the systematic use of serum PINP and β-CTX-I as reference markers of bone formation and resorption, respectively, for monitoring osteoporosis treatment [17]. The use of BTMs in treatment monitoring to identify response failure involves consideration of two concepts: least significant change (LSC) and reduction to within a reference interval (RI) [1▪▪]. The LSC is the smallest change in BTM measurement associated with a true change in the patient and can generally corresponds to about 3 times the biological variability (CVi) [21], whereas RI represents the decrease in BTM to the lower half of the premenopausal reference interval. These values are method dependent and should ideally be determined by each laboratory [20].

Antiresorptive therapies cause earlier and greater decreases in markers of bone resorption than in markers of bone formation [20]. A recent study compared the diagnostic accuracy of TRACP-5b with β-CTX-I and PINP for patient response to intravenous zoledronate, oral bisphosphonate therapy (alendronate, risedronate, ibandronate) and denosumab (evaluated at 1 year for all treatments). Similar results were observed for the three BTMs in the zoledronate and denosumab groups. In contrast, TRACP-5b showed lower accuracy in the oral bisphosphonates group (TRACP-5b: AUC 0.70; β-CTX-I: AUC 0.78; PINP: AUC 0.83, $P < 0.01$) [22]. The POSE study evaluated the use of PINP for the management of osteoporosis treatment in primary care. The study population was divided into two groups (a PINP-monitored group and a nonmonitored group) with similar baseline characteristics, notably in terms of BMD and major risk factors for fractures. The collected data showed that the PINP-monitored group was more likely to start treatment with an oral bisphosphonate (77.4% vs. 49.1%). The authors also observed an improvement in total hip BMD significantly higher in the PINP-monitored group (+2.74% vs. +0.42%, P-value = 0.003). In fact, their findings suggested that monitoring PINP during the first few months of treatment could encourage reassessment of compliance and identify poor responders, leading to a change in patient management, including a switch to zoledronate infusions. Finally, although the monitoring strategy came with additional costs, the authors' analysis suggested that PINP monitoring has the potential to be cost-effective [19▪].

Given the long skeletal half-life of bisphosphonates, the need for continued treatment of osteoporosis is reviewed after 5 years for oral therapies and after 3 years for intravenous therapies with an improved BMD measurement and the absence of incident fractures [23]. In addition, a break in long-term bisphosphonate treatment may minimize their rare adverse effects, such as atypical femoral fractures and osteonecrosis of the jaw [6,7,20]. The use of BTMs to monitor this offset using the LSC and RI methods was proposed in the TRIO extension study. After 48 weeks of treatment discontinuation, 66% of women had an increase greater than the LSC regarding β-CTX-I and 72% of women when PINP was evaluated. 64% and 42% of women had β-CTX-I and PINP levels above the reference mean, respectively. Women with the largest increases in BTMs had the greatest decreases in total hip BMD. The authors concluded that BTMs measurements after bisphosphonate withdrawal could be a useful tool to identify the likelihood of BMD decline and provide an indication for treatment resumption [24].

Anabolic agents such as teriparatide and abaloparatide, two synthetic peptides of the parathyroid hormone family, are able to uncouple bone remodeling and induce an enhanced and rapid increase in bone formation [25,26]. Abaloparatide is designed to selectively bind R^G-type PTHR1 and promote more transient signaling than PTH [1–34], resulting in a wider anabolic window [27]. A recent meta-analysis of eight randomized controlled trials showed that abaloparatide administration led to a significant enhancement in BMD at the lumbar spine, femoral neck and hip among postmenopausal women compared with the control group (placebo). Their findings highlighted the drug's ability to promote bone formation rather than bone resorption, as evidenced by a significant increase in PINP, while having no significant impact on β-CTX-I [27]. These results are consistent with other studies showing that daily subcutaneous injection of 80 μg abaloparatide for 48 weeks resulted in a rapid increase of PINP (140.7% above baseline at 6 weeks), while β-CTX-I increased slowly by 34.5% at 12 weeks [28,29].

USE OF BONE TURNOVER MARKERS IN CHRONIC KIDNEY DISEASE-ASSOCIATED OSTEOPOROSIS

Chronic kidney disease (CKD) is a major public health concern affecting an estimated 850 million people worldwide [30,31]. Impaired bone quality is observed early in the course of CKD [32]. These abnormalities are recognized as a systemic disorder characterized by dysregulation of bone turnover, mineralization and volume, accompanied by abnormalities in mineral metabolism and development of vascular or extra-vascular calcification and termed CKD-mineral and bone disorder (MBD) [33–35]. The resulting bone and mineral metabolism disturbances place CKD patients at high risk of fracture [33,36]. Nevertheless, the advanced CKD population has been systematically excluded of most major osteoporosis-treatment trials and limited evidence is available to support the treatment of patients with both osteoporosis and advanced CKD [14,37].

Bone involvement in CKD-MBD is referred to as renal osteodystrophy (ROD) [30,38]. Since the use of bone biopsy, the gold standard to evaluate ROD, is usually reserved for in-depth evaluation in select patients rather than for routine clinical workup and is not well suited for longitudinal monitoring response to treatment, there is a need for surrogate markers such as BTMs to assess bone turnover and help guide therapeutic decisions [32,39▪▪,40]. Unlike β-CTX-I and total PINP, BALP, intact PINP and TRACP-5b do not suffer from renal failure and should be considered in order to avoid bias related to

renal function [38,39▪▪]. Therefore, KDIGO (Kidney Disease Improving Global Outcomes) guidelines recommend measurements of PTH (with a target of 2–9 times the upper limit of normal in dialysis patients – there is no target range for nondialysis CKD patients) and BALP in the assessment of CKD-MBD. This group of experts suggests PTH and BALP measurements in patient with CKD G3a to G5D as significantly high and low values serve as predictors of the underlying bone turnover [41]. The KDIGO recommendations also include the monitoring of phosphate, calcium, and PTH with a variable temporal frequency depending on the severity of abnormalities and the degree of CKD progression [41].

Based on a transiliac bone biopsy and histomorphometry, ROD can be categorized in subtypes according to bone turnover, mineralization and volume into osteitis fibrosa (high turnover, normal mineralization), mixed bone disease (high turnover, abnormal mineralization), adynamic bone disease (low turnover, normal mineralization) and osteomalacia (low turnover, abnormal mineralization) [1▪▪,42]. With the progression of CKD, the worsening of sHPT and the increasing PTH resistance in bone, ROD may shift from one subtype to another. Only extremely high (>600 ng/l) or low (<100 ng/l) PTH levels may be good predictors of bone turnover in ROD but it should be remembered that PTH is a regulator of bone turnover and not its reflection *per se* [37,41,43]. Indeed, most CKD patients exhibit PTH levels between these extremes, which does not necessarily rule out the presence of adynamic bone disease or a high-turnover state [14,43]. Considering these pitfalls, the diagnostic accuracy of PTH, BALP, PINP and TRACP-5b against bone biopsy in ROD was investigated by Jørgensen *et al.* [39▪▪] in a retrospective cross-sectional study with CKD stage 3–5D and kidney transplant recipient (KTR). The collected data showed that all BTMs were able to discriminate high and low turnover (AUROC > 0.80), while PTH was slightly less accurate (AUROC > 0.75). The PINP diagnostic cut-off >120.7 ng/ml was a better predictor of high turnover (AUROC 0.85), while TRACP-5b < 3.44 U/l was better at predicting low turnover (AUROC 0.84). Furthermore, the highest diagnostic performance was achieved by combining BTMs, as seen with the association between PINP and TRACP-5b for high turnover (AUROC 0.84, accuracy 90%) and the association between BALP and TRACP-5b for low turnover (AUROC 0.86, accuracy 78%) (Fig. 1). The sclerostin/PTH ratio showed improved performance (AUC 0.79) compared to PTH (AUC 0.20) for the diagnosis of low bone turnover but better sensitivity (95.4%) and negative predictive value (93.8%) were reported for PTH (cut-off < 576.5 ng/l) [42].

Kidney transplantation (KTx), currently the optimal therapeutic approach for individuals at stage G5 of CKD, has the potential to alleviate many complications associated with CKD [44,45]. However, the risk of fracture is increased after KTx, especially in the early period following the transplant procedure, with an average decrease in BMD from 7% to 9% [44–46]. A recent study investigated the effect of pretransplant bone turnover category on the evolution of bone phenotype 1 year after KTx [40]. High bone turnover at baseline was associated with greater declines in BALP and TRACP-5b (−14.2 μg/l and −4.2 U/l respectively, $P < 0.001$). There was also a significant difference in the ΔBMD at the total hip (+4.4% vs. −1.7%, $P = 0.02$) and femoral neck (+5.3% vs. −1.1%, $P = 0.002$) in patients with a high turnover (gain in BMD) when compared to patients with normal turnover at baseline. The authors found that the circulating levels of BTMs paralleled the changes in bone histomorphometry and tended to decrease during the first post-transplant year: −23% for BALP, −47% for intact PINP and −42% for TRACP-5b. Conversely, a slight increase in BALP and PINP was observed in patients with low turnover at baseline, without any significant differences in ΔBMD compared to patients with normal turnover [40]. Another recent study examined the relationship between early changes in BTMs and subsequent changes in BMD during the first post-transplant year. The authors compared patients with significant BMD loss or gain at 1 year (<−2.5%/year and >+2.5%/year, respectively) with those who had no change in BMD. Their results showed that patients with a higher turnover at baseline, followed by a reduction in BTMs greater than the LSC at 3 months, were more likely to experience BMD improvement at 12 months, while a less marked decrease or an increase in BTMs was associated with bone loss [47].

In summary, although the diagnostic performance of BTMs has recently been found promising to discriminate high and low turnover bone diseases, the paucity of available data on precise targets and the inherent disparity of studies leading to different reference ranges and cut-offs have limited their use, warranting the need for further studies [48].

FUTURE PERSPECTIVES

Several novel biomarkers have recently emerged as future approaches to the management of bone disease, including the rapidly developing field of epigenetics. MicroRNAs (miRNAs) are short noncoding single-stranded oligonucleotides that regulate post-transcriptional gene expression by stimulating the degradation of messenger-RNAs (mRNAs) or repressing protein translation to modulate cell differentiation

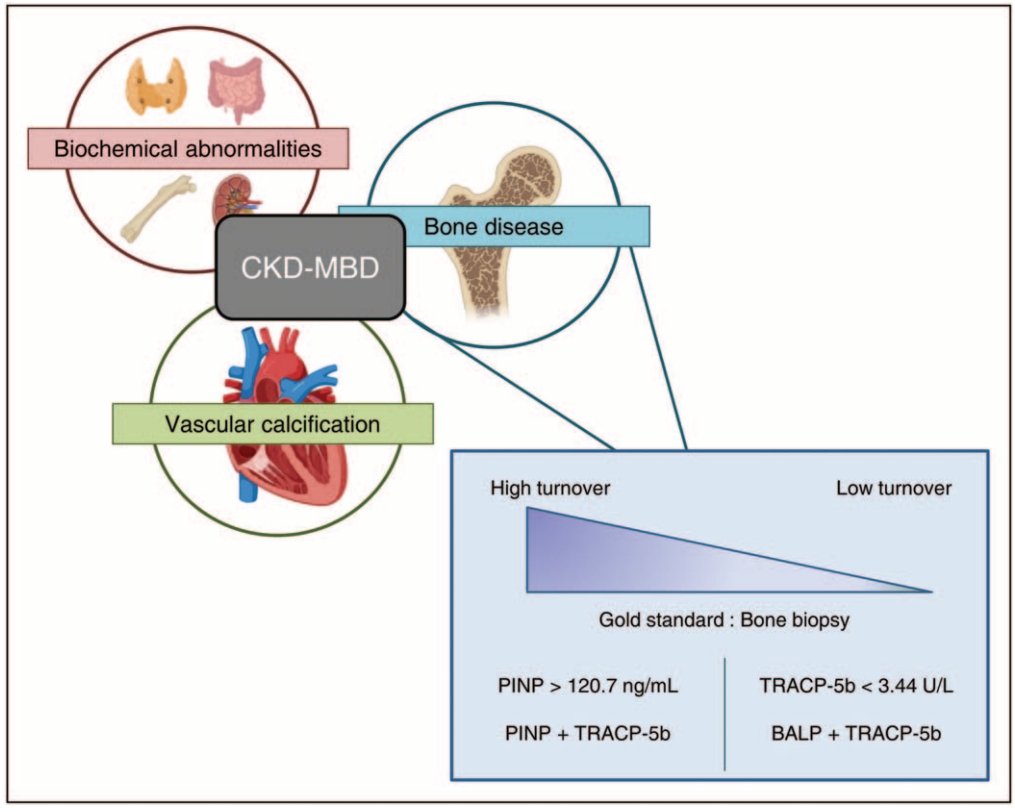

Figure 1. Proposed use of bone turnover markers to assess bone turnover in chronic kidney disease-mineral and bone disorder (CKD-MBD). CKD-MDB is one of the many complications associated with CKD. It is a systemic disorder characterized by biochemical mineral abnormalities (disturbances in calcium, phosphate, parathyroid hormone or vitamin D metabolism), bone fragility (dysregulation of bone turnover, mineralization, volume, growth or strength) and vascular calcification. Bone turnover markers could provide clinicians with useful information to classify patients according to their bone turnover status. The PINP diagnostic cut-off >120.7 ng/ml may be a good predictor of high turnover, while TRACP-5b <3.44 U/l may be better at predicting low turnover. Furthermore, the combination of PINP and TRACP-5b as well as BALP and TRACP-5b allows for higher diagnostic performance (for high and low turnover, respectively).

and metabolic processes [49,50]. As pivotal epigenetic regulators of bone homeostasis, miRNAs hold potential as targets for therapy and biomarkers of bone remodeling [51]. A recent prospective observational study investigated the usefulness of circulating miRNAs for monitoring denosumab therapy in women with postmenopausal osteoporosis [52]. The authors identified seven miRNAs that were significantly upregulated during a 24-month course of denosumab treatment compared to baseline, among which miR-454-3p and miR-584-5p were defined as top candidates based on amplitude degree of upregulation and correlation strength with BMD gain and BTMs suppression (β-CTX-I and PINP) [52]. Although miRNAs hold great promise, their application is limited by the lack of standardized methods and by studies failing to provide comparable results, requiring further investigation [50,51]. With the advances in metabolomics technology, there is also a growing interest in the impact of specific amino acids on skeletal health, especially for branched chain amino acids (BCAA), including valine, leucine and isoleucine, as essential components of bone [53–55]. Carbone *et al.* [53] found a significant association between higher leucine levels and higher total hip and femoral neck BMD, while Grahnemo *et al.* [55] identified that low circulating valine was a robust predictor of incident hip fractures. However, additional evidences are still needed before these biomarkers are ready for clinical prime time.

CONCLUSION

Recent literature has shown a growing interest in the use of BTMs in both research and clinical practice. Mounting evidence indicated that BTMs represent a simple, low-risk, rapid and convenient way to obtain data on total skeleton physiology, as well as a reliable alternative to bone biopsy. While they

may not be useful for diagnosing osteoporosis or predicting individual fractures, BTMs have proven valuable for monitoring the effectiveness of osteoporosis therapy and detecting inadequate response or noncompliance. Moreover, the acceptable diagnostic performance of nonkidney cleared BTMs to discriminate low and high turnover states, improved when they are used in combination, may increase their application in the management of CKD-MBD. Nevertheless, the lack of standardization or harmonization of commercial assays has led to disparities between studies and difficulties in providing consistent recommendations in clinical guidelines. There is still room for improvement to make BTMs universally accessible and affordable markers of bone disorders but they are on the right track for an increasing implementation in clinical practice.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

E.C. is a consultant to DiaSorin, IDS, Fujirebio, Roche Diagnostics, Snibe, Nittobo and bioMérieux.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Schini M, Vilaca T, Gossiel F, *et al.* Bone turnover markers: basic biology to ■■ clinical applications. Endocr Rev 2023; 44:417–473.

Comprehensive review of the most commonly used bone turnover markers and how they compare with other approaches to studying bone turnover, as well as their clinical utility and sources of variability.

2. Dincel AS, Jørgensen NR; on behalf of the IOF-IFCC Joint Committee on Bone Metabolism (C-BM). New Emerging Biomarkers for Bone Disease: Sclerostin and Dickkopf-1 (DKK1). Calcif Tissue Int 2022; 112:243–257.
3. Aggarwal J, Modi M, Gupta R, Pasha E. Utility of bone turnover markers in metabolic bone diseases. Santosh Univ J Health Sci 2023; 9:48.
4. Fusaro M, Pereira L, Bover J. Current and emerging markers and tools used in the diagnosis and management of chronic kidney disease–mineral and bone disorder in non-dialysis adult patients. J Clin Med 2023; 12:6306.
5. Makris K, Mousa C, Cavalier E. Alkaline phosphatases: biochemistry, functions, and measurement. Calcif Tissue Int 2022; 112:233–242.
6. Brown JP, Don-Wauchope A, Douville P, *et al.* Current use of bone turnover markers in the management of osteoporosis. Clin Biochem 2022; 109–110:1–10.
7. Vasikaran SD, Miura M, Pikner R, *et al.,* Bhattoa HP; the IOF-IFCC Joint Committee on Bone Metabolism (C-BM). Practical considerations for the clinical application of bone turnover markers in osteoporosis. Calcif Tissue Int 2023; 112:148–157.
8. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. J Am Med Assoc. 2001;285:785–95.
9. Kanis JA, Melton LJ, Christiansen C, *et al.* The diagnosis of osteoporosis. J Bone Miner Res 1994; 9:1137–1141.
10. Ivaska KK, McGuigan FE, Malmgren L, *et al.* Bone turnover marker profiling and fracture risk in older women: fracture risk from age 75 to 90. Calcif Tissue Int 2022; 111:288–299.
11. Diffenderfer BW, Wang Y, Pearman L, *et al.* Real-world management of patients with osteoporosis at very high risk of fracture. J Am Acad Orthop Surg 2023; 31:e327–e335.
12. Adami G, Fassio A, Gatti D, *et al.* Osteoporosis in 10 years time: a glimpse into the future of osteoporosis. Ther Adv Musculoskelet Dis 2022; 14:1759720X2210835.
13. Williams C, Sapra A. Osteoporosis markers. [Updated 2023 May 1]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK559306/.
14. Vasikaran S, Thambiah SC, Tan RZ, Loh TP; APFCB Harmonization of Reference Interval Working Group. The use of bone-turnover markers in asia-pacific populations. Ann Lab Med 2024; 44:126–134.
15. Schini M, Johansson H, Harvey NC, *et al.* An overview of the use of the fracture risk assessment tool (FRAX) in osteoporosis. J Endocrinol Invest 2023; 47:501–511.
16. Yang Z, Xuan S, Li W, *et al.* Clinical application of the fracture risk assessment tool in the general population and its correlation with bone turnover markers. Front Pharmacol 2023; 13:1013483.
17. Vasikaran S, Eastell R, Bruyère O, *et al.,* for the IOF-IFCC Bone Marker Standards Working Group. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int 2011; 22:391–420.
18. Bønløkke SE, Rand MS, Haddock B, *et al.* Baseline bone turnover marker levels can predict change in bone mineral density during antiresorptive treatment in osteoporotic patients: the Copenhagen bone turnover marker study. Osteoporos Int 2022; 33:2155–2164.
19. Mattia L, Davis S, Mark-Wagstaff C, *et al.* Utility of PINP to monitor osteo- ■ porosis treatment in primary care, the POSE study (PINP and Osteoporosis in Sheffield Evaluation). Bone 2022; 158:116347.

This study evaluates of a PINP monitoring algorithm for the management of osteoporosis treatment delivered in primary care and its cost-effectiveness compared with standard care without PINP monitoring.

20. Ashcherkin N, Patel AA, Algeciras-Schimnich A, Doshi KB. Bone turnover markers to monitor oral bisphosphonate therapy. Cleve Clin J Med 2023; 90:26–31.
21. Fraser CG; Changes in serial results. Biological variation: from principles to practice. Washington: Association for the Aid of Crippled Children Press; 2001; 67–90.
22. Gossiel F, Ugur A, Peel NFA, *et al.* The clinical utility of TRACP-5b to monitor antiresorptive treatments of osteoporosis. Osteoporos Int 2022; 33: 1357–1363.
23. Ahadzadeh Ardebili A, Fu T, Dunnewold N, *et al.* Bisphosphonates preserve bone mineral density and suppress bone turnover markers in early menopausal women: a systematic review and meta-analysis of randomized trials. JBMR Plus 2023; 7:e10748.
24. Naylor KE, McCloskey EV, Jacques RM, *et al.* Clinical utility of bone turnover markers in monitoring the withdrawal of treatment with oral bisphosphonates in postmenopausal osteoporosis. Osteoporos Int 2019; 30:917–922.
25. Lewiecki EM, Czerwinski E, Recknor C, *et al.* Efficacy and safety of transdermal abaloparatide in postmenopausal women with osteoporosis: a randomized study. J Bone Miner Res 2023; 38:1404–1414.
26. Mada S, Ibrahim S, Abarshi M, *et al.* Bone turnover markers for diagnosis of postmenopausal osteoporosis – a review. Int J Sci Glob Sustain 2023; 9:10.
27. Xu F, Wang Y, Zhu X. The safety and efficacy of abaloparatide on postmenopausal osteoporosis: a systematic review and meta-analysis. Clin Ther 2024; 46:267–274.
28. Matsumoto T, Sone T, Yamashita A, Inoue T. Abaloparatide dose-dependently increases bone mineral density in postmenopausal women with osteoporosis: a phase 2 study. J Bone Miner Metab 2023; 41:807–816.
29. Matsumoto T, Sone T, Soen S, *et al.* Abaloparatide increases lumbar spine and hip BMD in Japanese patients with osteoporosis: the phase 3 ACTIVE-J Study. J Clin Endocrinol Metab 2022; 107:e4222–e4231.
30. Xie D, Zhao L, Wu L, Ji Q. The levels of bone turnover markers and parathyroid hormone and their relationship in chronic kidney disease. Clin Chim Acta 2023; 548:117518.
31. Lin MY, Chiu YW, Lin YH, *et al.* Kidney health and care: current status, challenges, and developments. J Pers Med 2023; 13:702.
32. Smout D, Jørgensen HS, Cavalier E, Evenepoel P. Clinical utility of bone turnover markers in patients with chronic kidney disease. Curr Opin Nephrol Hypertens 2022; 31:332–338.
33. Wang Y, Ma W, Pu J, Chen F. Interrelationships between sarcopenia, bone turnover markers and low bone mineral density in patients on hemodialysis. Ren Fail 2023; 45:2200846.
34. Nitta K, Hanafusa N, Akiyama K, *et al.* Chronic kidney disease—mineral and bone disorder (CKD-MBD), from bench to bedside. Kidney Dial 2023; 3:46–55.
35. D'Arrigo G, Mallamaci F, Pizzini P, *et al.* CKD-MBD biomarkers and CKD progression: an analysis by the joint model. Nephrol Dial Transplant 2023; 38:932–938.
36. Oh TR, Myeong C, Song SH, *et al.* Association between serum osteoprotegerin level and renal prognosis in nondialysis patients with chronic kidney disease in the Korean Cohort Study for Outcomes in Patients with Chronic Kidney Disease (the KNOW-CKD Study). Kidney Res Clin Pract 2022; 41:200–208.

37. Ginsberg C, Ix JH. Diagnosis and management of osteoporosis in advanced kidney disease: a review. Am J Kidney Dis 2022; 79:427–436.

38. Fusaro M, Barbuto S, Gallieni M, *et al.* Real-world usage of chronic kidney disease-mineral bone disorder (CKD-MBD) biomarkers in nephrology practices. Clin Kidney J 2024; 17:sfad290.

39. Jørgensen HS, Behets G, Viaene L, *et al.* Diagnostic accuracy of noninvasive bone ■■ turnover markers in renal osteodystrophy. Am J Kidney Dis 2022; 79:667–676; e1.
This study investigates the diagnostic accuracy of nonkidney cleared bone turnover markers to categorize bone turnover in CKD patients.

40. Jørgensen HS, Behets G, Bammens B, *et al.* Natural history of bone disease following kidney transplantation. J Am Soc Nephrol 2022; 33:638–652.

41. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2017;7:1–59.

42. Pereira L, Magalhães J, Mendonça L, *et al.* Evaluation of renal osteodystrophy and serum bone-related biomarkers in a peritoneal dialysis population. J Bone Miner Res 2022; 37:1689–1699.

43. Haarhaus M, Aaltonen L, Cejka D, *et al.* Management of fracture risk in CKD—traditional and novel approaches. Clin Kidney J 2023; 16:456–472.

44. Keronen SM, Martola LAL, Finne P, *et al.* Clinical prediction of high-turnover bone disease after kidney transplantation. Calcif Tissue Int 2022; 110:324–333.

45. Sun L, Wang Z, Zheng M, *et al.* Mineral and bone disorder after kidney transplantation: a single-center cohort study. Ren Fail 2023; 45:2210231.

46. Marx D, Anglicheau D, Caillard S, *et al.* Urinary collagen peptides: Source of markers for bone metabolic processes in kidney transplant recipients. PROTEOMICS Clin Appl 2023; 17:2200118.

47. Jørgensen HS, Claes K, Smout D, *et al.* Associations of changes in bone turnover markers with change in bone mineral density in kidney transplant patients. Clin J Am Soc Nephrol 2023; 19:483–493.

48. Aguilar A, Gifre L, Ureña-Torres P, *et al.* Pathophysiology of bone disease in chronic kidney disease: from basics to renal osteodystrophy and osteoporosis. Front Physiol 2023; 14:1177829.

49. Bravo Vázquez LA, Moreno Becerril MY, Mora Hernández EO, *et al.* The emerging role of MicroRNAs in bone diseases and their therapeutic potential. Molecules 2022; 27:211.

50. Lombardi G, Delvin E. Micro-RNA: a future approach to personalized diagnosis of bone diseases. Calcif Tissue Int 2023; 112:271–287.

51. Smout D, Van Craenenbroeck AH, Jørgensen HS, Evenepoel P. MicroRNAs: emerging biomarkers and therapeutic targets of bone fragility in chronic kidney disease. Clin Kidney J 2023; 16:408–421.

52. Messner Z, Carro Vázquez D, Haschka J, *et al.* Circulating miRNAs respond to denosumab treatment after 2 years in postmenopausal women with osteoporosis—the MiDeTe study. J Clin Endocrinol Metab 2023; 108:1154–1165.

53. Carbone L, Bužková P, Fink HA, *et al.* plasma levels of branched chain amino acids, incident hip fractures, and bone mineral density of the hip and spine. J Clin Endocrinol Metab 2023; 108:e1358–e1364.

54. Lau KT, Krishnamoorthy S, Sing CW, Cheung CL. Metabolomics of osteoporosis in humans: a systematic review. Curr Osteoporos Rep 2023; 21: 278–288.

55. Grahnemo L, Eriksson AL, Nethander M, *et al.* Low circulating valine associate with high risk of hip fractures. J Clin Endocrinol Metab 2023; 108: e1384–e1393.