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REVIEW

CLINICAL UTILITY OF BONE TURNOVER MARKERS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Purpose of review

The burden of fractures is very high in patients with chronic kidney disease (CKD). It is increasingly recognized that knowledge of bone turnover is of paramount importance in guiding mineral metabolism and osteoporosis therapy in CKD. Bone histomorphometry is the gold standard to assess bone turnover, but is seldomly performed in clinical practice. Bone turnover markers (BTMs) may be the long awaited noninvasive diagnostic that may help to close the therapeutic gap in patients with advanced CKD presenting with bone fragility.

Recent findings

Mounting evidence indicates that BTMs may be useful in skeletal and nonskeletal risk stratification, in guiding mineral metabolism and osteoporosis therapy, and in monitoring the therapeutic response.

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Summary

BTMs provide information that is complementary to other clinical tests. It may be envisioned that in the near future, the assessment of nonkidney cleared BTMs may become part of routine clinical evaluation and monitoring of bone health in CKD patients, integrated with clinical risk factors, imaging data and, eventually, bone histomorphometry. Panels of BTMs will likely be more informative than single markers, and the same might hold true for trends as opposed to single time point data.

Keywords. bone fractures, bone histomorphometry, bone turnover marker, chronic kidney disease - mineral and bone disorder, chronic renal insufficiency

KEY POINTS

- Awaiting the results of additional studies validating BTMs against bone histomorphometry, a more liberal use of BTMs in patients with CKD should be considered.
- BTMs may be useful in skeletal and nonskeletal risk stratification, in guiding mineral metabolism and osteoporosis therapy, and in monitoring the therapeutic response in patients with CKD.
- Despite major advantages, none of the BTMs currently fulfills all of the criteria of an 'ideal' biomarker.
- Results obtained by different assays of the same BTM are not interchangeable.

INTRODUCTION

Derangements in mineral and bone metabolism occur early in the course of chronic kidney disease (CKD), become almost universal in patients with advanced stage disease and contribute to an excessively high fracture burden. The hip fracture risk is four times as high in patients on dialysis as compared with healthy controls [1], and further increases following kidney transplantation, at least transiently [2]. Multiple risk factors for fracture have been identified, some of which are modifiable [3]. Compared with CKD patients without fractures, those with fractures experience a multifold increased risk of mortality [4]. Fracture prevention focuses on fall risk reduction and restoring bone strength [5]. The latter implies optimal control of mineral metabolism disturbances and starting specific antiosteoporosis agents [6▪,7] (Fig. 1). Knowledge of bone turnover is of crucial importance to guide treatment decision. The histomorphometric analysisofatetracyclinedouble-labeled bone biopsy is the gold standard for evaluating bone turnover. However, taking a bone biopsy is invasive and requires the necessary skills, while its analysis is expensive and necessitates specific histopathological expertise, which is not widely available [8,9]. Noninvasive imaging techniques using isotopes (e.g. ^{18}F-sodium fluoride (^{18}F-NaF)-positron emission tomography) [10] may also inform on bone turnover, but further validation is needed prior to clinical implementation. Emerging data suggest that bone turnover markers (BTMs) might be used as surrogate of, or as adjunct to, a bone biopsy for the assessment of bone turnover. This review aims to present up-to-date evidence on the utility of BTMs in the setting of CKD. After discussing general aspects of BTMs, we will discuss the role of BTMs

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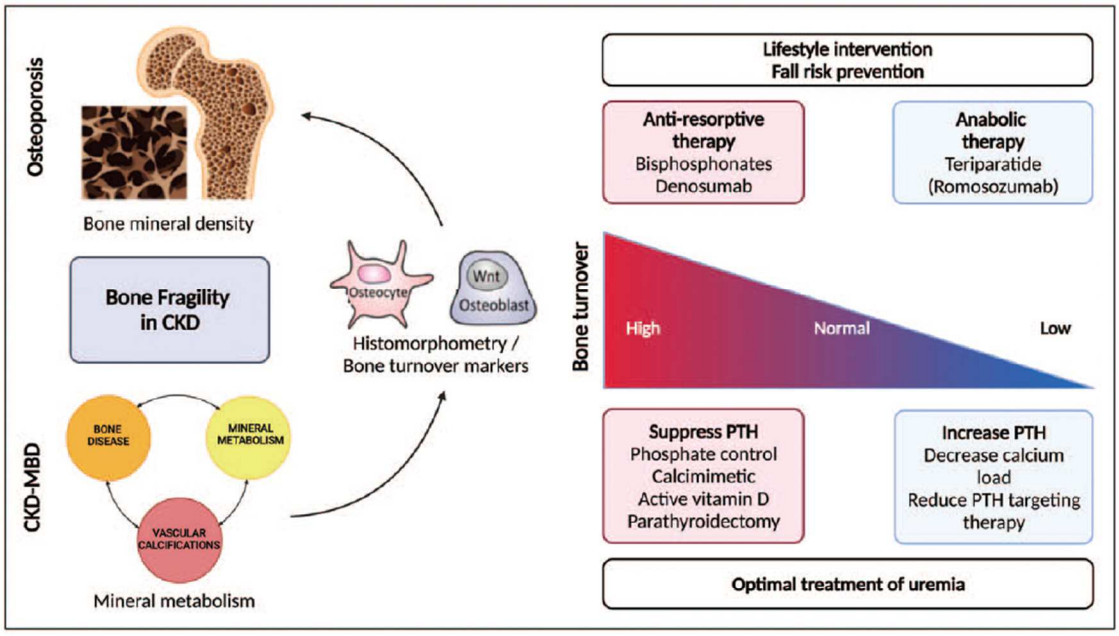

FIGURE 1. *An approach to a patient with advanced chronic kidney disease (stage 4–5D) presenting with bone fragility.* Therapy comprises optimal control of mineral and bone disturbances (commonly referred to as chronic kidney disease-mineral and bone disorder) and specific osteoporosis therapy. Knowledge of bone turnover is crucial in guiding treatment decisions in both pillars. Bone biomarkers may help to categorize bone turnover. If bone turnover is low, less parathyroid hormone suppression is indicated and anabolic agents could be considered. If bone turnover is normal, antiresorptive agents should be considered. Finally, if bone turnover is too high, parathyroid hormone suppression should be aimed for, and could be combined with antiresorptive agents. In all cases, lifestyle modification and optimal supportive therapy for chronic kidney disease should be part of the therapeutic action plan.

BONE TURNOVER MARKERS RELEVANT IN THE SETTING OF CHRONIC KIDNEY DISEASE

BTMs may be roughly classified as either circulating factors that affect bone turnover [e.g. parathyroid hormone (PTH), sclerostin] or markers that reflect bone cell number and/or activity. The latter are generallysubdividedintotwocategories:markersofbone formation and markers of bone resorption. Bone formation markers derive from osteoblastic activity and include bone-specific alkaline phosphatase (BALP), osteocalcin, N-terminal propeptide (PINP) and C-terminal propeptide of type-I procollagen. In the absence of liver dysfunction, total alkaline phosphatase (tALP) can be used as a surrogate marker of bone formation. The markers of bone resorption include degradation products of type-I collagen such as the intermolecular crosslinks pyridinoline and deoxypyridinoline, the C-terminal telopeptide (CTX), the N-terminal telopeptide (NTX) and matrix-metalloproteases (MMP)generated typeI collagenfragments – andosteoclasts enzymes, such as type 5b tartrate-resistant acid phosphatase (TRAP-5b) and cathepsin K. More recently, micro-RNAs (miRNAs) have entered the scene as promising BTMs. miRNAs are single-stranded noncoding

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oligonucleotides that negatively regulate translation of complementary mRNAs to modulate cell differentiation and metabolic processes. Several miRNAs play an important role in key mechanisms of bone homeostasis [11,12] and tissue expression is reflected by circulating miRNA levels [13■]. Recent observational studies have shown that circulating miRNAs may affect the secretion of PTH [14], a key regulator of bone remodeling and may provide accurate noninvasive identification of bone turnover in renal osteodystrophy [13■].

The deliberate use of BTMs requires knowledge about their strengths and limitations. Undoubtedly, the *easiness of sample collection* is an important asset of biochemical markers. Biochemical BTMs reflect changes in bone turnover more *rapidly* than changes in other clinical tests, such as bone mineral density (BMD) and bone histomorphometry. The concentration of bone biomarkers reflects the turnover rate of the *skeleton as a whole*, while histomorphometric indices represent bone turnover at a definite site, most commonly at the iliac crest. This may be relevant as heterogeneity of the skeleton (central/ distal skeleton,cortical/trabecular bone) exists, both with regard to the response to ageing, disease and therapy [15].

BTMs also have limitations, including *lack of tissue specificity* and *high variability*. Sources of variability can be preanalytical (related to patient characteristics and sampling conditions), analytical (related to the assay) [16] and postanalytical (including biological variability). Many of the circulating BTMs exhibit a circadian rhythm, which is most pronounced for markers of bone resorption and partly related to food intake. Some BTMs are retained in renal failure which hampers their interpretation in the setting of CKD. Other preanalytical confounding factors include age, sex, menopausal status, ethnicity, geographical location and therapy. Intermethod or intermanufacturer variability is uniformly high, mainly related to problems of antibody specificity and standardization, and automated methods are only available for a subset of BTMs. Lastly, most BTMs show substantial biological variability [17–19], although BTMs in blood do not suffer from biological variation to the same extent as the older BTMs that were measured in urine [20].

For clinical interpretation, this variability needs to be taken into account, most commonly by considering the '*least significant change'* (LSC) or critical difference. This helpful numerical is calculated based on the biological variation of the biomarker (intraindividual coefficient of variation, CV_I) as well as the analytical variation of the method (analytical coefficient of variation, CV_A). The calculation

$$(LSC = \sqrt{2} \times 1.96 \times (CVI^2 + CVA^2)^{1/2}$$

or approximately 3 x CV_I) reveals by what amount the biomarker needs to change before being considered *significant* – with a less than 5% probability of being attributable to random variation. In hemodialysis patients, LSCs for BALP, PINP and TRAP-5b have been found to be 23, 32 and 34%, respectively [17]. These figures are several fold higher than those observed for other common biochemical parameters such as creatinine [17]. Thus, in clinical practice, only changes in BTM levels greater than the LSC should be interpreted as representing a true change in the underlying skeletal remodeling rate. In patients with a recent fracture, BTMs should be interpreted cautiously, since, as a consequence of fracture healing, BTMs may be elevated for several months after the event [21,22]. Finally, one should be vigilant about the possible finding of defective bone mineralization in a patient presenting with bone fragility and high circulating tALP. Mineralization defects are rather uncommon

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in contemporary adult CKD patients [23], but should be excluded prior to initiating PTH suppressive therapy or antiresorptive agents. A synchronous elevation of other bone formation markers renders a mineralization defect very unlikely, especially in the absence of hypophosphatemia, metabolic acidosis and/or vitamin D deficiency. The above mentioned characteristics of BTMs may explain why the correlation between histomorphometric parameters obtained from the iliac bone and the integrated mean of the overall skeletal turnover represented by serum BTM concentration is at best only modest [24] (for a detailed discussion see [25]).

CLINICAL UTILITY

RISK STRATIFICATION

BTMs may help to predict risks, at least on the population level. Most studies have focused on bone outcomes. In the general population, higher BTM levels, particularly resorption marker levels directly associate with fracture risk [26]. Evidence, however, is not unequivocal [27] and the clinical utility of BTMs as stand-alone or as adjunct to BMD in osteoporotic fracture risk prediction remains ill-defined. The latter is also reflected by their absence in any of the currently available fracture risk calculators. In patients with CKD, tALP levels show a direct and linear relationship with fracture risk[28]. PTH levels, conversely, show a U-shaped correlation [29], with both high and low PTH levels associated with increased fracture risk. Residual confounding in the relationship between PTH and fracture might be suspected, as low levels of PTH are seen in states of severe morbidity in CKD, fx malnutrition and inflammation. These observations fuel the discussion as to whether low bone turnover *per se* is harmful, or if disease states associated with low PTH are the real drivers of dismal skeletal outcomes [30,31]. BTMs may also inform on BMD status and predict BMD change. In postmenopausal women, increased bone turnover is a major determinant of osteoporosis [32]. Similarly, in CKD patients, high levels of BTMs associate with low BMD [33] and BMD loss [34]. Bone loss, overall, is more strongly associated with bone resorption than with bone formation. Clinical utility of single time point values is limited owing to the high interindividual variability. Trends may be much more informative and will likely prove more useful for clinical decision-making. In de-novo kidney transplant recipients, changes in BTMs inversely associated with BMD changes [35]. Monitoring BTMs in these patients might help identify patients who might benefit the most from bone preserving measures.

BTM may also predict responses to, and complications of, CKD-Mineral and Bone Disorder therapy. High pretreatment levels of tALP identify patients at increased risk of hungry bone disease after parathyroidectomy [36]. A secondary analysis of the EVOLVE trial demonstrated that patients in whom FGF23 levels decreased by at least 30% following the initiation of cinacalcet, were characterized by higher tALP levels [37]. BMD gains in patients treated with antiresorptive agents are more pronounced in patients with high pretreatment levels of BTMs [38]. Finally, CKD patients with high BTMs at baseline are at higher risk for developing severe hypocalcemia following denosumab therapy [39].

BTMs may also predict nonskeletal outcomes. High tALP levels associate with higher risk of hospitalization, peripheral arterial disease and death in CKD patients, across stages of disease [28,40–

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44]. Bone disease is unlikely to account for these associations. Whether increased vascular calcification or inflammation is in the causal pathway requires further research.

GUIDING THERAPEUTIC DECISIONS

Osteoporosis therapy in CKD should be multileveled and comprise lifestyle measures, mineral metabolism control and specific pharmacological treatment, either with antiresorptive or anabolic agents, or with sequential therapy [6▪]. Knowledge of bone turnover is of crucial importance to define the best therapeutic approach. We recently studied the performance of 1– 84 PTH, and the nonkidney retained BTMs BALP, TRAP-5b and intact PINP for categorization of patients according to bone turnover [45▪]. The study enrolled 199 CKD patients, including both patients receiving maintenance dialysis treatment and recipients of a kidney transplant. All biomarkers differed across categories of low 33 (17%), normal 109 (55%) and high 57 (29%) bone turnover. Area under the curve values were in the range of 0.75–0.85. High negative predictive values (≥90%) were found for both high and low bone turnover, indicating the ability to rule out both conditions using the suggested BTM cutoffs. The highest diagnostic performances were seen with combinations of biomarkers, with overall diagnostic accuracies of 90% for high turnover, and 78% for low turnover. Results were similar for dialysis patients and kidney transplant recipients and align with findings in comparable studies of nonkidney retained biomarkers. Reassuringly, the suggested biomarker cutoffs are very similar across studies [45▪,46]. These cutoffs may be clinically implemented, pending additional external clinical validation studies. It must be acknowledged that diagnostic performance indices, specifically the positive and negative predictive values, are dependent upon the prevalence of a disease. Thus, for renal osteodystrophy phenotypes of low prevalence, for example high bone turnover, it is difficult to attain positive predictive values high enough to secure a diagnosis. On the other hand, the chosen cutoff will also affect diagnostic certainty – the higher the BTM, the higher the likelihood of high bone turnover, with less likelihood of a false-positive diagnosis [47].

A multicentric Kidney Disease Improving Global Outcomes (KDIGO) supported bone biopsy study concluded that BALP is not superior to PTH in categorizing patients according to bone turnover. This conclusion holds true in a population with a homogenous kidney function background (all patients in above-mentioned KDIGO study were on maintenance hemodialysis) but needs caution in the context of a population with a heterogeneous kidney function background [45▪]. In such context, variable PTH responsiveness may obscure the relation between circulating PTH levels and histomorphometric parameters of bone turnover [48].

MONITORING THERAPEUTIC RESPONSES

Though fraught with challenges [49], monitoring BTMs may be advocated to capture 'acute' effects of therapy. The absence of change in BTM levels following the onset of mineral metabolism or osteoporosis treatment may point to noncompliance. Noncompliance can be addressed by changing the treatment regimen: less frequent dosing, or intravenous injection rather than oral treatment can be tried [16]. Alternatively, the absence of posttreatment changes in BTMs may indicate a true lack of response, questioning the appropriateness of the therapy. In a CKD patient with osteoporosis, a lack of response to an antiresorptive agent may unmask low bone turnover disease,

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for which an anabolic agent may be a more appropriate therapeutic option. Conversely, a tentative diagnosis of high turnover may be strengthened by the expected decline in BTMs following suppressive therapy. In postmenopausal osteoporosis, decreases in BTMs >LSC (generally in the range of 30–40%) during the first 12 weeks of antiresorptive therapy predict the effect on BMD gain [50] and fracture risk reduction [51]; whether this is also true in CKD remains to be examined.

CONCLUSION AND FUTURE DIRECTIONS

At present, none of the BTMs fulfills all of the criteria of an 'ideal' biomarker (Table 1), defined as a biomarker that undergoes little degradation, shows minimal variability diurnally and longitudinally, and does not accumulate with glomerular filtration rate loss, nor is cleared by dialysis; can be analyzed by a high-throughput methodology that is accurate, reproducible and affordable; and provides information that adds to, or improves upon existing tests, aids risk assessment or enhances patient management (Table 1).

Intermethod variation of most, if not all

Table 1. Characteristics of an 'ideal' bone turnover marker

	PTH	Sclerostin	BALP	PINP	CTX	TRAP-5b
Description	Master regulator of bone remodeling	Wnt/β-catenin signaling inhibitor	Ectoenzyme of the osteoblast	Propeptide of type I procollagen	Peptide fragment of type I collagen	Enzyme produced by osteoclasts
Category	Factor affecting bone turnover	Factor affecting bone turnover	Bone formation marker	Bone formation marker	Bone resorption marker	Bone resorption marker
Preanalytical phase						
Stable, undergoes little degradation	+/−	+	+	+	+	+
Minimal variability diurnally and longitudinally	−	?	+	+	−	+
No accumulation with GFR loss, not cleared by HD	Fragments	Controversial	+	+ (Trimeric only)	−	+
Analytical phase						
High-throughput methodology; accurate, reproducible and affordable	+	−	+	+	+	+
Postanalytical phase						
Intraindividual variation (LSC, %)	24 (72%)	?	12 (36%)	10 (30%)	?	8/24
Clinical phase						
Measurement adds to, or improves upon, existing tests, aids risk assessment or enhances patient management	Yes, but only at extremes	Probable	Probable	Probable	Unlikely	Probable

BALP, bone-specific alkaline phosphatase; CTX, C-terminal telopeptide; GFR, glomerular filtration rate; LSC, least significant change; PINP, N-terminal propeptide; PTH, parathyroid hormone; TRAP-5b, type 5b tartrate-resistant acid phosphatase.

BTMs remains elevated. This compromises widespread clinical implementation and calls for further standardization and harmonization. The International Federation of Clinical Chemistry and the International Osteoporosis Foundation have established a Joint committee on Bone Metabolism, which is extensively working to improve harmonization or standardization of PTH, BTMs and vitamin D assays

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[52–54]. Meanwhile, clinicians should acknowledge that results obtained by different assays are not interchangeable.

BTMs do have several advantages, but also important limitations. Additional large cross-sectional and longitudinal studies that compare established and emerging (e.g. miRNAs) BTMs with the gold standard, that is bone histomorphometry are required. Very likely, a panel of BTMs will prove superior to a single parameter. The same holds true for trends over time as compared with a single time point measurement. BTMs provide information that is complementary to other clinical tests. It may be envisioned that in the near future the assessment of validated BTMs (panels) will be part of routine clinical evaluation and monitoring of bone health in CKD patients – integrated with clinical risk factors, imaging result and, eventually, bone histomorphometry data.

In conclusion, mounting evidence indicates that BTMs represent a useful adjunct, if not a reliable alternative, to bone histormorphometry. The 2009 KDIGO guidelines suggested that 'measurements of serum PTH or BALP can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover' (paragraph 3.2.3; grade 2B). PTH monitoring in advanced CKD is recommended every 3 months and tALP activity yearly, or more frequently if levels of PTH are elevated (paragraph 3.1.2; not graded) [55]. Time may have come to revisit this recommendation and to promote a more liberal use of BTMs in the evaluation and monitoring of bone health in patients with CKD.

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