3a Detection and Evaluation of CKD-MBD

The Use of Bone Turnover Markers in CKD-MBD

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Abstract

Bone turnover markers assist in fracture risk prediction, management and monitoring of osteoporosis in patients without CKD. The use in CKD-MBD has been limited as many of these markers and breakdown products are renally excreted, including the most commonly used and well standardised procollagen type I N propeptide (P1NP) and C-terminal cross-linking telopeptide of type I collagen (CTX). Of the markers unaffected by renal function, bone specific ALP (BSAP) is associated with mortality and fracture rate in CKD subjects and is now available on several automated analysers. When used in combination with PTH, BSAP as a bone formation marker correlated well with bone biopsy histomorphometry in predicting adynamic bone disease. Tartrate-resistant acid phosphatase 5b (TRAP5b) is a resorption marker which is under development for automation. Both high and low bone turnover in CKD-MBD patients are associated with increased fracture and mortality risk. Bone biopsy as the gold standard to differentiate between adynamic bone disease and osteitis fibrosa is limited by availability and cost. Appropriate use of bone turnover markers is vital in the decision to commence anti-resorptive agents, and to monitor efficacy in order to avoid over suppression of bone turnover which may lead to stress fractures. Further efforts are required to develop markers unaffected by renal function with standardised cut-off values and fracture as well as vascular calcification end-points.

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Introduction

The gold standard for assessment of bone turnover is the measurement of bone formation rate in an iliac crest bone biopsy specimen. This is limited by expense, invasiveness, and availability of local expertise. Plasma bone turnover markers (BTM) were developed in osteoporosis patients for fracture risk prediction,[1] assessment of medication compliance and anti-fracture efficacy, as well as monitoring bisphosphonate drug holiday. These markers have additional utilities in CKD-MBD, a condition with a higher prevalence of adynamic bone disease, whereby the use of anti-resorptive agents worsens microdamage accumulation and lead to further fractures. Therefore, it is of paramount importance in the management of CKD patients to distinguish high from low bone turnover state and have the ability to monitor turnover status periodically to titrate therapy. Aside from fragility fractures, BTM have been associated with arterial stiffness (1), and might help predict vascular calcification, which heralds the leading cause of mortality in these patients.

Two BTMs were flagged for standardisation by the IOF/IFCC procollagen type I N propeptide (P1NP) and C-terminal cross-linking telopeptide of type I collagen (CTX).[2] CTX is renally excreted and accumulates in CKD patients, P1NP is metabolised by the liver, however fragments are accumulated in CKD and therefore the intact P1NP assay (IDS-iSYS) is less affected than the total P1NP assay (Roche).(2)

Other markers unaffected in CKD include bone specific alkaline phosphatase (BSAP) and tartrate resistant acid phosphatase (TRAP) 5b. Both BSAP and total alkaline phosphatase (ALP) have good correlation with bone formation rate. (3) High parathyroid hormone (PTH), total ALP and BSAP levels are associated with increased mortality and fracture rate.(4-7) Low bone turnover is linked to vascular calcification and also associated with mortality.(8) Pyrophosphate inhibits vascular calcification while ALP increases pyrophosphate degradation and might therefore be an important

therapeutic target. Low bone turnover can develop with over-treatment from excessive doses or prolonged duration of anti-resorptive agents; this poses a concern regarding vascular risk in CKD patients.

KDIGO guidelines

The 2009 KDIGO guidelines recommended monitoring serum levels of calcium, phosphate, PTH and ALP beginning in CKD stage 3 (1C), and in CKD stages 4-5D that ALP be measured every 12 months, or more frequently in the presence of elevated PTH (not graded). In patients with CKD 3-5D, the guidelines suggested that measurement of serum PTH or BSAP could be used to evaluate bone disease, because markedly high or low values predict underlying bone turnover (2B). However, in patients with CKD 3-5D, routine measurement of bone derived turnover markers of collagen synthesis (such as P1CP) and breakdown (such as CTX, pyridinoline or deoxypyridinoline) was not suggested (2C). (9)

In the 2016 draft clinical practice update of the KDIGO guideline, no change to the bone turnover marker measurement was suggested. However, bone biopsy is now recommended only if the result will impact treatment decisions and not suggested for all CKD-MBD subjects prior to bisphosphonate commencement. Bone turnover markers will therefore be of paramount importance to exclude adynamic bone disease prior to anti-resorptive treatment and to avoid its development during treatment. The American Society of Bone and Mineral Research (ASBMR) task force for managing osteoporosis in patients on long-term bisphosphonate treatment recommends re-evaluating the need for bisphosphonate treatment after 3 years of intravenous or 5 years of oral therapies due to concern with risk of prolonged bone turnover suppression in patients with low absolute fracture risk. (10) The optimal duration of therapy for CKD-MBD subjects is unknown and requires further studies. Calcium, phosphate and PTH are routinely tested in CKD patients to titrate calcitriol, phosphate binder therapy and to monitor progression from secondary to tertiary hyperparathyroidism. Total ALP is a cheap enzymatic test, which as part of the liver panel is frequently performed in CKD patients. Whilst circulating ALP consists of mostly liver and bone isoforms, the inter-individual biological variation of ALP is large, in the order of 20%.(9) Subsequently, high BSAP can still result in a total ALP result which sits within the wide normative range of 30-110 IU/L.(10) A low total ALP on

the other hand suggests the low BSAP disorder of hypophosphatasia, a low bone turnover state which leads to stress fractures. In the setting of cholestatic liver disease with raised GGT, BSAP measurement will be required to ascertain the bone contribution to the raised ALP. In significant liver disease, the cross-reactivity of BSAP with liver ALP can be up to 20%, thereby failing to add clarity.(11) Nonetheless, some studies have found BSAP superior compared to total ALP and PTH in bone turnover determination.(3, 11) ALP has a longer half-life (1-2 days) compared to PTH (4 minutes) and has less day-to day fluctuation.

PTH is strictly speaking not a BTM as it is neither involved in the process of, nor is a direct product of bone resorption or formation. PTH release is regulated by low calcium concentration which increases osteoclastic activity and the release of calcium from the bone matrix. High PTH (> 300 pg/ml) is associated with high bone turnover and osteitis fibrosa on bone biopsy, but milder elevation has also been reported in adynamic bone disease due to PTH resistance. (12) A low PTH (< 150pg/ml) is more likely found in adynamic bone disease. The different generations of PTH assays, lack of standardisation amongst manufacturers, inadequate validation of the manufacturers' normative range and unstable drift of results due to lot-to-lot variation all add to the complexity of implementing a clinically relevant PTH cut-off. Combining a low PTH (< 150pg/ml) and a low BSAP (< 27 IU/L) improved the specificity of diagnosing adynamic bone disease in 103 dialysis patients with bone biopsy results.(13) In the newer automated Ostase BSAP assay, the cut off < 20 IU/L is used. This commercial patented reagent is more readily available and has good agreement when used on the Beckman Coulter Access, IDS-iSYS and Liaision analysers.(14)

C-telopeptide (CTX) and other collagen breakdown products are renally excreted and therefore elevated in CKD patients. Elevated results do not correlate with bone biopsy findings.(15) Despite the high baseline values, CTX concentration reduces by 60% post denosumab injection in renal failure, therefore a treatment effect can still be seen. However, the optimal therapeutic target in these patients remains unknown. CTX is cleared by dialysis and therefore predialysis sampling is required for longitudinal monitoring.

Osteocalcin is a non-collagenous protein found in bone matrix and cartilage. It is a marker of bone formation and is renally cleared. The combination of osteocalcin (< 41 ng/L) and BSAP (< 23 U/L) improved the positive predictive value for diagnosing adynamic bone disease in a CKD-5 cohort to 77%. (16)

TRAP5b is an enzyme released by osteoclasts to breakdown bone matrix. High serum levels therefore reflect increased osteoclastic activity and resorption. Levels correlate with PTH and ALP and are unaffected by renal function.(17) Its use is limited by availability of automated assays.

Implications for clinical practice

For patients with CKD, the bone formation marker BSAP has the advantage of specificity over total ALP. The automated Ostase assay is available on 3 analysers, it has good predictability either used alone or combined with PTH for adynamic bone disease and is associated with fractures and mortality. The other 2 formation markers, osteocalcin and intact P1NP, are less readily available and have limited normative range validation data in CKD patients. The bone resorption marker TRAP5b is to date the only resorption marker not affected by renal function. Its use is limited by availability of an automated assay.

Conclusion

High and low bone turnover states are associated with fractures and mortality in dialysis patients. Biomarkers are required as a surrogate to bone biopsy, which is an expensive, invasive and a limited resource. Longitudinal monitoring of CKD patients on bisphosphonates is required to avoid over suppression of bone turnover and stress fractures. Elevated total ALP generally reflects high bone turnover and can be used to monitor osteoblastic activity when liver function is intact. BSAP is useful in concurrent liver disease and to predict low bone turnover state. Combining low PTH and low ALP improves the predictive value for adynamic bone disease. TRAP5b is a potential resorption marker currently limited by availability of automation.

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