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Review

The need for a reliable bone biomarker to better assess chronic kidney disease mineral and bone disorder

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Abstract
Chronic kidney disease mineral and bone disorder is a metabolic bone disease present in almost all uremic patients. There are no good markers of bone resorption available for uremic patients. The validity of parathormone as a surrogate marker of bone and mineral disorders has been questioned over the past decade. We need to shift from Surrogate markers to bone markers.
Keywords: Chronic kidney disease, Mineral and bone disorder, Renal osteodystrophy, Parathyroid hormone, End- stage renal disease, Hypoparathyroidism
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Introduction

Chronic kidney disease, mineral and bone disorder (CKD-MBD) or formerly renal osteodystrophy (ROD) is a metabolic bone disease present in almost all uremic patients. In uremia, bone is relatively resistant to parathyroid hormone (PTH) action, such that supra-normal level of PTH is needed to maintain bone turnover. Relative hypoparathyroidism is associated with low-turnover or adynamic bone disease (1); severe secondary hyperparathyroidism leads to high turnover bone disease or osteitis fibrosa cystica (2). The classification and hence the management of ROD currently requires bone histomorphometry to calculate indices of bone turnover. Bone histomorphometry requires bone biopsy, a painful and invasive clinical test that is rarely performed in clinical practice. Histopathologically it ranges from high-bone turnover disease typical of osteitis fibrosa, mixed forms, and low bone turnover, mainly osteomalacia and adynamic bone disease. Adynamic bone disease is seen in 30%-50% of pre-dialysis patients, 40%-65% of chronic ambulatory peritoneal dialysis (CAPD) patients and 30%-40% of hemodialysis patients (3,4). ROD is also accompanied by a reduction in bone mineral density (5).

Materials and Methods

For this mini-review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was performed by using combinations of the following key words and or their equivalents; Chronic kidney disease, mineral and bone disorder, renal osteodystrophy, parathyroid hormone, end- stage renal disease, hypoparathyroidism, vitamin D, bone specific alkaline phosphatase, secondary hyperparathyroidism, bone histomorphometry, osteocalcin, renal failure, osteoblasts and alkaline phosphatase.

Diagnosis of CKD-MBD

Bone biopsy remains the gold standard for diagnosis of the high *versus* normal *versus* low turnover bone disease and for the assessing the response of renal bone disease to any intervention (6). However, the patients' acceptability and availability are often issues that prevent bone biopsies from being performed in the patients with chronic kidney disease (CKD). Serial bone biopsies are rarely used to follow progression of CKD-MBD or its response to therapy. Therefore, there is a need to develop non-invasive markers of bone turnover in the evaluation of ROD (7).
The current clinical practice is to infer the type of CKD-MBD present from plasma levels of intact PTH (iPTH) and/or bone specific alkaline phosphatase (BSAP). These markers are also used to guide treatment with calcitriol or other vitamin D analogs. However, the plasma intact PTH concentration mainly reflects the intensity of activity of the parathyroid glands, and given that the uremic condition is often accompanying with a resistance of bone cells to parathyroid actions (8). The relationship between plasma intact PTH levels and bone formation rate is not continuously maintained (9). Additionally, there is a non-PTH truncated fragment, i.e. PTH [7-84], which, in addition to PTH [1-84], is measured by most iPTH immunoradiometric assays, giving erroneously high

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Implication for health policy/practice/research/medical education

Currently, there are no good markers of bone resorption available for uremic patients. The validity of parathyroid hormone (PTH) as a surrogate marker of bone and mineral disorders has been questioned over the past decade. It has become obvious that instead of using surrogate markers to evaluate bone turnover, is better to use bone markers.

iPTH values. These fragments compete with PTH [1-84] for binding to the PTH receptor, accumulate in uremia and are an important cause of resistance to PTH action in uremic patients (10). Therefore, it has been proposed that the specific assay for whole PTH [1-84] may be more specific as a determinant for bone turnover in CKD-MBD. However, Coen et al have found whole PTH [1-84] to be only as good as iPTH in predicting bone turnover and hence the type of CKD-MBD (11). Therefore, there is a need to examine other non-invasive markers of bone turnover in uremic patients that can be used to predict bone turnover and thereby guide therapy with vitamin D analogs and antiresorptive agents.

Matrix molecules other than collagen and cellular components of bone cells are useful as markers of bone turnover. BSAP and osteocalcin levels are indicative of matrix maturation and mineralization phase of bone formation. The bone specific isoenzyme (BSAP) (molecular weight of 80 kDa) is neither dialyzable nor filterable by the kidneys so that, its plasma concentration is not altered by variations in kidney function. BSAP is exclusively produced by osteoblasts and is a marker of bone formation. It has high sensitivity and specificity for the diagnosis of different types of ROD in research studies but has limitations as a marker of bone turnover in individual patient. First, synthesis of BSAP and osteocalcin synthesis is directly stimulated by vitamin D, independent of an effect on bone turnover. Second, BSAP is over-estimated due to cross-reactivity, when liver disease leads to an elevation of total alkaline phosphatase (AP). Third, hormone imbalance and uremic milieu in end-stage renal disease (ESRD) patients may uncouple bone formation from bone resorption. In this situation BSAP would not reflect bone resorption, the single most important determinant used to define and treat ROD. Total AP is a poor marker of bone turnover, since it is comprised of six AP isoenzymes i.e. hepatic, intestinal, skeletal, renal, placental and tumoral (12-14).

Osteocalcin is the most abundant non-collagen protein of the bone matrix and human osteocalcin is produced by osteoblasts and odontoblasts under the control of 1, 25-(OH)2 D. There is a good correlation between osteocalcin and bone turnover in normal individuals, premenopausal women and osteoporotic women, but not in uremic patients since osteocalcin accumulates in the plasma in patients with renal failure (15).

Since 90% of the type I collagen is present in bone, type I procollagen breakdown products constitute good biochemical markers of bone formation and resorption. Procollagen type I carboxy-terminal propeptide (PICP) and procollagen type I amino-terminal propeptide (PINP) are peptides released from the carboxyl and nitrogenous terminals of procollagen where it is catabolized to form mature collagen. Cross-linked telopeptides from C- and N-terminals of type I collagen (ICTP and NTx respectively) are released into blood and excreted through the kidneys after bone resorption. These telopeptides are partly broken down further to release pyridinoline (PYD) and deoxypyridinoline (DPD) cross-links into the circulation which are also excreted in the urine. Although PYD has a wider tissue distribution, DPD is present almost exclusively in bone. Among these non-invasive markers urinary pyridinium crosslinks and urinary and serum NTx are presently considered the most specific markers of bone turnover in the general population. Urine NTx (U-NTx) is a specific and sensitive indicator of bone resorption and is able to distinguish normal premenopausal from late osteoporotic patients. NTx can be used as one of the diagnostic tools for osteoporosis, and to evaluate bone turnover in chronic kidney disease. Urinary measurements of NTx entail greater analytical and biological variability (i.e. urine NTx concentration is a function of urinary concentration and therefore expressed as a ratio of NTx to creatinine) (16-19).

Tartrate resistant acid phosphatase (TRAP), synthesized by osteoclasts, has been proposed as a potential marker of bone resorption. However, its activity was also detected in osteoblasts and osteocytes. The value of serum TRAP in uremic patients still remains to be established. A specific isoenzyme, TRAP 5b, is specifically produced by osteoclasts and not by other bone cells. It appears to be more specific than total TRAP for the assessment of bone resorption in patients with normal renal function. TRAP 5b isoform is elevated in ESRD and is related to bone turnover (20,21), but is available only as a research tool and its specificity to predict bone resorption in CKD-MBD remains to be established.

In renal failure, PYD, DPD and NTx are retained in the plasma and consequently serum concentrations are significantly higher in uremic plasma compared with normal plasma. PYD, DPD and NTx are excreted in the dialysate of patients on peritoneal dialysis and plasma concentrations decline in post-hemodialysis sera (22).

Conclusion

Currently, there are no good markers of bone resorption available for uremic patients. The validity of PTH as a surrogate marker of bone and mineral disorders has been questioned over the past decade (23,24). It has become obvious that instead of using surrogate markers to evaluate bone turnover, is better to use bone markers.

We need to shift from Surrogate markers to Bone markers. Markers of bone formation (BSALP) and resorption (TRAP-5b) can serve as predictors of cardiovascular

morbidity and mortality in CKD (25) and with the same rational in addition of U-NTx/Cr might be helpful in CKD-MBD evaluation (19,26).

Authors' contribution

RT and AG contributed equally to search and prepared the manuscript. All authors read and signed the final paper.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

The authors declared no competing interests.

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