

Relation Between PTH and Biochemical Markers of MBD



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Introduction

Progressive chronic kidney disease (CKD) ineluctably leads to mineral and bone disorders (MBD). Numerous biochemical alterations observed in CKD, namely the reduced natural and active vitamin D metabolites, hypocalcemia, hyperphosphatemia, high parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), sclerostin, and low klotho, independently or in concert affect mineral and bone metabolism (CKD-MBD), and ultimately bone quality and quantity [1]. Moreover, a significant number of medications aimed to control or normalize these biological alterations often directly or indirectly impact bone metabolism, including calcium salts, intestinal phosphate binders, vitamin D compounds, calcimimetics, bisphosphonates, and other emerging therapies.

The usual circulating biomarkers of bone metabolism, either alone or combined, are poor predictors of the type of renal osteodystrophy (ROD) in CKD-MBD [2]. Thus, to establish a firm diagnosis, the qualitative and quantitative histomorphometric evaluation of a bone biopsy still remains the gold standard. The bone histomorphometric nomenclature system describes essentially five types of ROD in CKD: osteitis fibrosa or high bone turnover, adynamic bone disease,

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osteomalacia, mixed lesions associating high bone turnover and osteomalacia, and osteopathies due to trace metal overload (aluminum, fluoride, strontium) [1]. This classification of CKD-MBD is mainly based on three parameters: bone formation rate (BFR) after tetracyclin double labeling, bone volume, and the amount of unmineralized osteoid surface or, in other words, the presence or not of a mineralization defect. Unfortunately, bone biopsy is still rarely indicated and performed in CKD patients, mostly because of difficulties in finding experienced teams and appropriate facilities to analyze them. Its invasive and largely perceived feeling that it is a painful procedure is an additional explanation. Therefore, considerable efforts are continuously devoted to the search of reliable noninvasive biomarkers of bone metabolism in CKD patients. These biomarkers of bone turnover in CKD-MBD would be of great importance in recognizing specific conditions, identifying patients at risk, and to guide patient tailored therapeutic intervention.

PTH is generally not considered as a biomarker of bone metabolism; however, PTH is one of the most important regulators of bone turnover and bone mineralization. Intermittent physiological doses of PTH increase bone formation and bone mass; however, extremely and constantly high or low PTH results in bone loss, increased risk of skeletal fractures and mortality [3, 4]. Regardless of the type of PTH assay, PTH values show a relatively good correlation with BFR and with most of histomorphometric parameters. However, approximately 30% of dialysis patients with normal/low BFR show PTH values between 200 and 600 pg/ml or 2–9 fold the upper limit of the reference value [5]. In spite of these findings, PTH, second and third generation assays, is the most used and useful biomarker in the diagnosis of ROD. However, one should keep in mind that PTH mostly reflects the degree of parathyroid activity and to some extent the degree of bone turnover.

Bone is composed of cells (10% osteoblasts and osteoclasts, and 90% of osteocytes) and of extracellular matrix (75% inorganic, mostly in form of hydroxyapatite, and 25% of organic proteins, mostly of type I collagen (85%) and non-collagenous compositions (15%)) [6]. Analyzing the metabolism of these proteins; collagen-related ones such as type I collagen C- and N-terminal pro-peptides (PINP and PICP), and collagen crosslinked molecules could be a useful tool in the assessment of ROD, as well as the non-collagenous proteins such as bone-specific alkaline phosphatase (BSAP) and tartrate-resistant acid phosphatase (TRAP5b). New molecules such as fibroblast growth factor 23 (FGF23), klotho, sclerostin and Dkk1 could also emerge as interesting biomarkers of bone metabolism. In this review we will briefly update the relation of PTH with old and the most recent biomarkers of bone metabolism.

PTH and Bone Remodelling

PTH is the principal molecule controlling bone remodeling. As previously mentioned, intermittent physiological doses of PTH increases bone formation and bone mass [7, 8]; however, extremely and constantly high PTH results in bone loss

and are associated with increased risk of mortality [9]. In CKD, with the decline in renal function there is alteration of the ratio between the intact and fragment forms PTH, translated by a decrease of circulating intact PTH and an increase of PTH fragments. Normal subjects have 80% of PTH fragments and 20% of intact PTH molecules, which comprises the intact PTH, N-terminal truncated PTH non 1–84 and amino-PTH [10]. On the other hand, CKD patients have 95% of PTH fragments and only 5% of the intact forms [10]. Nevertheless, whatever the type of PTH we measure, there is always a relatively good correlation between PTH, BFR and with all histological parameters as illustrated by several studies in the nineties [11, 12]. In one of these studies, which examined 96 bone biopsies from patients treated by hemodialysis or peritoneal dialysis, serum PTH levels positively and significantly correlated with BFR. It is important to note that some of these patients with normal or low BFR had serum PTH levels ranging between 200 and 600 pg/ml. Comparable results were also found in another study in 97 dialysis patients where more than one third of them had histological signs of low bone turnover while having serum PTH levels over 300 pg/ml. Altogether, these results contributed to the KDIGO guidelines and the recommendation of maintaining a PTH value between two and nine times the upper limit of normal value in dialysis patients [1]. However, although the controversies, serum PTH levels, either assessed by second or third generation assays are the most useful biomarker in the diagnosis of ROD.

PTH and Calcemia

PTH plays a vital role in maintaining calcium levels in a remarkably narrow area. PTH performs this role through its actions on the kidney, the bone and indirectly on the intestine [3, 13]. In the kidney, it stimulates calcium reabsorption in the broad ascending limb of Henle's loop and distal tubule. In bone, it stimulates bone remodeling and calcium release to the extracellular milieu. In the intestine, PTH indirectly stimulates calcium absorption via active vitamin D. In fact, it stimulates the activity of 1α -hydroxylase in the renal proximal tubule and the conversion of 25OHD to calcitriol, which directly stimulates several intestinal calcium transport proteins. Disorders of secretion of PTH synthesis and/or its mode of action on the skeleton are often associated with changes in serum calcium levels.

Serum calcium levels are maintained within a narrow range by the balance between urinary calcium excretion, intestinal calcium absorption and the amount of calcium released by the bone. Any change in serum calcium levels is detected by the parathyroid calcium sensing receptor (CaR), which adjusts PTH production [14]. Decreased serum calcium levels increase PTH, which increases renal tubular calcium reabsorption, bone resorption and calcium release. On the contrary, an increase in serum calcium levels activates the CaR, decreases PTH secretion, bone resorption, and increases urinary calcium excretion. In case of CKD, the CaR gene is normal, but its expression in parathyroid cells is reduced.

PTH acts in bone through the binding and activation of the PTH receptor type 1 (PTHr1) of osteoblasts. It stimulates cortical and trabecular bone remodeling and the release of calcium to the extracellular environment. The catabolic effect of PTH is mediated through the stimulation of RANKL (receptor activator of nuclear factor beta ligand) production and the reduction of sclerostin and osteoprotegerin (OPG) production by osteoblasts. This results in an increase in osteoclastogenesis, osteoclastic activity and bone resorption [3, 4, 15]. In case of excessive production of PTH, as in case of severe secondary hyperparathyroidism in CKD, it is possible to observe hypercalcemia, which is secondary to the excessive release of calcium from the skeleton following the PTH-induced increased bone resorption and the inability of the kidney to excrete this excessive load of bone-derived calcium (tertiary hyperparathyroidism). Paradoxically, high serum calcium levels can also be observed in case of extremely low bone turnover or adynamic bone disease because of the reduced buffer activity of the skeleton and the incapacity to uptake excessive calcium load coming either from the diet or from medications together with renal failure.

PTH and Phosphatemia

PTH was also the first hormone involved in the regulation of phosphatemia [3]. By stimulating bone resorption and calcium release, PTH also releases skeletal phosphate and may lead to hyperphosphatemia. However, PTH increases urinary excretion of phosphate due to the internalization of NPT2a and NPT2c cotransporters and the decrease of renal tubular phosphate reabsorption. For this reason, the measurement of the maximal proximal tubular phosphate transport has been used for long time, and prior to the availability of reliable PTH assays, as a marker of primary hyperparathyroidism [16]. In CKD, the phosphaturic effects of PTH are limited by the progressive loss of PTHr1 in renal cells [17]. Therefore, despite the increase in PTH and the fractional urinary phosphate excretion in CKD, the urinary excretion of daily phosphate diminishes at the late CKD stages leading to hyperphosphatemia [18]. Hyperphosphatemia decreases the expression and the sensitivity to calcium of the parathyroid CaR, making parathyroid cells less sensitive to the inhibitory action of calcium on PTH synthesis, resulting in hypersecretion of PTH [19, 20].

Bone plays an essential role in the control of phosphatemia, either by releasing phosphate during bone resorption or by storing phosphate during bone mineralization. The amount of phosphate provided by the bone depends on the degree of bone remodeling, which results from the balance between osteoblastic activity and osteoclastic activity. Bone is also responsible for the production of FGF23 by osteocytes [21]. Some examples illustrate the importance of bone in the regulation of phosphatemia, the first is that of the normalization of phosphatemia, following parathyroidectomy in cases of primary and SHPT [22]. The second is bone demineralization observed in subjects with disabling mutations of NPT2a

and hypophosphatemic hyperphosphaturia [23]. In CKD, accelerated bone remodeling, as in case of SHPT and mixed osteopathy, may be responsible for hyperphosphatemia. Conversely, low bone remodeling, as in osteomalacia, adynamic osteopathy and aluminum overload, can explain as well as certain hyperphosphatemias [24].

PTH and Magnesemia

Magnesium is the second most abundant intracellular cation in the body, only a tiny amount is found in the extracellular space (2%), and less than 1% is present in the plasma compartment. Magnesium is a crucial co-factor in numerous enzymatic reactions, and it is also involved in maintaining vascular tone, cardiac rhythm, platelet activity and bone formation [25]. The kidney plays a major role in magnesium metabolism through a fine-tuning regulation within the distal convoluted segment by the TRPM5 channels. In CKD, serum magnesium levels are usually increased, and it might impact bone metabolism because of its complex interdependence with PTH. PTH production by the parathyroid glands is physiologically controlled by calcium, but magnesium, although two times lesser, can also exert similar effects activating the CaR and suppressing PTH secretion [26, 27]. The suppressing effect of Mg upon PTH occurs mainly when a moderate low serum calcium concentration is present, while this effect is blunted by normal-to-high calcium concentrations [28]. Several studies have shown a negative correlation between serum magnesium and PTH levels [29, 30]. Therefore, chronic high serum magnesium levels may lead to low serum PTH levels and might play a role in the pathogenesis of adynamic bone disease, which is associated with a higher mortality risk [31, 32]. Moreover, as magnesium is a potent inhibitor of vascular calcification, low serum magnesium levels might also be involved in the setting and progression vascular calcification in CKD.

PTH and Vitamin D

Native vitamin D, cholecalciferol (D3) and ergocalciferol (D2), are pre-hormones that play an essential role in mineral and bone homeostasis. Vitamin D stimulates intestinal absorption, mainly through its dominant active metabolite $1,25\text{OH}_2\text{D}_3$, and kidney reabsorption of calcium and phosphate. In the parathyroid gland, vitamin D suppresses PTH production. Consequently, low circulating vitamin D levels invariably result in elevated serum PTH concentrations in healthy individuals as well as in CKD patients. In clinical practice, the measurement of vitamin D2 or D3 is never performed, and that of $1,25\text{OH}_2\text{D}_3$ is rarely assessed. What is usually assessed is the circulating concentration of its hydroxylated form 25OHD_3 , which is the standard biomarker of vitamin D status. However, this value does not reflect

the concentration of its active metabolite, 1,25OH₂D₃, but the two metabolites show a good correlation. Several institutions including WHO, institute of medicine, K-DOQI and KDIGO have defined vitamin D deficiency as a value lower than 15 ng/ml, insufficiency between 15 and 30, sufficiency greater than 30 and intoxication over 150 ng/ml. These values have been recommended based on the following four factors: the relation between vitamin D and PTH, with intestinal calcium absorption, with its association with bone mineral density or fractures, and with its relationship with fall, walk distance and muscle strength. However, most of the times the only criteria employed is its relationship with PTH.

In the general population, serum PTH and 25OHD levels are inversely correlated as it has been also found in CKD patients (Metzger). In the French cohort NephroTest™, including more than 1,000 CKD patients, we found that 80% of patients with CKD 3–5 were vitamin D deficient (25OHD < 15 ng/ml) or insufficient (25OHD 15–13 ng/ml), only 20% had normal vitamin D status [33]. In these patients, after adjusting for renal function, age, ethnicity and ionized calcium the circulating concentration of 25OHD at which PTH starts to significantly increase was of 20 ng/ml [33, 34]. Above this value of 20 ng/ml, serum PTH levels were likely to be within normal ranges. In a different smaller Spanish study, 25(OH) D < 20 ng/ml was an independent predictor of death and progression in patients with stage 3–5 CKD, with no additional benefits when patients reached the levels at or above 30 ng/ml suggested as optimal by CKD guidelines [35].

PTH and FGF23/Klotho Axis

PTH significantly increases serum FGF23 levels in healthy subjects due to a direct stimulatory effect on osteocytes and to an indirect effect through the stimulation of 1,25OH₂D₃ synthesis [36]. In CKD, serum phosphate levels increase with the decline of renal function, which directly and indirectly contributes to the skeletal fragility associated with CKD-MBD, through the stimulation of PTH and FGF23 production [37]. It is also accepted that serum FGF23 levels increase in CKD patients 10 to 15 ml/min of glomerular filtration rate (GFR) earlier than PTH (break-point at 57 ml/min for FGF23 compared to 46 ml/min for PTH) [38]. In normal conditions, FGF23 inhibits PTH production and parathyroid cell proliferation through the stimulation of parathyroid CaR and VDR expression [39, 40]. However, in CKD, the hyperplastic parathyroid cells show a hyporesponsiveness to the inhibitory effect of FGF23. FGF23 fails inhibiting PTH synthesis and does not affect the parathyroid expression of CaR and VDR, partially due to a reduced klotho and FGFR1 expression [39].

Circulating levels of FGF23 have also been found to be the most important factor predicting the development of refractory SHPT in dialysis patients. Indeed, it was observed that after 2-year of follow-up, and although with comparable basal PTH values, dialysis patients with basal cFGF23 >7500 n/L were those who significantly increased their serum PTH levels and become resistant to active vitamin

D therapy [41]. Moreover, in dialysis patients with severe SHPT there is a closed correlation between serum PTH and FGF23 levels, and the reduction of PTH by surgical parathyroidectomy is followed by a significant decrease in serum FGF23 concentrations [42]. Similarly, in dialysis patients with SHPT, the proportion of patients showing a reduction of >30% in FGF23 was higher in those treated by an oral or iv calcimimetic than with a placebo [43] [44]. In addition, the oral calcimimetic-induced reductions in FGF23 were associated with lower rates of cardiovascular death and cardiovascular events [43].

FGF23 is mainly produced by osteocytes and exerts its major physiological actions in the kidney stimulating urinary phosphate excretion and inhibiting calcitriol synthesis [45]. However, it has been suggested that FGF23 could also play an important role in the regulation of bone mineralization [46]. Indeed, in the absence of FGF23, as in FGF23 knockout animals, as well as in the excess of FGF23 such as in *klotho* knockout animals, there is a severe bone mineralization defect [45, 46]. Likewise, high FGF23 values have been associated with reduced osteoid thickness and osteoid maturation time, in children with normal renal function and in CKD dialysis children [47]. This enigma appears to be deciphered as illustrated by a recent publication where it has been demonstrated that FGF23 modulates bone mineralization by regulating the tissue non-specific alkaline phosphatase (TNAP) specifically through the FGFR3 and independently of *klotho*. FGF23 inhibits TNAP and by this pathway increases extracellular concentration of pyrophosphate, reduces the amount of free inorganic phosphate, and indirectly stimulates osteopontin gene expression, a known mineralization inhibitor [48].

Bone Formation Biomarkers

PTH and Alkaline Phosphatases

As mentioned before, the cellular constituent of bone tissue is composed by 10% of osteoblasts and osteoclasts, and 90% of osteocytes [49]. These cells produce an extracellular matrix which can be divided in inorganic matrix (75%), mostly in form of hydroxyapatite and organic matrix (25%), mostly constituted of type I collagen (85%) and non-collagenous proteins (15%). Therefore, analyzing the cellular metabolism and the proteins composing the 25% of the bone matrix can be a useful tool in the assessment of ROD. Among these proteins, bone-specific alkaline phosphatase and osteocalcin are the most used biomarkers of bone formation and TRAP of bone resorption [50].

Alkaline phosphatases are membrane-bound glycoprotein enzymes favoring phosphatase ester hydrolysis, and phosphate available for mineralization. The tissue-specific alkaline phosphatases (AP) are coded by 3 genes: intestinal, placental and stem cells [51]. The tissue-non-specific alkaline phosphatases (TNALP) are coded by a single gene and they differ by a post-transcription glycosylation, which gives rise to BSAP, liver and kidney isoforms. They are cleaved by phospholipase

C and D and released to the circulation. Three AP isoforms are usually found in the circulation, 50% as BSAP, 45% of liver AP and 5% of tissue-specific AP. In addition, a recent isoform that only circulates in the serum of CKD patients has been reported [52]. They are degraded by the liver and their serum concentration is not modified by the renal function. BSAP has a molecular weight of 80 kDa and a relative long half-life of 1–5 days.

Serum BSAP levels positively correlate with PTH in dialysis patients. Moreover BSAP distinguishes better than PTH and total alkaline phosphatases normal/low bone turnover disease from high bone turnover disease in dialysis patients. BSAP equal or higher than 20 ng/ml, alone or combined with PTH of 200 pg/ml, had the highest sensitivity, specificity, and predictability values for the diagnosis of high turnover bone disease and excluded patients with normal or low turnover bone disease (Table 1) [51, 53]. In another study carried out on 137 HD patients, those with reduced distal radius BMD had a significantly higher serum BSAP levels than those without BMD reduction [54]. High serum BSAP levels have also been demonstrated to be predictive of the skeletal response to active vitamin D treatment [55] and significantly increased in the first 3 months following surgical parathyroidectomy [22]. In conclusion, there is substantial evidence suggesting that serum BSAP level alone or in combination with PTH may be a useful tool for the biochemical estimation of the degree of bone turnover in CKD.

PTH and Osteocalcin

Osteocalcin is mainly produced by osteoblasts. Its gamma-carboxylated inactive form deposited in the extracellular bone matrix, which is transformed in the active, uncarboxylated (uOC) form, after bone resorption, and released into the circulation [56]. In the circulation, 74% of the total osteocalcin circulates in its intact form, and 26% as fragments. Among them, at least 4 fragments, N-terminal, mid-region N-terminal, mid-region C-terminal and C-terminal osteocalcin [57, 58].

Table 1 Plasma bone-specific alkaline phosphatase (BSAP) and parathyroid hormone (PTH) levels in dialysis patients with high bone turnover

High bone turnover	PTH \geq 200	Total AP \geq 200	BSAP \geq 20	PTH \geq 200 BSAP \geq 20
Sensitivity (%)	72	50	100	100
Specificity (%)	80	90	100	80
PPV (%)	92	94	84	94
NPV (%)	47	36	100	100

BSAP Bone-specific alkaline phosphatase; *PTH* Parathyroid hormone; *PPV* Positive predictive value; *NPV* Negative predictive value. BSAP equal or higher than 20 ng/ml, alone or combined with PTH of 200 pg/ml, had the highest sensitivity, specificity, and predictability values for the diagnosis of high turnover bone disease and excluded patients with normal or low turnover bone disease

Serum uOC levels are significantly and progressively lower in subjects with declining renal function compared with those of healthy individuals. They are also closely associated with the risk of subclinical atherosclerosis in CKD subjects [59]. It has been demonstrated that serum total OC levels are significantly and positively correlated with serum PTH and BSAP levels in dialysis patients. Moreover, dialysis patients with histologically proven high bone turnover have significantly higher serum OC levels than patients with normal/low bone turnover [51]. However, and in part because of the release into the circulation of multiples OC fragments during bone resorption, serum OC levels have a poor specificity (50%) in the diagnosis of low bone turnover and adynamic osteopathy [60].

PTH and P1NP

Type I collagen is produced by osteoblast cells and secreted into the extracellular space where it serves as the skeletal mineralizing matrix. Two molecules: procollagen type 1 N-terminal extension peptide (P1NP) and procollagen type 1 C-terminal extension peptide are produced by osteoblasts, released into the circulation and used as biomarkers of bone formation. However, the results of several studies showed that the utility of type 1 collagen-related molecules, either reflecting bone formation (P1NP and P1CP) or bone resorption have been inconclusive, still needing validation by larger studies [12, 51, 61]. One of the first studies measuring P1CP, the C-terminal peptide in 37 hemodialysis patients, with available bone biopsy data, did not find any difference in serum P1CP levels between patients with low or high bone turnover disease [12]. However, in another study, serum P1NP levels significantly differed between two groups of dialysis patients, being higher in those with greater annual BMD loss and the lowest in patients with the less BMD reduction [62, 63]. Similarly, the highest tertiles of P1NP were associated with the highest risk of skeletal fractures and the lowest values of BMD at the femoral neck [64]. Generally, serum PTH levels are positively correlated with P1NP in osteoporotic post-menopausal women and in dialysis patients, but confirmatory larger studies are needed [51, 62, 65].

Bone Resorption Biomarkers

PTH and TRAP5b

TRAP is a metalloenzyme with an optimal activity in acidic conditions, product of osteoclast activity. It is therefore used as a biomarker of bone resorption rate. Serum TRAP5b levels are not affected by the decline of renal function. CKD and dialysis patients show higher serum TRAP5b levels than healthy subjects [66]. The highest quartile of TRAP5b has been associated with the greatest BMD loss at

the distal radius in 58 dialysis patients [67]. Similar findings have also been found in another population of 103 dialysis patients, where the high TRAP5b quartile was associated with the lowest BMD value at the second metacarpal. Interestingly, this biomarker of bone resorption was well correlated with N-terminal telopeptide of type I collagen (NTX), another resorption marker [68]. Finally, serum TRAP5b levels are significantly higher in dialysis patients with SHPT than in control and in patients with normal PTH. Indeed, TRAP5b correlates better than PTH with osteoclast surface, osteoclast number, BFR and mineralization apposition rate [69].

PTH and Crosslaps

Several collagen-related molecules have been used to assess the degree of bone resorption including the NTX, the C-terminal telopeptide of type I collagen (CTX) and their crosslinked molecules pyridinoline (PYD) and deoxypyridinoline (DPD). NTX are cleared by the kidney; thus, in case of CKD, serum NTX levels increase as renal clearance decreases. However, it has been evaluated in a few studies. In CKD patients treated with a bisphosphonate (residronate), in order to prevent glucocorticoid-related bone loss, it was demonstrated that serum NTX levels decreased parallel to the reduction in bone resorption index [70]. In another study in 113 dialysis patients, the highest quartiles of NTX were associated with the greatest reduction of BMD at the distal radius [71]. Serum NTX concentration was evaluated in the Bonafide study. After one year of cinacalcet treatment of dialysis patients with SHPT, serum NTX levels significantly decreased from 378 to 249 nmol/liter, following the decreased of PTH and to the BFR [72]. Considering serum CTX levels, similar to ICTP, they did not differ between dialysis patients exhibiting high and low bone turnover (33 vs. 40 ng/ml) [12]. However, the cross-linked molecule PYD (pyridinoline) was significantly higher in patients with high bone turnover compared to low bone turnover. Serum PYD levels were also very well correlated with PTH, osteoclast surfaces and number, both markers of bone resorption [12]. Interestingly, another study in Japan corroborate our findings and found a good correlation between PYD and CTX. The highest quartile of CTX was associated with the faster bone loss at the distal radius [73]. In summary, collagen derived bone biomarkers, either of formation (P1NP and P1CP) or resorption (NTX, CTX, PYD and DPD) are eliminated by the kidney and accumulated in case of CKD. Their use as diagnostic tool in CKD-MBD need further and larger studies with bone histology.

Conclusions and Perspectives

In conclusion, CKD always leads to abnormal bone turnover, volume, and mineralization. Bone biopsy still remains the gold-standard for the diagnosis of renal osteodystrophy as well as for the monitoring of any therapy impacting bone

metabolism. The relation between serum concentration of PTH and biomarkers of bone metabolism is complex and not yet fully elucidated in case of patients with CKD or treated by dialysis. PTH is not always correlated with the degree of bone remodeling and in the absence of bone histology it cannot be considered as an accurate marker. Further studies, based on bone histomorphometry, are clearly needed to better understand the predictive diagnostic value of old and new, alone or combined with PTH or other biomarkers of bone metabolism in CKD-MBD.

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