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The Bone and Mineral Disorder in Patients Undergoing Chronic Peritoneal Dialysis

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Abstract

Disorders of mineral metabolism and bone disease are common complications in CKD patients. They are very complex and involve a number of feedback loops between the kidney, bone, intestine, and the vasculature associated with an increased morbidity and mortality and decreased quality of life of the patients. The work group of the kidney disease: Improving Global Outcomes (KDIGO) recommended in 2006 the use of the term chronic kidney disease-mineral and bone disorder (CKD-MBD) to describe a systemic disorder that incorporates these abnormalities. Compared to hemodialysis (HD), patients undergoing peritoneal dialysis (PD) appear to have an increased prevalence of low turnover bone disease defined as adynamic bone disease (ABD). The most important risk factors for ABD are age, oversuppression of parathyroid hormone (PTH) with vitamin D, diabetes, circulating antagonist PTH fragments, and frequent presence of a positive calcium balance, which may result in an oversuppression of PTH. PTH levels and bone phosphatase alkaline (bALP) should be assessed among such patients as the earliest markers of abnormal mineral and bone metabolism. Treatments considered are interventions to treat hyperphosphatemia, hyperparathyroidism, and bone disease. The optimal management of chronic kidney disease-mineral and bone disorder (CKD-MBD) includes the prevention of vascular calcifications.

Keywords: peritoneal dialysis, phosphate, calcium, adynamic bone disease, hyperparathyroidism

1. Introduction

Chronic kidney disease (CKD) is a global public health problem affecting 5–10% of the world population [1]. Disorders of bone and mineral metabolism and vascular calcification have been

identified as major risk factors for cardiovascular morbidity and mortality in patients with CKD. In the course of CKD appears a reduction in the ability of the kidney to excrete an adequate load of phosphate which leads to hyperphosphatemia. At the same stages of CKD in which phosphorus retention appears to occur, we are faced with calcium retention too. The main hormones and factors that contribute to the kidney regulation of phosphorus and calcium include parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), klotho and 1,25-dihydroxyvitamin D (1,25(OH)2D). It is now accepted that the increase in FGF-23 is an early event in the pathogenesis of mineral disorders in CKD. FGF-23 levels increase early in CKD, and may reflect an increased phosphorus load. This adaptive change favors the reduction of kidney 1-alpha-hydroxylase, which in turn results in lower levels of the active form of vitamin D 1,25(OH)2D3, decreasing intestinal calcium absorption and allowing a decrease in serum calcium. These changes allow increased PTH synthesis and its release. High level of PTH increases bone turnover and bone resorption, stimulates 1-alpha-hydroxylase, and increases phosphorus removal through reducing its kidney tubular resorption. Although FGF-23 and PTH having synergic effects regarding phosphorus removal, they have opposite effects on 1,25(OH)2D3 synthesis by inhibiting or stimulating 1-alpha-hydroxylase, respectively. During late Stage 4 CKD and into end-stage renal disease (ESRD), all these mechanisms become insufficient and most patients show hyperphosphatemia, high PTH, marked elevations of FGF-23, and reductions of klotho and 1,25(OH)2D3 [2–4]. All these changes together are critically important in the regulation of both initial bone formation during growth (bone modeling) and bone structure and function during adulthood (bone remodeling) [5]. High serum phosphorus was considered the most important uremia-related, non-traditional cardiovascular risk factor so controlling hyperphosphatemia was considered one of the most important goals in managing bone disorders in CKD patients [1].

Effective dietary phosphate restriction has resulted difficult in clinical practice so the use of phosphate binders has become the mainstay of efforts to decrease phosphate absorption from the intestine. The generalized usage in the past of aluminum-containing phosphate binders and calcium-containing phosphate binders was reported to be associated with increased incidence of adynamic bone disease (ABD) [6]. The mineral and hormonal changes in CKD patients go beyond bone alterations and are responsible for systemic consequences such as vascular calcification [1]. These changes have a major impact on morbidity and mortality [7] and consequently their control is of great importance in CKD patients. This chapter is a review that briefly discusses etiology, pathophysiology diagnosis of mineral bone disorders in chronic kidney disease patients on treatment with peritoneal dialysis and therapeutic options.

2. Overview on bone disease and mineral metabolism disorders in peritoneal dialysis patients

2.1. Etiology and pathogenesis

Disorders of mineral metabolism and bone disease are common complications in CKD patients. They are very complex and involve a number of feedback loops between the kidney, bone, intestine, and the vasculature. These are associated with numerous adverse clinical outcomes, in particular cardiovascular disease and increased fracture risk [8] which contributes in an increased morbidity and mortality and decreased quality of life of the patients [3].

The work group of the kidney disease: Improving Global Outcomes (KDIGO) recommended in 2006 the use of the term chronic kidney disease-mineral and bone disorder (CKD-MBD) to describe a systemic disorder that incorporates these abnormalities [9]. These systemic disturbances may manifest themselves by the presence of any one or a combination of the following three conditions: (1) laboratory abnormalities of calcium, inorganic phosphorus, PTH or vitamin D; (2) bone abnormalities in turnover, mineralization, volume, linear growth or strength, and (3) calcification of the vasculature or other soft tissues [8].

The work group recommended that the traditional term "renal osteodystrophy" be exclusively used to define alterations in bone morphology associated with CKD and stated that definitive diagnosis of renal osteodystrophy can only be made by bone biopsy [1].

It is well known that the traditional types of renal osteodystrophy have been defined on the basis of turnover and mineralization, with substantial differences in pathophysiology and treatment.

- Bone turnover and bone volume may both be classified as high, normal or low.

- Bone mineralization may be categorized as normal or abnormal.

In this way, it was suggested that bone biopsies in patients with CKD should be characterized by determining bone turnover (T), mineralization (M), and volume (V) (the TMV system) [9].

Six types of bone disorder are distinguished in the CKD-MBD complex [9]: hyperparathyroid bone disease (high turnover, normal mineralization, and any bone volume); mixed bone disease (high turnover with mineralization defect and normal bone volume); osteomalacia (low turnover with abnormal mineralization and low-to-medium bone volume); ABD (low turnover with normal mineralization and low or normal bone volume); and two distinct disorders due to specific causative agents, namely, amyloid bone disease and aluminum bone disease [10].

While the majority of studies focusing on CKD-MBD in dialysis patients involved hemodialysis (HD) patients, relatively few studies involving peritoneal dialysis (PD) patients have been published [1, 10]. It has been argued that features of CKD-MBD differ between patients undergoing PD and HD, secondary hyperparathyroidism remains the most common pattern in HD patients, and adynamic bone disease was more frequent in patients on PD [1]. This is based on a systematic review which analyzed studies carried out between 1983 and 2006 (**Table 1**). These findings strengthened the worldwide belief that PD is an important risk factor for ABD development.

ABD was first described in association with aluminum overload, being in the past the major cause of this bone lesion [11]. Aluminum deposition along the calcification fronts prevents the mineralization process and also inhibits the deposition of osteoid by directly damaging the osteoblasts [12].

Although there is a large difference between current and past clinical practice and patient characteristics regarding PD treatment (common use of aluminum- and calcium-based phosphate (P) binders, or PD modality mainly for elderly patients), in recent studies, bone histomorphometry persists to reveal lower turn-over parameters and worst mineralization in peritoneal dialysis patients when compared to hemodialysis ones [13, 14].

	PD	HD
Adynamic bone disease	50%	19%
Mild disease	20%	3%
Osteitis fibrosa	18%	34%
Mixed bone disease	5%	32%
Osteomalacia	5%	10%
Normal bone histology	2%	2%

Table 1. Prevalence of types of bone disease as determined by bone biopsy in patients with CKD-MBD.

Over time, it became apparent that adynamic bone or low bone formation exists without aluminum overload and became associated with abnormal calcium balance, the low levels of 1.25 dihydroxyvitamin D, metabolic acidosis, in addition to low levels of estrogen and progesterone, and systemic inflammation. It is referred to be linked with calcific arteriolopathy and cardiovascular disease (CVD) [15, 16].

There are a lot of specific factors which are reported to contribute in the pathogenesis of ABD in peritoneal dialysis:

- Accumulation of advanced glycation end products (AGEs) proteins reported in diabetes was also observed in PD patients. This happens during heat sterilization of PD conventional fluids, where glucose is degraded into products that include reactive carbonyl compounds [17]. Serum from uremic patients was also shown to contain high levels of these compounds derived not only from carbohydrates but also from lipids. The generation of high quantities of AGEs and advanced lipid end products modify bone matrix and participate in the processes which lead to the development of ABD [18]. In addition of elevated AGEs, PD patients have impaired glucose tolerance and high glucose levels during explosion to high glucose concentrations. High glucose levels were reported to inhibit bone mineralization in vitro by preventing calcium uptake by bone cells [19], a finding that could further support the altered bone structure in diabetic patients.

- High levels of calcium and magnesium found in dialysate. High magnesium concentrations may inhibit parathyroid hormone secretion just as high calcium concentrations do [20], being involved in the pathogenesis of adynamic bone in PD patients [21].

- Sclerostin is another factor with impact on ABD in PD patients. Sclerostin is a glycoprotein (22 kDa) product of the SOST gene in osteocytes, which leads to a negative regulation of bone formation by inhibiting differentiation and proliferation of osteoblasts. Recent investigations, demonstrated that increased plasma levels of sclerostin, were found to be associated with reduced bone turnover and osteoblast proportion in dialysis patients [14, 22].

- In PD patients, we are faced with high prevalence of hypoalbuminemia which came as a result of loss through the peritoneal membrane or malnutrition. It is reported that low level of albumin contributes to the development of ABD by reducing the plasma level of PTH. Serum intact PTH has been shown to positively correlate with serum albumin in PD patients [23].

The relationship between low PTH level, ABD, increased fracture risk [24], and vascular calcifications may at least partially explain the association of ABD with increased mortality rates. To achieve optimal bone and cardiovascular health, attention should be focused not only on classic control of secondary hyperparathyroidism but also on prevention of ABD, especially in the steadily growing proportions of diabetic, white, and elderly patients in PD [25].

2.2. Phosphate retention and hyperphosphatemia

It is generally accepted that the accumulation of phosphorus appears to begin in CKD Stage 3b and contributes to secondary hyperparathyroidism [3]. Persistent stimulation of the parathyroid glands by elevated extracellular phosphorus concentrations, especially when is accompanied by decreased extracellular ionized calcium concentrations, and markedly reduced serum calcitriol levels leads to increased parathyroid hormone (PTH) production [26]. This promotes diffuse polyclonal hyperplasia followed by monoclonal nodular hyperplasia, decreases the levels of calcium-sensing receptor and vitamin D receptor, lowering the activity of 1-alpha-hydroxylase and consequently decreases serum 1,25(OH)2D3 levels [27].

In severe hyperparathyroidism, hyperphosphatemia may be worsening via phosphorus efflux from the skeleton compromising its phosphorus reserve capacity. On the other side, in low bone turnover, the size of the exchangeable calcium and phosphorus pool is reduced and also is drastically reduced the buffer capacity of the skeleton for the excess of phosphorus. In this way, hyperphosphatemia links vascular calcification with low bone turnover.

Phosphate excess also has reported to be linked with endothelial dysfunction [28] and elevated FGF23, which contributes to left ventricular hypertrophy [29], being so an independent risk factor for mortality in ESRD [2].

Phosphate enters the body by intestinal absorption and is excreted through stools and dialysis fluids (plus urine output in patients with residual renal function). In dialysis patients, elimination of the inorganic phosphate by dialysis is a cornerstone of the management of hyperphosphatemia. The elimination characteristics of phosphate in HD and PD are unlike the urea and other low molecular weight toxins much more similar to those of typical middle molecules although the molecule is only 96D. This is explained with its negative charge, the aqueous cover that increases its effective molecular weight, and the slow intra/extracellular solute transfer rate [30].

In the case of daily dialysis or long nocturnal dialysis, P mass removal is usually large enough to reduce the need of dietary restrictions and the use of P binders. It does not happen in the case of well-nourished patients on standard three-times-a-week dialysis schedule, where to achieve a good P balance is needed an optimal dialysis removal, careful use of phosphate binders, and dietary P control [31].

Some studies suggest that continuous PD may be better in controlling hyperphosphatemia than intermittent hemodialysis [32–35]. This observation supports thesis that PD provides better phosphorus clearance through better preservation of renal failure and its continuous nature.

At the start of PD therapy, residual renal function (RRF) may contribute up to 65% of total phosphate clearance [30, 35]. Urinary phosphate excretion is found to highly correlate with

residual renal function and also a strong correlation between RRF and serum phosphate concentration on PD has been reported [32, 35]. It is well known that RRF declines with time on PD and the effect of this decline on phosphate homeostasis has been described in a few observational studies [34, 36, 37]. Phosphate removal is shown to correlate strongly with residual renal function, but it is dissociated from peritoneal Kt/V urea, creatinine clearance, and net ultrafiltration. Peritoneal creatinine transporter status and creatinine clearance cannot be used as surrogate markers of peritoneal phosphate transport and clearance. Prescription of high volume of dialysate is one of the strategies recommended to increase P removal in anuric patients [30]. Hyperphosphatemia is more frequent in patients with low transporter status, so they may achieve higher peritoneal P clearance under continuous ambulatory peritoneal dialysis (CAPD) regimens. In automated peritoneal dialysis (APD), hyperphosphatemia has been significantly associated with a lower number of automated peritoneal dialysis (APD) cycles and a shorter duration of nocturnal treatment, with insufficient dwell time. Here, recommended strategies to improve P management are increasing dwell times or transfer to CAPD [37]. Recently, Van Biesen et al., confirmed that for slow transporters, longer dwells resulted in higher peritoneal phosphate clearances, whereas for high transporters, shorter dwells were more optimal [38].

2.3. Fibroblast growth factor 23

FGF23 is a circulating peptide that plays a key role in the control of serum phosphate concentrations [4, 39]. It is secreted by bone osteocytes and osteoblasts in response to calcitriol, increased dietary phosphate load, PTH, and calcium [40, 41]. In CKD patients, we are faced with high level of FGF23 due to its decreased clearance too [4]. FGF23's primary function is to maintain normal serum phosphate concentration by reducing renal phosphate reabsorption and indirectly by decreased calcitriol production [42]. FGF23 inhibits the proximal tubular expression of 1-alpha-hydroxylase enzyme, leading to decreased calcitriol synthesis [43]. The net effect of both hormonal actions is to lower serum phosphate concentration. Increased FGF23 is considered as one of the earliest detectable biomarkers of CKD-MBD [44]. Is important to underline that treatments used to control CKD-MBD, such as vitamin D analogs and calcium-based phosphate binders, stimulate FGF23 production.

FGF23 also suppresses PTH secretion by the parathyroid gland [45]. Klotho expression declines progressively with decreasing GFR. Moreover, the decrease in klotho expression on hyperplastic parathyroid glands may contribute to the resistance and impaired parathyroid suppression by FGF23 [46].

In the PD patient population, data on FGF-23 are scarce. In a study by Isakova et al., the authors reported that longer dialysis vintage (R = 0.31), lesser RRF (R = −0.37), and lower renal phosphate clearance (R = −0.38) were associated with higher levels of serum FGF-23 [47]. Golembiewska et al. in her study highlights the strong positive association between serum phosphorus and FGF-23 in patients at the start of PD therapy independently from RRF [48]. It is suggested that FGF23 is a more stable marker of phosphate metabolism than PTH or phosphate itself, which could help explain its stronger association with outcomes and support the further development of FGF23 testing for clinical practice [47].

FGF23 levels are associated with increased risk of cardiovascular disease and mortality in patients with CKD [47]. Clinical and experimental studies have shown that FGF23 has a direct

pathogenic effect causing left ventricular hypertrophy [29]. However, FGF23 does not seem to promote cardiovascular calcification [49].

2.4. Calcitriol

Peritoneal dialysis (PD) patients have a high risk of developing vitamin D deficiency as 25(OH) vitamin D and the precursor of active vitamin D is lost during dialysis, apart from low exposure to sunlight and reduced dermal synthesis.

Plasma calcitriol concentrations generally fall below normal when the GFR is <60 mL/min/1.73 m^2 [8]. This initially happens due to the increase in FGF23 concentration rather than the loss of functioning renal mass [50]. However, further with the advanced CKD, hyperphosphatemia in addition to increased FGF23 levels contribute to the decline of calcitriol synthesis.

FGF23 decreases the synthesis of calcitriol by suppressing the activity of 1-alpha-hydroxylase, which converts 25-hydroxyvitamin D into calcitriol, and by stimulating the 24-hydroxylase enzyme, which converts calcitriol (1,25-dihydroxyvitamin D3) into inactive metabolites in the proximal tubule [43, 51]. Phosphate retention (or perhaps increased phosphate concentrations in the proximal tubule) can directly suppress the renal synthesis of calcitriol by inhibiting 1-alpha-hydroxylase activity [52]. Increased dietary phosphate load and increased calcitriol stimulate the secretion of FGF23 predominantly by bone osteocytes.

Low calcitriol concentrations increase PTH secretion by indirect and direct mechanisms:

- Indirect effects on PTH are achieved through decreased intestinal absorption of calcium and calcium release from bone, both of which promote the development of hypocalcemia, and hypocalcemia stimulates PTH secretion.

- Calcitriol normally acts on the Vitamin D Receptor (VDR) in the parathyroid gland to suppress PTH transcription but not PTH secretion. A decrease in calcitriol concentrations lowers the number of VDRs in the parathyroid cells. This is reported that can be corrected by taking supplementation with calcitriol [53]. The lack of calcitriol and the decreased number of receptors may promote both parathyroid cell hyperplasia and nodule formation. At a later stage of CKD, we have also the contribution of retained uremic toxins, by decreasing both receptor synthesis and the ability of the active hormone-receptor complex to bind to vitamin D response elements in the nucleus [54].

2.5. Skeletal resistance to PTH

In CKD, the skeletal resistance to the calcemic action of parathyroid hormone (PTH) is reported to contribute to the pathology of secondary hyperparathyroidism [55] due to downregulation of PTH receptors induced by the high circulating PTH concentrations; calcitriol deficiency and hyperphosphatemia [3, 56].

2.6. Disorders of calcium balance

Studies have suggested that disorders of calcium balance due to CKD-MBD may play a role in the high cardiovascular mortality in patients with CKD.

A positive calcium balance may arise, because the intestinal absorption of calcium overcomes the capacity of the diseased kidney for its excretion. The absorbed calcium enters in the extracellular space and is distributed in three compartments: blood, soft tissue, and bone. Bone contains 99% of total calcium being the major compartment of body calcium. It includes mineralized bone sites suggested to be partly mediated by PTH and a rapidly exchangeable calcium pool. The regulation of this exchangeable calcium pool might be altered in CKD.

The assessment of calcium balance in dialysis patients (including PD patients) becomes extremely complex. It has to take into account not only dietary calcium intake, but also calcium supplement dose, intake of vitamin D analogs (which increase intestinal calcium absorption), calcium uptake by soft tissue, stool calcium output, urinary calcium excretion, continuous calcium flux from the rapidly exchangeable calcium bone pool, and net bone remodeling or turnover, also influx from PD fluid across the peritoneum membrane if a high-calcium dialysate is used as a result of the concentration gradient or efflux of it when is used lower dialysate calcium [57].

Both hypocalcemia and hypercalcemia are associated with increased mortality in patients with CKD [7, 58].

Hypocalcemia is common among CKD patients and may be associated with increased PTH secretion and abnormal bone remodeling. Ca is a major regulator of PTH secretion. Minute changes in the serum ionized Ca are sensed by a specific Ca membrane receptor (CaSR), which is highly expressed on the surface of the chief cells of the parathyroid glands [59]. Changes in PTH secretion in response to serum Ca are tightly regulated by the CaSR. The fall in serum Ca concentration in CKD, as sensed by the CaSR, is a potent stimulus to the release of PTH. When Ca level goes persistently low, it appears to directly increase PTH mRNA concentrations via posttranscriptional actions and stimulates the proliferation of parathyroid cells over days or weeks [60].

A positive calcium balance, hypercalcemia, inhibits the secretion of PTH and stimulates the development of adynamic bone disease in patients undergoing PD. The risk of protein energy wasting (PEW), often referred as malnutrition, is higher especially in the elderly PD patients. This is associated with reduced bone mass [61] and increase fracture risk in this population [1, 62]. In addition, hypercalcemia has been implicated in the pathogenesis of extraskeletal calcification and is evaluated as an important factor in progression of calcification.

2.7. Vascular calcifications

In the last decades, although the number of peritoneal dialysis (PD) patients is increased, most of the studies related to vascular calcification development are mainly focused on HD population. The prevalence of cardiac valvular calcification is reported to be high in both modalities, ranges from 32–47% in PD patients [1, 63] to 19–84% in hemodialysis patients [64, 65] and greatly contribute on high cardiovascular mortality in this population [2, 66–68].

Recent studies suggest that vascular calcification is a process that involves more than simple precipitation of calcium and phosphate. A complex series of events causes predisposed vascular smooth muscle cells to differentiate into osteoblasts or bone forming cells. Chronic

Uremic toxins

Older age

ABD

Hyperphosphatemia

Higher dose of Vit D analogs

Higher dose of calcium-based phosphate binder

Hypercalcemia

Hypomagnesemia

Diabetes

Malnutrition, inflammation

High level of sclerostin

Low levels of fetuin-A

Table 2. Contributing factors to vascular/valve calcification in PD patients.

inflammation is one of the predisposing factors too. Serum fetuin-A, which is a potent inhibitor of extraskeletal calcification, is reduced in CKD patients with severe vascular calcification. A list of contributing factors in vascular/valve calcifications in PD is present in (**Table 2**).

The increased prevalence of risk factors for atherosclerosis [69], disordered mineral metabolism with a high calcium load and/or uncontrolled phosphate resulting in poor calcium-phosphate balance, as well as the loss of inhibitors of calcifications are considered largely responsible for the higher prevalence of valve and vascular calcification in dialysis patients [70] compared to age- and sex-matched individuals without the evidence of renal disease [71].

The treat-to-goal study revealed that after 3 years in dialysis, 83% of patients had vascular calcifications underlining the importance of the evaluation and control of all the parameters of CKD-MBD [68].

3. Diagnostic workup for disorders of bone and mineral metabolism in patients under peritoneal dialysis treatment

As stated above, regarding bone metabolism and morphology, differences may exist between chronic hemodialysis and peritoneal dialysis treatment. These differences apart from preservation of renal function are mainly linked to deficiency of vitamin D, which is lost in peritoneal fluid and to and poor adherence to oral vitamin D therapy in PD [72]. The latest guideline with new recommendations was provided by KDIGO in 2017, in order to better reflect the complex interaction between CKD-MBD laboratory parameters [73]. It is important to emphasize that there are no separate or different recommendations for diagnostic workup in PD.

3.1. Biochemical components: Ca, P, PTH, ALP, bALP, 25(OH)D

In the above mentioned guidelines in CKD Grade 5 in Dialysis (G5D) [73], it is stated with a nongraded level of recommendation, that it is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH in the presence and magnitude of abnormalities. Guideline evaluated as reasonable measurement of serum calcium and phosphate every 1–3 months, PTH every 3–6 months, and alkaline phosphatase activity every 12 months or more frequently in the presence of elevated PTH. The guideline also had a very weak (2D level) suggestion that instead of calcium-phosphate (CaxP) product, values of serum calcium and phosphate, evaluated together should be used in clinical practice.

PTH is a hormone with high biological variation because of feedback control and its short half-life. For instance, 26 blood samples are required in hemodialysis patients to determine the individual homeostatic set-point (within 10%) [74]. In PD patients, it is confirmed the U-shaped curve association between mortality and PTH concentration [75].

Alkaline phosphatase. The use of total alkaline phosphatase (ALP) as a biomarker in CKD-MBD is considered limited by its nonspecificity for bone disease, as only approx. 50% of blood activity is attributable to bone ALP. In contrast to the U-shaped curve for mortality and time-averaged PTH confirmed in PD patients [76], higher ALP activity (even within high-normal ranges) was found to be more linearly and independently associated with increased all cause and cardiovascular mortality in this population [77, 78]. In studies reporting a relationship between ALP and mortality in hemodialysis patients, it has been implied that the relationship is driven by vascular calcification mediated by the bone fraction of ALP [79].

Bone ALP is strongly and independently related to BMD, not accumulated with declining GFR and its concentration reflects directly osteoblastic activity [80], providing a "living biopsy" of bone activity. Most importantly, its biological variation is almost half that of PTH [81]. It is shown that higher b-ALP is an independent predictor of all-cause mortality in male HD patients [82] and high activities of b-ALP are strongly associated with cardiovascular mortality in dialysis patients, including PD population [83].

25(OH)D. Peritoneal dialysis (PD) patients have a high risk of developing vitamin D deficiency as 25(OH) vitamin D (the precursor of active vitamin D), is lost during dialysis. Vitamin D (25(OH) vitamin D) is measured to detect deficiency/insufficiency status. Defects of mineralization are presumably because of osteomalacia and hip fractures that associate its low levels [84]. Increase in mortality and hospitalization for patients on dialysis with severe 25-OH vitamin D deficiency was found [85] in a prospective cohort study. 2017 KDIGO guideline suggests (2C) in G5D patients, that 25(OH)D (calcidiol) levels might be measured, and repeated testing might be performed, determined by baseline values and therapeutic interventions.

In order to facilitate the appropriate interpretation of biochemistry data, it is moderately strongly recommended (1B) that clinical laboratories inform clinicians of the assay method or any change in method used, sample source (plasma or serum), or any specific relevant information [73]. It is also recommended (1C) that therapeutic decisions to be based on trends rather than on a single laboratory value and to take into account all available CKD-MBD parameters [73].

3.2. Biomarkers and tests for diagnosis of bone abnormalities in peritoneal dialysis

Parathyroid hormone (PTH) and total bone specific alkaline phosphatase (b-ALP) are bio-markers currently used in clinical practice despite some assay limitations. They may reflect bone turnover and bone formation. In an individual patient, no single biomarker or in combination is sufficient to diagnose low, normal, and high bone turnover although whole PTH, iPTH, and b-ALP levels are found associated with bone turnover. This was the conclusion of a recent cross-sectional retrospective diagnostic study of biomarkers and bone biopsies in 492 dialysis patients, with the objective to determine the predictive value of PTH [both intact PTH (iPTH) and total PTH], bone-specific alkaline phosphatase (b-ALP), and amino-terminal propeptide of type 1 procollagen (P1NP) as markers of bone turnover [86]. Rather than simple measurement of PTH, the continued use of trends in PTH is encouraged to guide therapy [73].

BMD testing. Identifying biomarkers and imaging test for non-invasive evaluation of patients at fracture risk is very important in dialysis patients, which in their 40s have a relative risk of hip fracture 80-fold that of age and sex-matched controls [87]. Multiple new prospective studies conducted in patients with CKD G3a-G5D demonstrated that lower dual-energy X-ray absorptiometry bone densitometry (DXA BMD) predicts incident fractures and the associations are comparable to the ones seen in the absence of CKD [76–79, 88]. In the light of these studies, in patients with G5D with the evidence of CKD-MBD and/or risk factors for osteoporosis, KDIGO guideline has a moderately strong suggestion for performing BMD testing to assess fracture risk, if results will impact treatment decisions (2B level) [73]. A DXA BMD result might also impact the decision to perform a bone biopsy [73].

Bone biopsy. In many centers, experience in performing and evaluating bone biopsies is limited [89]. In one side, DXA BMD does not distinguish among types of renal osteodystrophy. On the other side, (considering the short half-lives of the circulating biomarkers and the long (3–6 months) bone remodeling cycle), it is not surprising that cross-sectional studies have shown conflicting and non-conclusive data on the biomarkers use to predict underlying bone histology [89]. Biomarkers resulted of limited diagnostic use because of poor sensitivity and specificity. Although they correlate with some histomorphometric measurements in bone biopsy, studies have shown only modest positive predictive value of circulating PTH or bone-specific alkaline phosphatase levels for detection of states of high and low bone turnover, especially for adynamic bone disease [90–94].

Bone biopsy is the gold standard for the assessment of renal osteodystrophy, which is a component of the bone abnormalities of CKD-MBD. Its goals are to determine high- or low-turnover disease, identify a mineralization defect (both influencing treatment decisions), and rule out atypical or unexpected bone pathology. When trends in PTH are inconsistent, or in patients with progressively decreased BMD despite standard therapy, with unexplained fractures, refractory hypercalcemia, suspicion of osteomalacia or an atypical response to standard therapies for elevated PTH, a bone biopsy should be considered [73]. In the recent KDIGO guideline, it is stated that it is reasonable to perform a bone biopsy, if knowledge of the type of renal osteodystrophy will impact treatment decisions [73]. The bone biopsy is undertaken with a trocar preferably in the iliac crest. Double labeling with tetracycline according to a protocol is required to assess the turnover.

Bone turnover markers. During skeletal metabolic activity, bone turnover biomarkers are released into circulation and can be measured in the serum.

- **Serum marker of bone resorption** in which levels are not dependent in GFR (not renally cleared) is serum tartrate-resistant acid phosphatase (TRAP5b). Renally cleared markers of bone resorption are serum amino-terminal cross-linking telopeptide of type 1 collagen (s-NTX), serum carboxy-terminal cross-linking telopeptide of type 1 collagen (s-CTX), and carboxy-terminal crosslinking telopeptide of type 1 collagen (s-ICTP or CTX-MMP).

- **Serum markers of bone formation.** Serum alkaline phosphatase, bone specific alkaline phosphatase, and procollagen type IN propeptide (s-PINP) are not dependent in GFR and serum osteocalcin, procollagen type IC propeptide (s-PICP) are renally cleared [95]. 2017 guideline suggests not to routinely measure bone-derived turnover markers of collagen synthesis and breakdown (2C) [73]. Keeping in consideration their renal and dialytic elimination, those biomarkers and circulating fragments need to be studied and re-evaluated prospectively in CKD and ESRD population [95].

- **FGF23. FGF23 may be a more stabl**e marker of phosphate metabolism in ESRD compared to PTH or serum phosphate. Differently from parathyroid hormone (PTH), which fluctuates diurnally, acutely in response to changes in serum calcium and postprandially, FGF23 levels show minimal circadian and postprandial fluctuations in CKD [96, 97]. Despite no consensus about the ideal FGF23 assay, FGF23 showed significantly less within-subject variability compared to PTH and phosphate (measured contemporaneously). A single measurement of FGF23 could more accurately assess the phosphate metabolism disorder compared to markers actually in use. Prospective studies found elevated FGF23 to independently associate with mortality in incident hemodialysis patients [2, 98]. Accounting together these data further support usage of FGF23 testing.

3.3. Diagnosis of vascular abnormalities of CKD-MBD

An increasing number of data have shown the very high prevalence of cardiovascular calcification in dialysis patient population, including patients receiving long-term peritoneal dialysis treatment [63–69, 99]. Electron beam computerized tomography (EBCT) or multi-slice computerized tomography (MSCT) can measure coronary artery and valvular calcifications, but other more widely available tests as lateral abdominal X-ray and echocardiography also can measure calcifications. Vascular and valvular calcifications are important factors for determining the prognosis of patients on CAPD [100] and patients with confirmed vascular or valvular calcifications are at highest cardiovascular risk [68, 101]. This is the rationale of the use of vascular and valvular calcification information to guide the management of CKD-MBD. Despite the long and ongoing debate [102–105] about screening of ESRD population, according to 2017 KDIGO guideline, based on low quality of evidence (2C), a lateral abdominal radiograph and an echocardiogram can, respectively, be used (as alternatives to CT-based imaging) to detect the presence of vascular/valvular calcification in patients with G5D [73].

4. Treatment of CKD-MBD in patients on peritoneal dialysis

4.1. Treatment of CKD-MBD targeted at lowering high serum phosphate and maintaining serum calcium

4.1.1. Control of phosphorus and calcium in peritoneal dialysis patients

As outlined above, the risk of hyperphosphatemia has been clearly shown for population treated with both hemodialysis and peritoneal dialysis [31, 38, 106]. The role of hyperphosphatemia as a principle actor in the development and progression of vascular calcification has been well documented in this population [70].

Vascular calcifications are predictive of higher morbidity and mortality in dialysis patients. The main target of pharmacological research in the field has moved from bone toward the cardiovascular apparatus [107]. The control of serum phosphorus at all stages of CKD is considered one of the more important aspects to improve clinical outcomes in CKD-MBD.

On the other side, the complex relationship between abnormal CKD-MBD parameters suggests the need of optimal control of all CKD-MBD parameters in order to modify the mortality risk among PD patients and improve clinical outcomes.

Phosphate balance in dialysis patients depends on phosphate intake, absorption (minus phosphate binding), and dialysis removal. KDIGO guidelines in 2017 suggest lowering elevated phosphate levels toward the normal range in dialysis patients [73].

- Dietary restriction of phosphorus is an important part of phosphate control treatment in all dialysis modalities. The impact of phosphorus intake on patients is clear: higher levels of dietary phosphorus intake and a higher ratio of dietary phosphorus to protein are associated with an increased risk of death [3, 28, 108]. But because of other important risk factors for patient mortality and morbidity, such as malnutrition and hypoalbuminemia, dietary restriction may not be successful alone and cannot be effective without the help of other treatment measures, mainly the use of phosphate binders.

- Type of dialysis may also be an important factor in the adequacy of phosphorus control in dialysis patients [109, 110]. Chronic PD as a continuous dialysis modality has an expected theoretical superiority over intermittent hemodialysis [32–35].

Compared to hemodialysis (HD), patients undergoing PD appear to have an increased prevalence of low turnover bone disease defined as adynamic bone disease (ABD) [16–23, 111]. In PD, as discussed above, calcium transfer across the peritoneum is regulated by two different mechanisms known like diffusion and convection. These processes depend on serum calcium levels, calcium concentration in the dialysate, and dialysis dextrose concentration [8].

Moraes et al. reported that in patients with PTH < 150 pg/mL conversion to low calcium solutions (2.5 mEq/L) appears to be a simple and effective strategy to bring PTH levels to the

range determined by current guidelines when compared with 3.5 mEq/L calcium PD solutions [112]. This supports the finding of Spasovski et al. in HD patients where the lower dialysate calcium (1.25 mmol/l [2.5 mEq/l]) was found to improve bone and mineral parameters compared with the higher concentration of 1.75 mmol/l (3.5 mEq/l) in patients with adinamic bone disease [113].

There is no data on Ca balance in PD patients, so the safety limit for an elemental calcium dose in PD patients is currently uncertain but based on the opinion of Wang the maximal additional elemental calcium given daily in the form of calcium-containing phosphate binder should be kept to not more than 800 mg to avoid calcium overload [114]. Patients with a negative dialysate calcium balance may show an overall positive calcium balance, if they are concomitantly treated with calcium-containing phosphate binders, especially when coupled with vitamin D [114].

It is important to emphasize that the KDIGO 2009 guidelines recommend a 1.25–1.50 calcium dialysate for both HD and PD and this is an additional consideration that should be taken into account when choosing a phosphate binder [1].

Without phosphate-binding therapy, all patients undergoing PD are in a positive phosphorus balance, unless they are severely malnourished. As mentioned before, the reduction of oral phosphate intake, an adequate dialysis schedule and the use of intestinal phosphate binders are three strategies used to manage hyperphosphatemia in dialysis patients [114]. Inevitably, in the long term, patients rarely observe rigid dietary phosphate restriction, especially in the context of PD where a higher number of patients are prescribed a less restrictive diet with a higher content of dietary protein [115].

Phosphate binders are essential in control of phosphate overload and in the improvement of outcomes in peritoneal dialysis patients. Phosphate binders are used for their binding actions to reduce the absorption of phosphorus by the gastrointestinal lumen. First, it should be stressed that patient compliance is fundamental not only in limiting dietary intake of phosphorus but also in adhering to the prescribed protocol of phosphate binder administration, frequently linked to the number of pills the patient is required to take and the degree of gastric tolerance of the product prescribed.

There is insufficient evidence that any specific phosphate binder significantly impacts patient-level survival. The decision to use a phosphate binder should be followed by consideration of which currently available phosphate-binding agent is suitable for the patient. Ideally, a phosphate binder should effectively bind dietary phosphate regardless of pH have minimal systemic absorption, few side effects, good palatability, a low pill burden, and be available at a low cost [116]. Traditionally, phosphate binders are classified into calcium-containing phosphate binders and calcium-free phosphate binders.

4.1.2. Calcium-containing phosphate binders

Calcium-containing phosphate binders are available in two formulations: calcium carbonate and calcium acetate. Efficacy of calcium-based phosphate binders is known to be clinically satisfactory, especially when combined with adequate dialysis and dietary measures. Nowadays, calcium salts are considered not free of side effects. Great concern has been expressed about

their effect on raising serum calcium levels, especially when used in association with vitamin D or high calcium dialyzing solutions.

High calcium balance may over suppress PTH, exiting in a state of adynamic bone disease (ABD), which is as dangerous as a high bone turnover state [114]. Furthermore, the excess of calcium may lead to tissue and vascular calcifications, increasing cardiovascular mortality. Regarding the use of calcium-based phosphate binders in PD patients, there are limited data available. The majority of studies comparing calcium salts and sevelamer are performed in hemodialysis patients. These studies confirm the efficacy of calcium salts as phosphate binders and the potential role of them in developing calcifications.

Calcium salts should be administered carefully, considering the clinical status of each patient. KDIGO guidelines suggest restricting the dose of calcium salts in the presence of arterial calcification and/or adynamic bone disease and/or if serum PTH levels are persistently low [1].

4.1.3. Calcium-free phosphate binders

Aluminum salts were largely used as calcium-free phosphate binders, but this treatment was abandoned when cases of systemic aluminum toxicity were reported [117].

Sevelamer is a calcium- and aluminum-free phosphate binder, developed for hyperphosphatemia management in dialysis patients. There are also few data regarding sevelamer administration in PD patients. A study comparing the efficacy of sevelamer and calcium acetate showed the same efficiency of both treatments in control of serum phosphorus and PTH [118]. This study also evaluated the association between sevelamer administration and risk of peritonitis in PD patients, because it has been thought that a higher rate of diarrhea and constipation induced by sevelamer might increase the risk of peritonitis caused by Gram-negative microorganisms due to trans-mural migration of bacteria. Although peritonitis occurred in 11% of the patients in the sevelamer group and in 4% of the patients on calcium-containing phosphate binders, no significant increase in the risk of peritonitis was found [118]. Another study performed in PD patients in Canada showed the efficacy of sevelamer in ameliorating CKD-MBD parameters [119].

Lanthanum carbonate is another nonaluminum- and noncalcium-containing phosphate binder that has more recently become available for the management of hyperphosphatemia in dialysis patients. Unfortunately, less evidence and studies are available for patients undergoing PD [114]. An open, noncomparative study in patients with hyperphosphatemia undergoing continuous ambulatory PD evaluated safety and efficacy of lanthanum carbonate to reduce serum phosphate levels [120]. This study showed that lanthanum carbonate was generally well tolerated. Furthermore, majority of the patients reached the therapeutic target level in 2 months at doses between 750 and 2250 mg, suggesting that the efficacy dose was lower than that for HD patients.

A novel noncalcium iron-based phosphate binder, sucroferric oxyhydroxide is introduced for the management of hyperphosphatemia in dialysis patients. It is formulated as a chewable tablet containing 500 mg iron. Long-term efficacy and tolerability of the iron-based phosphate binder, sucroferric oxyhydroxide, was compared with that of sevelamer carbonate in an open-label Phase III extension study [121]. A representative proportion (9.3%) of patients receiving peritoneal dialysis was included in this long-term analysis of phosphate binders. Extension

study data demonstrate that the efficacy of sucroferric oxyhydroxide for controlling serum phosphorus concentration was robust, maintained over the long-term (1 year) and similar to that of sevelamer. Sucroferric oxyhydroxide was generally well tolerated over 1 year. The pill burden over 1 year of treatment was 62% lower with sucroferric oxyhydroxide than with sevelamer [121].

4.2. Treatment of secondary hyperparathyroidism in PD patients

Though the prevalence of secondary hyperparathyroidism (SHP) and the related mineral metabolism changes have been reported at almost the same rate in peritoneal dialysis as in hemodialysis patients, PD patients have a higher prevalence of adynamic bone disease suggesting that their bone is less sensitive for a given level of PTH [122].

It has also been widely reported that PD patients have lower vitamin D levels as compared with the HD patients [123]. Among the multiple causes which might explain the higher prevalence of vitamin D deficiency in PD patients, the peritoneal loss of vitamin D binding protein probably plays an overwhelming role.

It is suggested to correct vitamin D deficiency, using low doses of either cholecalciferol or calcifediol (800–100 UI/day), by adding calcitriol or paricalcitol only when, after the first two described steps, the PTH levels are stable at 450–500 pg/mL or show a clear increasing trend in the absence of relatively high calcium (>10.0 mg/dl) and/or phosphorus (>5.5 mg/dl) levels [122]. In these latter cases, it is suggested to start treatment with cinacalcet.

Most of studies on administration of calcimimetics in dialysis are performed in hemodialysis patients. Few studies that are PD have a very limited number of patients. So, most of the recommendations for peritoneal dialysis patients are simply transferred from the HD experiences. The calcimimetic cinacalcet was approved by the US Food and Drug Administration in 2004 and by European Committee for Medical Products for Human Use in 2005 to treat secondary hyperparathyroidism in patients on dialysis.

Cinacalcet acts directly upon the parathyroid cell calcium-sensing receptor (CaR). Upon binding CaR, cinacalcet allosterically increases its sensitivity to extracellular calcium thus suppressing PTH secretion without increasing serum calcium and phosphate levels [124]. A retrospective study was performed at a single PD unit based on 27 patients with moderate to severe SHPT (PTHi > 500 pg/mL with normal or elevated serum calcium levels) who were treated with cinacalcet. Cinacalcet was started due to the lack of response with conventional treatment: diet, phosphate binders, and vitamin D or inability to treat with vitamin D due to hyperphosphatemia >5.5 mg/dL or hypercalcemia >10.5 mg/dL [125]. This study showed that cinacalcet was a safe but not effective therapy in moderate to severe SHPT in PD patients. The gastrointestinal adverse factors made impossible the prescription of higher doses of cinacalcet and an eventual benefit of this therapy at higher doses in SHPT was impossible to evaluate.

On contrary with these conclusions were results of another study performed by Portoles et al. in PD patients. They evaluated efficiency and safety of cinacalcet in eighteen patients undergoing more than 4 months on PD with a severe SHPT (PTH > 500 pg/mL) resistant to conventional treatment with diet, chelants and vitamin D, in a prospective open-label study

[126]. The authors concluded that the addition of cinacalcet to conventional treatment in PD patients with resistant SHPT has improved the achievement of targets of K/DOQI guidelines and has been reasonably safe.

Lindberg et al. [127] evaluated a total of 395 patients on dialysis (349 on HD and 46 on PD). Two hundred and ninetyfour patients (260 HD and 34 PD) were treated with once-daily oral cinacalcet (titrated from 30 to 180 mg/day), while the remaining 101 patients (89 HD, 12 PD) were on placebo in addition to the ongoing standard therapy. This study confirmed that cinacalcet induced a more pronounced reduction of PTH in a larger percentage of patients as compared with standard therapy, with no major difference in the percentage of patients on HD and on PD treatment achieving a PTH level lower than 250 pg/mL (39 and 38%, respectively).

Cinacalcet treatment was associated with a slight, but significant, decrease in both calcium and phosphorus concentrations as compared with patients treated with the standard therapy only. Gastrointestinal symptoms were reported to be the most frequent adverse effects. However, no difference was observed between HD and PD patients in the incidence or type of the reported side events. A severe form of SHP is an unusual finding in PD patients. Furthermore, the control of phosphate is usually better in PD than in HD patients, at least until the residual diuresis is maintained. Another specific characteristic of patients treated with PD is the higher tendency to status of vitamin D deficiency which might make these patients more prone to hypo rather than hypercalcemia. For all these reasons, it is possible to predict that the need for the use of the most recent and potent drugs which are nowadays available for the control of SHP, including cinacalcet, might be lower in PD than in HD patients [122].

5. Nomenclature

The recommendation on diagnosis and management of CKD-MBD presented in this chapter are based on KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD).

The level of recommendations presented in these guidelines are:

Level 1—we recommend; Level 2—we suggest; the ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Quality of evidence presented in these guidelines:

Meaning A High: we are confident that the true effect lies close to that of the estimate of the effect.

B Moderate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

C Low: The true effect may be substantially different from the estimate of the effect.

D Very low: The estimate of effect is very uncertain and often will be far from the truth.

Conflict of interest

None to declare.

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