Chapter 12
Vitamin D and Bone in Chronic Kidney Disease

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Abstract The metabolic bone disorders induced by CKD have a major impact on bone fragility as illustrated by the high incidence of fractures in patients with CKD. These are the results of altered bone structure and mineralization both impairing the competence of bone to mechanical loading. Several mechanisms are involved such as the levels of bone remodeling and the production of hormones and soluble factors such as FGF23 and sclerostin. The main hormones are however parathyroid hormone (PTH) and vitamin D that closely regulate bone metabolism and structure. The levels of both native (Calcidiol or 25OH vitamin D) or active (Calcitriol or $1,25(OH)_2$ vitamin D) are low in patients with CKD. The failure of 1α hydroxylation in patients with CKD is responsible for low $1,25(OH)_2$ vitamin D levels that increase PTH levels and contribute to bone fractures. Administration of Calcitriol of derivatives reduces PTH levels, but insufficient data are available on the impact on bone mineral density and fractures. In contrast, Calcidiol fails to reduce PTH levels in end-stage renal disease, but contribute to ameliorate the mineralization and subsequently the bone capacity and pain. CKD-MBD is a complex disease involving several confounding factors that each contribute to the bone fragility. Improving the knowledge of the pathophysiology of CKD-MBD and the development of new tools are needed to identify patients at risk of fractures and improve their quality of life.

Keywords CKD-MBD • Fractures • Vitamin D • PTH • Osteoporosis • Renal osteodystrophy • Calcium • Phosphate • Bone mineral density

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12.1 Introduction

Metabolic bone disorders in chronic kidney disease (CKD) are the results of altered mineral and bone metabolism (MBD) due to impaired renal function [1]. The bone pattern are secondary to multiple metabolic abnormalities such as decreased synthesis of 1,25-dihydroxyvitamin D, hypocalcemia, hyperphosphatemia, metabolic acidosis, decreased klotho, increased fibroblast growth factor 23 (FGF23) and sclerostin, and insufficiently inhibited parathyroid hormone (PTH) by calcium, vitamin D and FGF23 because of the reduced expression of the calcium-sensing receptor, vitamin D receptor (VDR) and klotho in uremic parathyroid cells [2–4]. In addition, there is an insensitivity of bone cells to PTH because of the down-regulation of its receptor in osteoblast cells [5]. Bone diseases which are induced by these abnormalities are highly variable from one patient to another and influence the metabolism of calcium and phosphate through bone tissue which is the main mineral reservoir. Moreover, the bone diseases related to CKD are linked to major extra-skeletal complications such as vascular calcifications, making the regulation of the mineral disorder an important target to avoid other tissues alterations [6]. In this chapter, we will review the clinical effect of vitamin D on bone and the potential impact use for therapies. The identification of bone mineral mechanisms related to CKD will provide elements in order to prevent mineral disorders and fractures.

12.2 Metabolism of Vitamin D in CKD

Vitamin D is provided by diet (ergocalciferol or D2 and cholecalciferol or D3) or synthetized by the skin (D3) [7]. Cholecalciferol is then transported by vitamin D binding protein (DBP) to the liver where it is converted to 25-hydroxivitamin D (calcidiol) by the enzyme 25-hydroxylase. This native form is stored in the lipid tissues and available to progressively generate an active metabolite. The 1α hydroxylase then converts calcidiol to 1,25 dihydroxivitamin D (calcitriol) in the kidney. Calcitriol is the active form and acts as a hormone with several endocrine and immune functions. The synthesis of calcitriol is regulated by PTH, calcium, phosphate, and FGF23 whereas PTH increases 1 α hydroxylase activity. Anomalies of vitamin D metabolism are one of the most important factors in the pathogenesis of secondary hyperparathyroidism and features of CKD-MBD. In addition, many observational studies have shown an association with vitamin D disturbance, i.e. low circulating levels of vitamin D in CKD and cardiovascular disease [8].

Patients with CKD have low circulating calcidiol levels [9]. The levels of 25(OH)D are inversely associated with the glomerular filtration rate (GFR) in a dose-dependent manner. The low levels are observed at early stages of CKD, beginning before other mineral metabolism disturbances [10]. The prevalence of vitamin D deficiency (25(OH)D <15 ng/ml) in the population with CKD is higher than in the general population, ranging from 28 % for a GFR of 60 ml/mn to 51 % for a GFR below

15 ml/mn. The serum 25(OH)D levels are influenced by other known risk factor such as ethnicity, diabetes, hypertension and albuminuria [9]. In contrast, there is an association between bone disease in CKD and calcidiol level in small series that used bone biopsies. However, optimal 25(OH)D3 levels are required to allow the deposition of minerals in bone and prevent osteomalacia [11, 12]. Therefore, calcidiol might have a direct impact on bone mineralization by promoting the deposition of calcium.

Calcitriol levels are also low in CKD. Its production is stimulated by PTH and by low calcium while it is reduced by high phosphate and FGF23. The binding of 1α-25-dihydroxyvitamin D3 to its receptor induces gut absorption of calcium and phosphate, decreases PTH synthesis and stimulates FGF23. Calcitriol levels are low in CKD patients as the results of reduced renal 1a hydroxylase activity and low stock of its substrate calcidiol. This latter are the common causes shared with non-CKD patients such as low sun exposure or diet restriction which further decreased the generation of calcitriol in end-stage renal disease (ESRD). The raise in FGF23 levels occurs in early stages of CKD and precedes the decrease in calcitriol. The administration of low doses of calcitriol reduces serum PTH levels. A Renal Cochrane group assessed the impact of various active vitamin D compounds such as calcitriol in 894 patients with CKD on biomarkers [13]. Supplementation with active forms of vitamin D did not change the risk of mortality nor did postpone the need for dialysis. However, a 30 % reduction of serum PTH was achieved allowing a reduction of other treatment that targeted calcium and phosphate. All those metabolic effects influence the rate of bone turnover and subsequently bone mineral density, bone fragility and the risk of skeletal fracture (Fig. 12.1).

12.3 Different Forms of Renal Osteodystrophy in CKD-MBD

The classification of different forms of CKD-MBD has evolved in recent years. Several parameters has been included that are interrelated and participate to the bone fragility such as the levels of bone turnover, bone density and bone mineralization [14]. All these factors separately or synergistically contribute to skeletal fragility and the high risk of fractures in CKD [15]. However, these indices are poorly correlated because they measure different aspects of bone such as structure or mineral deposition in addition that some of them are variable during the course of CKD. Therefore, bone biopsy remains the gold standard for classifying different forms of renal osteodystrophy (RO) although more rarely done. The rate of bone turnover assessed by cycline double labeling and the thickness of osteoid are the main parameters that define the forms of RO [12, 16–18]. These indices allow separating high bone turnover forms from the low bone turnover ones including osteomalacia, which is characterized by a mineralization defect and adynamic bone disease mainly defined by a low bone remodeling rate. Using this definition, the prevalence of each bone disease has changed the last decades, adynamic bone diseases being the most common in contrast to a high frequency of high bone

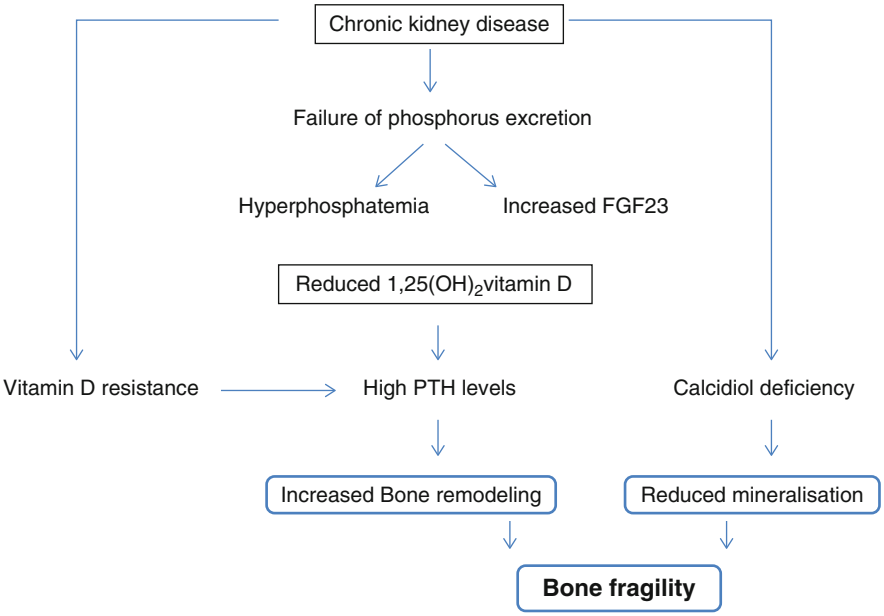

Fig. 12.1 Metabolic effects influencing the rate of bone turnover and subsequently bone mineral density, bone fragility and the risk of skeletal fracture

remodeling types that were observed in the late 1980s [19]. This illustrates the effort made by the nephrologists to reduce PTH secretion and to keep controlled secondary hyperparthyroidism. This new profile could however reflect moderately the current prevalence because of several biases. Bone biopsies are generally performed in symptomatic patients or at the inclusion of patients participating in clinical trials, which may not reflect the whole CKD population and may be limited by the presence of many confounding factors. Interestingly, the bone volume parameter has been added to the criterion of CKD-MBD in addition to bone remodeling rate, which clearly illustrates the interest for osteoporosis, an outgrowing bone complication that can lead to fractures.

The accuracy of serum PTH levels to predict or diagnose a given type of RO is low, which has led the experts of the Kidney Disease Improving Global Outcomes (KDIGO) to change the recommendations of the PTH target value in CKD, which is now targeting levels between two and nine times the upper normal value of the assays [15]. In non CKD patients, bone biomarkers are useful tools to assess the level of bone remodeling, which is a good predictive factor of bone fragility. Total and bone-specific alkaline phosphatase serum levels are the most used biomarkers on bone metabolism in addition to PTH. However, the sensitivity and the specificity of these two biomarkers are modest regarding the prediction of the type of RO. Indeed, the sensitivity and the specificity do not exceed 80 % for PTH value of 200 pg/ml in order to differentiate patients with high and low bone turnover diseases [20]. However, a significant number of patients with serum PTH levels between two

and four times the upper normal values have adynamic bone disease [21]. Serum total and bone-specific alkaline phosphatases have quite comparable sensitivity value to that of serum PTH to predict high bone turnover disease. However, serum total and bone-specific alkaline phosphatases do not have a good sensitivity to predict adynamic osteopathy, hence less than 60 % of subjects with bone-specific alkaline phosphatase value lower than 20 g/ml have histological signs of low bone turnover disease [20]. This was confirmed in 492 patients in whom PTH and alkaline phosphatase alone and in combination discriminated the extremes low or high bone remodeling diseases, as defined histologically and despite of their low sensitivity and specificity [22].

New circulating bone biomarkers could have an additive value for the prediction of bone fragility. FGF23 is synthesized by osteocytes and subjects with normal renal function and high levels of FGF23 have mineralization defects mainly attributed to hypophosphatemia. In contrast, in CKD patients treated by in dialysis, serum phosphate levels are high despite the extremely increased levels of circulating FGF23. No significant relationship could be demonstrated between biomarkers of bone turnover or bone mineral density (BMD) with serum FGF23 levels, suggesting that FGF23 had no direct effect on BMD in adult dialyzed CKD subjects [23], whereas serum FGF23 levels are inversely correlated with histomorphometric parameters of mineralization in CKD children tretaed by peritoneal dialysis [24]. Sclerostin and Dickkopf-1 (Dkk-1), Wingless integration site (Wnt) inhibitors that reduce bone formation, could also play a role in bone diseases related to CKD and might explain the low bone formation observed in some uremic forms [4]. Serum sclerostin levels were higher in CKD patients than in normal women [25]. Serum sclerostin levels are negatively correlated to PTH but not with bone-specific alkaline phosphatases or DKK-1. Surprisingly, serum sclerostin levels are positively correlated with BMD, bone microarchitecture, and histomorphometric parameters of bone turnover. In addition, high serum sclerostin levels have been associated with reduced risk of mortality in CKD patients treated by dialysis [25–27]. Basal serum levels of sclerostin and tartrate resistant acid phosphatase (TRAP), a marker of bone resorption, are good predictors of bone loss in CKD patients as measured by DEXA or QCT [28]. Overall, these biomarkers could reflect the severity of the bone disease, which may also partly explain the increased risk of the mortality.

12.4 Bone Fragility in CKD

Fractures are more common in patients with CKD than in the age and gender-matched peoples from the general population. They are dramatic events since they increase the rate of mortality and the length of hospital stay [29–32]. Data obtained from the United Stated and French registers with large number of patients showed that the risk of hip fracture is at least four times higher in subjects with CKD [32–34]. These skeletal fractures maily affect peripheral bones and vertebrae although this latter site is rarely documented [35]. The risk of femoral fractures increases

with age, female gender and a history of fracture of the femoral neck [30, 36, 37]. In addition to these common factors shared with patients with normal kidney function, diabetes and cardiovascular diseases such as hypertension and vascular calcifications are predominant and might explain part of the bone fragility [32, 34]. Nevertheless, no specific mechanism has been shown and this might be related to an amplification of comorbidity factors in relation to uremia and mineral disorders.

Fragility fractures related to low bone strength involves a reduction of both bone quantity and quality. Quantity of bone can be easily measured by the bone mineral density (BMD) which is a predictive factor as each reduction of one standard deviation (−1 SD) doubled the risk of fractures. Bone quality includes several factors such as the geometry, bone microarchitecture, the properties of the matrix and the rate of bone remodeling. The relationship between BMD and fracture is not clear in CKD patients. At the lumbar spine, this measurement is biased by spinal osteoarthritis and by the presences of vascular calcification particularly in CKD patients on dialysis [18]. The radius and the hip are better site for the assessment of the risk of fracture as the cortical component represent up to 90 % of the site proximal bone density. Indeed, there is a negative correlation between BMD at the radius and serum PTH levels [38]. In a recent meta-analysis carried out on six of these studies, it was observed the decrease of BMD at the spine and radius, but not at the femoral neck, was significantly associated with the risk of fractures [39]. However, the number of patients included in that meta-analysis was weak and the difference in BMD between patients with and without fractures was too small to allow guidelines for clinical practice. However, adding the assessment of FRAX indices to BMD could be an useful tool for risk fracture prediction [40]. Overall, BMD measure is not as useful in patients with CKD as in the general population. One of the reason is that there is no long term prospective study in CKD in which it is possible to assess the value of BMD to predict fractures and follows the patients. Moreover, the weak predictive value can be explained by the lack of discrimination of the measure of cortical bone which is the target of PTH. This could be now addressed by microcomputerized tomography (μCT). Indeed, the 1-year follow-up of 53 patients with CKD demonstrated that bone loss affects mainly the cortical bone [41]. The thickness of cortical bone was reduced due to increased bone resorption at the endocortical surface and was correlated to the serum levels of PTH, the levels of 25(OH) vitamin D being within the normal range. These results are consistent with a higher prevalence of peripheral fracture in patients with the highest PTH levels (above 900 pg/ml) in the DOPPS cohort [37]. The attempts to reduce PTH are also associated with a reduction of fracture occurrence in the presence of risk factors. Indeed, the 12 % incidence of peripheral fractures is similar with cinacalcet than with placebo in 3,883 patients on hemodialysis, but was significantly reduced when adjusted to factors predisposing to fracture such as fracture history or tobacco [42]. Finally, abnormalities of extracellular bone matrix due to diabetes (glycation of collagen, modification of crosslinks or accumulation of cations such as aluminum, fluoride, strontium) may well have a role in the bone fragility.

A major point is to liaise the above parameters that are available in order to draw guidelines. Each one of the parameters described above such as BMD, bone

histology, microarchitecture and the degree of bone remodeling contribute to bone fragility and the increase risk of fractures in CKD-MBD. However, the lack of correlation between them does not allow an accurate prediction. High bone remodeling assessed by PTH appears to be the more consistent. Indeed, in patients without CKD, high bone remodeling is associated with an increased risk of fracture while it is prevented by treatment that reduce bone turnover. This relationship is not clear-cut in CKD. Hip fractures occur in the presence of low PTH levels only in small cross-sectional studies [35, 43]. However, prospective studies demonstrated that high bone turnover assessed by PTH is the main risk factor. Undoubtedly, high PTH levels are one of the targets, but not the only one.

12.5 Impact of Low Vitamin D on Bone Metabolism in CKD

There are only a scarce number of studies looking at the impact of vitamin D insufficiency and deficiency on mineral metabolism, bone mineral density and the risk of bone fracture in CKD patients. In an Italian retrospective study carried out in 104 CKD patients undergoing chronic hemodialysis and not receiving any vitamin D compound, the bone histology showed that subjects with serum 25(OH)D lower than 15 ng/ml had decreased bone formation rate and lower trabecular mineralization surfaces than the control group, and these alterations were independent of PTH and calcitriol values [44]. A second study comprising 130 patients with CKD not yet treated by dialysis showed that patients exhibiting skeletal fractures had significantly lower serum 25(OH)D levels (15.8 ng/ml) than those without fractures (30.0 ng/ml), they were also more likely female, had longer duration of CKD and lower BMD values at the distal radius. In multivariate analyses serum 25(OH)D levels, radius BMD, and low PTH (<100 pg/ml), and history of fractures were independently associated with high risk of suffering a new skeletal fracture after initiation of dialysis therapy [45]. Another study in 69 hemodialysis patients showed a high prevalence of vitamin D deficiency (59 %), a significant negative correlation between serum 25(OH)D and PTH levels, and a positive correlation between 25(OH)D and BMD at the radius. Low vitamin D values were also independently associated with reduced BMD at the calcaneous as assessed by ultrasounds [46]. Vitamin D insufficiency has also been largely recognized to be associated with increased subperiostal bone resorption and with decreased BMD at the lumbar spine and the wrist in CKD dialysis patients [47, 48].

12.6 Treatment of Bone Fragility in Patients with CKD

The treatment of CKD-MBD should target the correction of mineral disorders, the prevention of osteoporosis and the reduction of the risk of fracture. The treatment of osteoporosis in CKD is restricted as the therapies available for the common

osteoporosis are contraindicated in CKD patients with a GFR below 30 ml/min. CKD reduces the elimination of bisphosphonates and strontium ranelate, which therefore may accumulate a greater extent with the potential risk of inducing a bone mineralization defect. Unlike common osteoporosis, fractures and low BMD in CKD can be accompanied by low or high bone turnover, which raised the question of the rationale of reducing bone resorption in the first situation. Therefore, antiresorptive treatment should not be prescribed in CKD without a prior bone biopsy in order to eliminate the presence of an adynamic bone disease that could be aggravated by such a therapy. This is reasonable also in the case of therapy by bisphosphonates, which appear to further decrease bone remodeling in case of CKD [18].

Because of these reasons, there is no randomized clinical trial in CKD assessing the effect of bisphosphonates on BMD and fracture risk. However, there are very few observational reports with these treatments whose results are not convincing in terms of BMD or risk of fractures, the number of events being too small. A controlled clinical trial carried out on 50 women with CKD undergoing hemodialysis and treated by raloxifene, a molecule not cleared by the kidney, showed an increase in BMD at the lumbar spine and the absence of important side effects [49], the treatment was restricted to postmenopausal women.

If fractures or low BMD are associated with high PTH levels, reduction of PTH levels should improve bone quality and decrease the risk of fracture. Indeed, analysis of 4 placebo controlled trials with Cinacalcet, designed to reduce PTH in CKD patients undergoing dialysis and with secondary hyperparathyroidism, also significantly reduced the incidence of fracture [50]. However, the large prospective randomized clinical trial EVOLVE failed to decrease the fracture risk in the intention-to-treat analysis [42]. One of the reasons of this failure might be the number of confounding factors that could influence the occurrence of fractures in these patients. Indeed, the fracture rate was lower in patients with risk factor such as history of fracture or tobacco use. These data demonstrate that a reduction in serum PTH levels should be reinforced in dialysis patients exposed to additional risk of fracture. Finally, Denosumab, an anti-RANKL biotherapy, efficient for the treatment of osteoporosis, has not been assessed for BMD and risk of fractures in patients with CKD. Although the use of Denosumab will be limited to patients with high bone remodeling, this treatment may also induce mineral disorders that should retain attention [51].

12.7 Treatment of Bone Fragility by Vitamin D in Patients with CKD

The treatment of CKD-MBD should also target the mineral disorders in particular should refrain PTH secretion by vitamin D. In subjects with normal kidney function, administration of natural vitamin D or calcidiol is necessary to reduce secondary hyperparathyroidism related to 25-hydroxy vitamin D deficiency. A supplementation of 50,000 IU of vitamin D weekly contributes to the significantly

reduction of PTH in subjects with CKD stage 3, but not with CKD stage 5 [52]. Such a treatment is however needed as calcidiol might also contribute to the mineralization of bone which is of particular interest in high remodeling states despite negative results [44] or reduce the risk of mortality [53, 54]. A recent meta-analysis, including 17 observational studies and 5 RCTs, showed that natural vitamin D supplementation, ergocalciferol or cholecalciferol, significantly increased serum 25(OH)D levels and reduced serum PTH concentration, which was more pronounced in dialysis patients. These changes were induced with a very low incidence of mild and reversible hypercalcemia (<3 %) and hyperphosphatemia (<7 %). However, in none of these studies bone related outcomes such as bone pain, BMD and bone fractures as well as cardiovascular outcomes were assessed. The studies were also of low to moderate quality [55].

Administration of calcitriol is based on the failure of 1a-hydroxylation, the supplementation of which might reduce PTH levels. Administration of calcitriol reduces serum PTH levels and improved the survival, but the impact on fractures is unknown [13, 56, 57]. The limitation is that doses of calcitriol (>3 μg/week) are associated with hypercalcemia and worse control of hyperphosphatemia. Several derivatives have been developed such as Paricalcidol, which provided similar effects [58] and can be used in association with Cinacalcet, however no clinical studies has assessed the protective effect on BMD and the risk of fracture.

In conclusion, the complexity of CKD-MBD relies on the presence of several confounding factors that include mineral metabolism and regulation of bone remodeling as well as the structure of bone. All these factors contribute to the bone fragility and the promotion of skeletal fractures, which when occurring greatly impair the quality of life of these subjects. Better understanding of the pathophysiology of CKD-MBD and the development of tools to identify patients at risk are needed to prevent skeletal fractures.

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