Clinic Rev Bone Miner Metab (2012) 10:119–127
DOI 10.1007/s12018-011-9119-1

ORIGINAL PAPER

Chronic Kidney Disease-Mineral Bone Disorder: Definitions and Rationale for a Systemic Disorder

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Published online: 15 October 2011

Abstract Over the past decade there has been an increasing awareness of the complexity of bone and mineral complications observed in chronic kidney disease (CKD) and recognition that the consequences of these abnormalities affect not only the skeleton, but also the cardiovascular system. These scientific advances led to the naming of a systemic disorder, "Chronic Kidney Disease-Mineral Bone Disorder" (CKD-MBD) defined as abnormalities in mineral-related biochemistries, bone modeling/remodeling and strength, and extraskeletal calcification. CKD-MBD begins early in the course of progressive CKD, at estimated glomerular filtration rates of 60 ml/min or earlier, with progression such that all dialysis patients have one or more components. The older term, renal osteodystrophy is one component of CKD-MBD and should be used exclusively to define the histopathologic abnormalities of CKD-related bone remodeling. This diagnostic criteria has been further refined using a new classification system "turnover, mineralization, and volume", that defines bone turnover, mineralization, and volume to allow for a more complete evaluation of renal osteodystrophy. The recognition of this inter-relationship between biochemical changes, bone, and extraskeletal calcification as the systemic disorder CKD-MBD allows for enhanced communication, increased awareness/diagnosis, and improved treatment approaches with the ultimate goal of improving morbidity and mortality in patients with CKD.

Keywords Bone · Calcium · Phosphorus · Vascular calcification

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Chronic kidney disease (CKD) is a significant worldwide health problem due to its high prevalence and contribution to cardiovascular morbidity and mortality. In patients with CKD, the prevalence of atherosclerosis and arteriosclerosis is increased, the course accelerated, and calcification is common, fueling the increased cardiac dysfunction and cardiovascular mortality [1–3]. Central to the underlying mechanism of accelerated CVD in CKD is disordered mineral metabolism, with elevated phosphorus, and abnormalities of the hormones regulating its homeostasis, associated with increased left ventricular hypertrophy, increased pulse wave velocity, vascular calcification (VC) of the arteries, and mortality in human observational studies [4]. In both CKD and the general population, cardiovascular calcification is inversely related to bone mineralization [5–8]. Furthermore, in the setting of uremia, vascular smooth muscle cells transdifferentiation to osteoblast/chondrocyte-like cells that mineralize in a manner similar to bone mineralization [2].

In uremia, disorders of mineral metabolism are common. With progressive CKD, phosphorus and calcium levels are kept in the normal range until late in the course or CKD through a complex, and not completely understood, homeostasis. One of the earliest observations is a downregulation of klotho expression in the kidney, and klotho null mice have an accelerated aging phenotype that resembles the clinical phenotype of CKD including bone demineralization and arterial calcification [9]. Early in the course of CKD (at 60–70% normal function), there is a

Table 1 Definition of chronic kidney disease-mineral bone disorder (CKD-MBD)

Chronic kidney disease-mineral bone disorder (CKD-MBD)
A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
1. Abnormalities of calcium, phosphorus, PTH or vitamin D metabolism
2. Abnormalities of bone turnover, mineralization, volume, linear growth or strength
3. Vascular or other soft tissue calcification
Renal osteodystrophy
An alteration of bone morphology in patients with CKD
It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy

This table was modified from Moe et al. [82], with permission

decline in klotho expression in the kidney, elevated FGF23 synthesis in the bone, increased PTH release from the parathyroid glands, and decreased conversion of vitamin D into the active form calcitriol in the kidney, altering intestinal calcium and phosphorus absorption [10]. These abnormalities affect four major target organs: bone, vascular smooth muscle cells, intestine, and parathyroid glands with cross-talk among these key organs.

It is this complex inter-play between biochemical abnormalities, bone and VC that led to a kidney disease: improving global outcomes (KDIGO) CKD-MBD Work Group in 2006 to define the disorder: "chronic kidney disease-mineral and bone disorder" (CKD-MBD). The rationale was that the consequences of disorders in mineral metabolism extend far beyond bone and thus the term renal osteodystrophy did not accurately reflect the systemic nature of the disorder. The definition of CKD-MBD is shown in Table 1. Importantly, the previous commonly used term "renal osteodystrophy" was restricted as a description of the histopathology of bone, which can be quantified using bone histomorphometry. The KDIGO group further expanded the term renal osteodystrophy to go beyond the more descriptive words that focused on bone turnover to fully assess turnover, mineralization, and volume (TMV) in a "TMV classification system". The pathophysiology of CKD-MBD is complex, and each of the components will be considered separately.

Biochemical Abnormalities

PTH is released from the parathyroid glands in response to low ionized calcium, and is inhibited by calcitriol, hyperphosphatemia, and FGF23 [11, 12]. PTH acts on bone to increase bone turnover by stimulating osteoblastic bone formation and osteoclastic bone resorption. PTH also increases the conversion of 25(OH)D to 1,25(OH)2D (calcitriol) in the kidney which then increases intestinal absorption of calcium and phosphorus, and enhances bone mineralization. PTH also increases the renal excretion of phosphorus and increases renal reabsorption of calcium.

More recently, there has been an increased interest in the phosphatonin fibroblast growth factor 23 (FGF23) which is secreted from osteocytes that are derived from osteoblasts. These osteocytes have primary cilia, and are embedded deep in bone, but are interconnected through a series of canaliculi. They serve as the chemo, mechano, and osmoreceptor cell of the bone and respond to biochemical changes [13]. FGF23 is stimulated in response to increased calcitriol, increased PTH, and increased phosphorus levels in the blood, and subsequently feedbacks to inhibit calcitriol synthesis and increase calcitriol degradation, inhibit parathyroid hormone secretion from the parathyroid gland, and increase renal excretion of phosphorus. In the kidney and parathyroid gland, FGF23 binds to its receptor and a co-receptor klotho [14, 15]. Thus, FGF23 and klotho provides a key link between bone and kidney, and bone and parathyroid glands; PTH links kidney and bone and calcitriol links kidney, parathyroid gland, bone and intestine. Finally, hyperphosphatemia and other factors present in uremic serum, induce vascular smooth muscle cells (VSMC) to undergo transdifferentiation into osteoblast/chondrocyte-like cells, with increased expression of bone-associated and mineralization regulating proteins, and increased extracellular matrix deposition [4]. Thus, phosphorus links PTH, FGF23/klotho and calcitriol to bone, vascular disease and the kidney (Fig. 1).

These complex multi-organ interactions clearly indicate that CKD-MBD is a systemic disorder that occurs when one of the major organs that control mineral homeostasis, the kidney, is damaged. The complexities also support how important it is to be able to assess multi-organ effects (both good and bad) in response to therapies. The exact mechanisms of all of these complex interactions remain to be fully elucidated, but the high prevalence of CKD worldwide and the increased risk of cardiovascular disease with CKD support that these derangements should be considered cardiovascular risk factors. Therefore, the diagnosis and management of these biochemical abnormalities in CKD should be moved from a bone-limited disorder to a systemic disorder (Fig. 1).

Disorders of Bone

Fragility

One of the bone components of CKD-MBD is fragility, which is defined as decreased strength (bone quality)

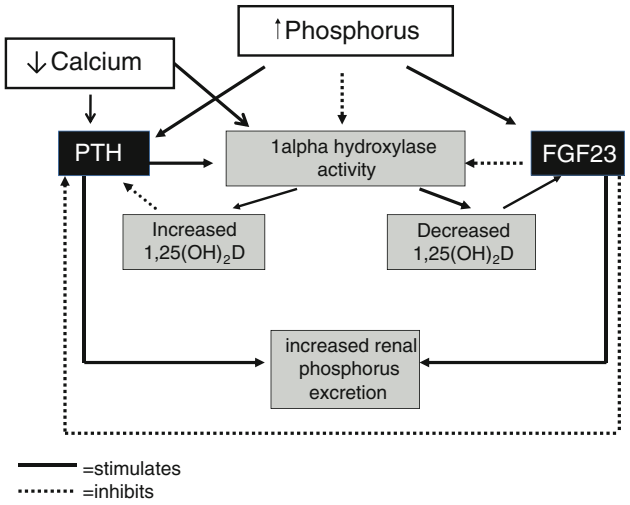

Fig. 1 Pathogenesis of abnormal mineral homeostasis in CKD: As phosphorus (Pi) levels increase (or there is a chronic Pi load), both PTH and FGF23 are increased. Both the elevated PTH and FGF23 increase urinary Pi excretion. The two hormones differ in respect to their effects on the vitamin D axis. PTH stimulates 1-alpha hydroxylase activity thereby increasing the production of $1,25(OH)_2D$, which in turn negatively feeds back on the parathyroid gland to decrease PTH secretion. In contrast, FGF23 inhibits 1-alpha hydroxylase activity, thereby decreasing the production of $1,25(OH)_2D$ feeding back to stimulate further secretion of FGF23. Lastly, there is some evidence that FGF23 also inhibits PTH secretion (*solid line* stimulates; *dashed line* inhibits). With permission from Moe and Sprague [83]

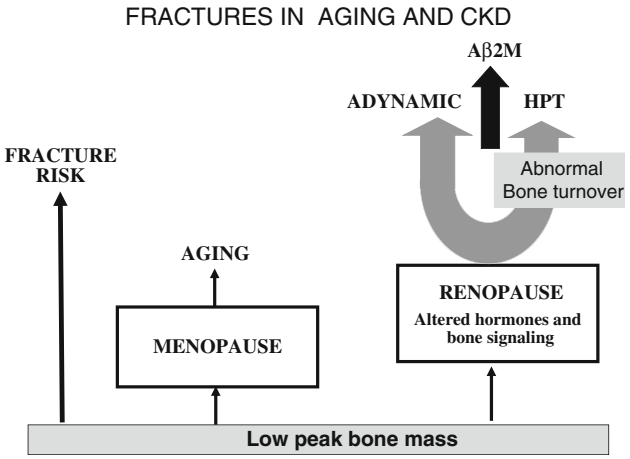

Fig. 2 Pathogenesis of bone fractures in CKD: for both the general population and CKD, the peak bone mass (achieved by age 30) is a major contributor to fracture risk and is determined by genetics and influenced by diet and exercise during childhood. In the general population, there is a slow decline in bone mass with normal aging, and an acceleration of loss during menopause. In CKD, these same age and menopause changes occur. In addition, there are other hormonal abnormalities and abnormal bone cell differentiation pathways ("menopause"), abnormalities of bone remodeling, and then deposition of beta-2-microglobulin that further decreases bone stability. As a result, fracture risk is increased and the etiology quite complex

predisposing to fracture. In animal models, the gold standard test for bone quality can be directly tested with three point bending engineering tests to determine the ability of the bone to resist fracture under strain. By definition, bone quality must be impaired in CKD, as there is an increased prevalence of hip fracture in dialysis patients compared to the general population across all ages [16, 17]. The risk disproportionately affects younger individuals due to the low prevalence of fractures in the young general population: dialysis patients in their 40 s have a relative risk of hip fracture 80-fold that of age and sex-matched controls [16]. Similar to the general population, a hip fracture carries increased mortality. That mortality is even greater in a dialysis patient with a doubling of the mortality observed in hip fractures in non-dialysis patients [17, 18]. In a multivariate analysis, the risk factors for hip fracture include age, gender, duration of dialysis, and presence of peripheral vascular disease [19]. Other analyses found race, gender, duration of dialysis and low or very high PTH levels as risk factors [17, 18]. In a study of Japanese men, 21% of prevalent dialysis patients (mean age 54 ± 9 years) had vertebral fractures by plain radiographs, supporting that fractures occur at both hip and lumbar spine and in all genders and races [20]. In addition to increased fractures in dialysis patients, the presence of CKD is also associated with increased risk of hip fractures [21–27] (Table 2), indicating that the pathogenesis of the decreased bone quality in CKD occurs early in the course of disease. In a rat model of CKD-MBD, impaired biomechanical strength occurred in animals with a 50% reduction in kidney function, at which time there was twice normal elevation in PTH and FGF23, and a marked decrease in blood 1,25D and kidney klotho expression yet normal calcium and phosphorus levels [10]. Thus, the abnormalities may go undetected unless CKD-MBD is recognized in CKD stage 3. Figure 2 illustrates some of the causes of increased fractures in CKD.

Both cortical and trabecular bones are important to bone strength and cortical bones resist bending or buckling, and trabeculae distribute force in cancellous bone. The strength of the skeleton depends on both its quality and quantity. Thus, the fragility of bone is due to changes in bone mass (assessed by dual X-ray absorptiometry and/or CT) and alterations in bone architecture. The latter is due to changes in bone turnover, mineralization, collagen structure/organization, and cannot be easily assessed clinically. Effective mineralization allows the bone to have adequate stiffness to resist bending and compression. Trabecular bone quality depends on bone volume and microarchitecture determined by trabecular thickness, number, connectivity, orientation, and preferable plate-like structures [28, 29]. Derangement of skeletal architecture found in the CKD population is regulated by several factors. Aging, hypogonadism,

Table 2 Studies of fracture risk associated with CKD

Study	Definition of kidney function	Fracture site	Fracture risk (95% CI)[a]
Dukas et al. [23]	<65 ml/min	Hip	OR 1.57 (1.18–2.09)
		Wrist	OR 1.79 (1.39–2.31)
		Vertebral	OR 1.31 (1.19–1.55)
Nickolas et al. [24]	<59 ml/min	Hip	OR 2.32 (1.13–4.74)
Ensrud et al. [25]	45–59 ml/min	Hip	HR 1.24 (0.60–2.56)
	<5 ml/min		HR 1.41 (0.59–3.36)
	45–59 ml/min	Trochanteric	HR 3.69 (1.21–11.24)
	<45 ml/min		HR 5.04 (1.38–18.45)
Jamal et al. [26]	<45 ml/min	Any fracture	OR 1.3 (1.0–1.6)[b]
		Vertebral	OR 2.5 (1.6–3.9)[b]
Fried et al. [27]	<60 ml/min	Hip	HR 1.38 (0.99–1.94)[b]
	Per s.d. increase in cystatin C	Hip	HR 1.16 (1.01–1.33)[b]

From Nickolas et al. [21], with permission

CI confidence interval, *CKD* chronic kidney disease, *HR* hazard ratio, *OR* odds ratio

[a] After multivariate adjustment

[b] Women only

diabetes mellitus, PTH, calcitriol, uremic toxins, inflammatory cytokines, and corticosteroids. The resolution of dual-energy X-ray absorptiometry (DXA) or ultrasonography is not high enough to distinguish cortical from trabecular bone density and it cannot illustrate trabecular microarchitectures. The new generation of high-resolution computed tomography (HRpQCT) and high-resolution magnetic resonance imaging (HR-MRI) have enhanced resolution and may allow for improved discrimination of architecture [30], with hopes to be used as a "virtual" bone biopsy. The role of DXA and other noninvasive bone imaging is described in more detail in a subsequent chapter.

Renal Osteodystrophy

After peak bone modeling and growth, normal bone is still dynamic and undergoes a remodeling process to heal micro-damage. Bone remodeling begins with activation of osteoclasts to resorb a resting bone surface, recruitment of osteoblasts, formation of bone matrix, and subsequent mineralization to complete new bone formation. The accurate assessment of abnormalities in bone turnover and mineralization requires bone biopsy with bone histomorphometry, the quantitative assessment of these histologic changes. Transiliac bone biopsy and histomorphometry with double-labeled tetracycline or its derivatives is the gold standard for diagnosis of renal osteodystrophy. It provides both static and dynamic data of bone quality and quantity.

Initial definitions of renal osteodystrophy [31], still commonly used, were more descriptive in nature and designed to allow classification for research purposes (Table 3). These are described in more detail in a subsequent chapter. The focus on this classification scheme was on bone turnover, and at the time, it was felt that PTH was the main regulator of bone remodeling. The prevalence of these various forms of renal osteodystrophy have changed over the years, with a decrease in osteomalacia and aluminum disease and an increased prevalence of adynamic bone disease (37–60% among dialysis patients), with a notably stable proportion of high-bone turnover disease at 40–50% [32–34]. These changes may be the result of a change in patient characteristics (older and more diabetics) and/or treatment modalities.

As noted above, the process of bone remodeling is very complex, and regulated by a number of local and systemic factors. In addition, patients with advanced CKD also suffer from age-related and menopausal-related bone loss and the manifestations of abnormal bone remodeling in CKD is also dependent on the state of bone when a patient developed CKD. This was brought to the forefront in 2006 with a study by Barreto et al. [35] who noted a high prevalence of low bone volume ("osteoporosis") in bone biopsy specimens, regardless of the mineralization or turnover. These observations led KDIGO to recommend a broadening of the original more descriptive definitions of renal osteodystrophy to a new nomenclature that evaluates TMV (Table 1 [36]).

Turnover (T) reflects cellular activity of osteoclasts and osteoblasts on new bone formation. The net bone turnover rate is determined by the balance of formation to resorption. In normal bone, formation and resorption are tightly coupled and in balance. But if either is abnormal, there will

Table 3 Turnover-based definitions of renal osteodystrophy

High turnover disease:
Osteitis fibrosa cystica: Severe hyperparathyroidism: increased BFR or activation frequency, increased osteoclast and osteoblast activity, increased fibrosis
Mild hyperparathyroid disease: All of the findings as in osteitis fibrosa cystic, but no fibrosis
Mixed disease: High BFR, increased osteoid
Low turnover disease
Osteomalacia: Low BFRs, increased osteoid
Adynamic: Low BFRs, no increased osteoid, low to absent cells

be net bone loss from resorption > formation, or net bone gain from formation > resorption. This net bone balance can be assessed with histomorphometry using the bone formation rate (BFR) because there is no direct method to measure the resorption rate. BFR can be measured with double tetracycline labeling. It is calculated by the length of tetracycline labels multiplied by the distance between the labels, then divided by the label interval. Activation frequency may be used instead of BFR, and better represents the activity of local bone remodeling units.

Mineralization (M) reflects how well a newly formed osteoid matrix is mineralized. It is regulated by how adequate the minerals, both calcium and phosphorus, enter into bone. Calcitriol deficiency and the deposition of some trace elements, such as iron and aluminum, during mineralization disturb the process. If abnormal mineralization occurs, high amounts of osteoid are presented. However, since the apparent increase of osteoid may be due to either accelerating bone formation or a mineralization defect, the amount of osteoid should be adjusted by a parameter of osteoblastic activity. The parameters osteoid maturation time (OMT) is the osteoid thickness divided by the distance between tetracycline-labeled per day. Mineralization lag time (MLT) is OMT adjusted for the percentage of tetracycline-labeled osteoid surface. For the KDIGO TMV system, MLT is recommended.

Volume (V) reflects the net bone balance resulting from the effects of bone turnover. If there is effective mineralization, bone density should correlate with bone volume and represent bone mass. In dialysis patients, bone volume on histomorphometry was not associated with trabecular connectivity by three dimensional imaging [37]. In the general population, bone mineral density by DXA can predict fracture risks in osteoporotic subjects who have never been treated with anti-resorptive agents. This association has not been validated in CKD patients because DXA only tells you how much mineral is present, not how the mineral is arranged. Thus, bone volume on histomorphometry can give you an estimate of the net bone balance over time.

Unfortunately, bone histomorphometry does not correlate well with noninvasive imaging (e.g., DXA), or biochemical tests and thus bone biopsy is needed if underlying histology will change clinical management. We typically measure PTH as a surrogate of bone turnover, but even the second generation "intact" assays provide limited sensitivity and specificity: 50–70% and 78–85%, respectively, for diagnosis of low-bone turnover disease at PTH levels <150 pg/ml, and 70–88 and 75–80%, respectively for diagnosis of high-bone turnover disease at PTH levels >300 pg/ml [38–40]. The predictability of the ratio of 1–84 PTH to C-terminal PTH levels less than 1.0 to diagnose adynamic bone disease showed initial promise but was not subsequently validated in other patient populations [41–43]. Furthermore, different PTH assays have had varying test results and standardization for the assays is not available [44]. A rising bone or total alkaline phosphatase alone or combined with intact PTH may be helpful to predict turnover. At this time, we have broad "targets" for PTH because of the lack of sensitivity and specificity and trends should be utilized to better determine appropriate therapies [36].

Linear Height

The final parameter of the bone abnormalities of CKD-MBD are alterations in linear height observed in children with CKD-MBD. Similar to abnormalities in bone remodeling, initial bone modeling is impaired in CKD. The etiology is likely similar to the pathogenesis of abnormal bone remodeling in adults, but are also due to impaired growth hormone-insulin-like growth factor axis, acidosis, and nutritional abnormalities [45]. Growth failure in children is associated with decreased quality of life, morbidity, increased hospitalizations, and a threefold increase in mortality [46].

Vascular Calcification

The term vascular calcification "VC" is used to describe arterial calcification, which can be within atherosclerotic plaques (intima), or medial in location. The presence of intimal calcification indicates advanced atherosclerotic disease and patients with this will present with ischemia. Arterial medial calcification, especially of the aorta and other mid- to large-size arteries, results in arterial stiffness that can manifest with increased pulse wave velocity. However, both types of calcification predict all-cause and cardiac mortality in dialysis patients (summarized in [36]).

The presence of coronary calcification in CT-based imaging studies cannot distinguish between intimal and medial calcium deposits. However, CT-based methods are

useful as they allow quantitation. The higher the coronary artery calcification score, the greater the risk of cardiovascular mortality in both general population [47] and CKD [48]. Coronary flow reserve is impaired in the subjects who are documented to have severe coronary calcification as the vessels cannot dilate to respond to increased myocardial metabolic demands. Caliskan et al. found that hemodialysis patients with coronary flow reserve <2.0 had more severe coronary calcification and were at twice the risk of cardiac events, compared to the ratio ≥2.0 [49, 50]. Plain radiographs demonstrate intimal calcification as discrete, irregular distribution of patchy radio-opaque lesions, and medial calcification as more uniform, linear lesions along the vessels. The presence of both types of calcification is associated with increased mortality [51].

Arterial calcification is more prevalent and usually more severe among CKD patients than in the general population. Over 50% of non-dialysis CKD patients [52] and 70–90% of prevalent dialysis patients have evidence of increased coronary artery calcification [53, 54]. On pathologic examination of the coronary arteries, a comparison of dialysis patients to non-CKD patients who died of a coronary event showed that dialysis patients had more calcification in the atheromatous plaques, but not more plaque. They also had a thicker tunica media [55]. Subsequent studies evaluating more distal segments of the coronary arteries found medial calcification adjacent to the internal elastic lamina [56]. In another study, only patients with stage 4 CKD and end-stage renal disease had evidence of calcification of the tunica media in coronary arteries whereas this was not found in the mild CKD and normal renal function [57]. In the inferior epigastric artery of patients undergoing a renal transplant, there was clearly isolated medial calcification observed in the absence of intimal atherosclerosis or internal elastic lamina disruption [58]. Thus, medial calcification can occur as an isolated finding suggesting that the pathogenesis is not the same as atherosclerosis. Thus, studies evaluating the pathophysiology of VC in CKD should discriminate between intimal/atherosclerotic and medial calcification.

In the past, arterial calcification was felt to be due to passive precipitation from a high calcium-phosphorus product in the blood of patients. But now, we know that the process is not passive, but in fact an active, cell-regulated process. In our previous reports, we have demonstrated the presence of core binding factor alpha-1 (Cbfa-1/RUNX2), a transcription factor critical for osteoblastic differentiation and downstream bone matrix proteins osteopontin and type I collagen in the calcified area of inferior epigastric artery obtained from hemodialysis patients [58]. Jono et al. [59] demonstrated osteoblastic transdifferentiation of vascular smooth muscle cells under high phosphate conditions through the up-regulation of sodium-phosphate co-transporter type III (Pit-1). Uremic toxins other than phosphate also induce osteoblastic changes and calcification of vascular smooth muscle cells [60]. In addition to the pro-calcifying uremic environment, patients with CKD also appear to be deficient in inhibitors of calcification. Approximately 10–40% of dialysis patients have no VC, and 80% of incident dialysis patients who have no coronary artery calcification at baseline continue to be free of calcification at 2 years [53], suggesting some patients are protected from calcification.

Fetuin-A is a systemic inhibitor which binds to calcium-phosphate crystals in the blood to presumably prevent deposition and low levels of fetuin-A are associated with increased mortality in dialysis patients [61]. Pyrophosphate is a locally synthesized inhibitor that is the same structural backbone as bisphosphonates; levels inversely correlate to baseline and 1-year progression of arterial calcium scores in hemodialysis patients [62]. Matrix gla protein (MGP) null mice have extensive medial artery calcification [63]. MGP must be carboxylated to be active, and circulating undercarboxylated MGP levels increase across the spectrum of CKD and positively correlates to aortic calcium scores in both non-dialysis and dialysis patients [64, 65]. Determining the regulation of the balance of pro-mineralizing to anti-mineralizing activity in CKD is an active area of scientific studies.

Hyperphosphatemia is a major risk factor for VC in CKD. In vitro, it induces the transdifferentiation of vascular smooth muscle cells to osteoblast/chondrocyte-like cells [4, 59]. The elevated phosphate can come from diet or from bone [2, 6, 66, 67], and sustained elevations require abnormal (inappropriate) urinary clearance. These findings have been supported by in vitro and ex vivo as well as animal experiments. Low phosphate diet attenuated aortic calcification in our CKD rat model [66], and in other models using phosphate binders [68]. Attenuation of hyperphosphatemia in klotho and sodium-phosphate cotransporter-2a double-knockout mice has shown a suppression of medial calcification despite the presence of hypercalcemia and hypervitaminosis D [69]. There is less clear data on the role of PTH. However, Neves et al. [70] and Graciolli et al. [71] published studies supporting that PTH had a pro-vascular calcification effect regardless of the level of phosphorus in nephrectomized rats. In a study of dialysis patients, both low and high turnover on bone biopsy was associated with increased coronary artery calcification [72]. Finally, studies in humans have demonstrated that lowering phosphorus levels with non-calcium containing phosphate binders compared to calcium containing binder attenuated coronary artery calcification [53, 73, 74], although one study did not find a difference [75]. Treating secondary hyperparathyroidism with cinacalcet, a calcimimetic, also appeared to slow the progression of

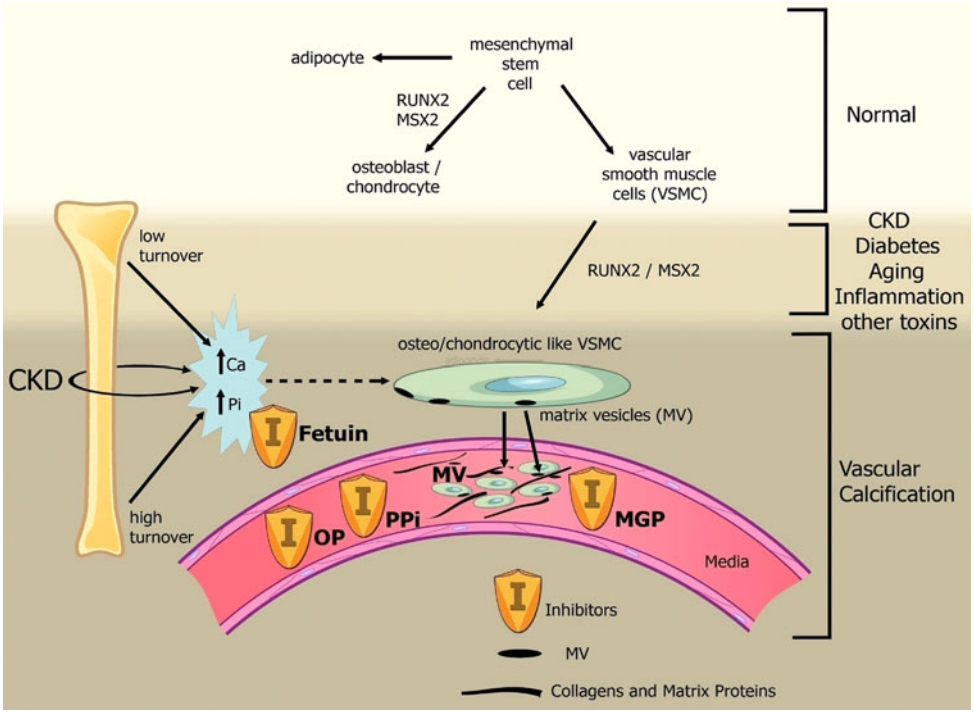

Fig. 3 Pathogenesis of VC in CKD: Normally, mesenchymal stem cells differentiate to adipocytes, osteoblasts, chondrocytes, and vascular smooth muscle cells. In the setting of CKD, diabetes, aging, inflammation and multiple other toxins, these vascular smooth muscle cells can de-differentiate or transform to a chondrocyte/osteoblast-like cells by upregulation of transcription factors such as RUNX-2 and MSX2. These transcription factors are critical for normal bone development and thus their upregulation in vascular smooth muscle cells is indicative of a phenotypic switch. These osteo/chondroctyic-like VSMC cells then become calcified in a process similar to bone formation. These cells lay down collagen and non-collagenous proteins in the intima or media AND incorporate calcium and phosphorus into matrix vesicles to initiate mineralization, and further grow the mineral into hydroxyapatite. The overall positive calcium and phosphorus balance of most dialysis patients feeds both the cellular transformation and the generation of matrix vesicles. In addition, the extremes of bone turnover in CKD (low and high or adynamic and hyperparathyroid bone, respectively) will increase the available calcium and phosphorus by altering the bone content of these minerals. Ultimately, whether an artery calcifies or not, depends on the strength of the army of inhibitors standing by in the circulation (fetuin-A) and in the arteries (*PPI* pyrophosphate, *MGP* matrix gla protein as examples). From Moe and Chen [2], with permission

coronary artery calcification [76]. Thus, both abnormal bone remodeling, and abnormal blood levels of biochemistries and hormones of mineral metabolism are involved in the pathogenesis of VC (Fig. 3).

Conclusion: CKD-MBD

Epidemiologic studies demonstrate an association of hyperphosphatemia, hypercalcemia, and significant hyperparathyroidism with cardiovascular events as well as mortality in hemodialysis patients; hyperphosphatemia and elevated FGF23 have the strongest risk [77–79]. Additionally, hypovitaminosis D is commonly found in the late stages of CKD and is related to increased all-cause and cardiovascular mortality in CKD [80, 81]. The pathogenesis of this cardiovascular mortality includes effects on left ventricular hypertrophy, endothelial dysfunction, coronary artery ischemia, and sudden death and hypertension [3]. Similarly, these mineral abnormalities are likely causative in the increased fractures observed in CKD, and mortality post-fracture is higher in patients with CKD than in the general population. Finally, both abnormalities in bone and mineral metabolism are involved in the pathogenesis of VC. Thus, the triad of abnormal mineral metabolism, abnormal bone, and VC inter-play to cause mortality, cardiovascular disease, and fractures in the systemic disorder of CKD-MBD. The clinical consequences of CKD-MBD are common and significantly impact the health and well-being of CKD patients. Understanding these interactions should lead to improved therapeutic approaches in the future.

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