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The Role of Bone in CKD-Mediated Mineral and Vascular Disease

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Abstract

Cardiovascular disease is the leading cause of death in pediatric patients with chronic kidney disease (CKD) and vascular calcifications start early in the course of CKD. Based on the growing body of evidence that alterations of bone and mineral metabolism and the therapies designed to treat the skeletal consequences of CKD are linked to cardiovascular calcifications, the Kidney Disease, Improving Global Outcomes (KDIGO) working group redefined renal osteodystrophy as a systemic disorder of mineral and bone metabolism due to CKD and this newly defined disorder is now known as “Chronic kidney Disease Mineral Bone Disorder (CKD-MBD)”. Elevated fibroblast growth factor 23 (FGF23), a bone derived protein, is the first biochemical abnormality associated with CKD-MBD and high FGF23 levels correlate with increased cardiovascular morbidity and mortality, suggesting that bone is central to both initiating and perpetuating the abnormal mineral metabolism and vascular disease associated with CKD-MBD. The current standard therapies for CKD-MBD affect FGF23 levels differently; non-calcium based binders with or without concurrent use of dietary phosphate restriction reduce FGF23 levels while calcium-based binders seem to either increase or have no effect on FGF23 levels. Active vitamin D sterols increase FGF23 levels whereas therapy with calcimimetics decreases FGF23 levels. Thus, the appropriate therapy that will minimize the rise in FGF23 and prevent cardiovascular morbidity remains to be defined.

Keywords

CKD-MBD; FGF23; PTH phosphate binders; Vitamin D; Vascular calcifications; Cardiovascular disease; children

Case Vignette:

A 5 year-old boy with end stage renal disease as a result of hemolytic uremic syndrome who was previously peritoneal dialysis dependent for two years was successfully transplanted. He had excellent allograft function, complicated only by mild hypertension, until at 10 years of age, when he suffered a heart attack. He recovered, however, over the next several years he lost his graft to chronic rejection, only to return to hemodialysis at 16 years of age. Two years later while on dialysis, he suffered a second massive myocardial infarction and died.

Epidemiology of Cardiovascular Disease in Chronic Kidney Disease

While the vignette is dramatic, the general theme is not uncommon. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality both in adults and children with end stage renal disease and it is highly prevalent post successful kidney transplantation. Childhood and adolescence are a crucial time for developing a healthy skeletal and vascular system; the alterations in bone modeling/remodeling and vascular biology that accompany kidney disease carry consequences that severely impact quality of life as well as life span. Five to 10% of the world's populations suffer from chronic kidney disease (CKD) [1]. In the US, the prevalence of CKD is 6.3% and in children, CKD is a growing problem, with an overall incidence of 15.2 per million between 2007–2011 and an increasing rate of renal replacement therapy [2].

The overall mortality is 30 fold greater in children with end stage renal disease (ESRD) than their healthy peers and a large percentage is due to CVD. In 2011, 3% of deaths in the general pediatric population were attributed to cardiac causes in contrast to 32%, 28% and 22% of deaths in patients treated with hemodialysis, peritoneal dialysis and post-kidney transplantation respectively [3–5] (Figure 1). Moreover, CVD appears to be increasing in prevalence in the pediatric CKD population. Between 2006–2010, the cardiovascular death toll rose 14.2% in children 0–9 years of age and by factors of 3.6x and 2.6x in children aged 10– years and 15–19 years respectively [2]. With time on dialysis the risk of cardiovascular death is further magnified up to 700 fold. Strikingly, the mortality rate for young adults treated with dialysis, 24–35 years of age, is on the same order of magnitude as that of healthy senior citizens [6].

In the general population CVD risk increases with age, but CKD is itself a risk factor for CVD [7]. In fact, a consensus statement from the American Heart Association classified children with CKD in the highest risk category for the development of CVD [8], which is particularly significant, as children lack many of the traditional risk factors associated with CVD found in adults. Even in adult patients with renal disease the amplified cardiovascular morbidity and mortality cannot be fully explained by traditional risk factors [9] and many investigators have attempted to elucidate the features inherent to kidney disease that contribute to the increased risk [10–13].

Extraskelatal calcification, including vascular calcification, is an established risk factor for cardiovascular disease in the general population and has also been clearly identified as a risk factor in both children as well as adults with CKD [14–18]. Milliner *et al.* demonstrated that soft tissue and vascular calcification were present in 60% of children with end-stage renal disease in a post-mortem analysis from 0 patients. The most common sites of calcification were blood vessels, lungs, kidneys, heart and coronary arteries [15]. In addition, Goodman *et al.* described a high prevalence of coronary artery calcifications assessed by electron beam computed tomography in young adults patients with childhood onset ESRD [17]. These original findings have subsequently been supported by other investigators utilizing different diagnostic tools [3, 16, 19, 20].

Structural and functional abnormalities and calcification in the large vessels begin in early CKD and are apparent as early as the first decade of life in patients with kidney disease. Russo *et al.* demonstrated that vascular calcifications were present in almost 40% of an adult cohort of patients with CKD stage 3 [21] and Temmar *et al.* revealed an increase in the prevalence of vascular calcifications with the decline of kidney function [22]. Further, Fang *et al.* found that extraskeletal calcification developed in a mouse model of CKD even before the advent of hyperphosphatemia [23].

In contrast to the calcifications of atherosclerotic plaques in the vascular intima that develop with age in individuals with normal kidney function, vascular calcification in the uremic milieu develops primarily in the vascular media [24, 25]. Medial calcification decreases the elasticity and compliance of arteries. The increase in arterial stiffness leads to an increase in systolic pressure, a widened pulse pressure and an increased strain on the heart. Recent data in children from the CKiD study cohort in the U.S. and the Escape trial in Europe demonstrates a high prevalence of both masked hypertension and left ventricular hypertrophy (LVH) in children. Eccentric and concentric LVH were found in 11–21% and 6–22% of children with kidney disease respectively [10, 26].

The complex process of media vascular calcification is incompletely understood, but is thought to involve a transition from vascular smooth muscle cells to osteoblast like cells in the setting of an inappropriate environmental milieu [27]. It is an active process with multiple contributing factors including micro-inflammation, apoptosis of vascular smooth muscle cells (VSMC) [28], induction of osteochondrogenesis, development of a calcifiable extracellular matrix, and mineral deposition [29, 30]. In addition, in CKD local and circulating inhibitors of soft tissue mineralization such as matrix Gla protein, pyrophosphate, Fetuin-A, Klotho, and osteopontin are diminished while promoters of calcification are up regulated [13, 27, 30–35]. The exact stimulus for the development of cardiovascular calcification remains unknown; however, a recent study correlated high tissue levels of Dkk1, a critical inhibitor of Wnt signaling, produced by diseased kidneys, with vascular calcification in mice with early stages of CKD. In these mice, neutralization of Dkk1 prevented vascular calcification, suggesting that this factor may play a role in the early development of CKD-mediated vascular calcification [13, 21, 23]. Interestingly, bone disease and deranged mineral metabolism, which are prevalent in patients with all stages of CKD, appear to be related to CVD. Furthermore, the current treatments for CKD-MBD, especially the control of calcium and phosphorous, have ramifications for the progression of CVD [36].

Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD)

Based on the growing body of evidence that alterations of bone and mineral metabolism and the therapies designed to treat the skeletal consequences of CKD are linked to cardiovascular calcifications and that cardiovascular disease is the leading cause of morbidity and mortality in CKD patients, in 2006, the Kidney Disease, Improving Global Outcomes (KDIGO) working group redefined renal osteodystrophy as a systemic disorder of mineral and bone metabolism due to CKD that is manifested by either one or a combination of the following: (1) abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D

metabolism; (2) abnormalities in bone histology, linear growth, or strength; or (3) vascular or other soft tissue calcification. This newly defined disorder is now known as “Chronic kidney Disease Mineral Bone Disorder (CKD-MBD)”. The term “Renal Osteodystrophy” refers only to the description of the bone pathology that occurs as a complication of CKD and is therefore only one aspect of CKD-MBD [36]. With the new definition for ROD, three different bone variables should be included in the assessment of bone biopsies: turnover (T), mineralization (M), and Volume (V) [36].

As originally described by Block *et al.* using data from the United States Renal Data System (USRDS), elevated serum phosphorus levels are an independent risk factor for death in the adult ESRD population [37]; this data has been consistently confirmed by other investigators [38–40]. Undeniably, high serum phosphorus contributes to the development of vascular calcification in those undergoing dialysis and in the general population, and thus, the control of serum phosphorus levels is a key component of ongoing clinical management [37]. Hyperphosphatemia seems to initiate a cascade of events that amplify the pathway to vascular calcification [41]. In *in vitro* studies, high phosphate concentrations enhance the uptake of phosphorus by VSMCs via the type III sodium phosphate co-transporter [42] and increase gene expression of osteogenic/chondrogenic genes such as runx2, osterix, alkaline phosphatase and osteopontin [43]. Concurrently, vascular expression of smooth muscle lineage markers, SM22 α and smooth muscle actin is down regulated [44].

Traditionally, the pathogenesis of secondary hyperparathyroidism of CKD has been attributed to early decreases in 1,25(OH)₂ D (1,25D) and replacement treatment has been advocated for the early control of serum PTH and bone disease [45]. However, over the past decade, the identification of fibroblast growth factor 23 (FGF23) and its co-factor Klotho [46] have led to a new conceptual framework in the understanding of the pathogenesis of the bone disease associated with CKD, challenging the current diagnosis and treatment of CKD-MBD. Acting together, these proteins reduce sodium phosphate co-transporter (NPT2a and NPT2c) expression in the proximal renal tubules, suppress renal 1- α -hydroxylase activity and increases 24- hydroxylase activity [47], thus regulating both phosphate and vitamin D metabolism. The absence of either FGF23 or Klotho thus results in hyperphosphatemia, hypercalcemia, elevated 1,25D levels and vascular calcification [47, 48]. FGF23 is produced by osteocytes and osteoblasts in bone [49] while Klotho is present at high levels in the brain, the parathyroid glands and the kidney and at low levels throughout the body, including vascular smooth muscle cells [50]. Interestingly, serum FGF23 levels and bone FGF23 expression increase early in the course of CKD, prior to detectable changes in serum mineral ion or PTH levels but at a time when renal bone disease [51, 52] and CVD [21] are already apparent. By contrast, expression of Klotho in vascular smooth muscle tissue appears to decline [50] while aberrant Klotho expression in calcified areas of vascular tissue appears to increase with progressive CKD. Increased Klotho expression within calcifications is likely a response to vascular damage [53] and in turn may induce end-organ resistance to the actions of FGF23, possibly further increasing circulating FGF23 values [50, 54].

The primary stimulus of FGF23 production in CKD has not been completely defined; nevertheless, oral phosphate loading stimulates FGF23 production suggesting that “phosphate load” may be an initial trigger [55–57]. Whether phosphate itself directly

stimulates FGF23 or whether its effect is mediated via transient changes in PTH, however remains unknown. Indeed, serum phosphorus levels remain within the normal range or are diminished in adult and pediatric patients with early CKD stages and phosphate balance is neutral in patients with CKD stages 3–4 [58]. Further, osteoblasts/osteocytes fail to produce FGF23 in response to extracellular phosphate *in vitro* [59].

Although PTH levels are normal, while FGF23 levels are elevated, in early CKD, some have suggested that transient increases in PTH may account for early increases in FGF23. In a recent experiment conducted in 18 healthy young adults with normal renal function, plasma PTH levels rose within eight hours of phosphate loading prior to significantly detectable changes in plasma FGF23. Subsequent increases in FGF23 were related to a decrease in PTH levels in these individuals [60]. In addition, PTH has been shown to increase FGF23 expression in a rat model of CKD [61] to stimulate osteocytic production of FGF23 in a murine model (DMP1-caPTHr1 transgenic mice) [62] and therefore may play a role in mediating the rise in FGF23 in response to phosphorous.

Alternatively, phosphate-independent mechanisms may predominantly contribute to the increase in FGF23 in CKD. Potential causes include a decrease in circulating and membrane-bound Klotho levels [63]; iron deficiency that stimulates FGF23 transcription in osteocytes [64]; increased levels of cleaved α Klotho (cKL) that regulate phosphate homeostasis by inducing FGF23 production [65]; abnormal metabolism of dentin matrix protein 1 (DMP1), a down-regulator- of FGF23 [66] and/or inflammation [67]. Furthermore, primary kidney disease may be an additional factor in increasing FGF23 levels. Portale *et al.* demonstrated that patients with glomerular diseases have higher FGF23 levels than those with congenital abnormalities despite no differences in phosphorus Z-scores or fractional excretion of phosphate. Such findings suggest that patients with glomerular disease may be resistant to the phosphaturic effect of FGF23 [68].

Increased circulating values of FGF23 in CKD, in addition to their implications for bone and mineral metabolism, have important systemic “off-target” effects. Several epidemiological studies have shown associations between elevated FGF23 levels and kidney disease progression, CVD, and mortality not only in CKD but also in the general population. FGF23 levels have been correlated with increased left ventricular mass index, left ventricular hypertrophy in adult and pediatric dialysis patients [69] and increased risk of mortality in incident dialysis patients, renal transplant recipients and in the general population [70–72]. Data from Faul *et al.* demonstrated that FGF23 has a direct effect on cardiomyocyte hypertrophy through a Klotho-independent mechanism [73]. Indeed, both adults and children with CKD have greater left ventricular mass than their non-CKD counterparts [74] even when they have similar blood pressures [75]. Since circulating levels of FGF23 have been identified as an independent risk factor for mortality in adult CKD patients and in the general population at large [76] and since dietary phosphate intake has been linked to increased circulating FGF23 levels in normophosphatemic patients, the prevention of intestinal phosphorus absorption in early CKD, when serum phosphorus levels are in the normal range, may be of critical importance in the future early management of CKD-MBD.

While several epidemiological studies have also shown associations between FGF23 levels and vascular calcifications, in dialysis patients, predialysis patients and subjects with normal renal function [41, 77], experimental studies have failed to confirm a pathogenic role for FGF23 in the development of vascular calcification [12], perhaps indicating that FGF23 acts as a marker of disease severity or inflammation [78]. However, normal expression of Klotho in vascular smooth muscle tissue appears to decline while expression of both FGF23 and Klotho appear to increase in calcified atheromas as CKD progresses, suggesting a link between the Klotho-FGF23-FGF receptor system and vascular pathology [53].

Impact of current therapy on CKD-MBD (Figure 2)

Phosphate binders

As early as the 1970s, aluminum based binders were used to control hyperphosphatemia, only to be replaced a decade later with calcium containing binders [79]. These agents were thought to be safe and cost effective and as a result are one of the mainstays of therapy for hyperphosphatemia today. However, large doses of calcium carbonate may lead to hypercalcemia, particularly in patients treated with vitamin D or those with adynamic bone disease. The elevated calcium-phosphorus product has been identified as a risk factor for vascular calcification in several studies [11, 17, 37]. Moreover, Hill et al. demonstrated that patients with CKD stages 3–4 are in positive calcium balance when they are given 2 g/day of calcium-based binders [58] and those patients with CKD stages 3–4 experience progressive vascular calcification [80]. *In vitro* studies of VSMC by Shroff *et al.* revealed that vessels from pediatric dialysis patients accumulate calcium and develop calcification in response to long term exposure to calcium and calcium and phosphorous together, in stark contrast to vessels from controls that do not calcify given the same environmental conditions [30].

Non-calcium based binders such as sevelamer hydrochloride, sevelamer carbonate and lanthanum carbonate have been found to effectively control hyperphosphatemia, and are a viable alternative to calcium based binders. A recent meta-analysis of clinical trials using calcium-based versus non-calcium based binders clearly demonstrated that calcium-based binders are associated with a greater degree of vascular calcification, cardiovascular disease and mortality in patients with CKD [81]. The choice of binder should therefore be based on both efficacy and safety. Of note, lanthanum is a heavy metal that accumulates in different tissues in animals with both normal and reduced kidney function and to date there are no published studies in the pediatric CKD population evaluating its safety profile.

Recently, Block *et al.* prospectively compared the effects of different phosphate binders in patients with moderate CKD, normal serum phosphorous, and mildly elevated levels of intact FGF23 (100s). In this cohort, the effects on intact FGF23 levels seemed to differ by binder type; intact FGF23 levels increased in those in the calcium acetate group, decreased in the sevelamer carbonate group and were no different from placebo in the lanthanum carbonate group [82]. Other small, short-term studies have demonstrated similar findings; non-calcium based binders with or without concurrent use of dietary phosphate restriction reduce FGF23 serum levels. By contrast, serum FGF23 levels remain unchanged with the use of calcium-based binders [80, 83–85]. More recently, ferric citrate has been shown to be an effective phosphate binder in pre-dialysis CKD patients and to markedly reduce FGF23

levels when compared to placebo [86]; while promising, this compound is yet to be FDA approved.

Vitamin D sterols

Active vitamin D sterols are currently recommended for the prevention and treatment of secondary hyperparathyroidism in patients with CKD. Calcitriol and alfacalcidol have been effective in decreasing PTH levels and preventing osteitis fibrosis cystica for decades [87] and large epidemiological studies have demonstrated a survival benefit with the use of low dose calcitriol in patients treated with hemodialysis [88–91]. However, treatment with both calcitriol and alfacalcidol in combination with calcium- based binders often results in hypercalcemia and hyperphosphatemia which contribute to the development of soft tissue calcification and potentially cardiovascular disease [15]; thus, additional vitamin D analogues were developed to minimize intestinal calcium and phosphorus absorption, while still suppressing PTH. Three of these active vitamin D analogues are used in patients with CKD: 22-oxacalcitriol in Japan and 19-nor-1,25- dihydroxyvitamin D2 (paricalcitol) and 1 α -hydroxyvitamin D2 (doxercalciferol) in the United States. While some studies showed that these newer analogues may confer a greater survival benefit than calcitriol [92–94], when oral calcitriol therapy was prospectively compared to doxercalciferol with the combined use of either calcium-based binders or sevelamer hydrochloride there were no differences in the number of hypercalcemic episodes, the serum calcium levels and the degree of control of the skeletal lesions of secondary hyperparathyroidism between both groups. Furthermore, mineralization defects persisted, irrespective of the binder-vitamin D combination used [95].

It is interesting to note, that therapy with active vitamin D sterols increases FGF23 levels, which is associated with higher mortality rates in dialysis patients; this paradox between the survival advantage of therapy with active vitamin D sterols and the increased mortality rate associated with elevated FGF23 remains to be resolved. Recently, Ito *et al.* demonstrated that 1,25D attenuates renal fibrosis by inhibiting TGF- β - SMAD signal transduction [96]. Thus, 1,25D may be essential for both cardiac health and the prevention of progressive renal dysfunction, a finding that could explain observational data suggesting that active vitamin D sterol therapy improves survival in patients treated with maintenance dialysis [88, 89, 92].

Calcimimetics

Calcium-sensing receptors (CaSR) are present in the kidney, the parathyroid glands and the vascular tissue and therapy with allosteric activators of the CaSR reduces serum levels of PTH by reducing the set-point for calcium-mediated PTH suppression. In animals, loss of function of the calcium-sensing receptor results in vascular calcification [97] and numerous case reports have reported an attenuation of cardiovascular calcification from calcimimetic use [98, 99]. However, the only large, prospective, randomized trial to date failed to find a survival benefit with Cinacalcet therapy in hemodialysis patients. In this large cohort of dialysis patients with secondary hyperparathyroidism, Cinacalcet resulted in a decline in the calcium–phosphorus ion product, a reduced rate of severe unremitting hyperparathyroidism, and a reduced rate of calciphylaxis; however no significant difference in cardiovascular outcomes was observed in an unadjusted analysis. Unfortunately a large number of patients dropped out from both arms of the study and there was a fair amount of cross-over between

study arms. Reduced risk for poor cardiovascular outcomes was shown after adjustment for differences of baseline characteristics between study groups -a % reduction in the primary endpoints, death or major cardiovascular events [100]. Cinacalcet is also associated with reductions in FGF23 levels [101].

Summary

In summary, CVD is the number one cause of morbidity and mortality in adult and pediatric patients with CKD. A substantial proportion of CKD patients develop vascular calcification; calcifications are present in almost 50% of adult patients with CKD stages 3–4, in patients new to dialysis and in pediatric CKD patients in whom traditional cardiovascular risk factors are absent. In contrast to the calcifications of atherosclerotic plaques in the vascular intima that develop with age in individuals with normal kidney function, vascular calcification in the uremic milieu develops primarily in the vascular media. Medial vascular calcification results in arterial stiffening, increased pulse pressure, and increased strain on the heart. The vascular calcification process is incompletely understood, but is thought to involve a transition from vascular smooth muscle cells to osteoblast like cells in the setting of an inappropriate environmental milieu and is associated with modifiable risk factors such as calcium intake from calcium-based binders, serum calcium and phosphorus levels, and the calcium-phosphate product.

FGF23 is the earliest biochemical abnormality of mineral metabolism associated with CKD and high levels of FGF23 correlate with increased cardiovascular morbidity and left ventricular hypertrophy. Additionally, high FGF23 levels appear to be associated with vascular calcification, even though experimental studies have failed to confirm a direct pathogenic role for FGF23. Current standard therapies for CKD-MBD that address hyperphosphatemia and secondary hyperparathyroidism affect FGF23 levels differently; non-calcium based binders with or without concurrent use of dietary phosphate restriction reduce FGF23 levels while calcium-based binders do not affect or increase FGF23 levels. Active vitamin D sterols increase FGF23 levels whereas calcimimetic therapy decreases FGF23 levels. Thus, the appropriate therapy that will minimize the rise in FGF23 and prevent cardiovascular morbidity remains to be defined. Future studies are needed to assess whether targeting FGF23 may delay the development of secondary hyperparathyroidism as well as the progression of CKD, CVD and overall mortality.

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Figure 1:

Leading causes of death in children with chronic kidney disease (CKD) and in the general population. Reprinted with permission from Mitsnefes MM et al (2012) Journal of the American Society of Nephrology 23:578.

Figure 2:
Effect of current therapies on bone FGF23 expression CKD. *PTH* parathyroid hormone, *FGF23* fibroblast growth factor-23, *CKD* chronic kidney disease