The bone-renal axis in early chronic kidney disease: an emerging paradigm

John Danziger

Renal Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

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Introduction

The prevailing paradigm of mineral metabolism in chronic kidney disease (CKD) is based on two principles. First, as the tradeoff hypothesis suggests, phosphate retention leads to hyperparathyroidism, a response that maintains normal levels of serum phosphorus until relatively late in the CKD process [1–3]. In addition, it is believed that dietary deficiency of 25 hydroxylated vitamin D (25OHD) is important in early CKD, with the deficiency of the activated version, 1,25-hydroxylated vitamin D (1,25OHD), developing only in the later stages. Since the hydroxylation to 1,25OHD is considered to be a renal-dependent mechanism, the deficiency of this activated form is thought to reflect renal dysfunction. Various mechanisms have been impugned, including loss of renal mass, hyperparathyroidism, hyperphosphatemia and uremic toxins. These two principles have shaped the current KDOQI guidelines for the treatment of mineral metabolism in CKD.

However, more recent data suggest that this approach to mineral metabolism in CKD may not be wholly accurate. A recent large trial has illustrated that 1,25OHD levels begin to fall at the earliest stage of renal decline, before the development of hyperparathyroidism, hyperphosphatemia or any changes in renal mass [4].

Furthermore, although loss of 1-alpha hydroxylase has been impugned as the cause of 1,25OHD deficiency, animal data suggest that this enzyme is not decreased in CKD [5]. In addition, 1-alpha hydroxylase is expressed in diverse tissues beyond the kidney, potentially providing an extra-renal source of 1,25OHD [6]. It seems that the 1,25OHD decline in CKD is actually a much more complicated process than originally proposed.

The recent discovery of the phosphatonin, specifically FGF-23, has added an interesting dynamic to our understanding of mineral metabolism, and in many ways, challenges the previous paradigm [7]. FGF-23 has important effects on phosphorus and vitamin D metabolism. Produced by the bone, it induces renal phosphaturia, inhibits renal production of 1,25OHD and down regulates PTH release. In turn, the consequent fall in 1,25OHD modulates the bone to reduce FGF-23 production, completing a feedback loop. This newly recognized bone-renal axis helps maintain phosphorus homeostasis.

How this bone-renal axis is affected by renal dysfunction remains an area of great interest. Emerging data suggest that FGF-23 levels begin to rise early in CKD, possibly before changes in parathyroid levels, and may be the culprit for the early decline of 1,25OHD. Several recent CKD trials have illustrated the physiologic importance of this bone-renal axis, and support the notion that FGF-23 is responsible for the early 1,25OHD decline in CKD patients. This review article summarizes the latest information on the bone-renal axis, and how it is affected in CKD.

FGF-23

FGF-23 is a 251 amino acid protein, with a molecular weight of 26 000 Da, and is cleaved into carboxyl-terminal (aa 180–251) and amino-terminal portions (aa 1–24). It is produced primarily in the femur, calvaria and teeth [8]. It binds to a family of FGF receptors, likely requiring a transmembrane protein, klotho, to facilitate cell surface interaction [9]. Although FGF receptors are ubiquitously expressed, the downstream effects of FGF-23 have been localized to the kidney, parathyroid and pituitary glands, suggesting a primary role in these organs [10]. FGF-23 has two important and well-described effects on the kidney. Acting on the renal tubular epithelial cells, it down regulates the activity of the type IIa sodium phosphate co-transporter (NaPi2a), preventing phosphate reclamation by the tubules [11,12]. In addition, FGF-23 suppresses renal 1-alpha-hydroxylase expression, preventing 1,25OHD production by the kidney [13]. The net effect is an increase in phosphaturia and decrease in renal production of activated vitamin D. Recent animal data have shown a direct effect
of FGF-23 on the parathyroid gland, decreasing both PTH gene expression and secretion [14,15]. Whether this will hold true in human studies remains uncertain, with some finding a relationship between FGF-23 and PTH [16], and others none [17].

The biochemical effects of FGF-23 explain the phenotype seen in several recently recognized clinical conditions of FGF-23 abnormalities. Tumor-induced osteomalacia, X-linked hypophosphatemia and autosomal dominant hypophosphatemic rickets, all with markedly elevated FGF-23 levels, are characterized by urinary phosphate wasting, hypophosphatemia, reduced 1,25OHD levels and osteomalacia [18–20]. Conversely, mutations, either in FGF-23 itself [21] or its klotho coreceptor [22], lead to severe tumoral calcinosis, characterized by hyperphosphatemia, increased 1,25OHD levels and ectopic calcification. These syndromes outline the importance of FGF-23 in maintaining normal physiologic balance.

The importance of FGF-23 in normal physiology
The mechanisms of phosphorus homeostasis in normal individuals remain an area of active research. Although the difference between oral intake and renal and gastrointestinal excretion will ultimately determine net phosphate balance, how this relates to serum levels remains unanswerd, and there are few true ‘balance’ studies in the literature. Given the multiple mechanisms that can influence serum phosphate, including acidosis, hypocalcemia and insulin release, along with a large potential depot of phosphate within the skeleton, serum phosphate levels may not reflect net phosphate homeostasis. And interestingly, although initial studies suggested that increasing serum phosphate levels, by inducing hypocalcemia, triggered a PTH-driven phosphaturic response, more recent data suggest that these phosphaturic responses occur independently of changes in serum phosphate levels. Slatopolsky has shown that dietary phosphate can stimulate PTH release without any changes in serum calcium. This occurs with the duodenal infusion of phosphonoformate, a nonabsorbable phosphate analog, suggesting a direct signaling mechanism from the gastrointestinal tract to the kidney [23]. In a similar manner, Kumar and colleagues have shown that dietary phosphate induces renal phosphaturia independently of serum calcium, phosphate, PTH and FGF-23 [24], further supporting the notion of an entero-renal axis.

The role of FGF-23 in phosphorus metabolism of normal individuals has recently been investigated. In the most recent study, Wolf and colleagues illustrated that a 500-mg phosphorus meal leads to an immediate phosphaturic response, yet without changes in FGF-23 [25]. Others have also suggested that the phosphaturic response to increased dietary intake is independent of FGF-23 [26,27]. However, Portale and colleagues showed that longer periods of high phosphate intake lead to increasing FGF-23 production. In a well-performed inpatient dietary study, 9 days of a high phosphate diet lead to an increase of FGF-23, along with a decline of 1,25OHD [16]. Others have also found that several days of high phosphate intake, rather than one meal, lead to increased FGF-23 levels [17]. Interestingly, in both these studies, the FGF-23 increase was associated with decreasing 1,25OHD, supporting the in vitro data that FGF-23 regulates 1,25OHD production. This reduction in 1,25OHD likely decreases further absorption of dietary phosphate, completing an important feedback loop and reestablishing homeostasis.

In summary, the normal response to oral phosphate intake involves multiple pathways of response, involving the parathyroid gland, bone and the GI tract itself. As seen in Figure 1, phosphate intake stimulates the entero-renal axis, PTH release and skeletal production of FGF-23, without requiring changes in serum levels of phosphate or calcium. The timing and relative importance of each axis in the daily control of phosphate balance remains uncertain at this point, with some suggesting that the entero-renal is the first response system, with FGF-23 changes occurring only after longer exposure to high phosphate intake. Nevertheless, FGF-23 adds another important component to our emerging understanding of phosphorus control. How FGF-23 is affected by changes in renal function is reviewed below.

FGF-23 in early CKD
FGF-23 levels are markedly elevated in ESRD, yet the effect of subtle changes of renal function is not fully known [28]. Studies of FGF-23 in early CKD are limited by the difficulty of accurately estimating GFR in mild renal dysfunction. In addition, the C-terminal portion of FGF-23 may be filtered by the kidney, suggesting that the loss of renal filtration could lead to FGF-23 accumulation. Whether this is true for the intact larger molecule remains unanswered [17]. Currently, there are two types of assays. Both are ELISA tests: one detects only the C-terminal portion of FGF-23 and is usually reported in RU/ml, whereas the other assay detects the intact peptide and is reported in pg/ml. At this point, there is no reliable relationship between these different measurements, and the normal ranges in different populations have not been fully elucidated.

Nevertheless, despite these caveats, several recent studies give insight as to when FGF-23 levels begin to increase in CKD. Shigematsu and colleagues, using 24-h urine collections and cystatin-C measurements, suggest that FGF-23 levels begin to increase as the GFR falls to between 30 and 80 ml/min [29]. A more recent study by Wolf and colleagues
suggests that FGF-23 levels increase once the GFR falls below 60 cc/min [30]. The most recent study of FGF-23 in CKD provides a slightly different timeline, suggesting that FGF-23 levels do not change until stage IV CKD [31]. The relative paucity of diabetic CKD patients in this study, and a potential relationship of FGF-23 to glucose metabolism, might explain these differences to the above studies [32]. Nevertheless, despite such differences in the exact timeline of when FGF-23 levels begin to increase in CKD and how that change may be affected by comorbidities such as diabetes, it is apparent that FGF-23 levels do increase in early CKD.

Effect of increasing FGF-23 on 1,25OHD levels

Ultimately, the recognition that FGF-23 levels rise early in CKD, combined with its inhibition of 1,25OHD production, suggests that FGF-23 may have an important clinical role in vitamin D metabolism. Admittedly, this field remains an area of uncertainty, and research is confounded by a relatively short half-life of the 1,25OHD molecule, large variations in serum levels and lack of consensus regarding the definition of ‘normal’ 1,25OHD levels. At this point, it is unknown how changes in serum 1,25OHD relate to biologic activity of the vitamin D axis, and the emerging importance of local, paracrine activation of 25OHD further complicates this issue [33]. Nevertheless, despite the uncertainty of how to interpret 1,25OHD levels, emerging data have shown that these levels begin to change early in CKD, challenging the traditional teaching that places 1,25OHD deficiency as a relatively late complication. There is little data as to exactly how renal 1-alpha-hydroxylase inactivity develops; yet although this was traditionally attributed to loss of renal mass [34], recent animal data find that enzyme activity remains relatively unaffected by loss of renal tissue [5].

In a recently published large cross-sectional study of >1800 CKD patients, the timeline of 1,25OHD decline has been revisited [4]. Levin et al. have shown that 1,25OHD levels actually begin to decline at the very mildest decrements of eGFR. This decline precedes measurable abnormalities of PTH, calcium or phosphorus. Although some have suggested that this decline in the activated 1,25OHD might be related to deficient 25OHD substrate [35], Levin found no statistical relationship between the two forms, as suggested by previous investigators [36]. Of the patients with low 1,25OHD, ~45% had normal 25OHD stores and PTH levels. This large study suggests that the decline in 1,25OHD begins early in the course of CKD, and precedes PTH elevations.

In the studies of FGF-23 in early CKD, both Shigematsu and Wolf found that the rise in FGF-23 levels was associated with a decline in 1,25OHD. Indeed, in multivariate analysis, FGF-23 was the strongest determinant of 1,25OHD levels, and adjusting for FGF-23 extinguished the association between renal function and 1,25OHD levels. Furthermore, even in healthy individuals, the FGF-23 increase induced by a prolonged high phosphorus diet is associated with a decline in 1,25OHD levels [16,17]. Thus, although some have suggested that 1-alpha hydroxylase is suppressed by various metabolic abnormalities seen in CKD, such as metabolic acidosis [37], uremic toxins [38] or hyperphosphatemia [39], these are unlikely to account for the initial 1,25OHD decline when the GFR is relatively well preserved. Given these inconsistencies, and the well-documented inhibitory effect of FGF-23 on 1,25OHD production, it seems plausible that FGF-23 may be primarily responsible for the decrement of 1,25OHD levels in early CKD.

In summary, with a mild decrement of renal function, skeletal release of FGF-23 increases, presumably to maintain phosphate balance (Figure 2). Ultimately however, because of impaired renal phosphate clearance, FGF-23 production continues unabated, leading to 1,25OHD deficiency. Further studies to assess whether reducing FGF-23 levels in early CKD might prevent 1,25OHD deficiency are needed. Initial animal data suggest that although the use of phosphate binders reduces FGF-23 levels, it does not improve 1,25OHD levels [40]. This question has not been evaluated in human studies.

Systemic effects of FGF-23 elevation and 1,25OHD deficiency

The ramifications of FGF-23 elevation and 1,25OHD deficiency seen in early CKD are just beginning to be explored, yet emerging data suggest that these changes may be clinically significant. FGF-23 acts through a downstream signal, early growth response (Egr)-1, a novel molecule recently found to have widespread influence on atherosclerosis [9,41]. In addition, since FGF-23 modulates type II sodium phosphate (NaP) transporters expression in the kidney, it might also influence the ubiquitously expressed type III NaP transporters. These potential mechanisms could link FGF-23 to vascular calcification, and might explain why calcification begins so early in CKD [42,43], prior to the development of hyperphosphatemia. One recent study suggests that FGF-23 levels predict the presence of vascular calcification independently of calcium, phosphate or PTH [44]. FGF-23 levels have also been correlated with progression of renal disease [45]. Ultimately, answering whether FGF-23, acting directly, through downstream signals or by inhibiting 1,25OHD production, has effects on vascular calcification will require further studies.
Although FGF-23 provides a mechanistic link between the skeleton and the kidneys, there is a paucity of data investigating whether the FGF-23 elevation seen in early CKD is associated with underlying bone disease. A single study has found no relationship between FGF-23 levels and bone mass in ESRD, yet this study relied on bone densitometry and circulating biomarkers rather than histology [46], making the results difficult to interpret. Ultimately, given the small number of clinical studies that obtain bone histology in early CKD, combined with the existing literature with widely disparate findings about bone disease in early CKD [47,48], it is difficult to make any conclusions about FGF-23’s relationship to underlying bone histology. However, a recent clinical study has suggested that 1,25OHD, rather than PTH, bests correlates with loss of bone density in early CKD [49]. Furthermore, treatment with activated vitamin D prevents further bone loss [50]. These findings suggest that FGF-23’s inhibition of 1,25OHD formation may be more clinically important than previously recognized.

Conclusion

FGF-23 has emerged as an important moderator in the physiology of phosphate homeostasis. Dietary phosphate stimulates an entero-renal axis, PTH and FGF-23, which in turn, induces phosphaturia. FGF-23 decreases 1,25OHD production, preventing further dietary phosphate absorption, thus helping to reestablish phosphorous homeostasis. This axis is disturbed in the early stages of CKD, and the potential downstream effects of FGF-23 elevation and early 1,25OHD deficiency remain not fully described.

This phosphate centric paradigm is in keeping with the idea that phosphate homeostasis can be independent of calcium and phosphate levels, as well as the parathyroid gland, and raises further questions as to how the body regulates and responds to this important anion. Phosphate has multiple biologic activities, and subtle changes in serum levels seem to have widespread physiologic consequence [51]. Although the exact sensing mechanisms remain unknown, with a potential phosphate receptor hitherto undiscovered, the manner in which phosphate regulates FGF-23 may ultimately provide insight into phosphate’s control of other biologic systems.

In addition, the emergence of this bone-renal axis will undoubtedly raise therapeutic questions, and challenge the current principles of mineral metabolism in early CKD. Although vitamin D therapy remains the mainstay of therapy in early CKD, the importance of dietary phosphate in stimulating FGF-23 release, and thus in perpetuating 1,25OHD deficiency, suggests that phosphate restriction might be the most appropriate early intervention. As increasing attention shifts to early CKD management, an understanding of the full spectrum of mineral metabolism will require further careful studies of FGF-23 and its clinical effects.

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