Editorial Comments

The role of fibroblast growth factor 23 in renal disease

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FGF23 is a phosphate regulator in physiology and pathology

Activating mutations in the fibroblast growth factor 23 (FGF23) gene were identified as the cause of autosomal dominant hypophosphataemic rickets (ADHR) [1]. This secreted protein was later shown to play a role in both physiological and pathological phosphate handling.

FGF23 may be the key pathogenetic molecule in three different diseases with hypophosphataemia and inappropriate regulation of vitamin D metabolism. In ADHR, the mutations stabilize the FGF23 protein, which leads to increased circulating levels [2]. In X-linked hypophosphataemia (XLH), a disease caused by inactivating mutations of the PHEX gene, the loss of a membrane-bound protease results in increased circulating levels of FGF23 [3]. Also, in the paraneoplastic syndrome of tumour-induced osteomalacia (TIO), tumors secrete large amounts of FGF23 [3–5]. Thus, in three disorders of inorganic phosphate (Pi) wasting, FGF23 circulates in increased amounts, suggesting a pathological role for the molecule.

Evidence for a physiological role for FGF23 in Pi handling comes from animal models of altered FGF23 expression. Fgf23 null mice have hyperphosphataemia and increased 1,25(OH)2D3 levels [6], and normal mice treated with Fgf23-blocking antibodies respond by a significant elevation in Pi and 1,25(OH)2D3 levels [7]. Transgenic mice that overexpress FGF23 show a phenotype in concordance with XLH, ADHR and TIO [8–10]. Thus, these animals have reduced serum P1 and 1,25(OH)2D3 levels. Furthermore, FGF23 levels change in response to changes in dietary Pi intake in both rodents and humans [11–13], suggesting a physiological regulation of FGF23 production in response to Pi availability.

Phosphate homeostasis and vitamin D metabolism in renal disease

Normal levels of Pi in plasma are maintained within a relatively narrow range (0.8–1.3 mmol/l). Processes that regulate intestinal absorption and renal excretion of Pi balance this level. In fact, the renal reabsorption of Pi is the single most important mechanism for maintaining Pi levels within this range. The activity of the NPT2 transporter located in the proximal tubules of the kidney is responsible for ~70% of the overall Pi reabsorption, and several known hormonal mechanisms, most notably that of parathyroid hormone (PTH), affect its activity [14]. In renal disease, the ability of the kidney to filter Pi decreases with the loss of functional nephrons, whereas intestinal absorption is unaffected. Therefore, in the early stages of chronic kidney disease (CKD), hyperparathyroidism develops as a compensatory mechanism to control serum levels of Ca, Pi and 1,25(OH)2D3, but as the glomerular filtration rate (GFR) falls bellow 25 ml/min, a rise in serum Pi levels will occur. Indeed, hyperphosphataemia is a hallmark of end-stage renal disease (ESRD) [15].

The increase in Pi levels is coupled to the development of complications such as hyperparathyroidism and vascular calcifications, and studies have shown a clear rise in mortality in ESRD patients with uncontrolled hyperphosphataemia [16]. High circulating levels of PTH induce the metabolic bone diseases osteitis fibrosa cystica and mixed renal osteodystrophy and contribute to cardiovascular complications that increase morbidity and mortality.

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As CKD progresses, the renal ability to activate vitamin D decreases. This also contributes to the generation and maintenance of parathyroid hyperplasia and increased synthesis and secretion of PTH. These two problems, hyperphosphatemia and low vitamin D activity, are the rationale for traditional therapy of a P_i-restricted diet in combination with intestinal P_i binders and vitamin D substitution. The question then arises, will our novel understanding of FGF23 actions on P_i handling and vitamin D metabolism affect future care of patients with renal disease?

The role of FGF23 in the dysregulation of phosphate/calcium/vitamin D homeostasis in CKD

FGF23 levels are increased in renal disease

With the development of immunoassays for the measurement of FGF23 in human serum or plasma, it became possible to study its role in disorders of P_i homeostasis [3,17]. The first studies focused on patients with hypophosphatemia, but we also reported that patients with renal failure have elevated levels of FGF23 [3]. There are currently three commercially available FGF23 assays. Immutopics, Inc. (www.immutopics.com) provides the original C-terminal assay and a newly developed intact assay. The C-terminal assay detects full-length protein and, in addition, the C-terminal fragments that are the result of proteolytical cleavage at the R179 site of the intact protein. Kainos Laboratories, Inc. (www.kainos.co.jp) provides an assay that uses epitopes on either site of the cleavage site which results in measurements of full-length FGF23 levels. Several studies, using both the Immutopics’ C-terminal and Kainos’ full-length assay, have corroborated the initial findings and it is now clear that immunoreactive FGF23 is highly elevated in both CKD and ESRD (~1000-fold) patients. After a successful renal transplant, the levels drop to near normal [18–21].

One potential reason for the high circulating FGF23 levels could be a decreased renal clearance of FGF23 [18,23] levels correlated significantly with increased fractional excretion of P_i, suggesting that, in early CKD, FGF23 maintains its phosphaturic actions. Concomitantly, FGF23 inhibits 1α-hydroxylase activity, thereby lowering the 1,25(OH)_2D_3 levels. This results in a relative hypocalcaemia which drives PTH secretion. 1,25(OH)_2D_3 also has direct effects on the parathyroid, inhibiting PTH gene transcription and parathyroid hyperplasia by suppressing the expression of autocrine growth signals [26]. In the same model, one injection of neutralizing antibodies against FGF23 improved the deranged renal phosphate excretion and serum 1,25(OH)_2D_3 levels [25], thus suggesting that FGF23 may be a major culprit in the development of secondary hyperparathyroidism in CKD. As GFR further declines, daily excretion of P_i declines in the face of a rise in the phosphaturic hormones PTH and FGF23. This further aggravates parathyroid dysfunction since increased P_i levels themselves stimulate the parathyroid cell [15].

Medical therapies including active vitamin D agents are effective in most cases of early secondary hyperparathyroidism. However, resistance to medical therapy occurs in cases with developed hyperparathyroidism through changes in the biological properties of parathyroid cells. It is possible that the...
hyperparathyroidism itself contributes to the increased FGF23 activity since one study showed a significant drop in FGF23 levels after parathyroidectomy [27]. However, this occurred with a concomitant drop in [Ca × P] and P levels. Therefore, the results could be explained by changes in the systemic Ca/P balance.

Are FGF23 measurements clinically useful in CKD patients?

So far, very few data are available to answer this question. Nakanishi et al. investigated 103 patients with early stages of CKD and found that patients with increased levels of FGF23 were more likely to develop severe secondary hyperparathyroidism [28]. Also, dialysis patients with the highest levels of FGF23 were the least likely to respond to vitamin D therapy, suggesting that FGF23 measurements may help in the management of these patients [29].

In conclusion, it is plausible that increased FGF23 levels are, at least partially, responsible for the reduction of 1,25(OH)2D3 levels in the early phase of renal insufficiency and that this contributes to the development of secondary hyperparathyroidism in chronic and end-stage kidney disease. Future development of anti-FGF23 therapy may be potentially beneficial for patients with early CKD, and measurements of FGF23 levels in this group of patients may help in deciding on an optimal treatment strategy.

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References

Ren sanus in corpore sano: the myth of the inexorable decline of renal function with senescence

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Changing structure of the aging kidney

The first notion of an inexorable loss of renal mass with age goes back to uncontrolled observations suggesting that the average kidney weight decreases by up to 40% from young adulthood to senescence [1]. It must be emphasized, however, that in none of these early studies were individuals with comorbid conditions excluded. These findings therefore conflict with observations where no significant decrease in renal mass was found in elderly patients who had suffered traumatic death and in whom renal disease and/or important comorbid conditions were excluded [2]. Moreover, imaging studies investigating changes of renal size and structure showed only a modest decrease until the age of 75 years, whereas thereafter kidney size, calculated volume and parenchymal thickness were clearly lower [3]. Thus, loss of renal mass with aging is moderate, at least until the age of 70 years, and it seems to affect the renal cortex preferentially.

An important factor that correlates with age-associated changes of renal haemodynamics is thought to be glomerulosclerosis—as much as 30% of glomeruli were found to be hyalinized or sclerosed in apparently healthy elderly individuals [4]. The results of studies on glomerular number in the human kidney have shown a high degree of variability, however, and hence only minor glomerular obsolescence was found in the elderly who had suffered traumatic death [5, 6]. Kasiske [6] also demonstrated that the severity of systemic atherosclerosis has a major impact on the degree of age-related glomerulosclerosis. Based on these findings, it has been concluded that the presence of glomerulosclerosis is indicative of subclinical renal injury from comorbid conditions affecting renal structure.

Increase of renovascular resistance as a hallmark of renal vascular aging

Although several past studies documented a decrease in glomerular filtration rate (GFR) in men as well as in women, most of these studies did not differentiate clearly between the effect of comorbid conditions and the effect of aging per se on renal function [7]. For example, in the seminal study by Davis and Shock [8] virtually all of the examined individuals >70 years of age had generalized atherosclerosis and/or disabling diseases, such as cancer. More recent cross-sectional and prospective studies documented only a modest decrease or even no change of GFR in the healthy elderly [9,10]. In these and other studies, many important factors accelerating the age-related decline of renal function were identified, e.g. hypertension, atherosclerosis (particularly of the lower limbs),...