The role of fibroblast growth factor 23 in renal disease

Kenneth B. Jonsson

Department of Surgical Sciences, Unit of Orthopedic Surgery, Uppsala University, Uppsala, Sweden

Keywords: CKD; ESRD; FGF23; hyperparathyroidism; hyperphosphataemia; phosphate; renal failure; vitamin D

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), tumours 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 Pi 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 below 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.
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, hyperphosphataemia and low vitamin D activity, are the rationale for traditional therapy of a Pi-restricted diet in combination with intestinal Pi binders and vitamin D substitution. The question then arises, will our novel understanding of FGF23 actions on Pi 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 Pi homeostasis [3,17]. The first studies focused on patients with hypophosphataemia, 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 in the diseased kidney. Some evidence for this exists since C-terminal FGF23 immunoreactivity is present in urine in both healthy individuals and in ESRD patients with residual urine production [20]. A more intriguing reason could be that FGF23 synthesis is stimulated by the hyperphosphataemia per se. As mentioned above, several observations suggest that FGF23 production is stimulated by hyperphosphataemia. Rodents and humans given high Pi diets increase their FGF23 production, and patients with hyperphosphataemia due to hyperparathyroidism also have increased levels [11–13,22]. Also, immunoprecipitation of FGF23 in serum from ESRD patients detects increased full-length immunoreactivity [19,20]. Together, this suggests that the elevation is, at least partially, due to increased production of FGF23.

In simple regression models, FGF23 levels have been found to correlate strongly with parameters of renal function in different populations of CKD patients. Other correlations include serum Pi, [Ca × Pi] and PTH. It is also of interest that in patients with normal or slightly depressed GFR, inverse correlations with serum 1,25(OH)2D3 appear to be very strong, which is in line with the known potent inhibitory actions of FGF23 on renal 25-hydroxyvitamin D-1α-hydroxylase (1α-hydroxylase) [18,23].

So its up, does it matter?

Several models of systemic overexpression of FGF23 have demonstrated that high levels of circulating FGF23 will result in basically four important changes: (i) hypophosphataemia due to decreased renal Pi reabsorption; (ii) decreased 1,25(OH)2D3 levels due to inhibition of the 1α-hydroxylase and stimulation of the 25-hydroxyvitamin D-24-hydroxylase activity; (iii) development of parathyroid hyperplasia; and (iv) osteomalacia or rickets. All of these effects may be relevant to CKD.

Two important but hitherto unpublished studies highlight this hypothesis [24,25]. In experimentally induced renal failure in the rat, FGF23 levels started to rise 10 days after injection of a nephritis-inducing antibody which coincided with the rise of serum creatinine. At day 20, serum PTH and 1,25(OH)2D3 levels were significantly changed from baseline and, only later, at day 30, did Pi levels significantly increase. Before the rise in serum Pi levels, FGF23 levels correlated significantly with increased fractional excretion of Pi, suggesting that, in early CKD, FGF23 maintains its phosphaturic actions. Concomitantly, FGF23 inhibits 1α-hydroxylase activity, thereby lowering the 1,25(OH)2D3 levels. This results in a relative hypocalcaemia which drives PTH secretion. 1,25(OH)2D3 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)2D3 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 Pi declines, and in the face of a rise in the phosphaturic hormones PTH and FGF23. This further aggravates parathyroid dysfunction since increased Pi 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
control of the circulatory system. This control is achieved through the maintenance of a balance between the absorption of calcium and phosphorus. The balance is maintained through the regulation of the levels of FGF23 and 1,25(OH)2D3, which are influenced by the absorption of calcium and phosphorus, as well as by the synthesis of 1,25(OH)2D3, which is mediated by the vitamin D receptor. Consequently, the levels of FGF23 and 1,25(OH)2D3 are closely related, and their levels can be influenced by the levels of calcium and phosphorus. Therefore, the levels of FGF23 and 1,25(OH)2D3 can be used as an indicator of the balance between calcium and phosphorus, which is important for the control of the circulatory system.

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doi:10.1093/ndt/gfh710

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

Danilo Fliser

Hannover Medical School, Hannover, Germany

**Keywords:** atherosclerosis; elderly; glomerulosclerosis; hypertension; renal function; renovascular resistance

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),

Correspondence and offprint requests to: Danilo Fliser, MD, Associate Professor of Medicine, Department of Internal Medicine, Hannover Medical School, Carl-Neuberg-Strasse 1, 30265 Hannover, Germany. Email: fliser.danilo@mh-hannover.de

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