FGF23 and mineral metabolism, implications in CKD-MBD

Mariano Rodríguez¹, Ignacio López², Juan Muñoz¹, Escolástico Aguilera-Tejero², Yolanda Almaden¹

¹ Servicio de Nefrología. Hospital Universitario Reina Sofía, REDINREN, IMIBIC, Córdoba
² Departamento de Medicina y Cirugía. Facultad de Veterinaria. Córdoba

Nefrología 2012;32(3):275-8

The regulation of mineral metabolism is achieved through a complex interaction of hormonal factors and target organs. Before the discovery of FGF23 we believed that the regulation of serum calcium and phosphate was mainly the result of changes in PTH and vitamin D acting on bone, kidneys and intestine. Parathyroids and kidneys were responsible for the production of PTH and 1,25(OH)2D3 respectively. Presently we know that FGF23 is produced by bone so the bone is not longer just a target organ but an active endocrine organ that participate in the regulation of mineral metabolism by sending signals through FGF23. Nephrologists are knowledgeable about the regulation of calcium and phosphate otherwise it is difficult to understand and manage the disturbances of mineral metabolism that are always present in patients with CKD. Changes in mineral metabolism in CKD are now described as chronic kidney disease-mineral and bone disorders (CKD-MBD).¹ The pathology derived from CKD-MBD includes not only bone abnormalities but cardiovascular disease with a devastating prevalence of vascular calcification. The severity of CKD-MBD is associated with increased mortality in CKD patients.

THE REGULATION OF SERUM PHOSPHATE

The regulation of calcium and phosphate was only partially understood until the discovery of FGF23. FGF23 increases phosphaturia a reduces the production of 1,25(OH)2D3 (Figure 1). Let’s think in a situation of hypocalcemia; the parathyroids recognize the decrease in serum calcium, elevated PTH acts on bone to increase the exit of calcium, but the calcium release from bone is also accompanied by the release of phosphate. The PTH acts also in kidneys increasing the tubular re-absorption of calcium so the calcium released by bone is kept in the extracellular space. The PTH produces phosphaturia so the phosphate released by bone does not build up in the extracellular space. This may not be sufficient to bring the calcium up to normal, therefore the elevated PTH stimulates renal production of 1,25(OH)2D3 which in turn stimulates intestinal calcium absorption. This regulatory system appears to be adequate to control serum calcium, however 1,25(OH)2D3 not only increase gut absorption of calcium but also the absorption of phosphate. It does not seem logical that a synchronized hormonal response to correct hypocalcemia had to be concluded with an excess of phosphate. FGF23 modulates the production of 1,25(OH)2D3 and the accumulation phosphate. Both high phosphate and 1,25(OH)2D3 stimulate the production of FGF23 which feeds back on the production of 1,25(OH)2D3 and induces phosphaturia. Thus the presence of FGF23 enables the system to restore the serum calcium without the trouble of phosphate accumulation (Figure 2).

PRODUCTION AND ACTIONS OF FGF23

FGF23 is a 32-kDa (251 amino acid) protein produced by osteocytes and osteoblasts which makes the bone an endocrine organ that communicates with other organs involved in mineral homeostasis. FGF23 acts on its receptor complex, klotho-FGFR1, in the kidney to cause phosphaturia and to decrease calcitriol synthesis.²⁻⁵ FGF23 induces phosphaturia by suppressing the expression of the Na-Pi cotransporters 2a and 2c in the brush border of renal proximal tubules. FGF23 suppresses renal production of 1,25(OH)2D3 by inhibiting 1α-hydroxylase (CYP27B1) activity which produces 1,25(OH)2D3 from 25(OH)D and also by increasing 24-hydroxylase activity which inactivates the 1,25(OH)2D3.²⁻⁶ Therefore the lack of FGF23, as in the FGF23 null mouse (FGF23⁻/) causes hyperphosphatemia and high levels of 1,25(OH)2D3 a situation that produces extrasosseous calcification.⁷ The endocrine action of FGF23 is dependent upon its binding and activation of the klotho-FGFR1 complex,⁷ therefore the absence of klotho as in the klotho⁻/⁻ mouse produces a phenotype similar to the FGF23⁻/⁻ mouse, elevation of phosphate and 1,25(OH)2D3 accumulation.
Hormonal response to hypocalcemia and the role of FGF23 to maintain phosphate balance. Ca: calcium; FGF23: fibroblast growth factor 23; P: phosphate; PTH: parathyroid hormone.
Nephrologists frequently ask whether or not it is advantageous to have elevation of FGF23. Certainly FGF23 helps to control phosphate balance but contributes to vitamin D deficiency. Furthermore recent experiments demonstrate a direct negative effect of FGF23 on the cardiovascular system. The fact that FGF23 is elevated indicates that the failing kidney needs the "help" of a phosphaturic hormone able to handle the phosphate load. Therefore the increase in FGF23 implies inadequate phosphate control. In patients with CKD a better control of phosphate is associated with a decrease in FGF23. Another question is whether FGF23 is a clinical useful tool to assess phosphate balance in CKD patients. FGF23 levels may not reflect acute changes in dietary phosphate; however high serum level of FGF23 may reveal a long period of positive phosphate balance. Certainly, clinical studies will have to be performed to prove the usefulness of FGF23 as a marker of phosphate balance. A considerable amount of clinical studies have shown that a high FGF23 level is independent predictor of mortality, progression of renal disease, left ventricular hypertrophy, vascular dysfunction, renal transplant outcome and experimental work have shown that FGF23 causes ventricular hypertrophy directly.

FGF23 IN ADVANCED SECONDARY HYPERPARATHYROIDISM

In dialysis patients serum FGF23 levels are markedly increased and they are positively correlated with serum PTH levels and with serum levels of phosphate. One may assume that the sustained accumulation of phosphate is the cause of a direct correlation between PTH and FGF23. Nevertheless, given the fact that FGF23 inhibits parathyroid function it is unexpected to observe a parallel increase in the serum concentrations of FGF23 and PTH. Experimental work in uremic rats with secondary hyperparathyroidism revealed that administration of FGF23 did not reduce serum levels of FGF23 in uremic rats; and, in vitro hyperplastic parathyroid glands from uremic rats did not respond to FGF23. Further experiments showed that hyperplastic parathyroid glands presented low expression of both FGF receptors and klotho. This results suggests a resistance of hyperplastic parathyroid gland to the inhibitory action of FGF23. Similar results were obtained by other group in another rat model of renal insufficiency. In parathyroid glands obtained from patients with advanced secondary hyperparathyroidism Klotho and FGFRIe expression decreased significantly particularly in glands with nodular hyperplasia.

FGF23 AFTER RENAL TRANSPLANT

After renal transplant many patients maintain high FGF23 levels suggesting that FGF23 may be the cause of post-transplant hypophosphatemia with a relative vitamin D deficiency. Before transplantation FGF23 levels are very high and after kidney transplantation the excess of FGF23 acts to promote phosphaturia and suppress 1,25(OH)2D production. It is not clear why FGF23 secretion is maintained after transplantation despite hypophosphatemia.

Conflict of interest


REFERENCES


