Role of FGF23 in Kidney Transplantation

Xoana Barros and Jose-Vicente Torregrosa*

Department of Nephrology and Renal Transplant, Hospital Clinic, Barcelona, Spain

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Introduction

Mineral bone metabolism disorders in Chronic Kidney Disease (CKD) has been traditionally related to alterations in serum levels of calcium and phosphate, calcitriol deficiency and subsequent development of secondary hyperparathyroidism. Recently, a new kind of molecules, named “phosphatonin”, has been described as an implicated factor, being fibroblast growth factor 23 (FGF23) the best known of them.

This bone-derived hormone regulates phosphate and calcitriol metabolism decreasing their serum levels in healthy subjects, CKD and renal transplant patients.

In this review, we summarize recent findings on FGF23 in the pathogenesis of bone-mineral disorders in CKD, emphasizing its role in kidney transplant recipients.

Fibroblast Growth Factor 23

FGF23 becomes to FGF19 subfamily, one of the 7 subfamilies of fibroblast growth factors (FGFs), formed by FGF19, FGF21 y FGF23. As a result of lower affinity for extracellular heparan sulfate, FGF23 becomes to FGF19 subfamily, one of the 7 subfamilies of fibroblast growth factors (FGFs), formed by FGF19, FGF21 y FGF23.

FGF23 is a 251 glycoprotein. The N-terminal portion of the peptide binds to FGF23-R in tissues and the C-terminal portion to Klotho; thus, both the N and C terminal portions are participants in the hormone’s activity [4].

The negative regulation of the PTH seems not to exert its effect in CKD animal models [10,11], probably in relation to a depressed expression of Klotho and FGF23-R in hyperplasic parathyroid glands from uremic patients, which suggest a resistance to FGF23 action [12,13].

Regulation of FGF23

Expression of Klotho and FGF23-R in hyperplasic parathyroid glands from uremic patients, which suggest a resistance to FGF23 action [12,13].

1,25-dihydroxyvitamin D stimulates FGF23 secretion by a vitamin D-response elements present in the FGF23 promoter as a counter-regulatory effect to increase renal phosphate clearance in the setting of enhanced gastrointestinal phosphate absorption [17,18].

A clinical study also showed that administration of calcitriol to diastysis patients results in increased serum FGF23 levels [19].

Determination of FGF23

Three assays for FGF23 are available: one assay to measure C-terminal FGF23 (cFGF23) (Immunotopics, San Clemente, CA, USA); a second assay to measure intact FGF23 (iFGF23) (Kainos, Tokyo, Japan); a third assay from Immunotopics to measure iFGF23, which has shown a high inter-assay variability, so it is preferably not used [20].

All three assays are sandwich enzyme-linked immunosorbant assays.

cFGF23 should be measured in plasma while Kainos assay recommends measuring iFGF23 in serum.

The antibodies in the C-terminal assay are directed against the C-terminal portion of the peptide.

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C-terminal region of FGF23, and therefore detect both C-terminal fragments and intact FGF23. The antibodies in the intact assay are described as being directed against the C-terminal and the N-terminal region of FGF23 and may therefore detect only iFGF23.

In vitro experiments showed that FGF-23 protein is proteolytically processed between Arg179 and Ser180, and only full-length FGF23 showed sufficient biological activity to cause hypophosphatemia [21].

Full length FGF-23 is present in the normal circulation and the reference range for healthy adults is 10–50 pg/ml, as established from 104 controls [22] or 29.7 +/- 20 pg/ml from 118 healthy pediatric controls [23]. The reference range of the C-terminal assay was reported to be less than 120–150 RU/ml [24,25].

There is a good correlation between cFGF23 and iFGF23 assays [23,25] except for FGF23 levels of less than 120 RU/ml by C-terminal assay [25]. The fact that the differences between two assays were found only in lower levels of FGF23 makes us think that both assays are comparable in CKD, dialysis and transplant patients when levels are above normal range.

**FGF23 and CKD**

An increase of FGF23 in early stages of CKD has been observed in several studies. The early increase in the production of FGF-23 and the fact that development of hypophosphatemia does not occur until advanced stages of CKD might be explained due to resistance to phosphaturic effect of FGF-23 as the number of nephrons decreases, with the consequent increase of FGF23 with decreasing glomerular filtration rate [26,27].

The relationship between mortality and hypophosphatemia [28] would suggest that increased FGF23 may have a beneficial effect by delaying the accumulation of phosphate in CKD. But current evidence based medicine shows FGF23 is not only a biomarker to asses phosphate load, but also a predictor of progression of CKD [29], development of refractory hyperparathyroidism [30,31] or mortality [32,33].

Several observational studies in adults suggest that increased FGF23 is independently associated with arterial stiffness, endothelial dysfunction and increased ventricular mass in elderly population, CKD and hemodialysis patients [34-38].

Recent clinical trials have shown that high FGF23 level was an independent predictor of mortality in both incident and prevalent dialysis patients independently of serum phosphate levels [32,33].

**Post-transplant alterations of bone mineral metabolism**

The extreme elevations of FGF23 in dialysis patients, who can manifest 100 to 1000-fold elevations above the normal range [26], sets the stage for tertiary FGF23 excess in the event of a kidney transplant.

After transplantation, there are some mineral alterations than could be related to FGF23 effects:

- Hypophosphatemia caused by inappropriate urinary phosphate wasting affects up to 90% of patients [39,40] in the early period following kidney transplantation and 6–27% of patients have persistently low serum phosphate levels for months to years [41,42]. In these patients, hypophosphatemia can contribute to complications such osteomalacia, muscle weakness and gradual bone demineralization, which in combination with steroids could predispose patients to an increased risk of fracture. Nephrocalcinosis has been proposed as a mechanism of phosphorus-associated renal toxicity [43-45], and post-transplant hypophosphatemia and hypercalcemia were associated with calcium and phosphate deposition in renal allograft [46].

Postransplant hypophosphatemia has been traditionally linked to persistence of severe secondary hyperparathyroidism from the dialysis period into post-transplant period (tertiary hyperparathyroidism) but inappropriate urinary phosphate wasting can occur despite low levels of PTH and it can persist after elevated PTH levels have normalized [47,48]. In addition, in most cases, hypophosphatemia following kidney transplantation is isolated and dissociated from concomitant hypercalcemia, which is the cardinal manifestation of hyperparathyroidism in the setting of normal renal function.

- Calcitriol deficiency persists in patients with a functioning allograft for several months following transplantation despite excessive PTH, a healthy allograft and hypophosphatemia, each of which should stimulate its production.

Currently, persistent excess of FGF-23 after transplant has been suggested as the main contributing factor to post-transplant hypophosphatemia and calcitriol deficiency despite a functioning allograft and the presence of persistent hyperparathyroidism.

**FGF23 and Kidney Transplant**

Data collectively suggest that although FGF23 levels decline to a range that is comparable to patients with CKD, ongoing elevations above the normal range contribute to early post-transplant hypophosphatemia, loss of bone mineral density, survival and allograft outcome.

**Hypophosphatemia:** Since 2006 several groups have published observational studies about FGF23 excess and post-transplant hypophosphatemia.

The first report studied 27 patients undergoing living donor kidney transplantation with a follow-up period of 6 months. 85% of patients developed hypophosphatemia (serum phosphate <2.6 mg/dL) and 37% severe hypophosphatemia (serum phosphate <1.5 mg/dL), without episodes of hypercalcemia in any recipient. cFGF23 (Immunotopics, San Clemente, CA, USA) decreased substantially during the first week following transplantation (means: 1218 +/- RU/mL to 557 +/- 559 RU/mL). FGF23 was independently associated with post-transplant serum phosphate levels, urinary fractional excretion of phosphate (FEPO4), and 1,25-dihydroxyvitamin D levels (inversely). In contrast, PTH was not independently associated with any of these parameters [39].

This association between FGF23 levels at time of transplant with post-transplant phosphate levels and FEPO4 was also described in following studies [39,42,49,50].

One year later, Evenepoel et al. [40] published another single-center prospective observational study including 41 recipients of a deceased donor kidney transplant with a follow-up period of 3 months. 90% of patients developed hypophosphatemia (serum phosphate <2.3 mg/dL). Serum phosphate levels reached a nadir of 1.48 ± 0.48 mg/dL at day 27 +/- 19 posttransplantation, being pretransplant iFGF23 the only significant predictor. Median levels of iFGF23 (Kainos, Tokyo, Japan) decreased from 1270 (498-5418) ng/L to 56 (43-89) ng/L at month three, remaining above normal range (>= 50 ng/L) in 61% of recipients.

In a subsequent longitudinal study [41], 50 renal transplant recipients (RTR) with a GFR above 30ml/min at month 12 after transplantation were compared with GFR-matched no transplanted CKD patients. Despite tremendous decrease post-transplantation, FGF23 levels at month 3 remained significantly higher in RTR as compared with CKD patients matched for GFR. However, afterwards, FGF23 levels and urinary fractional excretion of phosphate decline to reach similar concentrations to those CKD counterparts at month 12,
although these remained significantly elevated compared to normal volunteers. Another study showed normal or comparable levels of FGF23 for renal function after a year [42,51].

**Bone mineral density (BMD):** Relation between excess of FGF23 and BMD loss was assessed in 127 incident renal transplant recipients [52]. They found a weak association between high serum FGF23 levels and low PTH levels and risk for increased BMD loss during the first post-transplant year. And these associations were independent of serum phosphate levels at month three, thus it might be that BMD changes could be independent to hypophosphatemia.

**Survival and allograft loss:** In a prospective cohort of 984 stable kidney transplant recipients with a median follow up of 37 months (35 to 39 months) elevated levels of C-terminal FGF23 were independently associated with increased risk of all-cause mortality and allograft loss. C-terminal FGF23 was lower than in previous reports of CKD patients with comparable estimated GFR, but it could be explained because serum samples were assessed instead of plasma [53].

**Therapeutic alternatives**

Oral phosphate replacement and administration of calcitriol may be ineffective when hypophosphatemia is severe because these are the primary stimuli of FGF23 secretion and would be expected to raise FGF23 levels further. In addition, these therapies could theoretically contribute to nephrocalcinosis by markedly increasing phosphaturia [55].

A recent report suggested that cinacalcet, a calcimimetic that decreases serum PTH levels, might improve the metabolic parameters and reduce the doses of phosphate and calcitriol required to treat patients with X-linked hypophosphatemia [54]. However, additional studies are needed to determine the long-term efficacy in kidney transplant recipients.

Anti-FGF23 antibodies improve hypophosphatemia and calcitriol deficiency in animal studies of Hyp mice [56,57]. FGF23 blockade should be a target of therapy in transplant recipients with hypophosphatemia or even normal serum phosphate levels if FGF23 excess is found to contribute directly to bone loss, long-term allograft dysfunction, or cardiovascular disease, as we previously hypothesized.

**Conclusions**

In renal transplanted patients, recent data seems to emphasize the role of FGF23 excess in the pathogenesis of early posttransplant hypophosphatemia and its association with adverse clinical outcomes like loss of bone mineral density, survival and graft loss.

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