EDITORIAL COMMENT

FGF23 in kidney transplant: the strange case of Doctor Jekyll and Mister Hyde

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Abstract

During the last decade, a new view into the molecular mechanisms of chronic kidney disease-mineral bone disorder (CKD-MBD) has been proposed, with fibroblast growth factor 23 (FGF23) as a novel player in the field. Enhanced serum FGF23 levels cause a reduction in serum phosphate, together with calcitriol suppression and consequent hyperparathyroidism (HPT). In contrast, reduced serum FGF23 levels are associated with hyperphosphatemia, higher calcitriol levels and parathyroid hormone (PTH) suppression. In addition, serum FGF23 levels are greatly increased and positively correlated with serum phosphate levels in CKD patients. In this population, high serum FGF23 concentration seems to predict the occurrence of refractory secondary HPT and to be associated with higher mortality risk in incident haemodialysis patients. In living-donor kidney transplant recipients, a faster normalization of FGF23 and phosphate levels with a lower prevalence of HPT, may be considered a major pathway to investigate.

Key words: CKD-MBD, FGF23, PTH, secondary hyperparathyroidism

Kidney transplantation is the best renal therapy for eligible end-stage renal disease (ESRD) patients. Kidney transplant recipients have better survival rates than dialysis patients, with lower dialysis-related morbidity, reduced cardiovascular risk, improved quality of life and reduced health economic costs [1, 2].

Due to an organ shortage, however, most patients have to wait while on dialysis for a considerable period of time prior to transplantation, with unfavourable consequences such as compromised graft and patient survival. Living-donor kidney transplantation and pre-emptive kidney transplant, defined as transplant before dialysis, are valid options to expand the organ pool and reduce the waiting time of patients on the waiting list, and the short- and long-term outcomes seem to be favourable compared with deceased-donor kidney transplantation [3]. Abnormalities in serum calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23) and vitamin D levels occur early in the course of chronic kidney disease (CKD) to become a widespread complication in patients with advanced renal disease [4]. Mineral and bone disorders are common in patients who have undergone kidney transplantation [5]. Although for a long time it has been supposed that successful kidney transplantation to a large extent solves the problem of CKD-mineral and bone disorder (CKD-MBD), mineral and bone disorders are common in kidney transplant recipients, changing only its phenotype. These conditions are caused, to a large extent, by previous bone damage and CKD-MBD persisting after transplantation, de novo CKD-MBD and immunosuppressive therapy. The contribution of each component to the overall scenario changes over time.

In long-term kidney transplant recipients with a well-functioning graft (eGFR >30–45 mL/min), high PTH levels can still be observed in 30–60% at 1 year after transplantation [6]. Post-transplant hyperparathyroidism can be differentiated into a maladaptive response (‘persistent’ hyperparathyroidism) versus a compensatory–adaptive response (de novo hyperparathyroidism).
‘Persistent’ hyperparathyroidism results from pre-existing CKD-MBD with secondary hyperparathyroidism, likely complicating post-transplant follow-up with hypercalcaemia, hypophosphataemia, fracture risk [7], vascular calcification [8] and loss of graft function [9]. Conversely, de novo hyperparathyroidism results in elevated PTH levels, along with deterioration of graft function, to maintain normophosphataemia and normocalcaemia.

Serum levels of the bone-derived phosphaturic hormone FGF23 are extremely high in dialysis patients, reaching levels that can be 1000-fold above the normal range [4, 10], in an attempt to counteract hyperphosphataemia, producing a decrease of 1,25-dihydroxyvitamin D. Additional triggers for FGF23 in late CKD are secondary hyperparathyroidism and Klotho deficiency.

FGF23 levels decline 3 months after transplantation but remain higher than in CKD patients matched for eGFR. Further reductions in FGF23 levels were repeatedly observed over longer follow-up, approximating normal levels 1–3 years after transplantation [6, 11].

In contrast, in a cross-sectional observational study of 279 maintenance kidney recipients with CKD (stages 1–4), Sanchez Fructuoso et al. [12] found that FGF23 levels increased in long-term kidney graft recipients, even in the early stages of CKD, maybe as a result of previous chronic phosphate retention stimulating the secretion of FGF23. These findings support the notion of a persistent (or tertiary) hyperphosphatonimic that in the early post-transplant period mainly reflects previous mineral and bone disorders while in the long term mirrors renal function that is the major determinant of FGF23 serum levels, similar to what is observed in CKD patients. The interactions between FGF23 and PTH are very complex and cause a decrease in vitamin D metabolism. FGF23 and PTH mutually regulate each other in a negative feedback loop where PTH stimulates FGF23 production and FGF23, in turn, suppresses PTH synthesis acting via the Klotho–FGF receptor 1 (FGFR1) complex in the parathyroid gland and in the absence of Klotho via a phosphoinositide-specific phospholipase C gamma (PLCγ)-dependent activation of the calcineurin–nuclear factor of activated T cells (NFAT) pathway [13]. The mitogen-activated protein kinase (MAPK) pathway is likely the dominant pathway in physiology, although its relative contribution is unknown.

Hypophosphataemia is present in up to 90% of transplant recipients [14], with the majority (70%) of the cases being mild to moderate (serum phosphate level >1.5 to <2.3 mg/dL); phosphate levels remain low for longer than in patients with CKD matched for the GFR [15]. Acute or chronic post-transplant hypophosphataemia may cause detrimental effects. In the early post-transplant period, when serum phosphate levels are lower, muscle weakness may occur [16], whereas effects of chronic hypophosphataemia are less clear. There are few studies on the parallel effects previous mineral and bone disorders in kidney transplant recipients, until 6 months after transplantation. The pre-transplantation FGF23 level was the main predictor of urinary phosphate excretion and serum phosphate levels in the early post-transplantation period, whereas serum phosphate levels in the sixth month were mainly influenced by PTH at that time. In this study, FGF23 levels decreased within the reference range in 50% of patients in the first month after transplantation and in 77% of patients with pre-emptive transplants. Kidney function improvement was associated with a reduction in FGF23 levels after transplantation.

Prasad et al. [21] addressed this issue by analysing at 1, 3 and 12 months the post-transplantation changes in FGF23, iPTH and phosphate levels in 63 ESRD patients who underwent living-donor transplantation. FGF23 and phosphate levels remained above the normal range in 36.5 and 27% of patients, respectively, at 1 month, in 15.9 and 8%, respectively, at 3 months and in none of the patients at 12 months post-transplantation, while only 11% of patients had persisting hyperparathyroidism 12 months post-transplantation. The authors postulated that two factors were responsible for these results, i.e. the shorter dialysis vintage prior to transplantation and the inclusion of only living-donor transplantation in the study, as renal function and mineral metabolism normalize relatively faster than in deceased-donor transplantation [22]. In kidney transplant recipients, the pathogenesis underlying the imbalance between PTH and FGF23 levels is probably multifactorial, involving persisting bone abnormalities and the effects of immunosuppressive therapy. Except for mycophenolate, immunosuppressive drugs stimulate FGF23 production, impair vitamin D metabolism and consequently increase PTH production [23, 24]. Speculatively the clinical use of calcineurin inhibitors (CNIs) that block calcineurin signalling may increase the susceptibility to develop or may aggravate pre-existing hyperparathyroidism in patients with reduced Klotho expression, such as in kidney transplant recipients [13]. Nevertheless, Prasad et al. demonstrated
that FGF23 levels normalized and the prevalence of hyperparathyroidism was lower (when compared with deceased-donor kidney recipients) at 12 months after transplantation, even though all living-donor kidney transplant recipients underwent immunosuppressive schedules, including steroids and CNIs. This is an important finding of this study, but unfortunately there are only a few experimental studies on this specific issue, and the feasibility of clinical evaluations is hampered by the inability to assess the effects of the individual drugs, as they are always administered in combination.

Furthermore, the authors showed that the percentage decrease in FGF23 and iPTH levels was significantly associated during the entire follow-up. This interesting finding confirms the close interplay existing between FGF23 and PTH and suggests a substantial integrity/recovery of the receptor and signalling pathways in this cohort of living-donor kidney transplant recipients.

The study by Prasad et al. [4, 25, 26] independently associated with an increased risk of cardiovascular and all-cause mortality and allograft loss [10, 27]. There are several possible mechanisms that may explain this finding. In vitro and in vivo studies have shown that 1,25-dihydroxyvitamin D decreases T cell activation and proliferation and inhibits dendritic cell differentiation and maturation, while its supplementation may have beneficial effects on chronic allograft nephropathy [24]. FGF23-mediated suppression of 1,25-dihydroxyvitamin D is one possible mechanism through which high FGF23 levels could contribute to allograft loss. In kidney transplant recipients, phosphate depletion, in conjunction with high PTH levels, vitamin D deficiency and chronic steroid use, might worsen skeletal demineralization and contribute directly to fractures, which in turn could increase the risk of mortality. High levels of FGF23 may impair neutrophil recruitment, which could jeopardize antibacterial defence [28]. Moreover, if chronically increased FGF23 levels can directly stimulate FGF receptors in the kidneys and heart, independent of Klotho [29], FGF23 could mimic the known effects of FGF2 to induce glomerulosclerosis and cardiac hypertrophy and thereby contribute directly to chronic allograft nephropathy and death [30, 31, 32]. Finally, FGF23 is associated with endothelial dysfunction and atherosclerosis in patients with high, or even normal, serum phosphate levels [33, 34]. Post-transplant hypophosphataemia and hypercalcaemia were associated with calcium and phosphate deposition in renal allografts [35], although human studies have shown conflicting results on whether renal calcification contributes to worse allograft outcomes.

The study of Prasad et al. confirms once again that the post-kidney transplant period should be considered a unique phase in the natural history of disordered mineral metabolism associated with CKD that requires dedicated investigation. In living-donor kidney transplant recipients, faster normalization of FGF23 and phosphate levels, in addition to a lower prevalence of hyperparathyroidism, if confirmed in larger studies, could be one of the possible pathways towards better outcomes in living-donor kidney transplant recipients.
Conflict of interest statement

None declared.

(See related article by Prasad et al. FGF23 is associated with early post-transplant hypophosphataemia and normalizes faster than iPTH in living donor renal transplant recipients: a longitudinal follow-up study. Clin Kidney J (2016) 9: 669–676.)

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