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Elevated Fibroblast Growth Factor 23 Levels As a Cause of Early Post–Renal Transplantation Hypophosphatemia

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ABSTRACT

Background. Hypophosphatemia is a common complication after renal transplantation. Hyperparathyroidism has long been thought to be the cause, but hypophosphatemia can persist after high parathyroid hormone (PTH) levels normalize. Furthermore, calcitriol levels remain inappropriately low after transplantation, suggesting that mechanisms other than PTH contribute. Fibroblast growth factor 23 (FGF-23) induces phosphaturia, inhibits calcitriol synthesis, and accumulates in chronic kidney disease. We performed prospective study to investigate if FGF-23 early after renal transplantation contributes to hypophosphatemia.

Methods. We measured FGF-23 levels before and at 1, 2, 4, and 12 weeks after transplantation in 20 renal transplant recipients. Serum creatinine, calcium (Ca), phosphate (Pi), intact PTH (PTH), and 1,25-dihydroxy vitamin D ($1,25(OH)_2$VitD) were measured at the same time.

Results. FGF-23 levels decreased by 97% at 4 weeks after renal transplantation (PRT) (7,471 ± 11,746 vs 225 ± 295 pg/mL; $P < .05$) but were still above normal. PTH and Pi levels also decreased significantly after renal transplantation, and Ca and $1,25(OH)_2$VitD slightly increased. PRT hypophosphatemia of <2.5 mg/dL developed in 15 (75%) and 12 (60%) patients at 4 weeks and 12 weeks respectively. Compared with nonhypophosphatemic patients, the levels of FGF-23 of hypophosphatemic patients were higher (303 ± 311 vs 10 ± 6.9 pg/mL; $P = .02$) at 4 weeks PRT. FGF-23 levels were inversely correlated with Pi ($r^2 = 0.406$; $P = .011$); PTH was not independently associated with Pi ($r^2 = 0.132$; $P = .151$).

Conclusions. FGF-23 levels decrease dramatically after renal transplantation. During the early PRT period, Pi rapidly decreased, suggesting that FGF-23 is cleared by the kidney, but residual FGF-23 may contribute to the PRT hypophosphatemia. FGF-23, but not PTH levels, was independently associated with PRT hypophosphatemia.

HYPOPHOSPHATEMIA is a common complication of renal transplantation (RT).[1] Persistently increased levels of parathyroid hormone (PTH) due to secondary hyperparathyroidism associated with chronic kidney disease (CKD) have long been thought to be the cause of post–renal transplantation (PRT) hypophosphatemia, ie., tertiary hyperparathyroidism.[2] However, hyperparathyroidism does not appear to be the only mechanism of inappropriate urinary phosphate (Pi) wasting. Hypophosphatemia can persist after elevated PTH levels have normalized.[3] Furthermore, calcitriol levels are often inappropriately low after RT despite normal allograft function, hypophosphatemia, and hyperparathyroidism, which should stimulate increased calcitriol synthesis.[4] Therefore, mechanisms other than PTH contribute to the hypophosphatemia, uri-

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nary Pi wasting, and inappropriately low calcitriol levels after RT.

Fibroblast growth factor (FGF-23) has been shown to inhibit renal 1-α hydroxylase, lower calcitriol synthesis, and cause renal Pi wasting.[5] FGF-23 is a phosphatonin which plays a key role in the pathogenesis of inherited and acquired phosphorus wasting disorders. It has also been shown to have a physiologic role in normal phosphorus homeostasis. Serum concentrations of FGF-23 are known to be elevated in patients with CKD. Although the rise in serum FGF-23 may be due to its reduced renal clearance, the results from several studies have suggested that a progressive rise in FGF-23 may occur with the progression of CKD, possibly contributing to decreased 1,25-dihydroxy vitamin D ($1,25(OH)_2$VitD) synthesis.[6] In patients with CKD, serum Pi may also play a role in the secondary increase of serum FGF-23, which by enhancing urinary Pi excretion in the remaining nephrons mitigates the rise in serum Pi. In a prospective study conducted by Bhan et al, FGF-23 concentration decreased distinctly within the first week after transplantation, although its level continuously remained above normal.[7]

We hypothesized that persistently increased FGF-23 levels after RT contribute to PRT hypophosphatemia by increasing tubular Pi wasting and suppressing calcitriol synthesis. We prospectively followed parameters of mineral metabolism, including PTH and FGF-23, early after RT, and compared the strength of association between PRT hypophosphatemia and FGF-23 relative to PTH.

PATIENTS AND METHODS

We performed a prospective study of 20 patients who underwent renal transplantation from July 2010 to December 2010 at Keimyung University Dongsan Medical Center, Daegu, Korea. Blood samples were collected before transplantation and 1, 2, 4, and 12 weeks after transplantation. FGF-23 was measured with an ELISA kit (Millipore Corp), that measures intact FGF-23 as well as C-terminal fragments. Intact PTH and $1,25(OH)_2$VitD were measured with an immunoradiometric assay (Immuno-Tech). Serum creatinine, blood urea nitrogen (BUN), calcium (Ca), and Pi were measured with routine assays.

Patient characteristics are reported with standard descriptive statistics. All data were analyzed with SPSS 10. with comparisons for mean values performed with *t* tests. Correlations between the levels of FGF-23, PTH, and other blood chemistries were analyzed by analysis of variance linear regression analysis.

RESULTS

Characteristics of the Study Population

Among the 20 patients, 14 (70%) were men and 6 (30%) were women. Overall mean age of patients was 43.3 ± 11.4 years (range 21–60). Eighteen patients underwent hemodialysis, 2 patients peritoneal dialysis before RT. Two cases were preemptive RT. Mean duration of previous dialysis was 66.1 ± 59.3 months (range 9–216). Seventeen cases were first transplantation and 3 cases regraft. Maintenance immunosuppressant consisted of corticosteroids, tacrolimus, and mycophenolate mofetil.

Mineral Metabolism After Renal Transplantation

Pretransplantation and posttransplantation serum creatinine, BUN, and the parameters of mineral metabolism are presented in Table 1 Serum creatinine levels decreased quickly after transplantation. The mean pretransplantation serum Pi was 6.14 ± 1.79 mg/dL. Mean serum Pi decreased to 2.63 ± 1.21, 1.78 ± 0.55, and 1.90 ± 0.74 pg/mL at 1, 2, and 4 weeks after transplantation, respectively. Seventy-five percent (15 cases) and 60% (12 cases) of the patients developed PRT hypophosphatemia (defined as serum phosphate <2.5 mg/dL) at 4 weeks and 12 weeks after transplantation, respectively. Forty percent of patients (8 cases) developed severe PRT hypophosphatemia (defined as serum phosphate ≤1.5 mg/dL) at 4 weeks after transplantation.

The mean pretransplantation FGF-23 level was 7,471 ± 11,746 pg/mL. Mean FGF-23 levels significantly decreased to 225 ± 295 pg/mL at 4 weeks following transplantation, but these levels were still above normal (Fig 1). iPTH levels also decreased significantly after renal transplantation (295 ± 189.1 vs 151 ± 111.2 pg/ml, $P < .05$). $1,25(OH)_2$VitD increased slightly after renal transplantation (14.3 ± 10.6 vs 24.3 ± 12.2 pg/mL; $P < .05$). Compared with nonhypophosphatemic subjects, the levels of FGF-23 of hypophosphatemic patients were significantly higher (303 ± 311 vs 10 ± 6.9 pg/mL; $P = .02$) at 4 weeks after transplantation.

FGF-23 Versus PTH in PRT Hypophosphatemia

FGF-23 level was inversely correlated with Pi ($r^2 = 0.406$; $P = .011$); PTH was not correlated with Pi ($r^2 = 0.132$; $P = .151$; Fig 2).

Table 1. Parameters of Mineral Metabolism in Renal Transplant Recipients

	Before	1 wk	2 wk	4 wk	12 wk
BUN (mg/dL)*	63.2 ± 22.7	34.1 ± 23.6	20.0 ± 5.8	22.0 ± 7.6	18.9 ± 5.9
Serum creatinine (mg/dL)*	10.6 ± 3.28	1.84 ± 1.30	1.09 ± 0.30	1.07 ± 0.19	1.14 ± 0.28
Serum calcium (mg/dL)	9.59 ± 1.39	9.42 ± 1.21	9.54 ± 0.83	10.15 ± 1.08	10.34 ± 0.80
Serum phosphate (mg/dL)*	6.14 ± 1.79	2.63 ± 1.21	1.78 ± 0.55	1.90 ± 0.74	2.52 ± 1.00
Intact PTH (pg/mL)*	295 ± 189.1	144 ± 81.2	129 ± 70.1	151 ± 111.2	92 ± 84.3
$1,25(OH)_2$VitD (pg/mL)*	14.3 ± 10.60	28.9 ± 20.9	29.2 ± 20.5	24.3 ± 12.2	28.8 ± 14.2
FGF-23 (pg/mL)*	7,471 ± 11,746	1,500 ± 200	649 ± 1261	225 ± 295	55 ± 63

* $P < .05$.