Clinical Manifestations of Hypercalcemia and Hypophosphatemia After Kidney Transplantation

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ABSTRACT

Introduction. Abnormalities of calcium and phosphorus metabolism in end-stage renal disease patients can persist after transplantation. We investigated their natural courses after transplantation, their risk factors for posttransplantation hypercalcemia and hypophosphatemia, and their impacts on allograft outcomes.

Methods. We retrospectively analyzed a total of 490 adult patients who underwent kidney transplantations between 2000 and 2009.

Results. The serum calcium continued to increase, and reaching a plateau at around 3 months after transplantation. Thereafter it decreased, reaching a stable level by 2 years. Forty-four patients (9.0%) displayed hypercalcemia within 1 year; it persisted longer than that in 23 subjects (4.7%). Both longer dialysis duration (odds ratio [OR] 1.423; 95% confidence interval [CI], 1.192–1.699) and high intact serum parathyroid hormone (iPTH) level before transplantation (OR 1.002; 95% CI, 1.000–1.003) increased the risk for posttransplantation hypercalcemia. After a significant decrease during the first week, the serum phosphorus level increased, becoming stable between 1 and 6 months after transplantation. Hypophsphatemia occurred in 379 patients (77.3%) with 336 patients displaying hypophosphatemia without hypercalcemia. However, neither hypercalcemia nor hypophosphatemia influenced graft outcomes. Eight patients underwent pretransplantation parathyroidectomy, whereas 4 patients underwent posttransplantation parathyroidectomy. Neither group of patients experienced posttransplantation hypercalcemia.

Conclusions. Both hypercalcemia and hypophosphatemia are common after renal transplantation, especially among patients with a long history of dialysis before transplantation. Strict control of hyperparathyroidism including parathyroidectomy before transplantation may be the appropriate approach to these abnormalities.

POSTTRANSPLANTATION hypercalcemia is a common problem reported to occur in up to 53% of renal transplantation patients.[1] The clinical practice guidelines for treatment of bone disease in chronic kidney disease proposed by the National Kidney Foundation[2] triggered a paradigm shift in the treatment of secondary hyperparathyroidism. The focus of attention was shifted from control of parathyroid hormone levels toward prevention of cardiovascular calcification. Hypercalcemia is no longer considered an innocent complication, because it may impair graft

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function either acutely by inducing vasoconstriction[3] or chronically by mediating calcification of the tubulointerstitium.[4,5] Moreover, hypercalcemia may confer an increased risk for soft-tissue and vascular calcifications,[6] which in turn may adversely affect patient outcomes. As a result, calcium-containing phosphate binders, calcitriol supplements, and high-calcium dialysate baths have been increasingly replaced by non–calcium-containing phosphate binders, novel vitamin D analogs, and low-calcium dialysate baths, respectively. Because most studies that have investigated posttransplantation calcium metabolism were performed before the new guidelines,[2] we investigated the clinical manifestations of posttransplantation hypercalcemia and hypophosphatemia in the current era.

Posttransplantation hypophosphatemia can occur with hypercalcemia in cases of persistent hyperparathyroidism after renal transplantation. However, persistent hyperparathyroidism is not the only mechanism of posttransplantation hypophosphatemia. Previous reports have demonstrated that fibroblast growth factor 23 (FGF-23) may play a role in the development of posttransplantation hypophosphatemia.[7,8]

Therefore, we sought to determine the natural courses of calcium and phosphorus levels after kidney transplantation, the risk factors for hypercalcemia and hypophsphatemia, their impacts on graft outcomes, and the effects of pretransplantation and posttransplantation parathyroidectomy.

MATERIALS AND METHODS

Subjects

This single-center, retrospective, observational study of adult kidney transplantation patients (≥18 years) between 2000 and 2009 was approved by our institutional review board (IRB no: H-1104-098-359). The study adhered to the principles of The Declaration of Helsinki.

Data Collection

We reviewed the baseline clinical characteristics of age, gender, cause of end-stage renal disease (ESRD), modality and duration of renal replacement, donor type (deceased vs living), donor age, diabetes mellitus, hypertension, history of cardiovascular disease, and immunosuppressant treatment. The estimated glomerular filtration rate (eGFR) at 1 year after transplantation was calculated using The Modification of Diet in Renal Disease (MDRD) formula.[9] Posttransplantation hypercalcemia was defined as a serum total calcium level >10.5 mg/dL at least twice during the first year after transplantation. Posttransplantation hypophosphatemia was defined as a value <2.5 mg/dL at least twice during the first year after transplantation. We measured serum levels of calcium, phosphorus, intact serum parathyroid hormone (iPTH), and creatinine before transplantation as well as at 1 week, 1 month, 3 months, 6 months, 9 months, 1 year, 2 years, and 5 years after transplantation. Next, we identified patients who had undergone parathyroidectomy for persistent hyperparathyroidism before or after kidney transplantation, to check their control of hypercalcemia after the parathyroidectomy.

Data Analysis

After the overall natural course of the calcium and phosphorus levels after transplantation was analyzed, we compared the courses of hypercalcemic vs normocalcemic groups. We analyzed the risk factors for hypercalcemia and persistent hypercalcemia beyond 1 year after transplantation. Next, we investigated the impacts of hypercalcemia on cardiovascular events, as well as 1-year renal allograft function calculated using the MDRD formula.

The natural course of the hypophosphatemic and normophosphatemic groups were analyzed along with risk factors. Next, the hypophosphatemic cohort was subgrouped into a hypercalcemic hypophosphatemic and a normocalcemic hypophosphatemic group for comparisons. We also analyzed the impact of posttransplantation hypophosphatemia on graft function and complications.

Statistical Analysis

Continuous variables were expressed as mean values ± standard deviations. To compare continuous variables between the 2 groups we used Student *t* or the Mann-Whitney test. Categorical data were compared using the chi-square or Fisher exact test, as appropriate. Multiple logistic regression analysis was performed to identify risk factors for hypercalcemia or hypophosphatemia. Survival rates were calculated using the Kaplan-Meier method with log-rank tests for comparisons. $P < .05$ was considered statistically significant. All statistical analyses were performed using the SPSS statistics package version 17.0 (SPSS Inc, Chicago, Ill, United States).

RESULTS

Basal Characteristics of the Study Population

The 490 patients included in the study had a median follow-up duration of 38.6 months and an average age of 41.06 ± 12.23 years with 56.7% males. The most common cause of ESRD was glomerulonephritis (40.2%), followed by diabetes (14.1%), hypertension (9.2%), and autosomal dominant polycystic kidney disease (7.6%). The majority of patients had received a living donor kidney (73.3%), with 26.3% of cases as pre-emptive transplantations. Among patients who had received dialysis, the mean duration of treatment was 2.29 ± 3.18 months. All subjects were prescribed steroid, a calcineurin inhibitor, and a proliferation inhibitor.

Natural Courses of Calcium and Phosphorus After Kidney Transplantation

Serum calcium decreased to 8.72 ± 0.77 mg/dL at 1 week after transplantation, and then increased to 9.66 ± 0.70 mg/dL at 3 months (1 week vs 3 months; $P < .001$; Fig 1a). After a plateau between 3 and 9 months, it decreased until 2 years posttransplantation. The calcium content corrected according to the serum albumin level showed a similar trend (data not shown). The level of iPTH was 210.26 ± 259.00 before transplantation, decreasing to 184.03 ± 175.89 and 88.76 ± 89.68 at 6 and 12 months after transplantation, respectively. The serum phosphorus level began to increase, reaching the normal range at 1–6 months in all patients, after an abrupt decrease at 1 week after transplantation (2.52 ± 0.94 mg/dL; Fig 1b).

Posttransplantation Hypercalcemia

Posttransplantation hypercalcemia, which occurred in 44 patients (9.0%), persisted beyond 1 year in 23 subjects