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Original Article

Hypercalcemia After Kidney Transplantation: A Single-Center Experience

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ABSTRACT

Objective: To examine the causes of hypercalcemia developing after kidney transplantation and investigate its effects on graft functions.

Methods: The results of 104 patients were explored retrospectively. Patients assigned according to calcium levels at 12th month after transplantation as hypercalcemia group (Ca^{2+} >10.2) and normocalcemia (Ca^{2+} ≤10.2) group. Glomerular filtration rates were calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for each follow-up period.

Results: A total of 104 patients, 30 (29%) females and 74 (71%) males, were included in our study. Patients were divided into two groups as hypercalcemic (Ca^{2+} >10.2) (n=30, 29%) and normocalcemic (Ca^{2+} ≤10.2) (n=74, 71%) according to their 12-month follow-up results. While there was no significant difference in alkaline phosphatase levels (ALP) (p=0.720) at the time of transplantation, a significant difference was found in ALP in the 12th-month measurements (p<0.001). Both parathormone levels at the transplantation time (p=0.006) and 12th-month follow-up results (p<0.001) were significantly higher in the hypercalcemia group. When we evaluated the graft functions of the patients, no significant difference was found between e-GFR levels in the 1st, 3rd, and 12th months.

Conclusion: There is no association between posttransplant hypercalcemia and changes in graft function in kidney transplantation patients.

INTRODUCTION

Chronic kidney disease has become one of the most serious public health problems of the current century due to the increased awareness of the disease and the prolongation of life expectancy. Renal replacement therapies of chronic kidney disease include hemodialysis, peritoneal dialysis, and renal transplantation. Renal transplantation has become popular, especially in recent years, because it increases the life span and quality of the patient and is more advantageous than other replacement therapies in terms of treatment costs.

Prevention and treatment of complications are undoubtedly one of the most important steps in the follow-up and treatment of chronic kidney disease. One of these complications, metabolic bone disease due to chronic kidney disease, tends to improve after kidney transplantation. However, inadequate and ineffective treatment of secondary hyperparathyroidism in the uremic period may cause hyperparathyroidism-related symptoms such as hypercalcemia in the posttransplant period.[1]

Resistant hypercalcemia is observed at highly variable rates after kidney transplantation.[2,3] Inadequately treated secondary hyperparathyroidism in the uremic period is believed to be the most important etiological factor in the development of posttransplant hypercalcemia.[1] Hypercalcemia that occurred in the posttransplantation period may have negative effects on the hematological, gastrointestinal, and cardiovascular systems.[4] However, there is insufficient data on the relationship between posttransplantation hypercalcemia and graft functions. This study aims to examine the causes of hypercalcemia developing after kidney transplantation and to investigate its effects on graft functions.

MATERIALS AND METHODS

The patients who underwent kidney transplantation be-

tween 2002 and 2012 at Haydarpasa Numune Traning and Research Hospital and whose clinical and laboratory information was available before and one year after the transplantation were included in the study. Patients under the age of 18 and over 70 years, patients with pregnancy history after transplantation, patients who underwent parathyroidectomy before kidney transplantation, patients with delayed graft function, patients with posttransplant malignancy, patients with a history of calcimimetic agent use, and patients whose follow-up information cannot be obtained were excluded in our study. Transplantation ages, renal replacement therapy types, dialysis duration, and chronic kidney disease etiology of the remaining 104 patients were determined retrospectively from the patient follow-up files. Serum creatinine, parathormone, calcium, and phosphorus data of the patients were recorded before transplantation, 1 month after transplantation, 3 months after transplantation, and 12 months after transplantation. Glomerular filtration rates were calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for each follow-up period. Patients with calcium values >10.2 mg/dL at 12 months after transplantation and patients with normal calcium values were compared in terms of glomerular filtration rates.

Statistical Package for Social Sciences Software (SPSS 17.0 Chicago, IL) program was used for statistical evaluation in our study. Kolmogorov–Smirnov test and histogram curves were used to determine the distribution of variables. When comparing cases with and without hypercalcemia, Student's t-test was used for variables with parametric distribution, and Mann–Whitney U test was used for variables with the nonparametric distribution. The Chi-squared test was used to compare the proportions. In the results, p-value less than 0.05 was considered significant.

RESULTS

A total of 104 patients, 30 (29%) females and 74 (71%) males, were included in our study. The mean age of the patients was 39.6±8.4 years. Chronic kidney disease was developed in patients due to chronic glomerulonephritis (n=18, 18%), hypertension (n=18, 18%), vesicoureteral reflux (n=10, 9.6%), nephrolithiasis (n=6, 5.7%), diabetes mellitus (n=5, 4.8%), polycystic kidney disease (n=5, 4.8%), and undetermined cause (n=31, 29.8%) (Table 1). Before kidney transplantation, 81 of the patients received hemodialysis treatment and 14 of them received peritoneal dialysis treatment. Nine patients received preemptive kidney transplantation before renal replacement therapy was initiated. While 65 patients were transplanted from a living donor, 39 patients were transplanted from a cadaveric donor. Patients were divided into two groups as hypercalcemic (Ca^{2+} >10.2) (n=30, 29%) and normocalcemic (Ca^{2+} ≤10.2) (n=74, 71%) according to their 12-month follow-up results. When the hypercalcemia group and the normocalcemia group were compared, patient age (p=0.026, CI [0.59–8.99]), patient age at the time of transplant (p=0.020, CI [0.83–9.52]), duration of renal replacement therapy (p=0.022, CI [3.49–42.92]), and donor type (p=0.030) were found to be statistically significant. While there was no significant difference in alkaline phosphatase levels (ALP) (p=0.720) at the time of transplantation, a significant difference was found in ALP levels in 12th-month measurements (p<0.001). Both parathormone levels at the transplantation time (p=0.006) and 12th-month follow-up results (p<0.001) were significantly different. When we evaluated the graft functions of the patients, no significant difference was found between e-GFR levels in the 1st, 3rd, and 12th months (Table 2).

Table 1. Etiological factors of chronic kidney disease in patients

Etiological factor	HC (+)	HC (-)	Total
Unknown	8	23	31
Alport syndrome	1	0	1
Diabetes melitus	1	4	5
FMF	0	4	4
Glomerulonephritis	5	13	18
Hypertension	6	12	18
Drug nephrotoxicity	1	1	2
Nephrolithiasis	0	6	6
Polycystic kidney disease	3	2	5
Pyelonephritis	1	0	1
SLE	0	1	1
Trauma	2	0	2
VUR	2	8	10
Total	30	74	104

HC (+): Patients with hypercalcemia; HC (-): Patients without hypercalcemia; FMF: Familial Mediterranean fever; SLE: Systemic lupus erythematosus; VUR: Vesicoureteral reflux.

DISCUSSION

In our study, the causes of hypercalcemia that developed after transplantation and its effect on graft functions were evaluated. A statistically significant difference was found in patient age, transplantation age, renal replacement therapy duration, and donation type. There was a significant difference in pretransplant parathyroid hormone levels. A significant difference was also detected in both parathyroid hormone and ALP in the 12th-month follow-up results. Finally, there was no association between hypercalcemia and changes in graft function.

After kidney transplantation, bone and mineral disorders may persist in some patients.[5] One of these complications is hypercalcemia developing after transplantation. The studies evaluating the frequency of posttransplant hypercalcemia have reported variable results. In some studies, hypercalcemia frequency was below 5%; in other studies, the frequency was above 50%.[4] This variability is thought to be based on the ineffectiveness of the treatments for secondary hyperparathyroidism in the pretransplant period, the cross-sectional and retrospective design of the

Table 2. Comparasion of patients with posttransplant hypercalcemia and normocalcemia

	HC (+)	HC (-)	p
Age (years)	43.17±11.58	38.38±8.96	0.026*
Gender (female)	12 (35%)	34 (65%)	0.580
Dialysis type			0.256
Hemodialysis	23 (28.6%)	58 (71.6%)	
Peritoneal dialysis	6 (42.8%)	8 (57.2%)	
Preemptive	1 (12.5%)	8 (87.5%)	
Pre-transplant dialysis period (months)	71.87±40.70	48.66±42.85	0.022*
Donation type (living donation)	12 (18.5%)	53 (81.5%)	0.003**
IS treatment			0.903
CSI	27 (29%)	66 (71%)	
m-TOR inhibitor	3 (27.2%)	8 (72.8%)	
Age (when received transplantation)(years)	38.63±12.19	33.46±9.16	0.020*
Albumin (mg/dL) (12th month)	4.46±0.30	4.37±0.33	0.215
Phosphorus (mg/dL)	2.82±0.65	3.18±0.60	0.007*
Creatinine (1st month)(mg/dL)	1.38±0.69	1.28±0.49	0.431
Creatinine (3rd month)(mg/dL)	1.19±0.35	1.25±0.37	0.477
Creatinine (12th month)(mg/dL)	1.27±0.47	1.27±0.41	0.951
e-GFR (1st month)	69.13±27.53	73.01±26.41	0.513
e-GFR (3rd month)	74.23±20.63	72.36±22.42	0.695
e-GFR (12th month)	72.03±23.29	72±24.28	0.995
Basal parathormon level (pg/ml)	810 (68–2733)	352 (38–1852)	0.006***
Parathormon (12th month) (pg/ml)	298.3 (75.4–652.5)	108 (18–680)	<0.001***
Basal ALP level	131 (45–1362)	110 (9–1540)	0.125
ALP (12th month) (IU/L)	135 (39–460)	90 (6–545)	<0.001***

*Student's t–test, **Chi–squared test, ***Mann–Whitney U test, p<0.05. HC (+): Patients with hypercalcemia; HC (-): Patients without hypercalcemia; IS Treatment: Immunsupressive treatment; CSI: Calcineurin inhibitor; e-GFR: Estimated glomerular filtration rate (ml/min/1.73m^2); ALP: Alkaline phosphatase.

studies, the low number of patients in previous studies, and the fact that the calcium values used in the studies were taken at different times after transplantation.[4] The rate of hypercalcemia after kidney transplantation peaked after 8 weeks, and it was reported to be 29% in patients with low parathyroid hormone (PTH) levels and 48% in patients with high PTH levels. In patients who complete 1 year, this rate decreases to 11% and 25%, respectively.[6] In our study, the rate of hypercalcemia in the 3rd month was 30%, while patients with hypercalcemia at the end of the 12th month were 28.8%.

Although many etiological factors are proposed for posttransplant hypercalcemia development, the tightest relationship among them is thought to be related to persistent hyperparathyroidism.[7] In a multicenter cohort study, the identified independent predictors of posttransplant hypercalcemia at months 3, 6, 9, and 12 were high versus low baseline PTH stratum and baseline corrected serum calcium greater than 10.2 mg/dL.[6] In another study, posttransplant hypercalcemia was closely linked to pretransplant and posttransplant PTH levels.[8] Besides, it has been shown that hypercalcemia was reversible after parathyroidectomy surgery.[9] In the present study, parathormone levels both at the transplantation time and 12th-month follow-up results were higher.

It has been reported that urinary calcium excretion increased in patients with hypercalcemic course despite hyperparathyroidism. This observation suggests that tubular calcium absorption is suppressed by the activation of calcium sensitizing receptors in the early posttransplant period.[10] Another view put forward in terms of the etiology of hypercalcemia is that calcitriol synthesis increases due to increased parathyroid hormone levels and causes hypercalcemia by increasing gastrointestinal calcium absorption.[11,12] Finally, it has been shown that serum ALP increase in patients with hypercalcemia, which is thought to be associated with increased bone turnover.[13] This information agrees with the view that hypercalcemia seen after kidney transplantation occurs due to the increase in calcium release from the skeletal system via parathyroid hormone.

In previous studies, some mechanisms were proposed to explain the effects of posttransplant hypercalcemia on graft functions. The first is macroscopic nephrocalcinosis, characterized by coarse deposits of calcium salts both in the renal papillae and the urinary tract.[4] The second is microscopic nephrocalcinosis, which can be detected with only microscopic examination. Finally, biochemical and hemodynamic effects of hypercalcemia such as vasoconstriction; increased natriuresis and diuresis; and activation

of a huge number of enzymes, cytokines, and growth factors may induce renal damage.[4] However, the results of studies on hypercalcemia and nephrocalcinosis are inconsistent. Some studies have shown that hypercalcemia may be associated with calcium salt accumulation in the transplanted kidney and impaired graft survival.[14,15] On the other hand, Habbig et al.[16] could not show an association between hypercalcemia and graft function in the pediatric study population. In another cohort study, hypercalcemia was associated with an increased risk of mortality but not with graft failure.[17] Similarly, in our study, we could not confirm a relationship between calcium levels and graft functions at 1, 3, and 12 months after transplantation.

The present study has a few limitations. First, some patients were excluded due to missing data regarding the nature of the study's retrospective design. Second, only ALP was available to determine the source of calcium. Bone-specific ALP and bone densitometry of patients were not available. Third, graft functions were assessed with serum creatinine and creatinine-based e-GFR calculations. Cystatin-C, a successful biomarker in predicting cardiovascular events,[18] can also be used in these patients to determine graft functions. Fourth, the study lacked data about the drugs that can affect serum calcium levels. Finally, there was no follow-up of serum vitamin D levels of patients.

CONCLUSION

Hypercalcemia is one of the common complications after kidney transplantation. Although its effects on graft functions are controversial, it may be beneficial for patients with renal transplantation to be protected from hypercalcemia due to decreasing renal perfusion and negative effects on other systems. Therefore, it is important to take precautions when the patient is in the uremic period to prevent the development of hyperparathyroidism, which is known to be closely related to posttransplant hypercalcemia, especially in the uremic period.

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: M.G., G.Ş.M.; Design: M.G., G.Ş.M.; Supervision: G.Ş.M.; Fundings: M.G.; Materials: M.G.; Data: M.G.; Analysis: M.G., G.Ş.M.; Literature search: M.G.; Writing: M.G.; Critical revision: M.G., G.Ş.M.

Conflict of Interest

None declared.

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Böbrek Nakli Sonrası Hiperkalsemi: Tek-Merkez Deneyimi

Amaç: Böbrek nakli sonrası gelişen hiperkalseminin nedenlerini incelemek ve greft fonksiyonları üzerine etkilerini araştırmak.

Gereç ve Yöntem: Toplam 104 hastanın sonucu geriye dönük olarak incelendi. Hastalar nakil sonrası 12. ayda kalsiyum düzeylerine göre hiperkalsemi grubu (Ca^{2+} >10.2 mg/dl) ve normokalsemi (Ca^{2+} ≤10.2 mg/dl) grubu olarak belirlendi. Glomerüler filtrasyon hızları, her takip dönemi için Chronic Kidney Disease Epidemiology Collaboration formülü ile hesaplandı.

Bulgular: Çalışmamıza 30'u (%29) kadın, 74'ü (%71) erkek olmak üzere toplam 104 hasta dahil edildi. Hastalar 12 aylık takip sonuçlarına göre hiperkalsemik (n=30, %29) ve normokalsemik (n=74, %71) olarak iki gruba ayrıldı. Transplantasyon sırasında alkalin fosfataz düzeylerinde (p=0.720) anlamlı bir farklılık yokken, 12. ay ölçümlerinde alkalen fosfataz düzeylerinde anlamlı farklılık bulundu (p<0.001). Hem transplantasyon anındaki parathormon düzeyleri (p=0.006) hem de 12. ay takip sonuçları (<0.001) hiperkalsemi grubunda anlamlı olarak yüksekti. Hastaların greft işlevlerini değerlendirdiğimizde 1., 3. ve 12. aylarda e-GFR düzeyleri arasında anlamlı bir fark bulunmadı.

Sonuç: Böbrek nakli hastalarında nakil sonrası hiperkalsemi ile greft fonksiyonundaki değişiklikler arasında bir ilişki yoktur.

Anahtar Sözcükler: Böbrek nakli; greft fonksiyonları; hiperkalsemi.