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CLINICAL STUDY

Magnesium excretion and hypomagnesemia in pediatric renal transplant recipients

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Abstract

Background: We investigated magnesium excretion and rate of hypomagnesemia in pediatric renal transplant recipients. *Method*: The medical records of 114 pediatric renal transplant recipients were retrospectively evaluated. After exclusion of 23 patients, 91 patients were included in the study. We recorded serum magnesium levels at the time of measurement of urine magnesium wasting. *Results*: Mean serum magnesium levels were 1.73 ± 0.22 mg/dL and 38 of the patients (41%) had hypomagnesemia. There was a negative correlation between serum magnesium levels and estimated glomerular filtration rate and serum tacrolimus trough level ($r = -0.215$, $p = 0.040$ and $r = -0.409$, $p = 0.000$, respectively). Also, there was a statistically significant positive correlation between serum magnesium levels and transplantation duration ($r = 0.249$, $p = 0.017$). Mean fractional magnesium excretion was $5.9 \pm 3.7\%$ and 59 patients (65%) had high magnesium excretion. There was a significant negative correlation between fractional magnesium excretion and estimated glomerular filtration rate ($r = -0.432$, $p = 0.001$). There was a significant positive correlation between fractional magnesium excretion and serum creatinine ($r = 0.379$ $p = 0.003$). *Conclusion*: Patients with higher tacrolimus trough blood levels, lower glomerular filtration rate and at early posttransplant period had risk of hypomagnesemia.

Keywords

Cyclosporine, hypomagnesemia, hypermagnesuria, renal transplantation, tacrolimus

History

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Introduction

Magnesium is the fourth most abundant cation in the body and the third most common intracellular cation. It is an essential cofactor for numerous enzymes, some of them have a role in membrane stabilization and nerve conduction. Also, adenosine triphosphate (ATP) and guanosine triphosphate (GTP) need associated magnesium in the metabolic pathways by ATPase, cyclases and kinases. Renal excretion is the major regulator of magnesium balance of the body.[1]

In renal transplant recipients, hypomagnesemia is frequently reported due to the wide usage of calcineurin inhibitors (CNIs).[2–4] CNI's may cause obligatory renal loss and decrease transcriptional expression of the Mg transporter in the distal collecting tubule.[5] It is reported that hypomagnesemia is more common in tacrolimus-based regimens compared to cyclosporine (CsA).[6,7] Margretier et al.[5] found hypomagnesemia prevalence in patients on tacrolimus (TAC) as 6.6% and on CsA as 1.5%. Trompeter et al.[7] also found hypomagnesemia prevalence in pediatric renal transplant recipients on TAC as 34% and on CsA as 12.4%.

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The studies regarding the frequency of hypomagnesemia in pediatric renal transplant recipients are scarce; so, we aimed to study the frequency of hypomagnesemia and urinary magnesium excretion in this group.

Materials and methods

The medical records of 114 pediatric renal transplant recipients who were grafted at Akdeniz University Medical Faculty between May 2005 and February 2012 were retrospectively evaluated. After exclusion of 23 patients with the change of immunosuppressive therapy, graft loss, diuretic use and insufficient data, this retrospective single center study included 91 pediatric renal transplant recipients. Patient information was obtained from patient charts and hospital electronic database. We recorded serum magnesium levels at the time of measurement of urine magnesium wasting.

Urinary magnesium excretion of patients were measured as fractional magnesium excretion (FeMg) using the formula [(urine magnesium $\times$ plasma creatinine/serum magnesium $\times$ urine creatinine $\times$ 0.7) $\times$ 100].[8] A value >4% is indicative of inappropriate magnesium loss.[9] FeMg does not vary with age but it does change based on the serum magnesium concentration.[10] Hypomagnesemia was regarded as a serum magnesium level below 1.70 mg/dL.

The demographic features, donor type, renal transplantation duration and type of medications, serum creatinine,

cystatin C, serum calcium, phosphorus, uric acid, fasting blood glucose, triglyceride and total cholesterol, and CNI (tacrolimus and CsA) blood levels were recorded at the same time with serum magnesium and urine magnesium measurements. Blood levels of tacrolimus and cyclosporine were measured after 12 hours of last dose of CNI and after second hour of cyclosporine were also recorded. Estimated GFR (eGFR) was calculated according to the Schwartz formula with cystatin C.[11] Systolic and diastolic blood pressures were measured during physical examination.

In our centre, we began to investigate serum magnesium levels at each visit as a routine practice after November 2009; before this time only in cases with clinical necessity. There was a group of patients who had been using oral magnesium replacement as a therapy.

Tacrolimus blood levels were aimed to be 10–12 ng/mL during first month of post-transplant and 5–10 ng/mL later on; CsA trough and second hour level was 150–375 ng/mL and 850–1300 ng/mL during first 6 months of post-transplant and 50–100 ng/mL and 175–700 ng/mL later on.

Statistical analysis

Categoric variables are presented as frequencies and percentages. Continuous variables are expressed as mean ± SD, and we compared using student unpaired *t* test, analysis of variance or correlation analysis as appropriate. A *p* value <0.05 was considered to be statistically significant. All analyses were performed using SPSS software (SPSS 16, Chicago, IL).

Results

Patient characteristics

A total of 91 pediatric renal transplant recipients (43 girls and 48 boys) with a mean age of 13.6 ± 3.7 years were included in the study. The clinical and laboratory characteristics of the patients are shown in Table 1. Thirty-three of the patients (36%) had oral magnesium replacement due to previous investigation. Mean serum magnesium levels of patients with oral magnesium replacement and without oral magnesium replacement were 1.68 ± 0.20 mg/dL and 1.76 ± 0.22 mg/dL ($p = 0.236$). Mean FEMg levels of patients with and without oral magnesium replacement were $5.94 \pm 3.65\%$ and $5.91 \pm 3.72\%$ ($p = 0.869$).

Table 1. Clinical and biochemical characteristics of patients.

	Patients $n = 91$
Age (years)	13.6 ± 3.7
Male/Female	48/43
Donor type (cadaveric/living)	20/71
CNI type (cyclosporine/Tacrolimus)	18/73
MMF	91
Prednisolone	77
Oral magnesium replacement (yes/no)	33/58
Mean serum creatinine (mg/dL)	1.03 ± 0.57
Mean cystatin C (mg/L)	1.52 ± 0.67
eGFR (mL/min/1.73m^2)	67 ± 23
Mean serum magnesium (mg/dL)	1.73 ± 0.22
Mean serum calcium (mg/dL)	9.89 ± 0.42
Mean serum phosphorus (mg/dL)	4.38 ± 0.72
Mean serum uric acid (mg/dL)	5.13 ± 1.49
FEMG (%)	5.9 ± 3.7

Note: CNI: calcineurine inhibitor, MMF: mycophenolate mofetil, eGFR: estimated glomerular filtration rate, FEMg: fractional magnesium excretion.

Serum magnesium levels

Mean serum magnesium levels of patients were 1.73 ± 0.22 mg/dL and 38 of the patients (41%) had hypomagnesemia at the time of study. Most of the patients with hypomagnesemia (85%) had no symptom. Only 10 patients (10/91, 10%) had tremor as a symptom of hypomagnesemia; one patient had convulsion. Fifteen of the patients on oral magnesium replacement had hypomagnesemia at the time of study. The characteristics of patients with and without hypomagnesemia are shown in Table 2. The median period between renal transplantation and assessment of hypomagnesemia was 5.5 months (1–72 months, range). Hypomagnesemia was assessed in 35.7% of patients during the first month after renal transplantation. Earliest time of assessment of hypomagnesemia was at second week of renal transplantation.

There was a statistically significant negative correlation between serum magnesium levels and eGFR ($r = -0.215$, $p = 0.040$). There was no statistically significant correlation between serum magnesium and serum creatinine, cystatin C, serum calcium, phosphorus, uric acid and fasting blood glucose ($p > 0.05$ for all). Also, there was a statistically significant positive correlation between serum magnesium levels and transplantation duration ($r = 0.249$, $p = 0.017$). Mean serum magnesium levels, rate of hypomagnesemia and magnesium excretion of the patients on tacrolimus and cyclosporine are shown in Table 3. Mean serum tacrolimus trough blood levels were 6.7 ± 3.6 ng/mL. Mean cyclosporine trough and second hour blood levels were 135 ± 93 ng/mL and 454 ± 205 ng/mL, respectively. There was an inverse correlation between serum tacrolimus trough blood level and mean serum magnesium level ($r = -0.409$, $p = 0.000$). There was no correlation between cyclosporine trough and second hour blood levels and serum magnesium levels ($r = -0.186$, $p = 0.486$ and $r = 0.202$, $p = 0.407$, respectively).

Magnesium excretion

Mean FEMg levels of patients were $5.9 \pm 3.7\%$ and 59 patients (65%) had high magnesium excretion. Number of patients with hypomagnesemia and high magnesium excretion are shown in Table 4.

There was no significant correlation between FEMg and cystatin C ($r = 0.242$ and $p = 0.068$, respectively). There was a significant negative correlation between FEMg and eGFR ($r = -0.432$, $p = 0.001$). There was a significant positive correlation between FEMg and serum creatinine ($r = 0.379$, $p = 0.003$). There was no significant correlation between FEMg and serum calcium, phosphorus, uric acid and fasting blood glucose ($p > 0.05$ for all).

Magnesium excretion of patients on cyclosporine and tacrolimus were similar (Table 3). There was no statistically significant correlation between FEMg and both tacrolimus trough blood level and cyclosporine trough and second hour blood levels ($p > 0.05$ for all). There was no correlation

Table 2. The comparison of laboratory measurements between renal transplant recipients with hypomagnesemia and normal magnesium levels.

	Patients with normal magnesium levels $N=38$	Patients with hypomagnesemia $N=53$	p Value*
Age (years)	13.7 ± 3.8	13.5 ± 3.6	0.704
Transplant duration (months)	23 ± 16	18 ± 15	0.061
Serum creatinine (mg/dl)	1.10 ± 0.57	0.94 ± 0.56	0.051
Cystatin C (mg/L)	1.58 ± 0.69	1.43 ± 0.64	0.097
GFR (mL/min/1.73m^2)	65 ± 23	70 ± 24	0.180
Serum cholesterol (mg/dL)	172 ± 38	163 ± 36	0.224
Serum triglyceride (mg/dL)	133 ± 66	138 ± 69	0.822
Fasting blood glucose (mg/dL)	84 ± 10	86 ± 12	0.293
Systolic blood pressure (mmHg)	110 ± 11	107 ± 20	0.517
Diastolic blood pressure (mmHg)	66 ± 10	67 ± 10	0.786
FEMg (%)	6.47 ± 3.97	5.15 ± 3.22	0.135
Serum magnesium (mg/dL)	1.87 ± 0.14	1.53 ± 0.14	0.000
Serum calcium (mg/dL)	9.82 ± 0.42	9.98 ± 0.42	0.127
Serum phosphorus (mg/dL)	4.39 ± 0.72	4.36 ± 0.70	0.966
Serum uric acid (mg/dL)	5.13 ± 1.29	5.14 ± 1.75	0.623

Note: *Independent samples t test, $p<0.05$ is significant.

Table 3. Comparison of mean serum magnesium and FEMg of patients on tacrolimus and cyclosporine.

Variables	Patients on tacrolimus ($n=73$)	Patients on cyclosporine ($n=18$)	p Value
Serum magnesium (mg/dL)	1.67 ± 0.23	1.71 ± 0.17	0.446
FEMg (%)	5.60 ± 2.80	6.10 ± 3.80	0.952
Rate of hypomagnesemia (%)	32/73 (43%)	6/18(33%)	0.421
Rate of hypermagnesuria (%)	47/73 (64%)	12/18 (66%)	0.857

Table 4. The number of patients with hypomagnesemia and hypermagnesuria.

	Patients with normal FEMg $n=32$(35 %)	Patients with high FEMg $n=59$(65%)
Patients with normal magnesium levels $n=53$(58%)	16 (17.5%)	37 (40.5%)
Patients with hypomagnesemia $n=38$(42%)	16 (17.5%)	22 (24.5%)

between transplantation duration and FEMg ($r=0.166$, $p=0.214$).

Discussion

In the present study, we found the rate of hypomagnesemia in pediatric renal transplant recipients as 41% and the rate of hypermagnesuria as 65%. The rate of hypomagnesemia and hypermagnesuria were similar in patients on tacrolimus and cyclosporine. Serum magnesium levels were lower in patients with higher tacrolimus trough blood levels and shorter transplant duration. It may be because of the aim of higher CNI blood levels during early posttransplant period. Earliest time of assessment of hypomagnesemia was second week of posttransplant period.

Hypomagnesemia can develop as a result of deficient magnesium intake, gastrointestinal and renal losses and in the setting of diuretic and aminoglycoside use.[12,13] None of our patient group was using these medications. Twenty-eight patients had proton pump inhibitor (PPI) as another medication affecting serum magnesium level. Half of the patients (14/28) having PPI had hypomagnesemia. Twenty-two of patients (57%) with hypomagnesemia had higher magnesium excretion although 43% of them had normal magnesium excretion. It was reported that profound hypomagnesemia and renal magnesium wasting was associated with the use of cyclosporine in bone marrow transplant patients.[14] Later, it was reported that hypomagnesemia was also frequent and tacrolimus levels and renal function was found to have an effect on the excess renal magnesium excretion in adult renal transplant recipients.[15] Although most of the patients with hypomagnesemia in our study had high magnesium excretion there was a patient group who had hypomagnesemia with low magnesium excretion. One reason for this may be because FEMg may change at the state of hypomagnesemia. In the presence of hypomagnesemia renal conservation will occur as an adaptation mechanism.[1] Second reason may be that in our study we found an association between FEMg and serum creatinine, eGFR. After evaluation of features of patients with hypomagnesemia, eGFR levels of patients with normal FEMg were higher than patients with high FEMg ($p=0.048$). In patients who had hypomagnesemia at the time of study and with eGFR <60 mL/min/1.73 m^2, 83% of them (10/12) had high magnesium excretion. But in patients who had hypomagnesemia at the time of study and with eGFR ≥ 60 mL/min/1.73 m^2, 46% of them had high magnesium excretion. So we can say that especially in patients with lower GFR had higher magnesium excretion causing hypomagnesemia.

Nawaz et al.[16] reported that cyclosporine therapy in 50 renal transplant recipients lowered serum magnesium with a marked increase in FEMg in 50% of renal transplant recipients as compared to healthy controls; the authors concluded that FEMg may be a marker of chronic cyclosporine toxicity in stable transplant recipients. But in our study there was no association between cyclosporine blood levels (trough and second hour) and serum magnesium levels and magnesium excretion. As in our study the patients on CsA

were 18 the difference of result may be because of lower number of patients on CsA.

In another study it was reported that tacrolimus level was the best predictor of FEMg.[15] In our study there was no association between magnesium excretion and tacrolimus trough blood levels, but there was an association between serum magnesium levels and tacrolimus trough blood levels.

If the magnesium deficiency was chronic it was associated with the development of insulin resistance.[12] In our study there was no association between serum magnesium level and fasting blood glucose. There was no statistically significant difference at fasting blood glucose between patients with hypomagnesemia and normal magnesium levels. None of our patients had posttransplant diabetes mellitus. In 114 patients we had 5 patients diagnosed as newly onset diabetes after transplantation (NODAT) but we changed the immunosuppressive treatment of these patients we excluded the patient group diagnosed as NODAT. In adult renal transplant recipients, there were studies which found significant correlation between serum magnesium and fasting blood glucose.[17,18]

Hypomagnesemia causes hypocalcemia and the dominant symptoms of hypomagnesemia are due to hypocalcemia, e.g. tetany, positive Chovsteck and Trausseau signs and seizures. But most cases with hypomagnesemia are asymptomatic.[1] Our study population did not have hypocalcemia. Only 10 patients had tremor as a symptom of hypomagnesemia and one had convulsion.

In our study, we found the rate of hypomagnesemia as 41%. In adult renal transplant recipients, hypomagnesemia prevalence was found as 43% due to increased FEMg.[3] In another study on adult renal transplant recipients they found that the rate of hypomagnesemia was 10.2%. The authors advised to monitor serum magnesium levels especially in patients older than 50 years of age.[15] In our study we found high rate of hypomagnesemia in pediatric renal transplant recipients. So we could say that children have high risk of hypomagnesemia. So it should be better to monitor serum magnesium levels periodically.

In pediatric renal transplant recipients, the prevalence of hypomagnesemia was reported as 34% in patients on tacrolimus and as 12.9% inpatients on cyclosporine.[7] Magnesium wasting did not mentioned in this report. In our study, we found rate of hypomagnesemia in patients on tacrolimus and cyclosporine as 43% and 33%, respectively. These results were higher than the previous report. We also studied magnesium wasting in our study, so this is the first report that compare rate of hypomagnesemia and magnesium wasting in pediatric renal transplant recipients on tacrolimus and cyclosporine.

As a conclusion, rate of hypomagnesemia and hypomagnesuria were high in pediatric renal transplant recipients. Especially patients with higher tacrolimus trough blood levels, lower GFR and at early posttransplant period and had risk of hypomagnesemia. Mostly patients with hypomagnesemia were asymptomatic. So we advise to monitor serum magnesium levels in pediatric renal transplant recipients receiving CNIs periodically. This approach will also help to detect hypomagnesemic patients early without any symptom and replacement of hypomagnesemia will prevent its metabolic complications.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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