Hypomagnesemia in Pediatric Heart Transplant Patients Treated with Tacrolimus

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Abstract

Objectives: We aimed to investigate the frequency of hypomagnesemia and urinary magnesium excretion in pediatric heart transplant recipients.

Materials and Methods: In this study, 22 pediatric patients who underwent heart transplant at a single center between March 2014 and April 2015 and who were treated with oral tacrolimus were analyzed prospectively. Serum magnesium, creatinine, and tacrolimus levels and total amount of urinary magnesium excretion were measured. Serum tacrolimus levels were measured 12 hours after the last dose of tacrolimus.

Results: Our patient group included 11 boys (50%) and 11 girls (50%) with a mean age of 16.72 ± 4.78 years. Serum tacrolimus levels were in the therapeutic range, with a mean of 1.48 ± 0.13 ng/mL (range, 1.2-1.69 ng/mL), mean fractional magnesium excretion was 8.59 ± 5.9% (range, 3%-22%), and 24-hour urinary magnesium excretion was 90.2 ± 62.95 mg/d. Hypermagnesuria was assessed in 80% of patients. We found 24-hour urinary magnesium excretion to be higher than normal in 27% of patients. There was no association between serum tacrolimus levels and serum magnesium levels or urinary magnesium excretion.

Conclusions: Serum magnesium levels should be periodically measured in pediatric heart transplant patients treated with tacrolimus.

Key words: Child, Urine, Magnesium

Introduction

Renal excretion is the most important regulator of magnesium balance in the body.1 In renal transplant recipients, hypomagnesemia is frequently reported due to use of calcineurin inhibitors.2-4 Calcineurin inhibitors (tacrolimus, cyclosporine) cause renal loss and decrease transcriptional expression of the magnesium transporter in the distal tubules. Hypomagnesemia is more common with tacrolimus treatment than with cyclosporine treatment. Tacrolimus is a potent immunosuppressive agent administered after solid-organ transplant. Most pharmacodynamic data on tacrolimus are from studies in adults and in patients with kidney or liver transplant.5-11 In this study, we aimed to investigate the frequency of hypomagnesemia and urinary magnesium excretion in pediatric patients with heart transplant for the first time in the literature.

Materials and Methods

Study population

A total of 22 pediatric heart transplant recipients who were transplanted between March 2014 and April 2015 and were treated with tacrolimus were included in the study. Patients were prospectively recruited to the study at a single center. The study was approved by our Ethical Review Committee. All of the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from all patients and their families. All patients were started on oral magnesium at 0.015 to 0.05 mg/kg/d. The dose was adjusted according to serum level. All patients remained under additional treatment with mycophenolate mofetil and prednisolone. All patients diagnosed with hypomagnesemia were started on oral magnesium.

Laboratory examination

Patients included in the study had been receiving oral tacrolimus as primary immunosuppressant therapy and were undergoing drug monitoring. In our clinic, we began to measure serum magnesium...
levels at each visit as a routine practice. Serum tacrolimus levels were aimed to be 5 to 20 ng/mL. Serum tacrolimus levels were measured 12 hours after the last dose of tacrolimus. Serum levels of magnesium and total amount of urinary magnesium excretion were measured after tacrolimus was started. We recorded serum magnesium levels at the time of measurement of urine magnesium wasting. Patients were considered to be hypomagnesemic if serum magnesium concentrations were below 1.6 mg/dL. Renal magnesium wasting was diagnosed by the presence of hypomagnesemia and high urinary magnesium levels (24-hour urinary magnesium excretion of > 104 ± 6 mg/d). Urinary magnesium excretion levels were measured as fractional magnesium excretion, using the following formula: (urine magnesium × plasma creatinine / serum magnesium × urine creatinine × 0.7) × 100. Fractional magnesium > 4% was accepted as indicative of inappropriate magnesium loss. Normal ranges were 135 to 146 mmol/L for sodium, 3.5 to 5.2 mmol/L for serum potassium, 2.3 to 4.7 mg/dL for serum phosphorus, and 8.4 to 10.2 mg/dL for calcium. Glomerular function was assessed by measuring serum creatinine and estimated glomerular filtration rate. Creatinine-based estimated glomerular filtration rate was calculated according to the Schwartz formula: height (cm) × constant / serum creatinine (mg/dL). This constant was 0.55 for children and adolescent girls and 0.7 for adolescent boys.

Statistical analyses
Statistical analyses were performed with SPSS for Windows 14.0 software (SPSS Inc, Chicago, IL, USA). Data are expressed as arithmetic means ± standard deviations. Pearson’s correlation analyses were used for independent parameters. P < .05 was considered to be statistically significant.

Results
Our study group included 11 boys (50%) and 11 girls (50%) with a mean age of 16.72 ± 4.78 years (range, 3-21 y) (Table 1). The age of patients at the time of transplant ranged from 10 months to 17 years old. The mean period between heart transplant and assessment of hypomagnesemia was 55 ± 20 months (range, 1 month to 7 years). Serum sodium, potassium, phosphorus, urea, and creatinine levels were in normal ranges. Although tacrolimus levels were in the therapeutic range, mean serum magnesium levels were 1.48 ± 0.13 mg/dL (range, 1.2-1.69 mg/dL), mean fractional magnesium excretion was 8.59 ± 5.9% (range, 3%-22%), and 24-hour urinary magnesium excretion was 90.2 ± 62.95 mg/d. Mean glomerular filtration rate was calculated as 149.8 ± 43.1 mL/min/1.73 m² (Table 2). Twenty-one patients (95.4%) had hypomagnesemia at the time of study. Hypermagnesuria (fractional magnesium excretion > 4%) was assessed in 80% of patients. We found 24-hour urinary magnesium excretion to be higher than normal ranges in 35.2% of patients (Table 2). There was no association between serum tacrolimus levels and serum magnesium levels or urinary magnesium excretion. We found that hypomagnesemia and hypermagnesuria could be observed even when serum tacrolimus levels were in the normal range. There were no statistically significant correlations between serum magnesium levels and glomerular filtration rates, serum magnesium and serum creatinine levels, serum tacrolimus and serum magnesium levels, fractional magnesium excretion and glomerular filtration rate, fractional magnesium excretion and serum tacrolimus levels, and fractional magnesium excretion and serum creatinine levels.

Discussion
Magnesium is an important intracellular cation. Its homeostasis depends on balanced intestinal absorption and renal excretion. Its deficiency may result from reduced dietary intake, intestinal malabsorption, or renal loss. The control of magnesium homeostasis primarily resides in the renal tubules. Magnesium
depletion resulting from tubular dysfunction is usually secondary to another disease process or to a therapeutic agent (loop diuretics, aminoglycosides, cisplatin, and calcineurin inhibitors).

The calcineurin inhibitors cause hypomagnesemia by suppressing reabsorption of magnesium from renal tubules. Nephrotoxicity is the most common and clinically significant adverse effect with use of calcineurin inhibitors. Renal magnesium wasting is common due to drug effects on magnesium reabsorption. The association between high tacrolimus concentrations and toxicity, especially nephrotoxicity, is much stronger. Margreiter and associates found that the prevalence of hypomagnesemia was 6.6% in patients treated with tacrolimus and 1.5% in patients treated with cyclosporine, with corresponding results of 34% and 12.4% in the study of Trompeter and associates. In our study, we found that the prevalence of hypomagnesemia in pediatric heart transplant patients treated with tacrolimus was much more than in renal transplant recipients.

Hypomagnesemia with urinary magnesium excretion is a well-known adverse effect of tacrolimus treatment in solid-organ transplant recipients. Woodside and associates demonstrated that calcineurin inhibitors caused hypomagnesemia in patients with renal transplant. In adult renal transplant recipients, the prevalence of hypomagnesemia was found to range from 10.2% to 43%. Uslu Gökceoğlu and associates found that the rate of hypomagnesemia in pediatric renal transplant recipients (mean age of 13.6±3.7 y) was 41% and the rate of hypermagnesuria was 65%. In our study, we found that the rate of hypomagnesemia was high in pediatric heart transplant patients versus values reported in adult renal transplant recipients, which is consistent with other pediatric studies. Therefore, we suggest that children with heart transplant treated with calcineurin inhibitors have higher risk of hypomagnesemia than adults. This difference between children and adults may be due to the physiologic variations in the magnesium uptake in their nephron segments, as nephrons in children are not mature compared with those of adults and also due to insufficient magnesium uptake from the distal tubules caused by impaired distal tubular functions as a result of tacrolimus.

In hypomagnesemic patients with normal renal function, fractional magnesium excretion is a useful marker for the diagnostic approach to hypomagnesemia versus 24-hour urinary magnesium excretion. In our study, 24-hour urinary magnesium excretion was within reference ranges in 64.8% of patients, but fractional magnesium excretion was higher than the normal limits. It has been reported that tacrolimus level was the best predictor of fractional magnesium excretion.

Although it has been reported that serum tacrolimus levels and renal function were found to have an effect on excess renal magnesium excretion in adult renal recipients, we did not observe the same effect in pediatric heart recipients. In adults, the glomerular function is mostly evaluated by serum creatinine levels and glomerular filtration rates. However, tacrolimus usually affects tubular function rather than glomerular function; thus it leads to tubulopathy and not glomerulopathy. This could be another reason for this difference. In our study, increased serum creatinine levels and decreased glomerular filtration rates were not encountered in any patient; thus we concluded that tacrolimus did not impair renal glomerular function.

Hypomagnesemic patients exhibit other electrolyte abnormalities such as hyperkalemia, hypokalemia, hypophosphatemia, and hypocalcemia. Contrary to that shown with heart transplant, tubulopathy due to renal transplant may causes hypophosphatemia and hypokalemia. Hypophosphatemia is due to increased urinary excretion of phosphate. Al-Ibrahim and associates observed that hypomagnesemia requiring supplemental magnesium therapy occurred in 9% of renal transplant patients who received tacrolimus therapy. In the same study, hypophosphatemia was identified in 28% of patients, whereas hypokalemia was observed in 11.5%. Our study population did not have hypocalcemia, hypokalemia, or hypophosphatemia.

Conclusions

The rates of hypomagnesemia and hypermagnesuria were high in heart transplant recipients, independently of serum tacrolimus levels. Measuring serum magnesium levels periodically, particularly fractional magnesium excretion in patients treated with tacrolimus, could be helpful to detect and treat the tubulopathy and hypomagnesemia due to tacrolimus.
Study limitations
The number of patients was low to determine a full meaningful outcome. In addition, our study did not include a control group.

References