Serum Magnesium and Related Factors in Long-Term Renal Transplant Recipients: An Observational Study

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ABSTRACT

Background. Low serum magnesium (MgS) is a known risk factor for cardiovascular and mineral bone disease. In renal transplant recipients (RTRs), low MgS levels have been related to higher glomerular filtration rates (GFR) and with calcineurin inhibitors, particularly tacrolimus. We aimed to evaluate MgS in renal transplant recipients with over 1 year of follow-up to establish related risk factors and the impact of the use of cyclosporine versus tacrolimus.

Methods. Cross-sectional study of 94 RTRs with more than 12 months of follow-up. Hypomagnesemia was defined as serum magnesium level <1.5 mg/dL.

Results. Hypomagnesemia was found in 5.3% of patients. MgS showed a negative correlation with creatinine clearance. A positive correlation between MgS with urinary magnesium and phosphorus was found. Cyclosporine versus tacrolimus analysis did not show a significant difference regarding MgS when considering all the population and the subgroup of patients with GFR >45 mL/min/1.73 m^2. On the subgroup with GFR <45 mL/min/1.73 m^2, those on tacrolimus had lower MgS than those on cyclosporine, but those same patients presented with significantly different GFR, higher in the tacrolimus subgroup.

Conclusions. Hypomagnesemia has a low prevalence in RTRs with more than 1 year of follow-up. MgS levels evidenced a strong correlation with GFR. A significant difference on MgS levels between patients on tacrolimus and cyclosporine was found only when considering GFR <45 mL/min/1.73 m^2, in which patients on tacrolimus had significantly higher GFR than patients on cyclosporine, which may explain these results.

PATIENTS with chronic kidney disease (CKD) are now living longer and are consequently dealing with more complications secondary to this condition. Many efforts have been made to improve their quality of life, and nowadays emphasis is being put on the discovery and approach of risk factors for CKD complications. In the past decade, hypomagnesemia has been related to both cardiovascular disease and metabolic bone disease.

Considering cardiovascular disease, low levels of magnesium have been brought up in studies demonstrating a relationship between hypomagnesemia and the risk of developing atrial fibrillation in the general population [1]. It has also been implicated in the pathogenesis of arterial hypertension, endothelial dysfunction, dyslipidemia, and inflammation [2]. In CKD patients, associations were also made in hemodialysis patients between low serum magnesium (MgS) levels and increased atherosclerosis of the common carotid artery and evidence of increasing arterial calcification, mortality, and infection rates [3].

Low MgS levels have also been related to metabolic bone disease in patients with CKD, either by exacerbating osteoporosis [4] or by contributing to vascular calcification [5].

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Besides the above associations, some studies with renal transplant recipients concluded that hypomagnesemia was also an independent predictor of new-onset diabetes after transplantation (NODAT) [6] and was associated with decreased graft survival [7].

With this evidence, low MgS levels have become an important risk factor to consider in the vast spectrum of CKD patients.

Although with a small number or patients, some studies have evaluated the MgS status of renal transplant recipients in the early post-transplant period, reporting hypomagnesemia in 10% to 26% of the patients [8]. Furthermore, a relationship between low MgS and the use of calcineurin inhibitors was reported [9–11]. Accordingly, small studies have suggested that tacrolimus is responsible for lower MgS levels as compared with cyclosporine [12].

In this study, we aimed to evaluate the levels of MgS in renal transplant recipients with over 1 year of follow-up and to establish risk factors for this variable. Additionally, we aimed to examine the impact of the use of cyclosporine versus tacrolimus on MgS.

METHODS

A cross-sectional study including 94 renal transplant recipients over the age of 18 years and with more than 12 months of follow-up after transplantation at our unit was carried out. All patients were negative for hepatitis B and C. None of the patients were on furosemide, thiazide, or magnesium supplements. All patients were on calcineurin inhibitor, mycophenolate mofetil, and prednisone.

All patients were submitted to a medical observation. Laboratory tests were always performed by the same laboratory. We collected the following demographic data: age, sex, weight, height, duration of dialysis before transplantation, type of dialysis technique before transplantation, duration of follow-up after transplantation, and type of immunosuppression. We collected the following laboratory data: serum: creatinine, magnesium, calcium, phosphorus, iPTH, and 25OH-Vitamin D; 24-hour urine: magnesium, calcium, phosphorus, and proteinuria.

Glomerular filtration rate (GFR) was estimated by applying the CKD-EPI Creatinine Equation (2009), as recommended by the National Kidney Foundation. Hypomagnesemia was defined as serum magnesium level <1.5 mg/dL.

Statistical Analysis

Our statistical analysis was performed with the use of SPSS 21.0. Patients were characterized according to demographic and laboratorial parameters. For this characterization, we used percentage for nominal variables (type of dialysis, type of immunosuppression, history of acute rejection) and mean ± standard deviations (SD) for continuous variables. We applied a Pearson correlation to perform the correlation analysis for MgS levels. A multivariable linear regression analysis was then used to identify the influence of the variables collected on MgS levels.

The evaluation of the effect of the type of calcineurin inhibitor used was determined by 3 different tests according to the distribution of the variable: χ^2 for the type of calcineurin inhibitor and sex, Student t test for the age, and Mann-Whitney for the remaining variables.

We analyzed whether serum magnesium varied significantly according to the type of calcineurin inhibitor used and according to the estimated creatinine clearance of the patients by using a cut-off of 45 mL/min/1.73 m^2 for the comparisons.

RESULTS

The characteristics of the 94 patients are summarized in Table 1.

Levels of MgS <1.5 mg/dL were detected in 5 patients (5.3%).

Serum Magnesium and Other Variables

Pearson correlation coefficients were calculated for MgS and other laboratory variables. MgS showed a negative correlation with creatinine clearance significant at the .01 level. There was a positive correlation for serum magnesium with urinary magnesium and urinary phosphorus significant at the .05 level. These results were consistent also on simple linear regression analysis.

On multivariable linear regression analysis considering MgS levels as the dependent variable, we identified creatinine clearance and urinary magnesium as influenceable factors. No statistical significance was achieved for the type of calcineurin inhibitor used as presented in Table 2.

Type of Calcineurin Inhibitor and Analysis of Both Groups

The effect caused by the use of cyclosporine versus the use of tacrolimus on demographic and laboratory variables is shown in Table 3. All values of $P < .05$ confirm the presence of significant differences.

Cyclosporine versus tacrolimus analysis did not show a significant difference on MgS levels. We then divided each treatment group according to GFR, using 45 mL/min/1.73 m^2 as cut-off. The subgroup with GFR ≥45 mL/min/1.73 m^2 showed no difference in MgS levels. The subgroup with GFR <45 mL/min/1.73 m^2 had a significant difference on MgS levels with low MgS levels in the tacrolimus group, as shown in Table 4.

Table 1. Patient Characteristics (n = 94)

Sex	Male	59 (62.8%)
	Female	35 (37.2%)
Age (years)	Mean ± SD	52.6 ± 13.6
Body mass index (kg/m^2)	Mean ± SD	26.1 ± 4.5
Renal replacement therapy before transplantation	Hemodialysis	75 (81.3%)
	Peritoneal dialysis	13 (13.2%)
	Pre-emptive	6 (5.5%)
Duration of dialysis (months)	Mean ± SD	57.5 ± 53.6
Post-transplant duration (months)	Mean ± SD	103.1 ± 72.6
Type of calcineurin inhibitor used	Cyclosporine	57 (61.3%)
	Tacrolimus	36 (38.7%)
History of acute allograft rejection	Yes	10 (10.6%)
Estimated creatinine clearance (mL/min/1.73 m^2)	Mean ± SD	60.3 ± 23.8
Amount of proteinuria (mg/24 h)	Mean ± SD	662.9 ± 1355.9