Hypomagnesemia and Calcineurin Inhibitors in Kidney Transplant Recipients

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Abstract

Aim: Post-transplant hypomagnesemia is a frequently encountered and significant electrolyte disorder and is more common in patients using calcineurin inhibitors (CNIs). This study aimed to evaluate the frequency of hypomagnesemia and accompanying conditions in the outpatient follow-up of renal transplant recipients.

Methods: This cross-sectional study included 236 renal transplant patients. Demographic characteristics of the patients and their biochemical values, including drug levels, were recorded.

Results: Of the patients, 69 (29.2%) were female, and 194 (82.3%) were living donor recipients. The mean age of the entire group was 43.1 years. The frequency of hypomagnesemia was 40% (10/25) in the first 12 months, 26.1% (23/88) between the 12th and 60th months, 26% (32/123) after 60 months, and 27.5% (65/236) in all patients. In patients with higher levels of tacrolimus compared to those with the target level, the frequency of hypomagnesemia increased in those with a posttransplant period of 12-60 months (40.9% vs. 20.8%, p: 0.018) and over 60 months (44% vs. 26%, p: 0.046). In addition, the magnesium (Mg+2) level was lower in patients using tacrolimus compared to those using cyclosporine (CsA) (1.80±0.18 vs 1.91±0.25, p: 0.003). The effect of hypomagnesemia on graft functions was statistically insignificant in all groups.

Conclusion: Hypomagnesemia is a common electrolyte disorder in the early and late periods after transplantation. In our study, hypomagnesemia did not differ according to proton pump inhibitor (PPI) use, gender, fasting blood glucose, and glomerular filtration rate. However, the frequency increased in patients using tacrolimus and those with above-target serum tacrolimus levels.

Keywords: *Hypomagnesemia, kidney transplant, calcineurin inhibitor, posttransplant electrolyte disorders*

1. Introduction

Mg^{+2} is the fourth most abundant cation in the body and the second most crucial intracellular cation[1,2]. Approximately half of the total body Mg^{+2} is found in bones, and the rest is found in skeletal muscles and soft tissues[2]. Mg^{+2} involves physiological processes such as nerve and muscle function, cardiac rhythm, and blood pressure regulation. Low serum Mg^{+2} level (hypomagnesemia) is an electrolyte disorder frequently seen after renal transplantation[3].

It may cause symptoms such as muscle cramps or spasms, arrhythmias, numbness or formication in the extremities, mood swings or nervousness, loss of appetite, nausea, and vomiting. Hypomagnesemia may develop due to diuretics, acid-base imbalances, or Mg^{+2} loss due to renal tubular damage or gastrointestinal disturbances such as diarrhea, nausea, or vomiting. It is diagnosed by measuring serum Mg^{+2} levels. Treatment is primarily provided by supplementing Mg^{+2}, and the dosage and administration route depends on the deficiency level and the patient's clinical condition. Regular monitoring of Mg^{+2} levels is of great importance to ensure the effectiveness of the treatment and maintain the appropriate Mg^{+2} balance. Hypomagnesemia becomes more of an issue, especially in patients using CNIs[4].

In our study, we aimed to observe the frequency of hypomagnesemia in short (<12 months), medium (12-60 months), and long-term (>60 months) after renal transplantation and its relationship with the use of CNIs and biochemical and demographic characteristics.

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2. Materials and methods

2.1. Patients:

A total of 370 kidney transplant patients were evaluated. Of these 370 patients, 236 kidney transplant patients aged over 18 who underwent kidney transplantation between 2000 and 2016, who did not have acute rejection or acute kidney injury, who had a glomerular filtration rate of (GFR) >30 ml/min, who did not have any gastrointestinal or other critical diseases, who did not use diuretics, and who did not have uncontrolled diabetes were included in the study. Power analysis was performed for identifying the number of participants in the study conducted between 2016 and 2019, and two hundred and twenty patients were targeted. In the study, the frequency of hypomagnesemia in the first 12 months, between the 12th and 60th months, and after 60 months and the estimated glomerular filtration rate (e-GFR/CKD-EPI 2021), CNI levels (Tacrolimus C0 and cyclosporine A C2 level), and laboratory parameters were compared. In the study in which hypermagnesemia was not observed, patients were divided into two groups according to the Mg^{+2} level: hypomagnesemia (below 1.8 mg/dL) and normomagnesemia. Tacrolimus therapeutic target range was accepted as 8-12 ng/mL in the first 12 months, 5-8 ng/mL between 12 and 60 months, and 3-5 ng/mL after 60 months; C2 target level in patients treated with cyclosporine A (CsA) was accepted as 1000-1200 ng/ml (0-3 months), 600-1000 ng/ml (3-12 months), and around 600-800 ng/ml (>12 months). The study was designed as a cross-sectional and retrospective study. The study was conducted on outpatient kidney transplant patients admitted to the nephrology outpatient clinic of Cukurova University Faculty of Medicine.

Ethics committee approval was taken from Cukurova University Ethics Committee (Dated: 4/3/2016, Decision Number: 24). Informed consent was taken from all patients.

2.2 Statistical Analysis:

SPSS 18.0 for Windows was used for statistical evaluation. As a descriptive value, minimum, maximum, mean, and standard deviation were used for quantitative data. In intergroup comparisons, Chi-square and Fisher's exact tests were used for categorical variables, and a t-test was used for paired group comparisons. In evaluation, $p<0.05$ was accepted as the significance level.

3. Results

Of the patients included in the study, 69 (29.2%) were female, and 194 patients (82.3%) were transplant recipients from a living-relative donor. The mean age of the entire group was 43.1. Post-transplant hypomagnesemia was observed in 65/236 (27.5%) patients. The frequency of hypomagnesemia was 40% (10/25) in the first 12 months, 26.1% (23/88) between the 12th and 60th months, and 26% (32/123) after 60 months. The primary kidney diseases of the patients, the immunosuppressive drugs they used, and their demographic data are presented in Table 1.

Serum calcium and potassium levels were statistically significantly lower in the hypomagnesemia patient group compared to the normomagnesemic group (9.31±0.78 mg/dL vs. 9.59±0.59 mg/dL, p=0.008 - 4.14±0.48 mmol/L vs. 4.3±0.51 mmol/L, p=0.028, respectively). There was no statistically significant difference between patients with and without hypomagnesemia regarding age, gender, follow-up periods, e-GFR levels, living or cadaveric transplantation, serum levels of sodium, glucose, CNI, and PPI use (Table 2).

In cases where tacrolimus was above the target level, hypomagnesemia was statistically significantly more frequent than normomagnesemia in both the patient groups with a posttransplant period of 12-60 months and >60 months (42.9% vs. 20.4%, p=0.048 / 44% vs. 22.6%, p=0.046, p=0.046, respectively), but there was no significant difference in terms of the frequency of hypomagnesemia in patients with a posttransplant period of <12 months (p=0.665) (Table 3).

Table 1

Demographic characteristics of patients

Variables	
Female/Male, n (%)	69(29.2)/167(70.8)
Female/Male Mean age±SD	40.52±12.3/44.17±12.37
The mean age ±SD of the entire group	43.10±12.42
Cadaveric/living donor n (%)	42(17.7)/194(82.3)
Number of patients using PPI, n (%)	71(30.1)
Number of patients using tacrolimus	186/236
Number of patients using cyclosporin	33/236
Number of patients using mTOR inhibitor	10/236
Other immunosuppressive drugs	7/236
Primary Kidney Disease	n(%)
Hypertension	75(32)
Diabetes mellitus	56(24)
Idiopathic	37(14)
Chronic glomerulonephritis	36(16)
Kidney stone	10(4)
Polycystic Kidney Disease	19(8)
Tubulointerstitial Nephritis	3(2)

Abbreviations: mTOR: Mammalian target of rapamycin, PPI: Proton pump inhibitor

Serum Mg^{+2} levels were significantly lower in patients using tacrolimus (n=186) than in patients using CsA (n=33) (1.80±0.18 mg/dL vs 1.91±0.25 mg/dL, p=0.003). Sodium levels were significantly lower in cyclosporine patients than those using tacrolimus (136.47±2.54 mmol/L vs 137.98±2.74 mmol/L, p=0.004) (Table 4).

There was no statistically significant difference between cadaveric and living transplantation regarding the demographic and laboratory parameters (Table 5).

4. Discussion

In immunosuppressive regimens using CNIs after kidney transplantation, hypomagnesemia is frequently observed due to increased urinary excretion of Mg+2. CsA and tacrolimus are most recommended for maintenance immunosuppressive therapy, and both have a magnesium-lowering effect. CNIs down-regulate renal expression of epidermal growth factor and distal collecting tubule of Transient Receptor Potential Melastatin 6 (TRPM6), which absorbs distal magnesium[5,6]. Hypomagnesemia was observed in 6.6% of patients receiving tacrolimus and 1.5% receiving CsA[7] It has been reported that hypomagnesemia frequently develops in the first few weeks after transplantation and that serum Mg is at the lowest level in the second month after transplantation[8]. A cohort study on 49 kidney transplant recipients reported that 22.4% of patients developed hypomagnesemia six years after transplantation and that posttransplant hypomagnesemia could persist for a long time[9]. In our study, according to the follow-up period, the frequency of hypomagnesemia after renal transplantation was 40% (10/25) in the first 12 months, 26.1% (23/88) in between the 12th and 60th months, and 26% (32/123) after 60 months. The frequency among all patients was 27.5% (65/236).

Our study found that serum calcium and potassium levels were statistically significantly lower in the hypomagnesemia patient group than in the normomagnesemic patient group.

Table 2

Comparison of renal transplant patients with low and normal magnesium levels in terms of the follow-up period, calcium level, phosphorus level, graft function during transplantation, age, sex, donor source, and drug level

Variables	Serum magnesium (<1.8 mg/dL) (n=65, 27.54%)	Magnesium level normal (>1.8 mg/dL) (n=171, 72.46%)	P
<12 months (n=25)	10 (40%)	15 (60%)	
12-60 months (n=88)	23 (26%)	65 (74%)	
>60 months (n=123)	32 (26%)	91 (74%)	
Calcium (mg/dL)	9.31±0.81	9.58±0.59	0.018
Phosphorus (mg/dL)	3.37±0.84	3.30±0.66	0.450
Calcium x phosphorus product	31.15±5.96	31.51±6.04	0.689
Sodium level (mmol/L)	137.5±3.42	137.8±2.46	0.530
Potassium level (mmol/L)	4.14±0.48	4.3±0.51	0.028
Glucose level (mg/dL)	103.12±48.54	106.74±56.98	0.671
12 months e-GFR (ml/min)	75.63±38.66	68.73±23.48	0.583
12-60 months e-GFR (ml/min)	84.16±28.73	75.78±24.32	0.179
>60 months e-GFR (ml/min)	76.67±31.97	70.95±26.92	0.328
Age (year)	42.70±12.34	43.26±12.51	0.760
Sex (Female/Male)	22(32%)/47(68%)	43(26%)/124(74%)	0.337
Cadaveric transplantation (n=42)	13(20%)	29(17%)	0.585
Living transplantation (n=194)	52(80%)	142(83%)	
Tacrolimus level (ng/dL) (n=186)	5.78±2.46	5.13±2.38	0.098
Cyclosporin level (C2 level, ng/mL), (n=33)	336.06±301.06	251.34±191.83	0.386
Use of proton pump inhibitor (Yes/No)	22(34.4%)/43(65.6%)	50(29.5%)/121(70.5%)	0.475

Table 3

The frequency of hypomagnesemia in patients with serum tacrolimus levels in the target range and above the target level

Posttransplant period	Magnesium level	Number of patients	Number of patients with a tacrolimus level above the target value*	P
<12 months	Hypomagnesemia	10	3/10 (30%)	0.665
(n=24)	Normomagnesemia	14	3/14 (21.4%)	
12-60 months	Hypomagnesemia	21	9/21 (42.9%)	0.048
(n=75)	Normomagnesemia	54	11/54 (20.4%)	
>60 months	Hypomagnesemia	25	11/25 (44%)	0.046
(n=87)	Normomagnesemia	62	14/62 (22.6%)	

* The therapeutic target range for tacrolimus was accepted as 8-12 ng/mL for <12 months, 5-8 ng/mL for 12-60 months, and 3-5 ng/mL for >60 months.

Table 4

Comparison of patients' serum magnesium, glucose, and calcium levels using tacrolimus and cyclosporine as maintenance immunosuppressive.

Variables	Patients using tacrolimus (n=186)	Patients using cyclosporin (n=33)	P
Patients with hypomagnesemia, n (%)	53(28.5%)	6(18.2%)	0.218
Serum magnesium (mg/dL)	1.80±0.18	1.91±0.25	0.003
Serum calcium (mg/dL)	9.51±0.69	9.44±0.56	0.579
Serum phosphorus (mg/dL)	3.31±0.70	3.38±0.66	0.568
CalciumxPhosphorus product	31.34±5.74	31.94±6.30	0.585
Serum glucose (mg/dL)	107.93±58.57	94.61±16.56	0.259
Serum potassium (mmol/L)	4.26±0.47	4.34±0.61	0.388
Serum sodium (mmol/L)	137.98±2.74	136.47±2.54	0.004

Table 5
Comparison of renal transplant recipients according to the donor

Variables	Cadaveric Transplantation	Living Transplantation	P
Female/Male, n (%)	19(45.2%)/23(54.8%)	50(25.8%)/144(74.2%)	0.012
Age (year)	43.81±14.03	42.96±12.11	0.689
Tacrolimus level (ng/dL)	5.46±2.75	5.28±2.33	0.682
Cyclosporin C2 level (ng/mL)	354.57±204.67	257.96±214.63	0.462
Patients using tacrolimus, n (%)	39(92.9%)	147(83.1%)	
Patients using cyclosporine, n (%)	3(7.1%)	30(16.9%)	0.110
<12 months, n (%)	6(14.3%)	19(9.8%)	
12-60 months, n (%)	21(50%)	67(34.5%)	0.064
>60 months, n (%)	15(35.7%)	108(55.7%)	
Glucose level (mg/dl)	122.44±92.26	101.73±40.36	0.178
Calcium (mg/dL)	9.42±0.78	9.53±0.64	0.343
Phosphorus (mg/dL)	3.40±0.66	3.30±0.72	0.404
Calcium x phosphorus product	32.04±5.63	31.28±6.09	0.467
Serum sodium (mmol/L)	138.17±3.01	137.61±2.70	0.242
Serum potassium (mmol/L)	4.25±0.46	4.26±0.52	0.903
Serum magnesium(mg/dL)	1.78±0.19	1.82±0.21	0.218
<12 months e-GFR (ml/min)	80.53±40.36	68.63±26.53	0.407
12-60 months e-GFR (ml/min)	80.58±23.32	77.16±26.45	0.597
>60 months e-GFR (ml/min)	72.38±26.31	72.45±28.67	0.993
Patients using proton pump inhibitor, n (%)	16(39%)	55(29.1%)	0.212

In the study conducted by Suh et al., it was shown that the parathormone response might be impaired in hypomagnesemia conditions, and it was stated proposed that although the parathormone level increases, this may not be enough to provide sufficient calcium level[10].

CsA and tacrolimus lead to a 2- to 3-fold and 1.6- to 1.8-fold increase in urinary calcium and magnesium excretion, respectively, whereas rapamycin has no effect on calcium but doubles urinary magnesium excretion[10].

Our study showed that the potassium levels were within normal limits in hypomagnesemia patients but statistically significantly lower than in normomagnesemic patients. CNI were also examined according to the donor source, but no difference was found in potassium levels in both comparison groups. In the literature, there is no data on lower potassium levels within the normal range of posttransplant hypomagnesemia in the case of immunosuppressant use or other clinical processes. The possible reason for this might be associated with the potassium secretion-increasing effect of hypomagnesemia from the distal tubules.

Serum sodium levels of patients using CsA were significantly lower than those using tacrolimus. Contrary to our study, Higgins et al.[12] stated that serum Na^+ levels were lower in patients using tacrolimus, which could be associated with high glucose levels. Our study found that the mean fasting blood glucose (FBG) was 107 mg/dL in patients using tacrolimus and 94 mg/dL in patients using CsA and that there was no statistical difference between the groups. There are many findings in the literature stating that there is no difference in serum Na^+ levels of patients using tacrolimus and CsA[12,13].

Kidney Disease Improving Global Outcomes (KDIGO) recommended the target tacrolimus level as 5–15 ng/mL in the early post-transplant period[14]. However, in their study, Richards et al.[14] reported that tacrolimus concentrations of >8 ng/mL are required to reduce the frequency of early rejection in the first year after transplantation. In our study, the therapeutic target range for tacrolimus was determined as 8-12 ng/mL for <12 months, 5-8 ng/mL for 12-60 months, 3-5 ng/mL for >60 months and the frequency of hypomagnesemia was found to be increased in patients with tacrolimus above the target value for 12-60 months and over 60 months (40.9% vs. 20.8%, p=0.018 and 44% vs. 26%, p=0.046, respectively). In addition, it is known that tacrolimus increases renal Mg^{+2} excretion, which is more common in patients with high drug levels[15]. Serum Mg^{+2} levels were significantly lower in patients using tacrolimus than those using CsA. This has been shown in studies on Type 2 DM, which is newly developing in the posttransplant period[16].

The limitations of our study were the relatively small number of cases, examination at different stages of the posttransplant period, and the study's cross-sectional design.

5. Conclusions

Hypomagnesemia is a common electrolyte disorder seen in the early post-transplant period and the late period after five years. Interestingly, gender, proton pump inhibitors use, blood glucose levels, and GFR values did not differ for hypomagnesemia in our study. It was determined that using tacrolimus and above-target tacrolimus levels after the 12th month increased the frequency of hypomagnesemia after transplantation. Due to the long-term persistence of hypomagnesemia, monitoring the serum Mg^{+2} levels in renal transplant recipients is crucial.

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Statement of ethics
This study was approved from Cukurova University Ethics Committee (Dated: 4/3/2016, Decision Number: 24). Informed consent was taken from all patients.

Conflict of interest statement
The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

EO, SP: concepts, design, data acquisition, statistical analysis, manuscript editing and manuscript review.
ET: definition of intellectual content, literature search, data analysis, manuscript preparation and manuscript review.
MB, NCG, İA: clinical studies, data acquisition, manuscript review.
All authors read and approved the final manuscript.

References

1.Jahnen-Dechent,W, Ketteler, M. Magnesium basics. Clin. Kidney J. 2012; 5: i3–i14.
https://doi.org/10.1093/ndtplus/sfr163
2.Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. Lancet 1998 ; 352 : 391–6.
https://doi.org/10.1016/s0140-6736(97)10535-9
3.Garnier AS, Duveau A, Planchais M, et al. Serum Magnesium after kidney transplantation: a systematic review. Nutrients. 2018;10(6):729.
https://doi.org/10.3390/nu10060729
4.Stefanelli LF, Alessi M, Bertoldi G, et al. Calcineurin-inhibitor-induced hypomagnesemia in kidney transplant patients: a monocentric comparative study between sucrosomial magnesium and magnesium pidolate supplementation. J Clin Med. 2023; 12(3):752.
https://doi.org/10.3390/jcm12030752
5.Van Laecke S, Van Biesen W. Hypomagnesaemia in kidney transplantation. Transplantation Reviews. 2015; 29(3):154-60.
https://doi.org/10.1016/j.trre.2015.05.002
6.Ledeganck KJ, De Winter BY, Van den Driessche A, et al. Magnesium loss in cyclosporine-treated patients is related to renal epidermal growth factor downregulation. Nephrology Dialysis Transplantation. 2014; 29(5):1097-102.
https://doi.org/10.1093/ndt/gft498
7.Margreiter R. European tacrolimus vs. ciclosporin microemulsion renal transplantation study group efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: A randomized multicentre study. Lancet. 2002; 359: 741–6.
https://doi.org/10.1016/s0140-6736(02)07875-3
8.Stevens RB, Lane JT, Boerner BP, et al. Single-dose rATG induction at renal transplantation: Superior renal function and glucoregulation with less hypomagnesemia: RATGS minimizes glucose dysregulation. Clin. Transplant. 2012; 26:123–32.
https://doi.org/10.1111/j.1399-0012.2011.01425.x
9.Van de Cauter J, Sennesael J, Haentjens P. Long-term evolution of the mineral metabolism after renal transplantation: A prospective, single-center cohort study. Transplant. Proc. 2011; 43:3470–5.
https://doi.org/10.1016/j.transproceed.2011.09.030
10.Suh SM, Tashjian AH Jr, Matsuo N, et al. Pathogenesis of hypocalcemia in primary hypomagnesemia: normal end-organ responsiveness to parathyroid hormone, impaired parathyroid gland function. J Clin Invest. 1973; 52(1):153-60.
https://doi.org/10.1172/jci107159
11.Chien-Te Lee, Hwee-Yeong Ng, Yeong-Hau Lien, et al. Effects of cyclosporine, tacrolimus and rapamycin on renal calcium transport and vitamin D metabolism. Am J Nephrol. 2011; 34(1):87-94.
https://doi.org/10.1159/000328874
12.Robert Higgins, Karam Ramaiyan, Tanaji Dasgupta, et al. Hyponatraemia and hyperkalemia are more frequent in renal transplant recipients treated with tacrolimus than with cyclosporin. Further evidence for differences between cyclosporin and tacrolimus nephrotoxicities, Nephrology Dialysis Transplantation. 2004; 19(2): 444–50.
https://doi.org/10.1093/ndt/gfg515
13.Vincenti F, Jensik SC, Filo RS, Miller J, et al. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. Transplantation. 2002; 73: 775–82.
https://doi.org/10.1097/00007890-200203150-00021
14.Chapman JR. The KDIGO clinical practice guidelines for the care of kidney transplant recipients. Transplantation. 2010; 89:644–5.
https://doi.org/10.1097/tp.0b013e3181d62f1b
15.Gratreak BDK, Swanson EA, Lazelle RA, et al. Tacrolimus-induced hypomagnesemia and hypercalciuria require FKBP12 suggesting a role for calcineurin. Physiol Rep. 2020; 8(1): e14316.
https://doi.org/10.14814/phy2.14316
16.Augusto JF, Subra JF, Duveau A, et al. Relation between pretransplant magnesemia and the risk of new-onset diabetes after transplantation within the first year of kidney transplantation. Transplantation. 2014; 97(11): 1155-60.
https://doi.org/10.1097/01.tp.0000440950.22133.a1