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COMPARISON OF SERUM MAGNESIUM LEVELS IN RENAL TRANSPLANT PATIENTS RECEIVING TACROLIMUS VS CYCLOSPORINE

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Abstract

Objectives: *To evaluate the relationship between Tacrolimus and Cyclosporine on serum magnesium levels in kidney transplant recipients.*

Study design: *Prospective Cross Sectional Study*

Place and duration: *Armed Forces Institute of Urology conducted for six months April 2024- Jan 2025*

Methods: *This study involved 130 kidney transplant recipients over aged 20 years, who had followed up of over one year after their transplant at our centre. The participants were divided into two group Tacrolimus-Based (n=70) and Cyclosporine-Based (n=60). Data was analysed by SPSS 2.3 software. Descriptive and multivariate regression analyses were performed to determine independent predictors of hypomagnesemia, that was, duration of dialysis, history of previous acute rejection, and markers of kidney function.*

Results: *Serum magnesium levels were significantly lower in patients on Tacrolimus as compared to patients on Cyclosporine (β = -0.210, $p < 0.001$). Prolonged dialysis duration, history of acute rejection and impaired kidney function (serum creatinine) were associated with hypomagnesemia (β = -0.008, p = 0.010; β = -0.115, p = 0.006; β = -0.058, p = 0.018, respectively), whereas serum magnesium after 1 year correlated with kidney function, although weakly (β = 0.004, p = 0.045). Calcium, phosphate, iPTH, and vitamin D were not associated with significant difference.*

Conclusion: *Hypomagnesemia is increased by tacrolimus based immunosuppression in kidney transplant recipients. Furthermore, hypomagnesemia is also contributed to by prolonged dialysis duration, history of acute rejection, and worsening kidney function.*

INTRODUCTION

Kidney Transplantation is the preferred treatment in End Stage Renal Disease (ESRD), which provides better survival rate and quality of life than dialysis. However, electrolyte imbalances still remain a big metabolic concern after the transplant [1]. Of these, hypomagnesemia is frequently encountered and occurs more often in patients treated with calcineurin inhibitors (CNIs) like Tacrolimus and

Cyclosporine. Magnesium is essential in cellular function, enzymatic activity, neuromuscular conduction and cardiovascular stability and deficiency is a potential risk factor for adverse outcome in kidney transplant recipients [2, 3]. Tacrolimus and Cyclosporine are widely used to suppress T-cell activation and hence, improve graft survival. However, their nephrotoxic effects can result in an electrolyte disturbance such as hypomagnesaemia [4, 5]. Among immunosuppressives, tacrolimus should be more particularly mentioned since it has been known to lead to increased magnesium renal wasting as result of its direct effect on renal tubular transport mechanisms [6]. It decreases magnesium reabsorption from the distal tubules and increase urinary magnesium excretion. Tacrolimus treated patients are more at risk of hypomagnesemia than its effect of cyclosporine to the same degree [7].

Various complications such as increased risks of cardiovascular diseases, insulin resistance, osteoporosis and chronic allograft nephropathy are associated with hypomagnesemia in kidney transplant recipients [8]. Furthermore, magnesium deficiency may also play a role in increasing oxidative stress and inflammation, which could associate with greater rejection rates as well as poorer graft survival. Though these clinical implications exist, monitoring and supplementation of magnesium remains inconsistent in post transplant care leading to the need for further exploration into the burden and risk factors of hypomagnesemia [9]. Magnesium homeostasis is influenced by several factors after kidney transplantation. Dialysis for a prolonged period before transplantation can also adversely affect renal tubular function and make it difficult to control magnesium after renal transplant. Also, acute rejection episodes are associated with a history of unknown role of rejection related inflammation as well as adjustments of immunosuppressive therapy that may also contribute to alter magnesium metabolism [10]. Moreover, serum creatinine and estimated glomerular filtration rate (eGFR) are also important markers of kidney function and powerful predictors of development of electrolyte disturbances, mainly hypomagnesemia. Several metabolic factors, including calcium, phosphate, iPTH, folate and vitamin D, have been assessed in transplant recipients but much less is known about the relation of actual magnesium homeostasis [11].

Despite numerous studies examining the effect of Tacrolimus and Cyclosporine on post-transplant electrolyte disturbances, most of them are limited to short term results or small sample sizes. Moreover, despite Tacrolimus being well known to have a magnesium wasting effect, the risk difference between Tacrolimus and Cyclosporine in the real world is still shrouded in shadows. Additionally, there is limited research on independent predictors of hypomagnesemia including dialysis duration, acute rejection history, kidney function markers. In addition, it is unknown how metabolic parameters such as calcium, phosphate, iPTH and vitamin D affect magnesium levels. These gaps can be addressed that are relevant to improving post transplant care and for optimizing kidney transplant recipients' long-term outcome.

The aim of this study was to evaluate the relationship between Tacrolimus and Cyclosporine on serum magnesium levels in kidney transplant recipients. In addition, it aims to identify independent predictors of hypomagnesemia, the factors are dialysis duration, history of acute rejection and markers of kidney function. This study will also address these factors in order to contribute to better understanding of post transplant magnesium disturbances, and to define strategies for early detection and management.

Methodology

This was a cross-sectional study on renal transplant patients receiving either immunosuppression with Tacrolimus or Cyclosporine. This study was conducted for Ten months. This study involved 130 kidney transplant recipients over aged 20 years, who had followed up of over one year after their transplant at our centre. The participants were divided into two treatment group Tacrolimus-Based (n=70) and Cyclosporine-Based (n=60). No patients were hepatitis B or C positive status or taking furosemide, thiazide or magnesium supplementation were included. All patients were on an immunosuppressive regimen of a calcineurin inhibitor, mycophenolate mofetil and prednisone. Patients were evaluated medically and laboratory tests were performed in the same facility for consistency. Demographics data collected were age,

sex, weight, height, dialysis length before transplant, type of dialysis used prior to transplant, transplant length of follow up, and type of immunosuppressive therapy used. Blood was analysed for serum creatinine, magnesium, calcium, phosphate and measured 25 hydroxyvitamin D concentration (25OH VIT-D3), and 24 hour urine tests for magnesium, calcium, phosphate, and protein excretion. According to National Kidney Foundation, estimation of the glomerular filtration rate (GFR) was done by CKD-EPI Creatinine Equation. A serum magnesium level of less than 1.5 mg/dL constituted hypomagnesemia. SPSS 23.0 was used to do statistical analysis. Categorical variables, including dialysis type, immunosuppressive therapy, and history of acute rejection, were summarized for the patients in terms of percentages and continuous variables were described in terms of mean± standard deviation (SD). For examining the relationship between serum magnesium levels and other factors, Pearson correlation analysis was used. The impact of different variables on magnesium levels was determined by applying a multivariable linear regression model. Three statistical tests using different variable distribution (chi-square test for sex and class of calcineurin inhibitor, t for age and Mann-Whitney test for all others) were carried out to evaluate the effect of different calcineurin inhibitors. These analyses were used to determine, in kidney transplant recipients, the effect immunosuppressive therapy has on serum magnesium levels.

Results

The average age was 45.6 ± 12.3 years and was male predominant (61.5% male, 38.5% female) of 130 kidney transplant recipients. The average BMI of the patients was 24.3 +/- 3.8 kg/m² and most patients (73.1%) were on hemodialysis prior to transplantation. The mean follow up was 36.2 ± 10.7 months. Tacrolimus based was 53.8% and cyclosporine based was 46.2%. In 19.2% of patients an acute rejection was seen in history. These data show that tacrolimus was the more commonly used immunosuppressant and a large proportion had prolonged dialysis prior to transplant see Table I.

Table I: Demographic Characteristics of Study Participants (N=130)

Variable	Mean ± SD or n (%)
Age (years)	45.6 ± 12.3
Sex	
- Male	80 (61.5%)
- Female	50 (38.5%)
Weight (kg)	68.2 ± 14.5
Height (cm)	167.4 ± 9.2
Body Mass Index (BMI) (kg/m²)	24.3 ± 3.8
Dialysis Duration Before Transplant (months)	24.8 ± 8.5
Type of Dialysis Before Transplant	
- Hemodialysis	95 (73.1%)
- Peritoneal Dialysis	35 (26.9%)
Follow-up Duration After Transplant (1 year)	36.2 ± 10.7
Type of Immunosuppressive Therapy	
- Tacrolimus-Based	70 (53.8%)
- Cyclosporine-Based	60 (46.2%)
History of Acute Rejection	
- Yes	25 (19.2%)
- No	105 (80.8%)

It was found that tacrolimus use was significantly associated with lower serum magnesium levels compared to cyclosporine (β = -0.210, p < 0.001) with the multivariable linear regression analysis. Furthermore, decreased magnesium levels were also associated with the duration of dialysis before transplantation (β = -0.008, P = 0.010) and a history of acute rejection (β = -0.115, P = 0.006). Magnesium also exhibited a negative correlation with higher serum creatinine (β = -0.058, p = 0.018) suggesting worsening kideny function might contribute for hypomagnesemia. Other variables, such as age, BMI, follow up duration, serum calcium, phosphate, iPTH, or vitamin D levels were not associated in any significant way. Immunosuppressive therapy, dialysis history, and kidney function were the key determinants of serum magnesium levels in renal transplant recipients and overall model accounted for 42% of the variance (R2 = 0.42, p < 0.001) see Table II.

Table II: Multivariable Linear Regression Analysis for Serum Magnesium Levels

Independent Variables	β (Regression Coefficient)	95% Confidence Interval (CI)	p-value
Age (years)	-0.012	(-0.025, 0.001)	0.075
Sex (Male vs. Female)	-0.042	(-0.095, 0.011)	0.124
BMI (kg/m²)	-0.021	(-0.043, 0.002)	0.067
Duration of Dialysis (months)	-0.008	(-0.015, -0.002)	**0.010**
Follow-up After Transplant (1 year)	0.006	(-0.002, 0.014)	0.145
Tacrolimus vs. Cyclosporine	-0.210	(-0.312, -0.108)	**<0.001**
History of Acute Rejection (Yes vs. No)	-0.115	(-0.198, -0.032)	**0.006**
Serum Creatinine (mg/dL)	-0.058	(-0.106, -0.010)	**0.018**
Serum Calcium (mg/dL)	0.023	(-0.035, 0.081)	0.432
Serum Phosphate (mg/dL)	-0.033	(-0.095, 0.029)	0.287
iPTH (pg/mL)	-0.002	(-0.005, 0.001)	0.201
25OH-Vitamin D (ng/mL)	0.005	(-0.002, 0.012)	0.148

These results show that the patients receiving tacrolimus had significantly lower serum magnesium levels compared to the patients receiving cyclosporine (1.49 ± 0.22 mg/dL vs. 1.78 ± 0.26 mg/dL; p < 0.001) and confirm that patients on tacrolimus are at higher risk of hypomagnesemia. Moreover, the history of acute rejection was significantly more frequent in the tacrolimus group (27.1%) compared to cyclosporine group (10.0%, p = 0.017), which might be explained by different types of immune responses or effects of the used drugs. The other covariates such as age, BMI, dialysis and follow up duration and serum creatinine, calcium, phosphate, iPTH and vitamin D levels were not different between the groups. This shows that serum magnesium levels should be monitored regularly, and care of the individual risk of acute rejection taken, particularly in renal transplant patients taking tacrolimus see Table III.

Table III: Comparison of Patients on Cyclosporine vs. Tacrolimus

Variable	Cyclosporine (n=60)	Tacrolimus (n=70)	p-value
Age (years, mean ± SD)	46.8 ± 11.9	44.5 ± 12.6	0.342
Male (%)	36 (60.0%)	44 (62.9%)	0.743
BMI (kg/m², mean ± SD)	24.8 ± 3.7	23.9 ± 3.9	0.211

Duration of Dialysis (months, mean ± SD)	23.6 ± 7.9	25.8 ± 9.0	0.158
Follow-up After Transplant (months, mean ± SD)	37.4 ± 11.2	35.2 ± 10.3	0.279
History of Acute Rejection (%)	6 (10.0%)	19 (27.1%)	**0.017**
Serum Creatinine (mg/dL, mean ± SD)	1.45 ± 0.32	1.52 ± 0.38	0.287
Serum Magnesium (mg/dL, mean ± SD)	1.78 ± 0.26	1.49 ± 0.22	**<0.001**
Serum Calcium (mg/dL, mean ± SD)	9.2 ± 0.6	9.1 ± 0.7	0.452
Serum Phosphorus (mg/dL, mean ± SD)	3.6 ± 0.8	3.5 ± 0.7	0.523
iPTH (pg/mL, mean ± SD)	58.3 ± 21.4	55.7 ± 23.1	0.518
25OH-Vitamin D (ng/mL, mean ± SD)	23.5 ± 5.8	22.9 ± 6.2	0.649

Discussion

This study demonstrates that tacrolimus treatment is associated with significantly lower serum magnesium levels than cyclosporine. Tacrolimus can induce hypomagnesemia more often than other preparations as it can affect renal magnesium handling. The association between patient electrolyte imbalances and magnesium levels lower than that observed, as well as prolonged dialysis before transplantation, supports the hypothesis that kidney dysfunction is tremendously important in electrolyte imbalances of transplant recipients [12, 13].

Impacts of immunosuppressive therapy, specifically Tacrolimus and Cyclosporine on serum magnesium level in renal transplant recipients were investigated in our study. Findings show that the Tacrolimus based immunosuppression is associated significantly with lower level of serum magnesium than Cyclosporine based therapy ($p < 0.001$). Also, the hypomagnesemia was associated with greater duration of dialysis prior to transplantation ($p = 0.010$), history of acute rejection ($p = 0.006$), and worsening kidney function serum creatinine: ($p = 0.018$). Taken together, these results suggest that Tacrolimus predisposes kidney transplant patients to hypomagnesemia which is independent of calcium, phosphate,parathyroid hormone (iPTH), and vitamin D levels [14].

Our findings are in keeping with previous studies showing that Tacrolimus seems to be associated with a higher incidence of hypomagnesemia compared

with Cyclosporine. Alternatively, there is one proposed mechanism by which this difference occurs, which is increased renal magnesium wasting result from Tacrolimus inhibition of transient receptor potential melastatin 6 (TRPM6) and TRPM7 channels in the distal renal tubule, resulting in reduced magnesium reabsorption. In agreement with this, Onan et al. (2023) showed that Tacrolimus treated patients had significantly higher urinary magnesium excretion compared to Cyclosporine treated patients [15]. Moreover, studies regarding the degree of Tacrolimus–induced hypomagnesemia have determined also these hypomagnesemic levels to be positively correlated to the dose range of Tacrolimus used by patients resulting in a dose dependent hypomagnesemia. In our study, we did not stratify the patients based on the dose of Tacrolimus used and future work may inquire if higher doses contribute to further depletion of magnesium [16].

Moreover, we showed a significantly higher prevalence of acute rejection in Tacrolimus group (27.1%) in comparison with that in Cyclosporine group (10.0%, $p = 0.017$). It is in line with Gummert et al. (2018) who found that although Tacrolimus has stronger potency against rejection, it also causes a different alteration of the immune homeostasis than Cyclosporine [17]. Acute rejection episodes themselves lead to renal dysfunction and thus may worsen Tacrolimus-induced hypomagnesemia by further injuring the tubules and further increasing urinary losses of magnesium. In addition, serum magnesium had a negative correlation with serum creatinine ($\beta = -0.058$, $p = 018$), indicating that hypomagnesemia is due to worsening kidney function. This finding is consistent with Stefanelli et al. (2023), who proved that reduced functioning of the kidney promotes magnesium loss due to reduced reabsorption in the face of elevated magnesium loss caused by Tacrolimus [18].

We found no significant association of serum magnesium with such variables as age, BMI, level of

serum calcium, phosphate, iPTH, and vitamin D [19]. On the contrary, studies by Ehrenpreis et al. (2022) suggested that, unlike in the present case, hypomagnesemia could result from hypovitaminosis D. That would be different if the population that we studied had significantly fluctuating vitamin D levels, which many people found in the population did but was not found in our study population [20].

These findings are clinically important in that they raise concern for the need to routinely monitor magnesium in kidney transplant recipients, especially those on Tacrolimus based immunosuppression. Because Tacrolimus treated patients are at significant higher risk of hypomagnesemia, serum and urinary levels should be regularly assessed in follow up of post transplant patients. In addition, magnesium supplementation or dosage adjustment may be helpful especially in patients with a background of previous episodes of acute rejection or prolonged pretransplant dialysis. Whether hypomagnesemia itself increases the risk of acute rejection or if it ensues as a result of Tacrolimus therapy remains to be determined in future studies. Finally, interventional trials testing whether magnesium supplementation decreases the rejection rate would be informative.

Conclusion

The current study shows that Tacrolimus-based immunosuppression leads to a significantly low level of serum magnesium in the renal transplant recepients. Furthermore, hypomagnesemia is also contributed to by prolonged dialysis duration, history of acute rejection, and worsening kidney function. Such findings emphasize the necessity for repeated magnesium surveillance and recommend that specific immunosuppressive schemes to minimize magnesia loss may be adopted in renal transplant patients. Given the potential clinical consequence of magnesium deficiency, management of this deficiency may improve the transplant outcome if it is proactive with supplementation as needed. However, research is still warranted to find out whether these results will impact graft survival or patient health long term.

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Authors Contribution:

Author	*Contribution*
MS	*1. Substantial Contribution to study design, analysis, acquisition of Data* *2. Manuscript Writing* *3. Has given Final Approval of the version to be published*
FI	*1. Substantial Contribution to study design, acquisition and interpretation of Data* *2. Critical Review and Manuscript Writing* *3. Has given Final Approval of the version to be published*
AS	*1. Substantial Contribution to acquisition and interpretation of Data* *2. Manuscript Writing* *3. Has given Final Approval of the version to be published*
SS	*1. Contributed to Data Collection and Analysis* *2. Critically reviewed the article* *3. Has given Final Approval of the version to be published*
NK	*1. Substantial Contribution to study design and Data Analysis* *2. Manuscript Writing and Critical review of the article* *3. Has given Final Approval of the version to be published*
MFH	*1. Contributed to study concept and Data collection* *2. Critical review of the manuscript* *3. Has given Final Approval of the version to be published*

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