Hypomagnesemia During Early Post Renal Transplantation Period

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ABSTRACT:

BACKGROUND:

In renal transplantation, hypomagnesemia is a frequent disturbance associated with the use of calcineurin inhibitors (Cyclosporine and Tacrolimus) and sirolimus. They may cause obligatory renal loss and decrease transcriptional expression of the Mg transporter in the distal collecting tubule.

OBJECTIVE:

Evaluation of serum Magnesium in patients during the first four days post renal transplantation and to find any correlation with different variables.

PATIENTS AND METHOD:

A cross sectional descriptive study was performed at Nephrology and Kidney Transplantation Center- Medical City-Baghdad, Iraq from first of January, 2012 to first of December, 2012. Serum Magnesium was followed in forty patients underwent renal transplantation during the first four days post transplantation. Other variables also was studied to find any correlation with serum Magnesium, include (age, sex, duration dialysis of , calcineurin inhibitors (types and dose) , diabetes mellitus, loop diuretics, urine volume . electrolytes (serum Potassium and s. Calcium) and s.creatinine .

RESULT:

The mean serum Magnesium was (2.87 ± 0.5 mg/dl) pre transplantation, on 1st day it was (2.3±0.49) and 4thday (2.31±0.67). The mean Post transplantation serum Magnesium was significantly lower than pre transplantation, ($P<0.01$). Serum Magnesium had statistically significant direct correlation with serum Potassium and s.creatinine and statistically significant inverse correlation with s. Calcium and urine volume. It was significantly lower in those using loop diuretics at 1st day post-transplant ($P=0.039$). Tacrolimus was associated with lower serum Magnesium level than cyclosporine.

CONCLUSION:

Serum Mg post transplantation was significantly lower than pre transplantation level, and sometime may reach to significant hypomagnesemia. This was significantly correlated with S.K , S.Ca, and S Creatinine,

KEY WORDS: hypomagnesimia, renal transplantation

INTRODUCTION:

Magnesium is the eighth most common element in the crust of the Earth.(1) Magnesium salts dissolve easily in water and are much more soluble than the respective calcium salts, as a result, magnesium is readily available to organisms.(2) Being the second most common intracellular cation after potassium, with both these elements being vital for numerous physiological functions.(3,4)

About 99% of total body magnesium is located in bone, muscles and non-muscular soft tissue.(5)Bone provides a large exchangeable pool to buffer acute changes in serum magnesium concentration.(7) About 1-5% intracellular magnesium concentrations range is ionized, the remainder is bound to proteins. Extracellular magnesium accounts for ~1% of total body magnesium which is primarily found in serum and red blood cells (RBCs).(2,6,7,8)

Magnesium is a cofactor in >300 enzymatic reactions.(3)Thus, one should keep in mind that ATP metabolism, muscle contraction and

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relaxation, normal neurological function and release of neurotransmitters are all magnesium dependent, it is also important to note that magnesium contributes to the regulation of vascular tone, heart rhythm, platelet-activated thrombosis and bone formation.[8,9]There is also evidence that magnesium and calcium compete with one another for the same binding sites on plasma protein molecules.It was shown that magnesium antagonizes calcium-dependent release of acetylcholine at motor endplates, ‘calcium antagonist’.While calcium is a powerful ‘death trigger’,[10,11,12] magnesium is not, it is anti-apoptotic.[13]

The daily requirement for magnesium is 310–360 mg and 400–420 mg for adult women and men, respectively.[6]While drinking water accounts for ~10% of daily Mg intake, chlorophyll (green vegetables) is the major source. Nuts, seeds and unprocessed cereals are also rich in magnesium, fruit, meat and fish have an intermediate magnesium concentration. Low magnesium concentrations are found in dairy products.[14]

Magnesium—just like calcium— is absorbed in the gut and stored in bone mineral, and excess magnesium is excreted by the kidneys and the feces. Magnesium is mainly absorbed in the small intestine,[7,15]

Parathyroid hormone (PTH), Antidiuretic hormone (ADH), glucagon, calcitonin and estrogen all have a role for Mg absorption.[6]

In moderate Chronic Kidney Disease, increases in the fractional excretion of magnesium largely compensate for the loss of GFR to maintain normal serum magnesium levels.However, in more advanced CKD (as creatinine clearance falls <30 mL/min), this compensatory mechanism becomes inadequate such that overt hypermagnesaemia develops frequently in patients with creatinine clearances <10 ml/min.[16,17]Dietary calcium and magnesium may affect the intestinal uptake of each other, though result are conflicting, and likewise the role of vitamin D on intestinal magnesium absorption is somewhat uncertain.[18] In Peritoneal and hemodialysis , the concentration of magnesium in the dialysate will affect the S. Mg accordingly.[19,20,21,22,23,]

In renal transplantation, hypomagnesemia is a frequent disturbance associated with the use of Calcineurin inhibitors (cyclosporine and tacrolimus), and sirolimus (obligatory renal loss and decrease transcriptional expression of TRMP-6/TRMP-7 in the distal collecting tubule).Other important factors include recovery from Acute tubular necrosis, post obstructive polyuria, loop diuretic therapy, and Renal tubular acidosis.[24]

AIM OF THE STUDY:

Evaluation of serum Mg in patients during the first four days post renal transplantation to evaluate the correlation with different variables like age, gender, dialysis duration, CNI_s (types and dose) , S.Creatinne, Diabetes mellitus (DM), loop diuretics, urine volume and electrolytes (S.K, S.Ca.).

PATIENTS AND METHODS:

This study is a cross sectional descriptive study, conducted atNephrology and Kidney Transplantation Center – Medical City, from 1st of January 2012 – 1st of December 2012.

Patient characteristics:

Forty patients underwent kidney transplantation wereinvolved in this study. For each patent a full history, clinical assessment was done including drugs history, and family history of kidney disease.

The following investigations were doneat days (one day before transplantation, 1st and 4th post operative) : blood urea, serum creatinine, serum Potassium, serum Calcium, serum Magnesium and 24 hours urine volume were done for all patients.

Serum Magnesium was measured by Magnesiumliquicolor(photometric colormetrictest for magnesiumwith lipid clearing factorLCF) Normal values for S. Magnesium(1.6-2.5 mg/dl)

Statistical Analysis:By using statistical package for social sciences (SPSS) version 17, for windows software, data of all patients were entered and analyzed. For comparing means ANOVA test was used to compare 3 means of continues variables (S.Mg, S.K, S Ca, S.Cr, CNI dose and urine volume), to compare 2 mean variables standard T test was used. Level of significance was set at P≤0.05 to be considered as significant difference or correlation.

The direction of correlation considered as inverse when the correlation coefficient (R) value was negative signed and as direct correlation when the (R).

RESULTS :

Forty patients underwent renal transplantation at Nephrology and KidneyTransplantation Center-Medical City-Baghdad, Iraq, 26 (65%) of them were male and 14 (35%) were female; the mean age was 42±6.5 SD.Table (1).

Table 1: Demographical characteristics of study group (N=40).

Variable		No.	%
Age	< 35	16	40.%
	35-55	20	50.0%
	> 55	4	10.0%
	Mean	42 ± 6.5	
Gender	Male	26	65.0%
	Female	14	35.0%
Causes	Diabetes mellitus	9	22.5%
	Hypertension	7	17.5%
	Obstructive uropathy	2	5.0%
	Congenital	4	10.0%
	Others	18	45.0%
Dialysis Period	< 1month	10	25.0%
	1-12 Month	25	62.5%
	> 12 Month	5	12.5%
CNI type	Cyclosporine	9	22.5%
	Tacrolimus	31	77.5%
Patients kept on diuretic(furosemide)	No	21	52.5%
	Yes	19	47.5%

Table (2), shows the mean values of serum electrolytes in addition to CNI dose and urine volume, the mean S.Mg was (2.87±0.5) pre transplantation, on day 1 it was (2.3±0.49) and on the day 4 (2.31±0.67). The mean Post transplantation S.Mg was significantly lower than pre transplantation, (P<0.01). The same picture was found with the mean S.K, and S.Creatinine and urine volume (P<0.05), while no significant difference had been found in S.Calcium and CNI dose (Cyclosporine and Tacrolimus) (P>0.05).

Table 2: Mean values of Serum electrolytes, Calcinurineinhibitor dose and urine volume.

Parameter		One day pre-transplant	Day one post-transplant	Day fourpost-transplant	P.value
S. magnesium mg/dl		2.87 ± 0.5	2.3 ±0.49	2.31 ± 0.67	<0.01*
S. Potassiummmol/l		4.56 ± 1	3.89 ± 0.74	3.7 ± 0.72	<0.01*
S. Calcium mg/dl		8.33 ± 1.1	7.82 ± 1.43	8.13 ± 0.95	0.15*
S. Creatinine mg/dl		6.28 ± 2.6	2.70	1.97 ± 1.2	<0.01*
Dose of NI	Cyclosporine mg/kg	6.31 ± 1.76	7.22 ± 0.83	6.84 ± 1.82	0.46
	Tacrolimus mg/kg	0.085 ± 0.05	0.11 ± 0.05	0.1 ± 0.06	0.21
Urine volume ml/24Hrs		-	12821±6344	4408 ± 1767	<0.01**

Table (3) shows no significant correlation between mean S.Mg at day (-1), day (1) and day (4) and different variables (age, gender, CNI type and DM) (P> 0.05), but we found that mean S.Mg at day (1) significantly lower in those using loop diuretics than non using (P=0.039).

Table 3:Correlation of mean Serum Magnesium with other variables in the study. (ANOVA test and students t test were was used in comparison).

Variable		Mean Serum Magnesium		
		One day pre-Transplantation	Day one Post-transplant	Day four Post-transplant
Age	<35	2.79	2.26	2.29
	35-55	2.94	2.33	2.39
	>55	2.82	2.28	2.05
	P.value	0.622	0.815	0.815
Gender	Male	2.88	2.30	2.32
	Female	2.84	2.29	2.29
	P.value	0.821	0.965	0.895
CNI type	cyclo.	2.83	2.19	2.09
	Tac.	2.88	2.33	2.38
	P.value	0.818	0.454	0.264
Loop diuretics	no diuretic	2.82	2.15	2.31
	loop diuretic	2.92	2.46	2.31
	P.value	0.566	0.039	0.986
Diabetes Mellitus	Diabetic	2.7	2.3	2.5
	Non diabetic	2.9	2.3	2.3
	P.value	0.29	0.83	0.38

As it shown in table (4), there were no significant correlation between mean S.Mg and other electrolyte (S.K and S.Ca)at day -1. It had been significantly found that mean S. Mg was directly correlated with the mean S.K in day 1(P=0.01) and at day 4 (P=0.019).
The table also shown significantly direct correlation between mean S.Mg and mean S.Cr at day 1 and 4 (P=0.004 and 0.002 respectively) . Also there was a inverse statistically significant correlation between mean S.Mg and mean S.Ca at day 1 and 4, in both comparison (P<0.05).
The same thing also found between the mean S.Mg and the mean urine volume at day 1 and 4 (significant inverse correlation) (P=0.04 and 0.014 respectively).
We found there was no significant correlation between the dose of CNI (Cyclosporine and Tacrolimus) and mean S.Mg at day (-1),(1) and (4) apart from significant inverse correlation between mean S.Mg and the mean Tarolimus dose at day (4) (P=0.002).

Table 4: Correlation of Serum Magnesium with other electrolytes (Pearson's correlation was used).

		Mean S. Mg			
		Day (-1)	Day (1)	Day (4)	
Mean S.K (day -1)	correlation coefficient (R)	0.223			no significant correlation
	P. value	0.167			
Mean S.K(day 1)	correlation coefficient (R)		0.405		direct correlation
	P. value		0.010		
Mean S K(day 4)	correlation coefficient (R)			0.369	direct correlation
	P. value			0.019	
Mean S.Ca (day -1)	correlation coefficient (R)	0.170			no significant correlation
	P. value	0.295			
Mean S.Ca (day 1)	correlation coefficient (R)		-0.365		inverse correlation
	P. value		0.021		
Mean S.Ca (day 4)	correlation coefficient (R)			-0.393	inverse correlation
	P. value			0.012	
Mean S.Cr(day -1)	correlation coefficient (R)	0.206			no significant correlation
	P. value	0.202			
Mean S.Cr(day 1)	correlation coefficient (R)		0.440		direct correlation
	P. value		0.004		
Mean S.Cr(day 4)	correlation coefficient (R)			0.466	direct correlation
	P. value			0.002	
Cyclosporine day (0)	correlation coefficient (R)	0.211			no significant correlation
	P. value	0.586			
Cyclosporine day (1)	correlation coefficient (R)		0.041		no significant correlation
	P. value		0.917		
Cyclosporine day (4)	correlation coefficient (R)			-0.189	no significant correlation
	P. value			0.626	
Tacrolimusday (0)	correlation coefficient (R)	-0.096			no significant correlation
	P. value	0.606			
Tacrolimusday (1)	correlation coefficient (R)		-0.322		no significant correlation
	P. value		0.077		
Tacrolimusday (4)	correlation coefficient (R)			-0.526	inverse correlation
	P. value			0.002	
Mean urine volume day(1)	correlation coefficient (R)		-0.322		inverse correlation
	P. value		0.043		
Mean urine volume day(4)	correlation coefficient (R)			-0.387	inverse correlation
	P. value			0.014	

S.K Serum Potassium , S Ca Serum Calcium SCr Serum Creatinine

DISCUSSION:

To our best knowledge this is the 1st study focused on Iraqi patients who underwent renal transplantation to measure and follow up serum magnesium level one day before renal transplantation and at day one and day four after transplantation, also we studied if there was any correlation of the level of serum magnesium with different variables, We found that serum magnesium significantly decrease post transplantation in comparison with pre transplantation levels, although it still in the normal range but 6 (15%) of patients were suffered from hypomagnesemia ((S.Mg< 1.6 mg/dl). Al-Ghamdi SMG et al also found the same result.[25]A high flow state (large volume of urine)as might be seen in patients with excess extracellular fluid volumeor in the diuretic phase of (ATN) can reduce magnesium reabsorption,another explanation is the effect of CNI on renal tubular reabsorption of magnesium (Nijenhuis T et al and Alexander RT et al)).[26,27]Other factors include recovery post obstructive polyuria, renal tubular acidosis and loop diuretics effect.The level of the serum potassium run parallel to the serum creatinine which significantly decreased post renal transplantation in comparison with pre transplantation.Urine volume was dramatically increased at day one (polyuria) in comparison with pre transplantation day where most of our patients suffered from (oliguria), it started to decrease later on to reach to the mean of ~4000 ml/day at day 4, all these results may be explained by diuretic phase post transplantation, used of loop diuretics, recovery from ATN, post obstructive polyuria, and RTA.The serum calcium was slightly decreased at day 1 in comparison with pre transplantation level and returned back to increase at day 4 but all these changes were not significant.Pieter evenepoel et al also goes with our result a (biphasic pattern).[28]High pre transplantation PTH level protect against hypocalcemia later.There was no significant difference of the mean serum Mg with the different age group (we didn´t have patients with extreme age.(The Mg intake of old people tend to be low (Vir and Love),[29] and their intestinal absorption decrease with age (Mountokalakis et al.).[30]We found there was no significant difference of the mean serum Mg in relation to CNI type and gender.We found there was no significant difference in the mean of serum Mg between diabetic and non-diabetic .

Pham PC et al, Guerrero-Romero F et al and Barbagallo M et al found the reverse (osmotic diuresis or decreased magnesium reabsorption due to insulin resistance).[31-33]While Kao WH et al and Guerrero-Romero F et al also found that hypomagnesemia may play a causal role to impair glucose tolerance through decreased insulin secretion, reduced cellular transport of glucose.[34,35]The mean S. Mg decrease significantly at day one in those patients on loop diuretics this may be explained by the remote effect of loop diuretics which may interfere with Mg reabsrption at thick ascending limb of loop of henle. (Ellison DH et al), In our study there was significant direct correlation between mean serum Mg and mean serum K which goes with most of other results.

Whang R et al ,Huang CL et al (increased potassium secretion in the loop of Henle and the cortical collecting tubule).[36,37]There was also significant direct correlation between mean serum Mg and mean serum creatinine i.e. with decrease level of Mg there was decrease level of creatinine.This most probably related to diuretic phase post renal transplantation which also may explain the significant inverse correlation between mean serum Mg and mean urine volume.

We found there was significant inverse correlation between mean serum Mg and mean serum Ca .There are several contributing factors interact between them lead to this result,persistent secondary hyperparathyroidism (Cundy T et al),[38]Post transplant severe hypophosphatemia through stimulation of renal proximal tubular 1α-hydroxylase,resolution of soft tissue calcifications, high dose corticosteroid therapy, and immobilization .On the other hand Schlingmann KP et al showed that hypomagnesemia decrease PTH release and end-organ responsiveness.[39]

There was inverse correlation between the mean serum Mg and the mean CNI dose which is not significant apart from substantial correlation at day 4 with tacrolimus.NijenhuisTet al, Alexander RT et al and Ikari A et al found the reverse (CNI may cause obligatory renal loss and decrease transcriptional expression of the Mg transporter in the distal collecting tubule).[26,27,40]Higgins RM et al showed that the rise in S.Mg among patients undergoing elective conversion from tacrolimus to cyclosporine which goes with our result that hypomagnesemia is more severe with tacrolimus.[41]

CONCLUSION:

1. Serum Magnesium significantly decreases post kidney transplantation in comparison with pre transplantation levels.
2. There is a significant correlation between the Serum Magnesium and (urine volume, serum of (Potassium, Calcium , Creatinine) and the medications used (diuretics and CNI -types and dosages)

Recommendation

We recommend to close monitoring of serum Magnesium pre and post kidney transplantation and to be part of the routinefollow up of patients with chronic kidney disease.

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