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Original Article

Biochemistry Section

Effect of Haemodialysis on Serum Magnesium Level in Patients with Chronic Renal Failure: A Cross-sectional Study

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ABSTRACT

Introduction: The dialysate Magnesium (Mg) concentration is the primary determinant of serum Mg levels in individuals on maintenance haemodialysis. A stable dialysate Mg content of 0.5 mmol/L is currently recommended. An alteration in this concentration can lead to altered serum magnesium levels. Few studies indicate that dialysate Mg concentration needs to be altered for maintenance of stable serum magnesium level.

Aim: To compare pre and postdialysis serum magnesium levels in patients with chronic renal failure and the effect of drug intake and duration of dialysis on serum magnesium levels.

Materials and Methods: This prospective observational cross-sectional study was conducted in a tertiary care hospital of Coimbatore, Tamil Nadu, India, for a period of three months, from June 2021 to August 2021. The predialysis and postdialysis serum magnesium levels of 100 chronic renal failure patients undergoing maintenance haemodialysis were measured. Parameters such as dialysis period, predialysis weight, predialysis routine blood chemistry variables (estimated glomerular filtration rate, serum urea, serum creatinine, serum sodium, serum potassium and serum calcium, serum phosphate measurements) history of diabetes, history of hypertension and history of medications, were assessed for all the patients. Statistical analysis of the data were done using Analysis Of Variance (ANOVA), Students' t-test and Pearson's correlation coefficient.

Results: Total 71% of the study population were males and 29% were females. The mean age of the study population was found to be 51.34 years. The mean predialysis serum magnesium levels was 2.28±0.48 mg/dL. The mean postdialysis serum magnesium level was 1.69±0.52 mg/dL. Total 2% of the chronic renal failure patients had hypomagnesemia before dialysis, while 27% of the patients developed hypomagnesemia after dialysis. There was significant difference between pre and postdialysis Mg levels, $p<0.001$. There was no significant correlation between pre and postdialysis magnesium levels and drug intake. Patients undergoing dialysis for more than 300 days had a significantly decreased serum magnesium levels than those undergoing dialysis for less than 90 days.

Conclusion: The risk of hypomagnesemia is definite in patients undergoing dialysis. Uniformity of dialysis fluids for all patients may not be advisable. Dialysate should be titrated in individual patients according to the predialysis serum magnesium levels.

Keywords: Hypermagnesemia, Hypomagnesemia, Postdialysis magnesium, Predialysis magnesium

INTRODUCTION

Chronic Kidney Disease (CKD) is a global health issue that affects millions of individuals (57.2 million) around the world [1]. In India, CKD is one of the common noncommunicable diseases with high mortality, morbidity and economic costs [2,3]. Approximately 1,75,000 people in India are on haemodialysis, resulting in a haemodialysis prevalence of 129 per million population [4].

The CKD staging is done based on the estimated Glomerular Filtration rate (eGFR) as follows: eGFR more than or equal to 90 mL/min is Grade 1 (G1) CKD, eGFR of 60-89 mL/min is G2 CKD, eGFR of 45-59 mL/min is G3a CKD, eGFR of 30-44 mL/min is G3b CKD, eGFR of 15-29 mL/min is G4 CKD, eGFR of <15 mL/min is G5 CKD [5]. Maintenance Haemodialysis (MHD) forms the cornerstone of management of patients with CKD [6]. Magnesium ions are the second most abundant intracellular cations and the fourth most abundant group of ions in the body [7]. Owing to the major role of kidneys in electrolyte homeostasis, Mg homeostasis is altered in patients with End Stage Renal Disease (ESRD) [8]. Dialysis removes excessive magnesium. Both hypomagnesemia and hypermagnesemia, are associated with vascular calcification, left ventricular hypertrophy, and death in individuals with CKD [9]. Vascular calcification is common in patients undergoing haemodialysis [10].

According to Alhosaini M and Leehey DJ, [11], there are two factors that can alter the serum magnesium levels during dialysis. This includes concentration gradient across the dialysis membrane and Gibbs-Donnan effect. The main determinant of magnesium flux across the dialysis membrane is the concentration of magnesium in the dialysate fluid. If the serum magnesium is higher than that of the dialysate fluid magnesium, then the magnesium will be removed from the blood. Thus, the main determinant of concentration of serum magnesium in dialysis patients is the dialysate fluid magnesium concentration. Apart from the dialysate fluid magnesium concentration, intake of certain drugs like proton pump inhibitors can cause disturbances in the magnesium balance [12].

The dialysate Mg concentration is the primary determinant of serum Mg levels in individuals on maintenance haemodialysis [13]. A stable dialysate Mg content of 0.5 mmol/L is currently recommended. An alteration in this concentration can lead to altered serum magnesium levels [14]. Van de Wal-Visscher ER et al., and Leender et al., have concluded that dialysate Mg Concentration needs to be altered for maintenance of stable serum magnesium levels [12,13]. During literature search, a very few studies [15-17] were available where predialysis and postdialysis magnesium levels were compared. Hence, present study was conducted to find the changes in serum Mg levels among patients undergoing dialysis in a tertiary care centre in south India.

MATERIALS AND METHODS

This prospective observational cross-sectional study was conducted in a tertiary care hospital of Coimbatore, Tamil Nadu, India, for a period of three months, from June 2021 to August 2021. After obtaining the Institutional Human Ethical Committee (IHEC) approval (21/IHEC/2021). Written informed consent from all the participants was taken for inclusion in the study.

Inclusion criteria: All chronic renal failure patients undergoing maintenance haemodialysis in the hospital during the study period were included in the study.

Exclusion criteria: Chronic renal failure patients for whom renal transplantation was done and those receiving magnesium supplements were excluded from the study.

Sample size calculation: According to Han Z et al., [17], the mean predialysis magnesium level was 1.11±0.14 and the mean postdialysis magnesium level was 0.97±0.10. Sample size was calculated using the formula:

$$n = \frac{2s_p^2\left[z_{1-\alpha/2} + z_{1-\beta}\right]^2}{\mu_d^2}$$

$$s_p^2 = \frac{s_1^2 + s_2^2}{2}$$

where Z score (1.96), S-standard deviation, μ-population mean. The required sample size was found to be 13. So convenient sampling was done with the sample size of 100 patients.

Study Procedure

Required details of the patients were obtained from patients records maintained at Department of Nephrology using a preset proforma [PROFORMA]. It included age, gender, dialysis period, predialysis weight, post dialysis weight, predialysis routine blood chemistry variables (eGFR, serum urea, serum creatinine, serum sodium, serum potassium, serum calcium, serum phosphate-all these parameters were done within one week before dialysis) history of diabetes, history of hypertension and history of medications.

Total 3 mL of blood sample was collected immediately before and after dialysis. The collected samples were kept for 25-30 minutes at room temperature to clot and then serum was separated by centrifuging at 3000 rpm for 15 minutes. Then the predialysis and postdialysis serum concentrations of magnesium were analysed in Cobas 6000 c501 chemistry analyser (Roche diagnostics ltd). Serum magnesium was estimated by xylidyl blue method and the normal reference range for serum magnesium level was 1.4-2.6 mg/dL [18]. Serum magnesium levels less than 1.4 mg/dL is hypomagnesemia whereas serum magnesium level more than 2.6 mg/dL is hypermagnesemia [19,20].

Serum Urea, creatinine, calcium and phosphate were estimated in Cobas 6000 c501 chemistry analyser (Roche diagnostics ltd). Serum sodium and potassium were estimated using by direct potentiometry using ion selective electrode. The methods used for the estimation of these analytes and their normal reference ranges are shown in [Table/Fig-1] [21]. All the collected data were recorded for further statistical analysis.

Name of the serum analyte	Normal reference range	Method of analysis
Urea (mg/dL)	15-40	Urease method
Creatinine (mg/dL)	0.7-1.4 (males)	Modified Jaffe's method
	0.6-1.2 (females)	
Calcium (mg/dL)	8.7-10.2	NM-BAPTA method
Phosphate (mg/dL)	2.5-4.3	Phosphomolybdate method
Sodium (meq/L)	136-146	Direct potentiometry
Potassium (meq/L)	3.5-5	Direct potentiometry

[Table/Fig-1]: Routine biochemical parameters.
NM BAPTA: 1; 2: Bis (o-aminophenoxy) ethane-N,N,N′; N′: Tetraacetic acid

STATISTICAL ANALYSIS

The data was statistically analysed using the Statistical Package for the Social Sciences (SPSS) software version 28.0. For continuous variables, descriptive statistics such as mean with Standard Deviation (SD) were used, whereas for categorical variables, frequencies and percentages were used to express the data. The means of predialysis and postdialysis magnesium levels in different subgroups of patients were compared using Student's t-test and ANOVA. A p-value of less than 0.05 was deemed significant. Pearson's correlation coefficient was used to determine the degree of correlation between the parameters.

RESULTS

A total of 100 patients were included in the study. 71% of the study population were males and rest 29% were females. The mean age of the population was 51.34±14.46 years. Total 66% of the study population had systemic hypertension and 15% had both systemic hypertension and diabetes mellitus. In 19% of the subjects, there were no co-morbid illnesses. In the study population, 41% were undergoing dialysis for <90 days, 31% were having dialysis for more than 90 days but less than 300 days, 28% were undergoing dialysis for >300 days. The demographic and comorbidity details, duration of dialysis, are shown in the [Table/Fig-2].

Variable	Total no. of patients
Gender	
Male/female	71/29
Age (years)	51.34±14.46
Co-morbidities	
Hypertension	66
Diabetes and hypertension	15
No known co-morbidities	19
Duration of dialysis	
≤90 days	41
91-300 days	31
≥301 days	28

[Table/Fig-2]: Patient characteristics (N=100).

About 84% of the study population had haemodialysis access via arteriovenous fistulas and 16% had haemodialysis catheters in place. The mean predialysis weight was 59.9±11.9 Kg, ranging from 33-109 kg, while the mean postdialysis weight was 57.6±11.6 Kg, ranging from 32-99 kg. There was no statistically significant association between body weight and serum magnesium levels in the study population (p-value=0.66)

Total 34% of the study population did not have history of intake of any magnesium lowering drugs. The remaining 66% of the study population had history of intake of drugs like insulin, diuretics and proton pump inhibitors. History of medications taken by the patients is shown in [Table/Fig-3].

Drug intake	Frequency
No drug	34
Proton pump inhibitors	15
Diuretics	12
Proton pump inhibitors+insulin	2
Insulin+diuretics	4
Proton pump inhibitors+diuretics	5
Proton pump inhibitors+insulin+diuretics	2
Antacids	17
Insulin+antacids	1
Diuretics+antacids	4
Insulin+diuretics+antacids	4
Total	100

[Table/Fig-3]: History of medications taken by the patients.

Almost all the patients (98%) included in the study population had eGFR <15 mL/min/1.73 m^2 i.e., they had stage five chronic kidney disease. The rest (1% each) had stage four chronic kidney disease (eGFR 15-29 mL/min/1.73 m^2) and stage three chronic kidney disease (eGFR 30-59 mL/min/1.73 m^2).

The mean predialysis serum magnesium level was 2.28±0.48 mg/dL. Total 69% of the study population had magnesium levels in the normal reference range of 1.5-2.6 mg/dL, 2% had serum magnesium levels <1.4 mg/dL and 29% had levels >2.6 mg/dL. The mean postdialysis serum magnesium levels in the study population was 1.69±0.52 mg/dL, 71% of the study population had magnesium levels in the normal range and 27% had levels <1.4 mg/dL [Table/Fig-4].

Mean Mg level (mg/dL)	Predialysis frequency	Postdialysis frequency
1.5-2.6	69	71
<1.4	2	27
>2.6	29	2
Mean Mg value	2.28±0.48	1.69±0.52
p-value	0.007	

[Table/Fig-4]: Mean predialysis, postdialysis magnesium values.

There was no significant correlation between pre and postdialysis magnesium levels and drug intake (p-value >0.05) as shown in [Table/Fig-5].

Variables		Insulin Injection	Proton pump inhibitors	Diuretics	Antacids
Predialysis Mg	Pearson correlation	-0.059	-0.158	-0.158	0.035
	p-value (2-tailed)	0.559	0.117	0.117	0.728
Postdialysis Mg	Pearson correlation	-0.061	-0.026	-0.026	-0.003
	p-value (2-tailed)	0.548	0.796	0.796	0.979

[Table/Fig-5]: Correlation between predialysis, postdialysis magnesium and drug intake.

Patients undergoing dialysis for more than 300 days had a significantly decreased serum magnesium levels than those undergoing dialysis for less than 90 days as shown in [Table/Fig-6].

Dependent Variable	(I) Duration of dialysis	(J) Duration of dialysis	Mean Diff (I-J)	p-value
Predialysis Mg	≤90 days	91- 300 days	-0.05980	0.960
		≥301 days	0.01394	0.998
	91- 300 days	≤90 days	0.05980	0.960
		≥301 days	0.07373	0.949
	≥301 days	≤90 days	-0.01394	0.998
		91- 300 days	-0.07373	0.949
Postdialysis Mg	≤90 days	91- 300 days	-0.09520	0.700
		≥301 days	-0.30488*	0.036
	91- 300 days	≤90 days	0.09520	0.700
		≥301 days	-0.20968	0.241
	≥301 days	≤90 days	0.30488*	0.036
		91- 300 days	0.20968	0.241

[Table/Fig-6]: Analysis of relationship of duration of dialysis, predialysis magnesium and postdialysis magnesium using ANOVA.

The mean serum creatinine was 7.4±2.41 mg/dL, serum urea was 93.3±32.7 mg/dL, serum sodium was 136.9± 3.5 meq/L, potassium 5.0±0.7 meq/L, calcium 8.7±1.2 mg/dL, phosphate 4.74±1.8 mg/dL. There was no significant correlation between postdialysis serum magnesium level and Serum creatinine, Serum urea, serum sodium, s. potassium and s. calcium. There was a positive significant correlation between magnesium level and serum phosphate (r-value- 0.212, p-value- 0.034) [Table/Fig-7].

Serum analyte	Mean value	Pearson Correlation	p-value (2-tailed)
Serum creatinine (mg/dL)	7.40±2.41	0.148	0.143
Serum urea (mg/dL)	93.31±32.71	-0.029	0.772
Serum sodium (meq/L)	136.91±3.58	0.065	0.520
Serum potassium (meq/L)	5.03±0.71	-0.066	0.513
Serum calcium (mg/dL)	8.79±1.28	-0.003	0.976
Serum phosphate (mg/dL)	4.74±1.80	0.212	0.034

[Table/Fig-7]: Correlation between postdialysis serum magnesium levels and routine biochemical parameters.

DISCUSSION

The predialysis serum magnesium levels in the study population ranged from 1.48 mg/dL to 4.09 mg/dL. The mean predialysis magnesium was 2.28±0.48 mg/dL. Findings of this study were similar to those of Han Z et al., [17] where mean predialysis magnesium was 2.77±0.34 mg/dL. But this is in contrast with the findings of the study done by Patel H et al., [16] where the mean magnesium levels were in the higher range of 4.34±1.38 mg/dL. About 69% of the study population had magnesium levels in the normal reference range of 1.5-2.6 mg/dL. 2% had serum magnesium levels <1.4 mg/dL. 29% had serum magnesium levels >2.6 mg/dL. These findings were in contrast with those of Han Z et al., [17] where predialysis hypermagnesemia was seen in 73.65% of the population.

The postdialysis serum magnesium levels in our patients ranged from 0.98-6 mg/dL. The mean postdialysis magnesium was 1.69±0.52 mg/dL. This is similar to the study by Han Z et al., [17] where the postdialysis magnesium was 2.36±0.24 mg/dL. Total 71% of the study population had postdialysis magnesium levels in the normal reference range of 1.5-2.6 mg/dL, 27% had serum magnesium levels <1.4 mg/dL and 2% had serum magnesium levels >2.6 mg/dL.

It was observed that the mean serum magnesium had decreased from 2.28 mg/dL to 1.69 mg/dL postdialysis. Before dialysis, 2% of the patients had hypomagnesemia, while 27% had hypomagnesemia after dialysis.

This observation was confirmed by doing a paired t-test between predialysis and postdialysis magnesium levels and there was a significant difference between the two as shown by a significant p-value of <0.05. These findings are in line with the findings of Leenders NHJ et al., [12] where there was a significant decrease in the mean serum magnesium levels postdialysis. This is in contrast with the findings of Patel H et al., [16] and Han Z et al., [17] where there was an elevation of serum magnesium levels postdialysis.

Only 34% of the study population did not have history of intake of any magnesium lowering drugs. The remaining 66% of the study population had history of intake of drugs like insulin, diuretics and proton pump inhibitors, which can lower magnesium levels. Of these, insulin lowers the magnesium level by interfering with Na^+/Mg^{2+} exchanger SLC41A1 resulting in increased renal magnesium loss. Proton pump inhibitors interfere with active magnesium absorption by interfering with channels TRPM6 and TRPM7 and increase renal magnesium loss. Diuretics cause reduced TRPM6 expression, reduced paracellular magnesium reabsorption and increased renal magnesium loss [12].

Farhanghi MA et al., [22] have observed in their study that serum magnesium levels were significantly lower in obese individuals when compared to non obese individuals. There was no significant correlation between body weight and serum magnesium levels in our study population (ANOVA: p-value=0.66).

In the study population, 41% were undergoing dialysis for <90 days, 31% were having dialysis for more than 90 days but less than 300 days, 28% were undergoing dialysis for >300 days. Patients undergoing dialysis for more than 300 days had a significantly decreased serum magnesium levels than those undergoing dialysis for less than 90 days.

On analysing the co-morbidities, 66% had systemic hypertension and 15% had both systemic hypertension and diabetes mellitus. In 19% of the subjects, there were no co-morbid illnesses. The temporal

and the causal relationship between systemic hypertension and chronic kidney disease is not known in the study group. Systemic hypertension could have been the cause of chronic kidney disease or CKD could have resulted in systemic hypertension [23].

There was no significant correlation between serum magnesium levels (postdialysis) and serum urea, creatinine, sodium, potassium and calcium. There was a significant correlation between serum magnesium and serum phosphate levels similar to the study done by Han Z et al., [17].

Magnesium homeostasis is altered in renal failure and it is one of the important ions maintained by haemodialysis. It is a cofactor in about 300 enzyme systems and also involved in the active transport of calcium and potassium ions across cell membranes. It may be dialyzed readily, in both ionized and complexed forms. Dialysis patients' magnesium balance is strongly reliant on the magnesium level of their dialysate [12]. Magnesium concentrations of 0.75 mmol/L in dialysis fluid have been linked to mild hypermagnesemia, while concentrations of 0.25 mmol/L have been linked to hypomagnesemia. Magnesium concentrations in dialysate has been a point of indecision, with the levels being steadily decreased over time, owing to early research expressing concerns that hypermagnesemia was a significant factor in osteomalacia or concerns about hypermagnesemia induced by kidney failure. A stable dialysate Mg content of 0.50 mmol/L is currently recommended. Leenders NHJ et al., have shown in their study that in most haemodialysis patients, plasma magnesium levels are likely to be too low. Haemodialysis on a regular basis causes the concentration of magnesium in the blood to drop even lower. So, there is a danger of continuous magnesium depletion, especially in patients who are malnourished or taking proton pump inhibitors [12].

Limitation(s)

The total magnesium concentration and not the ionic magnesium, which is a better indicator of magnesium status of patients was measured in this study.

CONCLUSION(S)

In this study, it was found that majority of the patients undergoing maintenance haemodialysis had postdialysis hypomagnesemia. This showed that dialysate fluid magnesium concentration needs to be adjusted according to the patient's predialysis magnesium level to reduce the mortality and morbidity associated with disturbances in magnesium homeostasis. There was no significant correlation between pre and postdialysis magnesium levels and drug intake. In present study it was found that patients undergoing dialysis for more than 300 days had significantly decreased serum magnesium levels than those undergoing dialysis for less than 90 days. A multi centric study can be done to confirm the findings of this study in a large variable population.

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PROFORMA

Patient Id number:
S.No:
Age: Gender:
Predialysis weight:
Clinical condition:
Duration of dialysis :
Blood chemistry parameters:
Serum magnesium (predialysis)
Serum magnesium(postdialysis)
eGFR reported
Serum creatinine reported
Serum urea reported
Serum calcium reported
Serum phosphorous reported
Serum potassium reported
Serum sodium reported
Others:
History of diabetes
History of hypertension
History of medications