

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 Mg levels. Few studies indicate that dialysate Mg concentration needs to be altered for maintenance of stable serum Mg level.

Aim: To compare pre and postdialysis serum Mg levels in patients with chronic renal failure and the effect of drug intake and duration of dialysis on serum Mg 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 to August 2021. The predialysis and postdialysis serum Mg 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 Mg levels was 2.28±0.48 mg/dL. The mean postdialysis serum Mg level was 1.69±0.52 mg/dL. Total 2% of the chronic renal failure patients had hypomagnesaemia before dialysis, while 27% of the patients developed hypomagnesaemia after dialysis. There was significant difference between pre and postdialysis Mg levels, $p < 0.001$. There was no significant correlation between pre and postdialysis Mg levels and drug intake. Patients undergoing dialysis for more than 300 days had a significantly decreased serum Mg levels than those undergoing dialysis for less than 90 days.

Conclusion: The risk of hypomagnesaemia 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 Mg levels.

Keywords: Hypermagnesaemia, Hypomagnesaemia, 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 (Mg) 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 Mg. Both hypomagnesaemia and hypermagnesaemia, 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, there are two factors that can alter the serum Mg levels during dialysis [11]. This includes concentration gradient across the dialysis membrane and Gibbs-Donnan effect. The main determinant of Mg flux across the dialysis

membrane is the concentration of Mg in the dialysate fluid. If the serum Mg is higher than that of the dialysate fluid Mg, then the Mg will be removed from the blood. Thus, the main determinant of concentration of serum Mg in dialysis patients is the dialysate fluid Mg concentration. Apart from the dialysate fluid Mg concentration, intake of certain drugs like proton pump inhibitors can cause disturbances in the Mg 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 Mg levels [14]. Leender NHJ et al., and Van de Wal-Visscher ER et al., have concluded that dialysate Mg concentration needs to be altered for maintenance of stable serum Mg levels [12,13]. During literature search, a very few studies were available where predialysis and postdialysis Mg levels were compared [15-17]. 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 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 Mg supplements were excluded from the study.

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

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

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

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, postdialysis 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 Mg were analysed in Cobas 6000 c501 chemistry analyser (Roche diagnostics Ltd). Serum Mg was estimated by xylydyl blue method and the normal reference range for serum Mg level was 1.4-2.6 mg/dL [18]. Serum Mg levels less than 1.4 mg/dL is hypomagnesaemia whereas serum Mg level more than 2.6 mg/dL is hypermagnesaemia [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 Mg levels in different

subgroups of patients were compared using Student's t-test and Analysis Of Variance (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 Mg levels in the study population (p-value=0.66).

Total 34% of the study population did not have history of intake of any Mg 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 m² 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 m²) and stage three CKD (eGFR 30-59 mL/min/1.73 m²).

The mean predialysis serum Mg level was 2.28 ± 0.48 mg/dL. Total 69% of the study population had Mg levels in the normal reference range of 1.5-2.6 mg/dL, 2% had serum Mg levels <1.4 mg/dL and 29% had levels >2.6 mg/dL. The mean postdialysis serum Mg levels in the study population was 1.69 ± 0.52 mg/dL, 71% of the study population had Mg 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's correlation	-0.059	-0.158	-0.158	0.035
	p-value (2-tailed)	0.559	0.117	0.117	0.728
Postdialysis Mg	Pearson's 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 Mg 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 Mg level and serum creatinine, serum urea, serum sodium, serum potassium and serum calcium. There was a positive significant correlation between Mg level and serum phosphate (r-value=0.212, p-value=0.034) [Table/Fig-7].

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

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

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

This observation was confirmed by doing a paired t-test between predialysis and postdialysis Mg 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., where there was a significant decrease in the mean serum Mg levels postdialysis [12]. This is in contrast with the findings of Patel H et al., and Han Z et al., where there was an elevation of serum Mg levels postdialysis [16,17].

Only 34% of the study population did not have history of intake of any Mg 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 Mg levels. Of these, insulin lowers the Mg level by interfering with $\text{Na}^+/\text{Mg}^{2+}$ exchanger SLC41A1 resulting in increased renal Mg loss. Proton pump inhibitors interfere with active Mg absorption by interfering with channels TRPM6 and TRPM7 and increase renal Mg loss. Diuretics cause reduced TRPM6 expression, reduced paracellular Mg reabsorption and increased renal Mg loss [12].

Farhanghi MA et al., have observed in their study that serum Mg levels were significantly lower in obese individuals when compared to non obese individuals [22]. There was no significant correlation between body weight and serum Mg levels in present 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 Mg 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 CKD is not known in the study group. Systemic hypertension

could have been the cause of CKD or CKD could have resulted in systemic hypertension [23].

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

Mg 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 dialysed readily, in both ionised and complexed forms. Dialysis patients' Mg balance is strongly reliant on the Mg level of their dialysate [12]. Mg concentrations of 0.75 mmol/L in dialysis fluid have been linked to mild hypermagnesaemia, while concentrations of 0.25 mmol/L have been linked to hypomagnesaemia. Mg concentrations in dialysate has been a point of indecision, with the levels being steadily decreased over time, owing to early research expressing concerns that hypermagnesaemia was a significant factor in osteomalacia or concerns about hypermagnesaemia 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 Mg levels are likely to be too low. Haemodialysis on a regular basis causes the concentration of Mg in the blood to drop even lower. So, there is a danger of continuous Mg depletion, especially in patients who are malnourished or taking proton pump inhibitors [12].

Limitation(s)

The total Mg concentration and not the ionic Mg, which is a better indicator of Mg 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 hypomagnesaemia. This showed that dialysate fluid Mg concentration needs to be adjusted according to the patient's predialysis Mg level to reduce the mortality and morbidity associated with disturbances in Mg homeostasis. There was no significant correlation between pre and postdialysis Mg levels and drug intake. In present study, it was found that patients undergoing dialysis for more than 300 days had significantly decreased serum Mg 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