
Changes in the serum magnesium in chronic kidney disease patients receiving multiple maintenance haemodialysis over a period of two months – A New Insight

Arun Harith^{*1}, Kanchan Kulhari², Suraj Pratap Singh³ and Srinivas Iyengar⁴

¹Southern Command Hospital, Wanowrie, Pune, Maharashtra 411040 India

²MD Biochemistry, Base Hospital, Delhi Cantt, India

³III MBBS student, Army College of Medical Sciences, Near Base Hospital, Brar Square, New Delhi, Delhi 110010, India

⁴DM Nephrology, Command Hospital, Air Force, Bangalore, India

***Correspondence Info:**

Dr. Arun Harith,
Southern Command Hospital,
Wanowrie, Pune, Maharashtra 411040 India
E-mail: arunharith@gmail.com

Abstract

Objective: Magnesium is an important divalent cation with protean functions. Chronic Kidney disease (CKD) is the most common cause for hypermagnesemia. It is possible that CKD patients on Maintenance Haemodialysis (MHD) could have hypermagnesemia due to inadequate clearing of magnesium during dialysis. It is also possible that periodic haemodialysis could result in excess clearing of serum magnesium leading to a progressive hypomagnesemia. Information of the serum magnesium levels in patients with multiple sittings of MHD is not available. This study was undertaken to evaluate the impact of MHD on serum magnesium levels following multiple sittings of MHD.

Material and Methods: 44 CKD patients on MHD were enrolled in the study after obtaining informed consent. Pre and Post dialysis samples were assayed for serum magnesium on a fully automated clinical chemistry analyser along with other renal parameters.

Results: There was no significant difference between the mean of the pre and post dialysis serum magnesium levels. However, over a period of two months, it was found that there was a gradual decrease in the serum magnesium levels, and this difference was found to be statistically significant.

Conclusion: The study shows that there is a mild but progressive decrease in the serum magnesium levels over multiple sittings of MHD. This needs to be monitored and supplemented as hypomagnesemia is associated with increased cardiovascular events in CKD patients.

Keywords: Serum Magnesium, Chronic kidney disease, Haemodialysis

1. Introduction

Magnesium is the second most important intracellular cation present in the body. It is an essential co-factor to numerous enzymes, chiefly involved in the ATP production [1,2]. The major homeostasis of magnesium is maintained between the amount absorbed by the gut and the amount excreted by the kidney [1]. Hence it is not surprising that in Chronic Kidney Disease patient, the homeostasis of magnesium gets deranged. The signs and symptoms of hypomagnesemia and hypermagnesemia are very subtle and not easily detected, unless specifically looked for [1]. This is further compounded by the fact that the diagnostic facilities for estimating serum magnesium are not universally available. However, both hypomagnesemia and hypermagnesemia have profound clinical impact [3-10]. It is possible that in patients who

are undergoing continuous haemodialysis there could be a systematic derangement of serum magnesium that is not being picked up. It is possible that the haemodialysis is not removing the excess of serum magnesium which is expected in cases of CKD making the patient prone to hypermagnesemia. On the other hand, it is also possible that excess of magnesium is being removed by the dialysis and hence patients on CKD would be prone to developing hypomagnesemia on the long run with its own associated complications [9-11]. This study was undertaken to evaluate and monitor the serum magnesium levels in CKD patients who were receiving MHD at our center over a period of two months with a view to study if MHD had any impact on the serum magnesium levels.

2. Material and Methods

44 CKD patients on MHD were included in this study after obtaining their informed consent. The patients usually received MHD two to three times as week, for a duration of 2-4 hours. The dialysing fluid used was bicarbonate based and had a magnesium concentration of 1.5 mEq/l. Pre and Post dialysis samples were collected every alternate week from each of these patients at the time of their dialysis setting and sent to the laboratory for estimating the serum urea, creatinine, sodium, potassium and magnesium levels. A total of four such samples were sent for every patient over a period of two months. Serum magnesium was estimated by the Xylidyl Blue dye binding method on a fully automatic clinical biochemistry analyser using the Transasia System pack as per the manufacturer’s instruction. The principle of estimation was that Serum Magnesium reacts with Xylidyl Blue to form a colored compound in alkaline solution. The intensity of which is proportional to the magnesium concentration in the sample. Samples were repeated in duplicates and the average was taken as the final reading. The normal range of serum magnesium as per this method was 1.6 – 2.6 mg/dL. In this method, the interference with calcium was prevented by the use of GEDTA. In every batch of sample

analysis, Bio Rad QC sample was also run. As the study was designed to evaluate the impact of haemodialysis on the serum magnesium levels, the medication that the patient was receiving was not considered as a confounding factor. However, in none of the patient’s phosphate binding agents (known to contain magnesium) was freshly introduced in the treatment regimen during the study.

Statistics: Paired t Test was done for comparing the means of the groups analysed.

3. Results

A total of 44 patients were included in this study which included 28 males and 16 females. The mean age of the patients was 58 ± 9.3 yrs, with the youngest patient being 23 yrs old and the oldest being 87 years old. All the patients were receiving atleast two sittings of haemodialysis per week. The average serum creatinine in the patients (pre-dialysis levels) was 7.6 ± 3.1 mg/dL. There were 28 who had diabetic nephropathy leading to CKD. In three cases Adult Poly cystic kidney disease was the etiology for CKD. However in 13 cases in which the etiology of CKD was obscure.

The pre and post dialysis serum urea, creatinine and electrolytes of the patients are shown in Table 1.

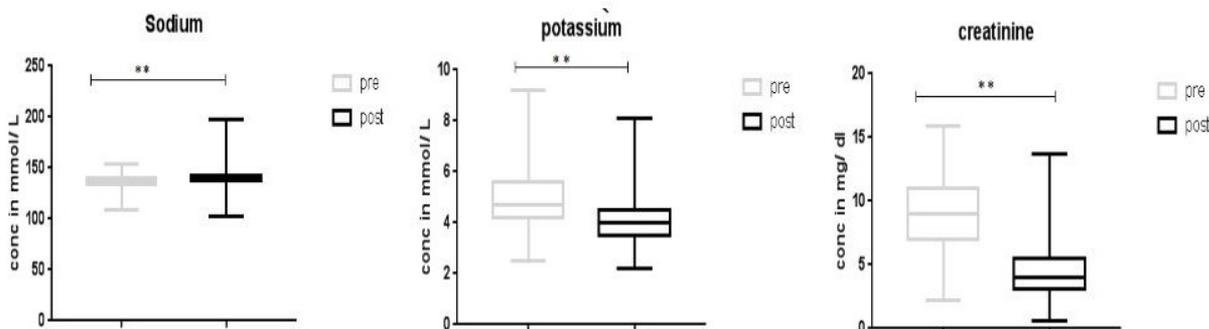
Table 1: Results of the pre and post dialysis samples

Parameter	n	Pre dialysis		Post dialysis		p Value
		Mean	SD	Mean	SD	
Urea (mg/dL)	166	154.9	49.15	101.09	42.02	< 0.05
Creatinine (mg/dL)	166	8.97	2.8	4.5	2.1	< 0.05
Sodium (mEq/L)	166	137.21	6.29	141.49	7.8	<0.05
Potassium (mEq/L)	166	4.89	1.04	4.05	0.82	<0.05
Magnesium (mg/dL)	166	3.29	1.31	3.22	1.22	0.61

Figure 1 shows the box and whisker plot of the pre and post dialysis samples of serum sodium, potassium and creatinine. A paired t Test was used to see if there was any difference between the levels of the electrolytes in the

pre and post dialysis sample. It was found that there was significant difference between the mean levels of creatinine, sodium and potassium in the pre and post dialysis sample.

Figure 1: Box and Whisker plot for serum sodium, potassium and creatinine levels in the pre and post dialysis sample.



In this study, we found that the mean pre-dialysis serum magnesium levels were 3.29 mg/dL (SD 1.31). In the first pre-dialysis sample, there were 35 cases who had hypermagnesemia with 16 patients having serum magnesium more than 3.6 mg/dL (significant hypermagnesemia). 3 samples had hypomagnesemia and there were 6 samples in which the serum magnesium levels were within the normal range. A paired t Test was done to evaluate the difference between the mean serum magnesium levels in the pre and post dialysis sample. This difference was not statistically significant (p = 0.61).

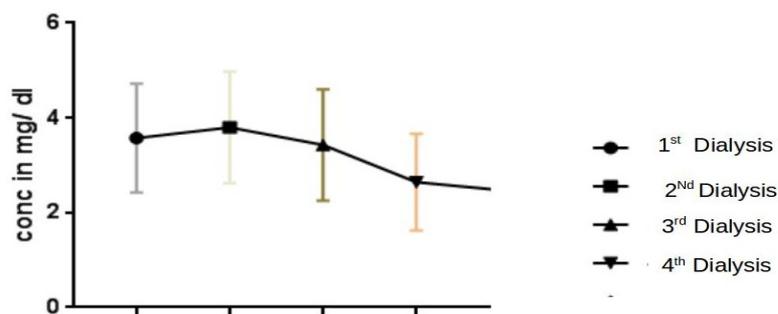
Table 2 shows the data of the mean pre dialysis serum magnesium levels the four samples collected two weeks apart. There was a gradual decrease in the mean serum magnesium concentration over the period of 8 weeks A paired t Test done between the first sample and the other three samples individually showed that there was a progressive trend of decrease in serum magnesium levels in the sample, with the difference between the mean of the first and fourth sample only being statistically significant (p=0.046). Figure 2 shows the mean serum magnesium levels over the eight week period.

Table 2: Bi weekly Pre dialysis serum magnesium levels

Week	n	Mean	SD	p value (compared to the first week sample)
First sample	166	3.57	1.2	
Second sample	166	3.7	1.3	0.35
Third sample	166	3.36	1.27	0.124
Fourth sample	166	3.31	1.31	0.046

Figure 2: Graphical representation of the serum magnesium levels of the four samples collected for each patient in the study.

Mean Serum Magnesium levels during the four visits



4. Discussion

CKD is a common disease that is associated with lot of morbidity and mortality in the patients. Renal transplant has come as a therapeutic boon to a large number of patients of CKD. However, renal transplant is not universally available to meet the demands of the CKD population. Pending renal transplant, or as an alternative treatment protocol, MHD has provided a lease of life to many of the CKD patients. In India, diabetes is the most common cause of CKD. Sadly though, there are a significant number of CKD patients in whom the exact etiology is not clear. In our study, we had 13 cases (29%) in which we did not have a clear etiology for the CKD.

Disorders of the serum magnesium (both hypermagnesemia and hypomagnesemia) have been associated with worse outcome. Hypermagnesemia is known to affect the conduction of impulse in the heart [5]. Hypermagnesemia affect bone metabolism and PTH secretion adversely [12]. In a study by Celi et al [6] hypermagnesemia was associated with lowering of blood pressure, and in patients at the ICU who had a serum

magnesium level > 2.6 mg/dL, there was a greater likelihood of requiring vasopressors. Hayashi et al [7] reported a case of HELLP syndrome who when into coma due to excess administration of magnesium sulphate and recovered following haemodialysis and reduction of the serum magnesium level. Hypermagnesemia is known to have some beneficial effects also, in that it is known to improve insulin sensitivity [13,14] retard the rate of vascular calcification in CKD patients. [15-16]

Limaye demonstrated that in critically ill patients who had hypomagnesemia, there was increased incidence of mortality, requirement of ventilatory support and longer duration of stay in the hospital [8]. It was also found that patients with hypomagnesemia tend to have a rapid deterioration of renal function and development of cardiac events [17]. In a meta analysis conducted by Upala et al, they found that critically ill patients with hypomagnesemia had a significantly higher risk of mortality (RR = 1.9) and requirement of ventilatory support (RR = 1.65) [9]. Hypomagnesemia was associated with poor glycemic control [10,11] and magnesium

supplementation was associated with improved glycemic control [13,14]

In this study, we evaluated the serum magnesium levels in the pre and post dialysis sample of patients over a period of two months. As the study was designed to see the impact of MHD on the serum magnesium levels in a temporal profile over a period of two months, we did not go into details of the treatment that patient was getting. However, phosphate binding agents, a known source of magnesium, was not started on any of the patients in the study.

The nature of the dialysis fluid used has an impact on the serum magnesium levels. In a study done by Elsharkawy et al, it was found that acetate based dialysate resulted in a decrease in the bicarbonate levels following standard dialysis procedure and bicarbonate based dialysis fluid caused an increase in the serum magnesium levels [18]. In our study the dialysis fluid was bicarbonate base with a concentration of on 1.5mEq/L. We did not find any significant difference between the mean pre and post dialysis magnesium levels.

In this study we found that nearly 79% (35 out of 44) CKD patients had hypermagnesemia in the first pre-dialysis sample with over 34% having significant hypermagnesemia. This needs to be viewed seriously and calls for a better monitoring of the serum magnesium levels in CKD patients considering the adverse clinical outcome of hypermagnesemia. Although there was no significant difference between the pre and the post dialysis serum magnesium levels in our study, we noticed that, when our patients were followed over a period of two months, there was a gradual decline in the level of serum magnesium (Figure 2).

This study has been done on a small cohort of patients and for a short duration of time. A larger multicentric study on CKD patients with probably a longer duration of follow up may give us a better understanding of the dynamics of serum magnesium following MHD in CKD patients. It is also known that the ionic form of magnesium is the metabolically active form [1,2]. Escuela et al found that in a study were 52.5% of the patients admitted to the ICU were hypomagnesemic. However only 9.7% of them had actual ionic hypomagnesemia [19]. As our center did not have facilities for doing ionic magnesium level assay, we used a colorimetric method to estimate total serum magnesium levels. A study in which ionic magnesium is tested will probably throw more light on the hemodynamics of serum magnesium in CKD patients on MHD.

5. Conclusion

Our study has shown that a significant proportion of our patients on MHD (79%) have hypermagnesemia

with nearly 39% having significant hypermagnesemia. Progressive MHD shows a gradual trend of decrease in the serum magnesium. While this may be beneficial in the wake of the light that most of our patients had hypermagnesemia, it also suggests risk of developing hypomagnesemia in the long run (with its associated complications) and hence needs to be monitored periodically.

References

- [1] Ángel L. M.e de Francisco, Rodríguez M. Magnesium - its role in CKD. *Nefrologia* 2013; 33(3):389-99.
- [2] Wisit C, Thongprayoon C, Qian Q. Dymagnesemia in Hospitalized Patients: Prevalence and Prognostic Importance *Mayo Clin Proc.* 2015; 90(8):1001-1010.
- [3] Jhang WK, Lee YJ, Kim YA, Park SJ, Park YS. Severe hypermagnesemia presenting with abnormal electrocardiographic findings similar to those of hyperkalemia in a child undergoing peritoneal dialysis. *Korean J Pediatr.* 2013; 56:308-11.
- [4] Yoon HE, Kim YW, Ha KS, Sim EH, Go SW, Shin SJ. Hypermagnesemia accompanied with colonic perforation in a hemodialysis patient. *Yonsei Med J.* 2013; 54:797-800.
- [5] Huey CG, Chan KM, Wong ET, Nelson JM, Durand M. Los Angeles County-University of Southern California Medical Center clinical pathology case conference: extreme hypermagnesemia in a neonate. *Clin Chem.* 1995; 41:615-618.
- [6] Celi LA, Scott DJ, Lee J, Nelson R, Alper SL, Mukamal KJ, Mark RG, Danziger J. Association of hypermagnesemia and blood pressure in the critically ill. *J Hypertens.* 2013; 31:2136-4.
- [7] Hayashi K, Oshiro M, Takara I, Iha H, Sugahara K. Coma caused by hypermagnesemia in a pregnant woman complicated with HELLP syndrome]. *Masui.* 2003; 52:783-5.
- [8] Limaye CS, Londhey VA, Nadkarni MY, Borges NE. Hypomagnesemia in critically ill medical patients. *J Assoc Physicians India.* 2011; 59:19-22.
- [9] Upala S, Jaruvongvanich V, Wijarnpreecha K, Sanguankeo A. Hypomagnesemia and mortality in patients admitted to intensive care unit: a systematic review and meta-analysis. *QJM.* 2016 Jul; 109:453-9.
- [10] Arundhati Dasgupta, Dipti Sarma, and Uma Kaimal Saikia. Hypomagnesemia in type 2 diabetes mellitus. *Indian J Endocrinol Metab.* 2012; 16(6): 1000-1003.
- [11] Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. *Clin J Am Soc Nephrol.* 2007; 2:366-73.
- [12] Kanbay M, Goldsmith G, Uyar UK, Turgut F, Covic A. Magnesium in Chronic Kidney Disease:

- Challenges and Opportunities. *Blood Purif* 2010; 29:280–292.
- [13] Rodríguez-Morán M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care*. 2003; 26(4):1147-1152.
- [14] Guerrero-Romero F, Rodríguez-Morán M. Magnesium improves the beta-cell function to compensate variation of insulin sensitivity: double-blind, randomized clinical trial. *Eur J Clin Invest*. 2011; 41(4): 405-410.
- [15] Sakaguchi Y, Fujii N, Shoji T, Hayashi T, Rakugi H, Isaka Y. Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis. *Kidney Int*. 2014; 85(1):174-181.
- [16] Courivaud C, Davenport A. Magnesium and the risk of all-cause and cardiac mortality in hemodialysis patients: agent provocateur or innocent bystander? *Kidney Int*. 2014; 85(1):17-20.
- [17] van Laecke S, Nagler EV, Verbeke F, Van Biesen W, Vanholder R. Hypomagnesemia and the risk of death and GFR decline in chronic kidney disease. *Am J Med*. 2013 Sep; 126:825-31.
- [18] Elsharkawy MM, Youssef AM, Zayoon MY. Intradialytic changes of serum magnesium and their relation to hypotensive episodes in hemodialysis patients on different dialysates. *Hemodial Int*. 2006 Oct; 10 Suppl 2:S16-23.
- [19] Escuela MP, Guerra M, Anón JM, Martínez-Vizcaíno V, Zapatero MD, García-Jallón A, Celaya S. Total and ionized serum magnesium in critically ill patients. *Intensive Care Med*. 2005 Jan; 31:151-6.