

Serum Magnesium and Its Association with Vascular Calcification in Chronic Kidney Disease Patients on Haemodialysis

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Article History	Abstract
Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 25 Nov 2023	Background: Cardiovascular disease is one of the leading causes of death in chronic kidney disease (CKD). It has been observed that haemodialysis patients have a high prevalence of cardiac risk factors with further risk due to abnormal mineral metabolism. A study has demonstrated that a higher serum magnesium significantly decreased the mortality risk in haemodialysis patients and lower serum Mg level has been found to be associated with increased mortality in them. The aim of the study was to characterize the relationship between Mg level and vascular calcification in CKD patients. Methods: It was a cross sectional study conducted in 100 CKD patients attending outpatient and inpatient ward of Tagore Medical College and Hospital, Chennai, Tamil Nadu, India. Serum magnesium levels will be measured using Xylidyl blue method. Carotid intimal medial thickness will be measured using Doppler. Results: In the study 10 patients did not show the sign of any calcification. Among the remaining 90 patients, 42 patients showed calcification and 48 patients showed stenosis. The statistical analysis showed a spearman correlation coefficient value of 0.201 thus showing only a weak association. Conclusion: The present study showed that only a weak relationship exists between the magnesium level and vascular calcification. Keywords: Chronic kidney disease, Haemodialysis patients, Magnesium level, Vascular calcification
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1. Introduction

Cardiovascular disease is one of the leading causes of death in chronic kidney disease (CKD).¹ It has been observed that haemodialysis patients have a high prevalence of cardiac risk factors with further risk due to abnormal mineral metabolism.² Vascular calcification is a process characterized by thickening and loss of elasticity of muscular arteries walls.³ The increased calcification of the large arteries including the aorta may result in increased arterial wall stiffness and pulse pressure and also causes the decreased myocardial perfusion during diastoles contributing to the high incidence of cardiovascular mortality.^{4,5} Intimal calcification is associated with atherosclerotic plaques whereas the medial calcification is characterized by vascular stiffening and arteriosclerosis and more common in patients with CKD.⁶ During the early course of CKD, the process of vascular calcification may start, even much before the start of dialysis. It will worsen progressively, often in an accelerated fashion compared with the general population.^{7,8} Disturbances in mineral and bone metabolism have found to play a major role in the pathogenesis of rapid progression of vascular calcification.⁹⁻¹¹ Several in vitro studies have shown that magnesium can have an inhibitory effect on the calcification process.¹² Both in-vitro and animal studies have found that the Mg addition to vascular smooth muscle cells inhibits the increase in mineralization associated with increase in expression of anti- calcification proteins, and down regulates pathways necessary for the development of vascular calcification.¹³⁻¹⁹ A study has demonstrated that a higher serum Mg significantly decreased the mortality risk in haemodialysis patients and lower serum Mg level has been found to be associated with increased mortality in them.²⁰⁻²³ In the present study, a cross sectional study has been conducted to characterize the relationship between Mg level and vascular calcification.

2. Materials And Methods

It was a cross sectional study conducted in CKD patients who attended outpatient and inpatient ward between July 2018 to December 2018 of Tagore Medical College and Hospital, Chennai, Tamil Nadu, India. A total of 100 CKD patients were selected for the study. Patients on calcium magnesium phosphate binder, magnesium containing medications were excluded from the study. The ethical clearance was obtained from institutional ethical committee prior to the start of the study. An informed consent was obtained from each participant. Detailed history and clinical examination will be taken using the patient information sheet prepared for this study. Serum magnesium levels will be measured using Xylidyl blue method. It is a direct colorimetric assay based on the Xylidyl Blue-I method without deproteinization of the sample. The magnesium determination is based on the reaction of magnesium with Xylidyl Blue-I (as chelator) at alkaline pH, which yields a purple coloured complex. The intensity of the colour formed is proportional to the calcium concentration in the sample. Absorbance of the Mg^{2+} -complex is measured at 660 nm. Carotid intimal medial thickness will be measured using Doppler. The patient was positioned lying face-up on an examination table that can be tilted or moved. Patients may be turned to either side to improve the quality of the images. A clear water-based gel was applied to the area of the body being studied to help the transducer make secure contact with the body and eliminate air pockets between the transducer and the skin that can block the sound waves from passing into your body. The transducer is placed on the skin in various locations, sweeping over the area of interest or angling the sound beam from a different location to better see an area of concern. Comparison between serum magnesium levels and the condition of carotid intimal medial thickness was assessed in CKD patients on haemodialysis was analysed with cross-tabulations and chi square test.

3. Results and Discussion

A total of 100 CKD patients were taken for the present study among which 52 were males and 48 were females. The patients with different age group ranging from 24 to 70 with a mean age of 52.56 ± 12.05 were seen in the study. The maximum number of individuals were above the age of 60 years followed by the age group of 41 to 50 years (Table 1).

TABLE 1. Age distribution of CKD patients.

Age Group in Years	Total No. of Individuals
20 to 30	4
31 to 40	16
41 to 50	26
51 to 60	18
Above 60	36
Total	100.0

TABLE 2. Levels of the magnesium and the condition of carotid intimal medial thickness in CKD patients.

		Calcification			Total
		No calcification	Calcification	Stenosis	
	1 to 1.2	0	6 (75.0%)	2 (25%)	8 (100%)
	1.2 to 1.4	0	2 (20%)	8 (80%)	10 (100%)
	1.4 to 1.6	4 (50%)	4 (50%)	0	8 (100%)
	1.6 to 1.8	0	8 (100%)	0	8 (100%)
Magnesium	1.8 to 2	2 (20%)	4 (40%)	4 (40%)	10 (100%)
level in	2 to 2.2	0	2 (25%)	6 (75%)	8 (100%)
mg/dL	2.2 to 2.4	0	2 (33.3%)	4 (66.7%)	6 (100%)
	2.4 to 2.6	4 (18.2%)	6 (27.3%)	12 (54.5%)	22 (100%)
	2.6 to 2.8	0	6 (60%)	4 (40%)	10 (100%)
	2.8 to 3	0	0	4 (100%)	4 (100%)
	Above 3	0	2 (33.3%)	4 (66.7%)	6 (100%)
Total		10	42	48	100

The magnesium level was measured and was compared to carotid intimal medial thickness for its correlation by spearman rank correlation test.

The Table 2 shows the levels of the magnesium and the condition of carotid intimal medial thickness. In the study 10 patients did not show the sign of any calcification. Among the remaining 90 patients, 42 patients showed calcification and 48 patients showed stenosis. The statistical analysis showed a spearman correlation coefficient value of 0.201 thus showing only a weak association.

It has been proved that vascular calcifications are common in chronic kidney disease (CKD) is one of the primary causes of death in CKD patients.²⁴ In CKD patients the glomerular filtration rate decreases, thereby the phosphate (Pi) levels rises. This will lead to disturbed mineral and bone metabolism affecting vascular integrity and function.²⁵

Many studies have been conducting magnesium as the independent factor affection the carotid intimal medial thickness with varying results.^{26,27}

In the present study, the magnesium level did not show any correlation with the vascular calcification in CKD patient under HD. Even though experimental studies have shown that the magnesium has the inhibitory of calcification, the calcification is a multifactorial and hence other factors can contribute for calcification in spite of high magnesium level.¹⁹

It should also be considered that serum Mg levels poorly reflect the intracellular Mg content and that in patients with renal failure hypermagnesemia may be accompanied by tissue Mg depletion or normal tissue Mg content, thus results of the serum magnesium levels many not show proper correlation with the calcification process.²⁸

4. Conclusion

Recently, several epidemiological studies showed a significant inverse relationship between serum magnesium and survival in CKD patients.²⁸ The present study shows that only a weak relationship exists between the magnesium level and vascular calcification. Even though there is conclusive evidence that the magnesium decreases the calcification process in vitro, one should not overlook the other factors that may influence the process of calcification in CKD patients.

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References:

1. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol.* 1999;10:1606-15.
2. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol.* 2004;15:2208-18.
3. Hunt JL, Fairman R, Mitchell ME. Bone formation in carotid plaques: a clinicopathological study. *Stroke.* 2002;33:1214-9.
4. Blacher J, Demuth K, Guerin AP. Influence of biochemical alterations on arterial stiffness in patients with end-stage renal disease. *Arterioscler Thromb Vasc Biol.* 1998;18:535-41.
5. Speer MY, Giachelli CM. Regulation of cardiovascular calcification. *Cardiovasc Pathol.* 2004;13:63-70.
6. Giachelli CM. The emerging role of phosphate in vascular calcification. *Kidney Int.* 2009;75:890-97.
7. Shroff RC, McNair R, Figg N. Dialysis accelerates medial vascular calcification in part by triggering smooth muscle cell apoptosis. *Circulation.* 2008;118:1748-57.
8. Temmar M, Liabeuf S, Renard C, et al. Pulse wave velocity and vascular calcification at different stages of chronic kidney disease. *J Hypertens.* 2010;28:163-9.
9. Shroff RC, McNair R, Skepper JN. Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. *J Am Soc Nephrol.* 2010;21:103-12.
10. El-Abbadi M, Giachelli CM. Mechanisms of vascular calcification. *Adv Chronic Kidney Dis.* 2007;14:54-66.
11. Nikolov IG, Mozar A, Drueke TB. Impact of disturbances of calcium and phosphate metabolism on vascular calcification and clinical outcomes in patients with chronic kidney disease. *Blood Purif.* 2009;27:350-59.
12. Boskey AL, Posner AS. Effect of magnesium on lipid-induced calcification: an in vitro model for bone mineralization. *Cal Tissue Int.* 1980;32:139-43.
13. Inagaki O, Syono T, Nakagawa K, Nishian Y, Takenaka Y, Takamitsu Y. Influence of magnesium deficiency on concentration of calcium in soft tissue of uremic rats. *Ren Fail.* 1996;18:847-54.
14. Montezano AC, Zimmerman D, Yusuf H, Burger D, Chignalia AZ, Wadhera V, et al. Vascular smooth muscle cell differentiation to an osteogenic phenotype involves TRPM7 modulation by magnesium. *Hypertension.* 2010;56:453-62.
15. Kircelli F, Peter ME, Sevinc Ok E, Celenk FG, Yilmaz M, Stepan S, et al. Magnesium reduces calcification in bovine vascular smooth muscle cells in a dose-dependent manner. *Nephrol Dial Transplant.* 2012;27:514-21.
16. Salem S, Bruck H, Bahlmann FH, Peter M, Deetjen PJ, Kretschmer A, et al. Relationship between magnesium and clinical biomarkers on inhibition of vascular calcification. *Am J Nephrol.* 2012;35:31-9.
17. Louvet L, Buchel J, Stepan S, Deetjen PJ, Massy ZA. Magnesium prevents phosphate-induced calcification in human aortic vascular smooth muscle cells. *Nephrol Dial Transplant.* 2013;28:869-78.

18. Oca MA, Guerrero F, Martinez-Moreno JM, Madueno JA, Herencia C, Peralta A, et al. Magnesium inhibits Wnt/beta-catenin activity and reverses the osteogenic transformation of vascular smooth muscle cells. *PLoS One*. 2014;9:e89525.
19. Xu J, Bai Y, Jin J, Zhang J, Zhang S, Cui L, et al. Magnesium modulates the expression levels of calcification-associated factors to inhibit calcification in a time-dependent manner. *Exp Ther Med*. 2015;9:1028-34.
20. Li L, Streja E, Rhee CM, Mehrotra R, Soohoo M, Brunelli SM, et al. Hypomagnesemia and mortality in incident hemodialysis patients. *Am J Kidney Dis*. 2015;66:1047-55.
21. Fein P, Weiss S, Ramos F, Singh P, Chattopadhyay J, Avram MM. Serum magnesium concentration is a significant predictor of mortality in peritoneal dialysis patients. *Adv Perit Dial*. 2014;30:90-3.
22. Ishimura E, Okuno S, Yamakawa T, Inaba M, Nishizawa Y. Serum magnesium concentration is a significant predictor of mortality in maintenance hemodialysis patients. *Magnes Res*. 2007;20:237-44.
23. Matias PJ, Azevedo A, Laranjinha I, Navarro D, Mendes M, Ferreira C, et al. Lower serum magnesium is associated with cardiovascular risk factors and mortality in haemodialysis patients. *Blood purification*. 2014;38(3-4):244-52.
24. London GM, Guérin AP, Marchais SJ. Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*. 2003;18:1731-1740.
25. Markowitz GS, Perazella MA. Acute phosphate nephropathy. *Kidney Int*. 2009;76:1027-34.
26. Del Gobbo LC, Imamura F, Wu JH, Oliveira Otto MC, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2013;98(1):160-73.
27. Nilsson P, Johansson SG, Danielson BG. Magnesium studies in hemodialysis patients before and after treatment with low dialysate magnesium. *Nephron*. 1984;37:25-29.
28. Sakaguchi Y, Hamano T, Nakano C. Association between density of coronary artery calcification and serum magnesium levels among patients with chronic kidney disease. *PLoS One*. 2016;11:e0163673.