International Journal of Research in Medical Sciences
Gulati Y et al. Int J Res Med Sci. 2023 May;11(5):1671-1675
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20231334

Original Research Article

Study of relationship between serum magnesium and carotid atherosclerosis in hemodialysis versus non-hemodialysis dependent CKD patients

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Received: 05 March 2023
Revised: 09 April 2023
Accepted: 14 April 2023

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ABSTRACT

Background: Cardiovascular diseases are the most important causes of morbidity and mortality in CKD mainly due to accelerated atherosclerosis. Mg2+ possesses an anti-atherosclerotic effect, because of its anti-inflammatory and antioxidant properties. Mg2+ deficiency promotes hydroxyapatite formation and calcification of VSMC thus leading to accelerated plaque formation. To evaluate relationship between serum Mg2+ level and atherosclerotic changes in CKD patients who are hemodialysis dependent versus who have not undergone hemodialysis.
Methods: This hospital based observational cross-sectional study has been carried out in Department of K.P.S Institute of Medicine, GSVM Medical College, Kanpur.58 subjects (29 being dialysis dependent and other 29 who have not undergone dialysis sessions yet. All the subjects underwent routine tests and intima media thickness (IMT) of carotid artery was measured via Doppler study.
Results: In our study the mean value of Mg was 2.25 mg/dl + 0.81 with 17 patients had hypomagnesemia. IMT of carotid artery with a mean value of 0.91mm + 0.24, was found to be increased in 16 patients, these were the patients who were on hemodialysis and had lower magnesium levels. Serum Mg2+ was negatively correlated (Pearson correlation coefficient was -0.677 and -0.704) with CIMT with statistical significance as ($P<0.001$) , only in patients who have underwent series of hemodialysis sessions.
Conclusions: We concluded that serum Mg might be considered as a modifiable risk factor of atherosclerosis (and thus, cardiovascular mortality) in Hemodialysis dependent CKD patients.

Keywords: Mg^{2+}, Carotid Intima-media thickness, Cardiovascular mortality, Hemodialysis, Chronic kidney diseases

INTRODUCTION

Cardiovascular diseases are the most important causes of morbidity and mortality in CKD patients mainly due to accelerated atherosclerosis. The pathogenesis of atherosclerosis in CKD is also affected by other factors such as genetic factors, inflammation, hyperparathyroidism, malnutrition as against general population.[1] Early atherosclerosis can be evaluated by measurement of CIMT with ultrasonography, which is a simple, reliable, non-invasive method. Magnesium being one of the major intracellular cations, is a vital element in human metabolism. Recently, through increasing evidence an association between low serum Mg^{2+} levels and CVD in CKD as well as in general population has been suggested.[2]

Vascular calcification in CKD is associated with distribution of various mineral disturbances including high Calcium and Phosphorus concentrations, loss of

mineralization inhibitors, including carboxylated matrix gla protein (carboxylated MGP) and fetuin A , apoptosis of vascular smooth muscles, and an active process of osteogenic transformation of vascular smooth muscle cells (VSMCs). The nanocrystals of Calcium and phosphorus after being taken by endocytosis by VSMCs are released intracellulary, which leads to expression of osteogenic transcription factors including Runx2 and BMP2 , mineralization of Extracellular matrix , decreased expression of calcification inhibitory proteins including MGP.[3] The intracellular burst of calcium causes apoptosis and release of apoptotic bodies containing Calcium and phosphate particles , which along with decreased amounts of calcification inhibitors (including Fetuin A and MGP) provide a nidus for mineral nucleation and maturation.[4]

Dietary magnesium may counteract vascular calcification by inhibition of intestinal phosphate uptake as a result of phosphate binding, by systemic effects on both promoting and inhibiting factors of calcification, or by local effects at the vascular tissue level.[5]

Second, Mg2+ inhibits calcium influx via L-type calcium channels in VSMCs and this affects vascular tone. Third, magnesium acts on the calcium- sensing receptors (CaSR) and stimulation of the CaSR by calcimimetics inhibits VSMCs calcification.[6] Fourth, magnesium inhibit Wnt/beta-catenin signalling, which is a mediator of osteogenic transformation.[7]

Along with severely depressed intestinal Mg2+ absorption , use of Low Mg^{2+} dialysate (0.25 mmol/L or 0.5 mEq/L) is a risk factor for hypomagnesemia I patients on both hemodialysis and peritoneal dialysis . Usually we consider calcium, LDL and Parathyroid hormone like variables to be only associated with cardiovascular risk associated with CKD patients but evaluating serum Magnesium levels in dialysis dependent patients can bring revolutionary changes in preventing cardiovascular mortality in ESRD patients.

Thus, the present study was designed to evaluate the association of carotid atherosclerosis and calcification with serum Magnesium levels in hemodialysis dependent CKD patients as compared to those CKD patients who haven't been dialyzed , since accelerated atherosclerosis has been postulated to be one of the most important causes of cardiovascular mortality dialyzed CKD patients, in particular.

METHODS

This hospital based observational cross-sectional study was conducted in PG department of Medicine, GSVM Medical college, Kanpur .Patients suffering from CKD attending medicine OP/IPD/ICU, admitted in medicine ward were screened and recruited for the study .It was conducted from December 2020 to August 2022 on 58 patients, 29 of who were hemodialysis dependent and had undergone numerous sessions of dialysis and other 29 had not undergone any dialysis session. The study was approved by ethical committee of GSVM Medical College Kanpur, India.

Inclusion criteria of the study include patients of age >18 years old diagnosed with Chronic Kidney disease, in stage IV and V (patients with either kidney damage or decreased glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m2 for atleast 3 months; according to CKD-EPI Classification).

Exclusion criteria includes patients with chronic liver disease, heart failure or unstable coronary artery disease, malignancy due to use of immunosuppressants, chronic infections tuberculosis (due to use of ATT) and chronic use of proton pump inhibitors.

The cases were subjected to following investigations, Hb, TLC, DLC, Serum Urea, Serum creatinine, Serum magnesium (Technology, Photometry, Method, Modified Xylidyl Blue Reaction Method), LFT (including serum albumin), Serum $Na^{+}/K^{+}/Ca^{++}$, Serum alkaline phosphate, Serum phosphorus, intact Para thyroid hormone ,Serum lipid profile, Hba1C, Carotid Doppler ultrasonography to measure intima-media thickness of common carotid artery, Urine routine and microscopy, Ultrasound whole abdomen.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Survey (SPSS) version 21.0. The collected data was summarized in the form of mean±standard deviation (SD) and range for measurable data and frequency and percentage for qualitative data. Comparisons amongst various study groups were done using Students t test. Association between variables was considered statistically significant if p value was <0.05.

RESULTS

Out of 58 patients, males represent 64% and females represent 36% of the patients. The result of our study showing CKD more common in males than females (Figure 2). In our study, the mean age of patients with ESRD was 52.6 years old (+12.75) (Table 2).

The level of Magnesium was found out to be low in 17 CKD patients which was lesser than 1.9 mg/dl. (Table 3). The correlation of various variables like Serum calcium, Phosphorus and Parathyroid hormone were not found to be statistically significant with CIMT values and thus cardiovascular risk in CKD patients. The mean value of Right CIMT was 0.9 mm (+0.24) and that of Left CIMT was 0.91 mm (+0.25) (Table 4).

CIMT was found to be elevated (>1 cm) in 16 CKD patients dependent on hemodialysis who had low magnesium levels (Table 1). Through our study it was

found that Serum Magnesium level was found to be negatively correlated to CIMT of bilateral carotid arteries (p<0.001) (Figure 1) in CKD patients who have been on maintenance hemodialysis. Thus showing, accelerated atherosclerosis associated with vascular calcification of intima and media layers and arterial stiffening is a frequent finding in CKD patients having hypomagnesemia. Hence, Mg2+ can be considered as the modifiable risk factor for cardiovascular morbidity in CKD patients, especially if on maintenance hemodialysis.

Table 1: Association of risk of CVD according to magnesium level (n = 58).

	Serum Magnesium level	CVD risk absent	CVD risk present	p-value
Right CIMT	Low (< 1.9)	2	15	<0.001
	Normal (1.9 – 3.1)	38	1	
	High (> 3.1)	2	0	
	Mean (SD)	2.64 (0.44)	1.23 (0.67)	<0.001
Left CIMT	Low (< 1.9)	2	15	<0.001
	Normal (1.9 – 3.1)	38	1	
	High (> 3.1)	2	0	
	Mean (SD)	2.65 (0.38)	1.21 (0.73)	<0.001

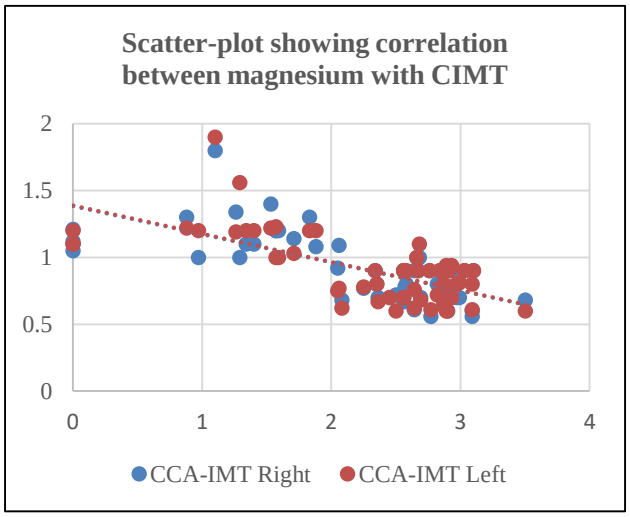

Figure 1: Correlation of serum magnesium with CIM.

	Pearson correlation coefficient	p-value
CIMT – Right	-0.704	<0.001
CIMT – Left	-0.677	<0.001

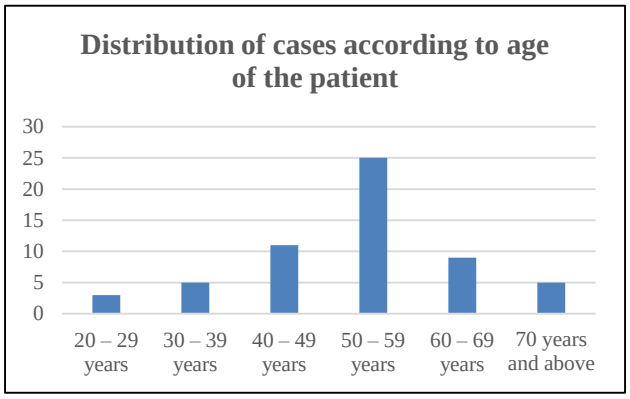

Figure 2: Distribution of cases according to age of the patient (n=58).

Table 2: Distribution of cases according to sex of the patient (n=58).

Sex of the patient	Number of cases
Male	37
Female	21

Table 3: Distribution of cases according to serum calcium, magnesium and phosphorus (n=58).

Marker	Number of cases
Serum calcium	
Mean (SD)	4.38 (0.56)
Range	3.04 - 5.28
Serum Magnesium	
Low (< 1.9)	17
Normal (1.9 – 3.1)	39
High (> 3.1)	2
Mean (SD)	2.25 (0.81)
Serum Phosphorus	
Low (< 2.4)	15
Normal (2.4 – 5.1)	43
High (> 5.1)	0
Mean (SD)	5.93 (1.43)
iPTH	
Normal (12 - 88)	12
Raised (>88)	46
Mean (SD)	156.15 (196.64)

Table 4: Distribution of cases according to Right and Left CIMT measurements (n=58).

	Right CIMT	Left CIMT
Mean (SD)	0.9 (0.24)	0.91 (0.25)
Number of patient with normal CIMT	42	42
Number of patients with increased CIMT	16	16

DISCUSSION

A growing body of evidence from in vitro investigations, animal models and both observational as well as interventional clinical studies point to the possibility that low magnesium levels are associated with vascular calcification. Moreover, several observational studies suggest a relationship between increased serum magnesium concentrations and better survival rates for patients receiving long-term dialysis treatment. Preliminary results from an uncontrolled interventional trial suggest that long-term intervention with magnesium in dialysis patients may retard arterial calcification. However, many questions remain unanswered and hard evidence is as yet lacking.[9]

The result of our study showing that CKD more common in males than females , where males represent 64% and females represent 36% of the patients , this was in agreement with Yorifuj M. et al who documented in their study that 69% of the patients were males and 31% were females.[10] In our study, the mean age in patients with ESRD was 52.6 (±12.75 years). The results have shown that patients with hypertension were 49 and DM were 18. This was in agreement with Parati G. et al. who showed that hypertension is highly prevalent in CKD particularly in patients with ESRD receiving hemodialysis.[12] In our study, serum calcium levels were significantly lower than normal value. This was in agreement with Ali Y. et al who reported in their study that serum phosphate, alkaline phosphatase and iPTH levels were significantly more elevated, whereas serum Ca levels were significantly lower in the study patients than the healthy controls.[15] In our study, 79.31 % of studied patients have higher iPTH while 20.6% have normal iPTH and the mean level of iPTH was (156.15+96.64 pg/ml). This was in agreement with Chutia H and Abraham A. who found that 95.2% show hyperparathyroidism and 4.8% show normal iPTH levels.[16] In our study, the mean value of Magnesium was 2.25 mg/dl (+ 0.81) with 17 patients has hypomagnesemia, 39 patients had normal Mg^{2+} level and 2 patients had hypermagnesemia and this was in agreement with Zaher M. et al. who found a significant decrease in serum magnesium levels in children with CKD on regular HD than in the controls. Spiegel D. showed that serum Mg^{2+} of HD patients significantly decreases after hemodialysis sessions.[17] Van de Wal-Visscher E. et al. reported that hypomagnesaemia is even more common (5–33%) when a 0.5 mEq/L dialysate Mg2+ is used.[24]

Hypomagnesaemia can be explained by reduced gastrointestinal uptake due to acidosis, poor nutrition and absorption. Patients with CKD normally have severely depressed intestinal Mg^{2+} absorption compared to healthy individuals, probably due to a deficiency of active vitamin D. Also, use of Low-Mg^{2+} dialysate (0.25 mmol/L or 0.5 mEq/L) is a risk factor for hypomagnesaemia in patients on both hemodialysis and peritoneal dialysis.[18] Also our study revealed no significant correlation between serum Mg^{2+} and laboratory data (Ca^{2+}, P, iPTH, urea and creatinine) and also this was in agreement with Yorifog M. et al who found in their study no significant differences in the PTH and vitamin D levels between two categories of Mg^{2+} levels, lower and normal. Khatami M. et al found no significant correlation between serum Mg^{2+} levels and serum Ca^{2+}, PTH and the other studied parameters. This may be attributed to small number of patients and short duration of CKD and dialysis.[19]

In our study, serum Mg^{2+} was negatively correlated with CIMT with statistical significance as ($P<0.001$) and this was in agreement with Ortega O. et al who founded that accelerated atherosclerosis associated with vascular calcification of intima and media layers and arterial stiffening is a frequent finding in hemodialysis patients and is a strong risk factor for increased morbidity and mortality.

In hemodialysis patients, an inverse association between serum Mg^{2+} and the common CIMT has been observed and some observational studies have confirmed the superior survival of dialysis patients with serum Mg^{2+} levels above the normal range, this survival advantage could be related to the inhibition of vascular calcification, phosphate lowering effect, and to reduction of oxidative stress. Ari E. et al. founded that Mg^{2+} may be negatively associated with CIMT, and a risk factor of CVD in CKD patients.[20]

CONCLUSION

Serum Mg^{2+} level assessment should also be included along with Ca^{2+}, K^{+} , phosphorus levels while managing CKD patients, considering the association of low level of serum Mg^{2+} with increased risk of atherosclerosis in CKD patients, particularly who are on haemodialysis. Though further prospective studies on larger population will be required to assess if Long term administration of oral Magnesium supplements to CKD patients on intermittent haemodialysis therapy might retard arterial calcification, thus decreasing the risk of cardiovascular mortality in such patients. Hence, Mg^{2+} can be considered as the modifiable risk factor for cardiovascular morbidity in dialysis dependent CKD patients.

Limitations

Limitation of the study were the sample size is small and larger similar studies are required in future to confirm the conclusion, it is not a multi-centre trial, Other mechanism by which Magnesium leads to altered milieu in cardiac myocytes leading to arrythmias and arterial stiffness and its interaction with other minerals like Na+ Ca2+ etc. was not considered in the study, which also increase cardiovascular mortality in CKD patients, a follow up of patients with reduced Magnesium levels with increased carotid intima-media thickness was not done to account for increased mortality in such CKD patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Gulati Y, Rastogi I, Giri R. Study of relationship between serum magnesium and carotid atherosclerosis in hemodialysis versus non-hemodialysis dependent CKD patients. Int J Res Med Sci 2023;11:1671-5.