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Original Research Article

Study of role of serum magnesium in preventing carotid atherosclerosis in chronic kidney diseases patients

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ABSTRACT

Background: Cardiovascular diseases are the most important causes of mortality and morbidity in CKD mainly due to accelerated atherosclerosis. Mg^{2+} possesses an anti-atherosclerotic effect, because of its anti-inflammatory and antioxidant properties, by inhibiting endothelial proliferation and inhibiting the upregulation of PAI 1 and VCAM 1. Mg^{2+} deficiency promotes hydroxyapatite formation and calcification of VSMC thus leading to accelerated plaque formation. Aim and objectives of current study were to evaluate relationship between serum Mg^{2+} level and atherosclerotic changes in patients with CKD.
Methods: This hospital based observational cross-sectional study has been carried out in department of KPS institute of medicine, GSVM Medical College, Kanpur. 58 subjects were recruited and underwent routine tests including Serum urea, creatinine, calcium, phosphorus, iPTH, Magnesium and intima media thickness (IMT) of carotid artery via Doppler study.
Results: In our study the mean value of Mg^{2+} was 2.25 mg/dl±0.81 17 out of 58 patients (29.3%) had hypomagnesemia. Intima Media thickness of carotid artery had an observed mean value of 1.0 cm±0.24, with mostly increased in those who had hypomagnesemia. Serum Mg^{2+} was negatively correlated (Pearson correlation coefficient was -0.677 and -0.704) with CIMT with statistical significance as $p<0.001$. Also, our study revealed no significant correlation between serum Mg^{2+} and other laboratory data (Ca^{2+}, P, iPTH, urea and creatinine.
Conclusions: We concluded that serum Mg^{2+} may be considered as a modifiable risk factor of atherosclerosis (thus, cardiovascular mortality) in CKD patients.

Keywords: Magnesium, Carotid Intima-media thickness, Cardiovascular mortality, Chronic kidney diseases

INTRODUCTION

CVD are the most important causes of mortality and morbidity 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. This 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, magnesium 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] Thus, the present study was designed to evaluate the association of carotid atherosclerosis and calcification with serum Magnesium levels in CKD patients, since accelerated atherosclerosis has been postulated to be one of the most important causes of cardiovascular mortality in CKD patients.

METHODS

The study was conducted in PG department of Medicine, GSVM Medical college, Kanpur. Patients suffering from CKD attending medicine OPD/IPD/ICU, admitted in medicine ward were screened for the study. It was prospective cross-sectional study conducted from December 2020 to August 2022 on 58 patients. The study was approved by ethical committee of GSVM Medical College Kanpur, India.

Inclusion criteria

Inclusion criteria for current study were; patients of age >18 years old diagnosed with chronic kidney disease, in stage IV & 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

Exclusion criteria for current study were; 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.

Procedure

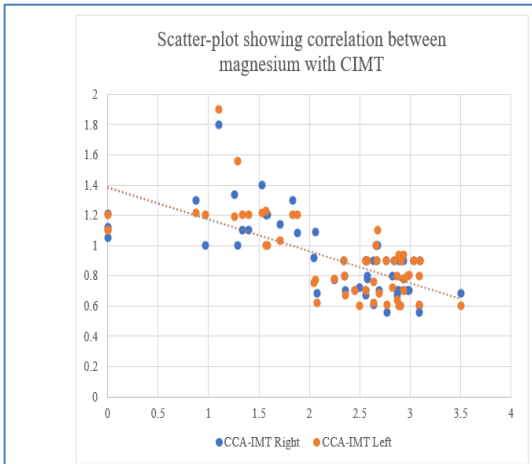
The cases were subjected to following investigations: Hb, TLC, DLC, Serum Urea, Serum creatinine, Serum magnesium (Technology: Photometry; Method: Modified Xylidyl Blue Reaction Method), LFT (including serum albumin), Serum Na+/K+/Ca++, Serum alkaline phosphate, Serum phosphorus, Para thyroid hormone, 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 (Table 2). The result of our study showing CKD more common in males than females. In our study, the mean age of patients with ESRD was 52.6 years old (±12.75) (Figure 2).



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

Figure 1: Correlation of serum magnesium with CIMT.

The results have shown that 84.4% patients had hypertension and 31% of the 58 patients had diabetes mellitus. There was no significant relationship found between age and CIMT, nor did the management varied with different ages, and efforts to identify risk factors for progression of CKD have generally focused on patient characteristics other than age.

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

Location	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

The value of CIMT was not found to be related to sex of the patient, or any comorbidity like diabetes mellitus and hypertension (Table 6). The mean value of urea and creatinine were 118.72 mg/dl (±61.77) and 8.68 mg/dl (±3.93).

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

Sex of the patient	N
Male	37
Female	21

Table 3: Distribution of cases according to mean biochemical markers (n=58).

Biochemical marker	N
HDL	
Normal	31
Deranged	27
Mean (SD)	42.81 (10.2)
LDL	
Normal	56
Deranged	2
Mean (SD)	98.89 (24.61)

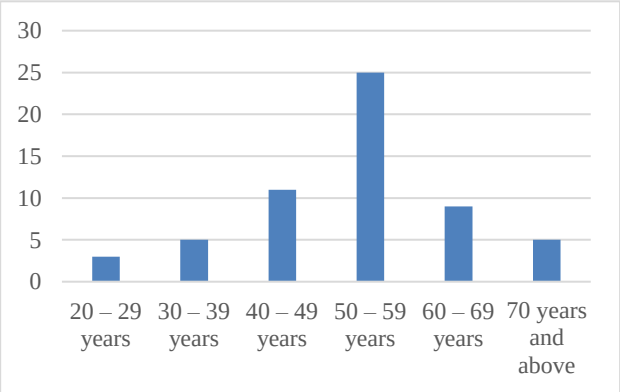


Figure 2: Distribution of cases according to age of the patient (n=58).

The level of calcium was found to be low and those of phosphorus and parathyroid hormone were found to be elevated. The level of Magnesium was found out to be low in 17 CKD patients which was lesser than 1.9 mg/dl (Table 4).

Table 4: 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 5: Distribution of cases according to right and left CIMT measurements (n=58).

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

The kidney size was found to bilaterally small, with size of right kidney ranging from 6-7.9 cm and that of left kidney ranging from 5.3-8 cm. 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 (Table 7-8). The mean value of Right CIMT was 0.9 mm (±0.24) and that of Left CIMT was 0.91 mm (±0.25) (Table 5). CIMT was found to be elevated (≥1 cm) in 16 CKD patients who had low magnesium levels (Table 1).

Table 6: Association of risk of CVD according to comorbidity reported (n=58).

Location	Comorbidity	CVD risk absent	CVD risk present	P value
Right CIMT	DM	14	4	0.540
	HTN	35	14	0.695
Left CIMT	DM	13	5	0.983
	HTN	34	15	0.229

Table 7: Association of risk of CVD according to iPTH level (n=58).

Location	Serum iPTH level	CVD risk absent	CVD risk present	P value
Right CIMT	Normal (12-88)	8	4	0.617
	Raised (>88)	34	12	
	Mean (SD)	172.53 (223.95)	113.15 (84.43)	0.308
Left CIMT	Normal (12-88)	7	5	0.220
	Raised (>88)	35	11	
	Mean (SD)	175.39 (223.83)	105.65 (78.99)	0.231

Table 8: Association of risk of CVD according to serum phosphorus level (n=58).

Location	Serum phosphorus level	CVD risk absent	CVD risk present	P value
Right CIMT	Low (<2.4)	10	5	0.563
	Normal (2.4-5.1)	32	11	
	Mean (SD)	5.89 (1.42)	6.05 (1.51)	0.701
Left CIMT	Low (<2.4)	11	4	0.926
	Normal (2.4-5.1)	31	12	
	Mean (SD)	5.87 (1.41)	6.12 (1.52)	0.560

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). 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.

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 supplementation with magnesium in dialysis patients may retard arterial calcification.[11] The result of our study showing that CKD more common in males than females , was in agreement with Yorifuj et al who documented in their study that 69% of the patients were males and 31% were females.[10] The results of patients having hypertension and Diabetes Mellitus was in agreement with Parati et al who showed that hypertension is highly prevalent in CKD particularly in patients with ESRD receiving hemodialysis.[12] As regard to serum urea the mean value was 118.72$\pm$61.77mg/dl. There was a significant increase in serum urea in studied group and this was in accordance with those of Ali et al who reported that the mean of serum was 139.69$\pm$27.59 mg/dl and in the control group 22.59$\pm$6.30 mg/dl with statistical significance as $p<0.001$.[13] As regard to serum creatinine the mean value was 8.68 ($\pm$3.93mg/dl) and this was in agreement with those of Sliem et al who reported that mean of serum creatinine in the hemodialysis patients was (8.6$\pm$2.2 mg/dl) and in the control group was (0.7$\pm$0.2 mg/dl) with statistical significance as $p<0.001$.[14] In our study, serum calcium levels were significantly lower than normal value . This was in agreement with Ali 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 pg/ml $\pm$96.64). This was in agreement with Chutia and Abraham, 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 et al who found a significant decrease in serum magnesium levels in children with CKD on regular HD than in the controls. Wal-Visscher et al reported that hypomagnesaemia is even more common (5-33%) when a 0.5 mEq/l dialysate Mg^{2+} is used. 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 and laboratory data (Ca^{2+}, P, iPTH, urea and creatinine) and also this was in agreement with Yorifog 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 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 et al who founded that accelerated atherosclerosis associated with vascular calcification of intima and media layers and arterial stiffening is a frequent finding in haemodialysis patients and is a strong risk factor for increased morbidity and mortality. The superior survival of dialysis patients with serum Mg^{2+} levels above the normal range, could be related to the inhibition of vascular calcification, phosphate lowering effect , and to reduction of oxidative stress. This brings all of us to consider Magnesium deficiency as one of the modifiable risk factors while taking into account other mineralisation factors and other well-known pathophysiology underlying cardiovascular morbidity and mortality in CKD patients.

Limitations

Limitations of current 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.

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 CKD patients.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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