Serum magnesium level in maintenance hemodialysis and cardiovascular calcification

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Background Patients with chronic kidney disease have a high prevalence of vascular calcification, and cardiovascular disease is the leading cause of death. Magnesium (Mg) is a natural calcium antagonist and many studies have shown that low circulating levels of Mg are associated with vascular calcification.

Aim of the work The aim of the study was to assess the relationship between serum Mg levels and vascular calcification in chronic hemodialysis (HD) patients.

Patients and methods A cross-sectional study conducted on 60 patients with end-stage renal disease on regular HD in Al-Zahraa University Hospital (group I) compared with 30 healthy controls (group II), from June to December 2017. Patients with evidence of infection, chronic diarrhea, ileostomy, and those receiving Mg-based phosphate binders were excluded from the study. All studied groups were submitted to clinical examination, renal function, lipid profile, serum albumen, calcium, phosphorus, intact parathyroid hormone, Mg, carotid duplex, echocardiography, ECG, and lateral view plain abdominal radiograph.

Results There were highly significant differences regarding Mg and carotid intimal medial thickness (CIMT) in group I compared with group II: 1.51±0.28, 0.89±0.30 and 2.47±0.18, 0.45±0.08 respectively, $P<0.001$. Echocardiographic findings showed calcified mitral and aortic valves in 12 (20%) patients and calcified abdominal aorta by abdominal X-ray radiograph in 20 (33.33%) patients. There were highly significant negative correlation between serum Mg and CIMT and abdominal aortic calcification in group I.

Conclusion The patients on maintenance HD have lower serum Mg levels. It was associated with increased CIMT and vascular calcification if compared with healthy group and concomitant use of proton pump inhibitors may aggravate this hypomagnesemia. So serum Mg level in maintenance HD patients could be a potential biomarker for cardiovascular calcifications.

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Introduction

Magnesium (Mg) plays an important role in the regulation of vascular tone and heart rhythm. Mg deficiency has been reported to promote inflammation, and it decreases the specific immune response [1]. Mg also reduces total peripheral resistance by stimulation of nitric oxide synthesis and is a potent inhibitor of vascular calcification [2].

Serum Mg concentration is maintained in a narrow range by the kidneys and the digestive tract in healthy control. In dialysis patients, where the kidney function is abolished, serum Mg concentrations are elevated and its balance depends on the intake and most importantly dialysate Mg concentration [3]. However, there is a wide variability in Mg balance in dialysis patients and it is not surprising that Mg balance may be normal or even low in this population [4].

Cardiovascular disease is the leading cause of mortality and morbidity in patients with chronic kidney disease (CKD). Several traditional and nontraditional risk factors have been identified as risk factors for the increased mortality of end-stage renal disease patients. Vascular calcification is highly prevalent in end-stage renal disease (ESRD) patients, occurs decades earlier than in the general population, and its progression accelerates dramatically once a patient initiates regular dialysis. This is of great clinical significance, as the presence and degree of calcification independently predicts future cardiovascular events, as well as mortality [5].

Animal models have shown an association between lower Mg levels and cardiovascular disease. In both uremic and nonuremic rats, Mg-deficient diet with subsequent hypomagnesemia was associated with widespread tissue calcifications, increased large-artery media thickness, collagen content, higher pulse pressure, and mortality [6].

In ESRD patients receiving hemodialysis (HD), some data suggest that hypomagnesemia is associated with

increased all-cause and cardiovascular mortality [7]. However, these studies were conducted outside Egypt and thus may not be generalizable to the Egyptian dialysis population, given the varying dialysate Mg concentrations used in different countries. Therefore, we conducted what is to our knowledge the first study investigating the association between serum Mg and vascular calcification in adult Egyptian HD patients.

Patients and methods

This cross-sectional study of 60 patients with ESRD on regular HD in Al-Zahraa University hospital dialysis unit (group I) was compared with 30 age-matched and sex-matched healthy controls (group II). The study was done during the period from June to December 2017. Patients included in group I were on regular HD for more than 6 months, three times/week, 4 h/ session with a dialysate Mg concentration of 0.5 mmol/L, without evidence of infection confirmed with negative CRP and willing to participate. Group I was further subdivided into two groups: group Ia included patients on regular intake of proton pump inhibitors (PPI) and group Ib included patients not on PPI. Any patient who had a history of chronic diarrhea, ileostomy or colostomy, malignancy, receiving diuretics, or unwilling to participate were excluded from the study. None of the patients were receiving Mg-based phosphate binders or other Mg-based medications. Written informed consents were taken from all studied groups.

Full medical history and clinical examination were done for all studied groups. All patients and control were subjected to the following: blood urea, serum creatinine, serum albumin, total calcium, phosphorus, total cholesterol, triglycerides, intact parathyroid hormone (iPTH), and serum Mg were measured using standard kits. The blood samples were taken before dialysis in a midweek session before anticoagulation to avoid interference with heparin. Comprehensive transthoracic two-dimensional, M-mode echocardiography, and Doppler were done in standard views for the detection of ejection fraction, valvular calcification, left ventricular hypertrophy (LVH), segmental wall motion abnormalities using the VIVD7GE system (KPI HEALTHCARE INC., Yorba Linda, CA, USA). Lateral view plain abdominal radiograph for the assessment of abdominal aortic calcification score was performed in the standing position using standard radiographic equipment. Calcification of abdominal aorta was graded using the scoring system described by Kauppila *et al.* [8], in which both the location and the severity of calcific deposits at each lumbar vertebral segment (L1–L4) were evaluated as follows : A score of 0 denoted no aortic calcific deposits, 1 denotes small scattered calcific deposits filled less than one-third of the longitudinal wall of the aorta; 2 denotes one-third or more but less than two-thirds of the longitudinal wall of the aorta was calcified; and 3 two-thirds or more of the longitudinal wall of the aorta was calcified. A separate score was determined for the anterior and posterior aorta, and the values were summed across the four vertebrae, resulting in an abdominal aortic calcification index that could range from 0 to 24 points. High-resolution B-mode ultrasonography multifrequency 5–10 MHZ linear probe (Siemens Sonoline G, Garnerville, NY, USA) was used to measure carotid intimal medial thickness (CIMT) of both carotid arteries which were done in supine position while the patient neck rotated to the opposite side with little hyperextension.

Data analysis

Data were analyzed by Microsoft Office 2003 (excel) and Statistical Package for Social Sciences, version 16 (SPSS Inc., Chicago, Illinois, USA). Parametric data were expressed as mean±SD, and nonparametric data was expressed as number and percentage of the total. A comparison of the mean±SD of the two groups was done using paired and unpaired Student's *t*-test and measurement of the mutual correspondence between two values was done using the Spearman's correlation coefficient. A *P* value of greater than 0.05 is considered insignificant; a *P* value of 0.05 or less is considered significant; and a P value of less than 0.01 is considered highly significant.

Results

Sixty patients with ESRD were on regular HD for more than 6 months (group I); 26 (43.3%) of them were women; 34 (56.6%) were men; their ages ranged from 22 to 76 years, with a mean±SD of 55.25±12.45 years (Table 1). Thirty apparent healthy persons served as the control group (group II); 14 (46.6%) of them were women and 16 (53.3%) were men; their ages ranged from 22 to 72 years with a mean±SD of 52.43± 14.27 (group II) (Table 1). The apparent causes of ESRD were : 28 (46.6%) patients were hypertensive, 17 (28.3%) patients diabetic and hypertensive, six (10%) patients of unknown cause, three (5%)

Table 1 Demographic data of groups I and II

Variables	Group I	Group II	*P*
Sex [*n* (%)]			
Males	34 (56.6)	16 (53.3)	–
Females	26 (43.3)	14 (46.6)	–
Age (mean±SD) (years)	55.25±12.45	52.43±14.27	NS

patients having polycystic kidney disease, two (3.3%) patients analgesic nephropathy, two (3.3%) patients renal amyloidosis,one (1.6%) patient systemic lupus erythematosus, and one (1.6%) patient with obstructive nephropathy.

Among 60 HD patients none of them had hypermagnesemia; however, 27 (45%) patients had hypomagnesemia and 33 (55%) patients had normal Mg levels.

Table 2 showed a highly significant comparison between groups I and II as regarding blood urea, serum creatinine, cholesterol, triglycerides, serum iPTH, serum phosphorus, and serum Mg ($P<0.001$) (Fig. 1), while there was no significant difference between serum albumin and total calcium in both groups ($P=0.979$ and 0.124, respectively).

There were no significant difference between men and women on comparing both groups I and II as regards age and all laboratory parameters.

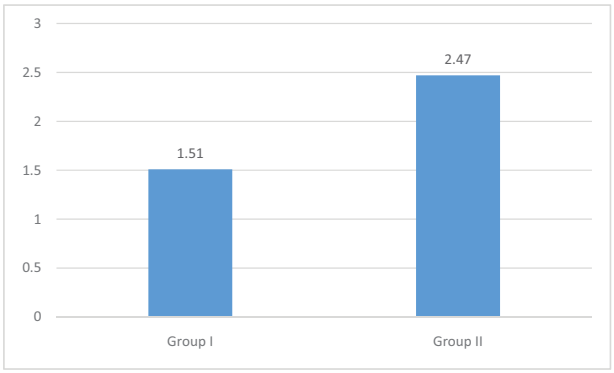
There were highly significant increases in mean±SD of CIMT in group I compared with group II ($P<0.001$) (Fig. 2).

Table 3 shows the echocardiographic findings of group I; we found 12 (20%) patients who had calcific aortic and mitral valves, five (8.33%) patients who had calcified aortic valve, two (3.33%) patients who had calcified mitral valve, and 21 (35%) patients who had LVH with segmental wall motion abnormalities. Five (8.33%) patients had atrial fibrillation by ECG. Abdominal lateral view radiograph showed 20 (33.33%) patients with calcification of abdominal aorta affecting all four lumbar segments with an abdominal aortic calcification score of greater than 1.

The correlation study in group I was done between serum Mg and laboratory parameters. We found a highly positive significant correlation with serum albumin ($r=0.350$, $P<0.01$) and a negative significant correlation with iPTH ($r=-0.253$, $P<0.05$) (Figs. 3 and 4) and nonsignificant correlation between blood urea, serum creatinine, total cholesterol, triglycerides, serum calcium, and phosphorus.

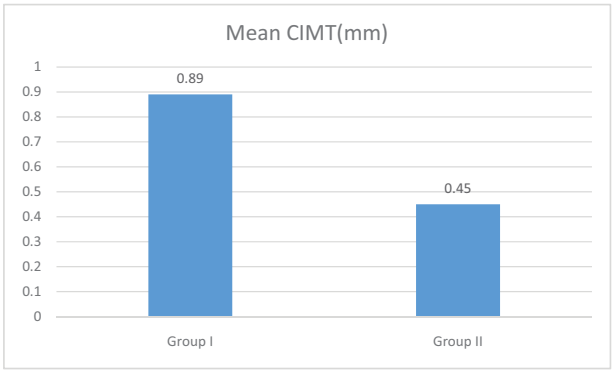
In this study, we found a significant negative correlation between serum Mg and mean CIMT of both sides in group I ($r=-0.265$, $P<0.05$) (Fig. 5).

Figure 1



Comparison between serum±SD of Mg in groups I and II.

Figure 2



Comparison between mean carotid intimal medial thickness (CIMT) in groups I and II.

Table 2 laboratory data for groups I and II

Variables	Group I (mean±SD)	Group II (mean±SD)	*P* value	Significance
Blood urea (mg/dl)	134.52±38.09	28.00±6.59	<0.001	HS
Serum creatinine (mg/dl)	8.88±2.61	0.75±0.19	<0.001	HS
Total cholesterol (mg/dl)	161.23±37.52	125.37±30.71	<0.001	HS
Serum TG (mg/dl)	134.75±48.68	89.93±18.96	<0.001	HS
Serum albumin (g/dl)	3.80±0.34	3.80±0.24	0.979	NS
iPTH (pg/dl)	567.02±469.24	42.23±11.09	0.001	HS
Total Ca (mg/dl)	8.81±0.75	9.01±0.47	0.124	NS
Serum Ph (mg/dl)	5.48±1.80	3.29±0.68	<0.001	HS
Serum Mg (mg/dl)	1.51±0.28	2.47±0.18	<0.001	HS

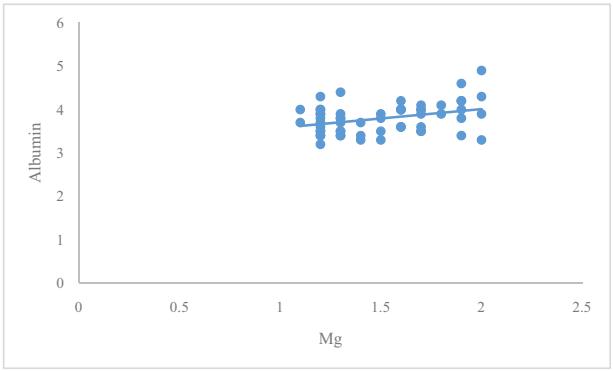
Ca, calcium; HS, highly significant; iPTH, intact parathormone hormone; Mg, magnesium; Ph, phosphorus; TG, triglycerides.

Table 3 Echocardiographic, ECG, and radiologic findings in group I

Findings	*n* (%)
Calcific aortic and mitral valve	12 (20)
Calcified aortic valve	5 (8.33)
Calcified mitral valve	2 (3.33)
Segmental wall motion abnormalities and LVH	21 (35)
AF (by ECG)	5 (8.33)
Abdominal aorta calcification (abdominal radiograph, lateral view)	20 (33.33)

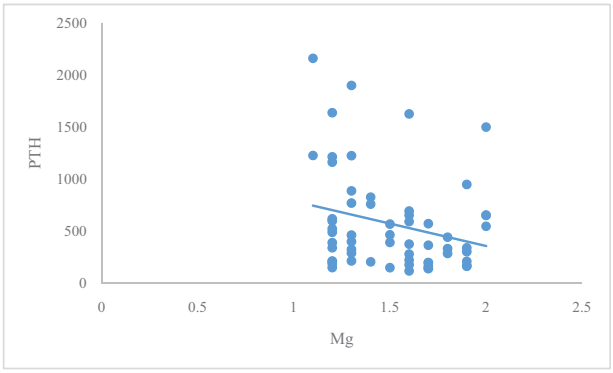
AF, atrial fibrillation; LVH, left ventricular hypertrophy.

Figure 3



Correlation between serum Mg and serum albumin in group I.

Figure 4



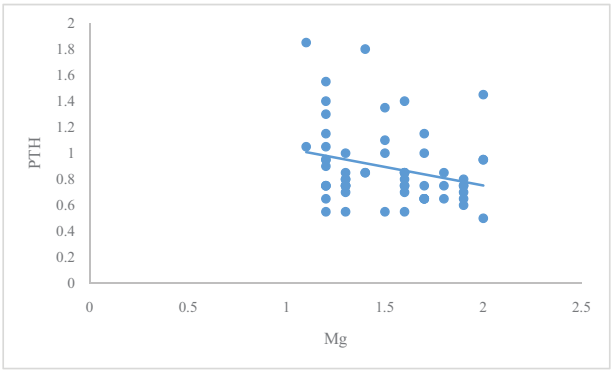
Correlation between serum Mg and intact parathyroid hormone (iPTH) in group I.

According to the use of PPI we found highly significant decrease in serum Mg in group Ia compared with group Ib (1.39±0.21 vs. 1.69±0.27; $P<0.001$), while there were nonsignificant differences with other laboratory parameters (Fig. 6).

We found nonsignificant increase in CIMT in group Ia compared with group Ib.

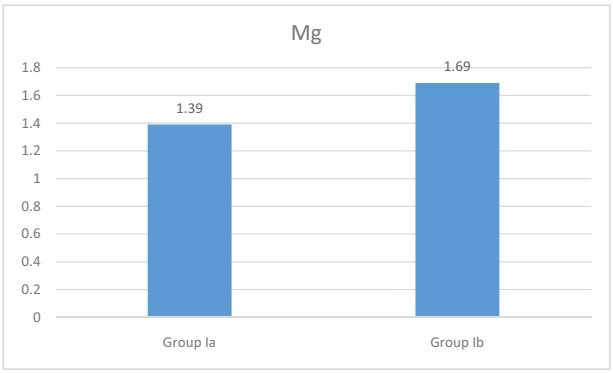
There were highly significant negative correlation between serum Mg and iPTH ($r=-0.485$; $P<0.001$) and significant negative correlation with triglycerides

Figure 5



Correlation between serum Mg and mean carotid intimal medial thickness (CIMT) in group I.

Figure 6



Comparison between Mg level in groups Ia and Ib.

($r=-0.263$; $P<0.05$), while no significant correlation with other laboratory parameters in group Ia (Table 4).

There were significant negative correlations between serum Mg and CIMT in group Ia, ($r=-0.316$, $P<0.001$), while in group Ib there were no significant correlations between serum Mg and CIMT (Table 5).

Discussion

Studies from the general population have linked Mg deficiency with endothelial dysfunction, insulin resistance, hyperaldosteronism, and inflammation all of which are associated with vascular calcifications [9].

Many studies suggest that hypomagnesemia occurs more frequently among dialysis patients than previously realized. This can be attributed to dietary restrictions for ESRD patients who limit the intake of Mg-rich foods including, nuts, seeds, dried fruits, and dairy products and concomitant use of loop and thiazide diuretics. In dialysis patients, the dialytic

Table 4 Correlation between serum magnesium and different laboratory parameters in group Ia

Variables	*r* value	Significance
Urea (mg/dl)	–0.049	NS
Creatinine (mg/dl)	0.063	NS
Cholesterol (mg/dl)	–0.209	NS
Triglycerides (mg/dl)	–0.263	S
Albumin(g/dl)	0.203	NS
Calcium (mg/dl)	0.095	NS
Phosphorus(mg/dl)	0.132	NS
iPTH (pg/dl)	–0.485	HS

HS, highly significant; iPTH, intact parathormone hormone; S, significant.

Table 5 Correlation between serum magnesium and CIMT in group Ia

Variables	*r* value	Significance
CIMT (mean) (mm)	–0.316	HS

CIMT, carotid intima-medial thickness; HS, highly significant.

procedure has the primary function of Mg removal; therefore, the serum Mg concentration parallels the dialysate Mg content [10].

In this study, Mg levels in patients on maintenance HD were significantly lower than the control group. These results are in agreement with the study done in pediatric patients by Zaher *et al*. [11], while Metwalli in 2016 in a study done on Saudi patients found that most of his patients have hypermagnesemia, but around 25% had below normal Mg level. He also added that patients on peritoneal dialysis had lower levels of serum Mg when compared with the HD group [12].

In our study, we found that patients echocardiographic findings such as mitral valve, aortic valve calcification, LVH, or arrhythmia had lower Mg level than those without. These findings are in agreement with the study by Silva *et al*. [13], which found an association between mitral valve calcification in diabetic predialysis patients. Also results from a large prevalent HD population conclude that low Mg levels are a good cardiovascular risk marker, associated with higher left ventricle mass and vascular calcification, and a good predictor of all-cause and cardiovascular mortality [9].

Several theories have been advanced to explain the onset and progression of vascular calcification, during which a central role is played by the vascular smooth muscle cells. Endothelial cells' exposure to low Mg levels causes them to express an inflammatory phenotype, and in-vivo hypomagnesemia is associated with increased leukocyte and macrophage activation, C-reactive protein, NF-kB, platelet aggregation, and cytokines. Increased endothelial permeability increases lipid penetration into the vascular media, leading to the formation of foam cells, plaques, and increased oxidative stress [14].

A meta-analysis report a 30% increase in cardiovascular disease for every 0.49 mg/dl decrease in serum Mg within the normal range [15].

In the present study, we found that abdominal aorta calcification was detected by lateral view radiograph and this agreed with the study done by some authors who added that the abdominal aorta calcification score is decreased by the addition of Mg supplementation to dialysis patients and they suggests that Mg may act as a possible inhibitor of vascular calcification [16].

In the current study we found significant negative correlation between serum Mg and carotid intimal thickness in the patient group; this is in agreement with Turgut *et al*. [17] who reported a negative association between serum Mg levels and carotid intima-media thickness in patients undergoing HD, which was improved after 2 months supplementation of oral Mg citrate.

In the current study, we found a negative correlation between serum Mg and PTH in HD patients compared with the control group; this could be explained on the bases that Mg was thought to bind the calcium-sensing receptors in the parathyroid gland and might cause reduced PTH release [18]; this in agreement with the results of some authors Mitwalli [12] and João Matias *et al*. [9], while other authors found no correlation between Mg level and PTH in predialysis CKD patients [19] and in peritoneal dialysis population [20] and HD patients [21].Mg supplementation has been reported to reduce carotid intima-media thickness in dialysis patients. Mg is also well recognized to prevent soft tissue calcification by inhibiting hydroxyapatite formation and increasing natural inhibitors of calcification such as fetuin A, osteoprotegerin, and undercarboxylated-matrix Gla protein [22].

The US Food and Drug Administration has issued a warning that the prolonged use of PPIs may cause low serum Mg levels, and recommends obtaining serum Mg levels before prescribing PPI treatment in patients who are expected to use these drugs for long term [23].

The high-gastric pH present in PPI users may alter Mg transport resulting in a tendency to gastrointestinal Mg loss in all patients using PPIs [24].

In our study, we found that serum Mg is lower in patients on daily intake of PPI, this is consistent with many studies [24–27], while other studies did not find any relation between serum Mg and PPI in HD patients [28].

Conclusion

Hypomagnesemia is frequent among adult Egyptian HD patients. It is associated with increased CIMT and abdominal aorta calcification; meantime the use of PPI could aggravate hypomagnesemia. Further study is required to determine the effect of use of different dialysate Mg concentrations on serum Mg level in HD patients and we recommend maintaining a serum Mg level in a high normal range either by diet modification or by increased dialysate Mg concentration. We can conclude that serum Mg level in maintenance HD could be a potential biomarker for cardiovascular calcification for further investigations.

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Nil.

Conflict of interest

There are no conflicts of interest.

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