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Study of the relationship between serum magnesium and atherosclerotic changes in hemodialysis patients

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Abstract: Background: Cardiovascular disease is the most common complication of chronic kidney disease and the most common cause of death. Atherosclerosis progress more dynamically in hemodialysis patients than in the general population. Mg depletion may be the missing link between cardiovascular risk factors and atherosclerosis. **Aim of the study:** The aim of this study was to evaluate the relationship between serum Mg and atherosclerotic changes in hemodialysis patients**. Methods:** The study was conducted on 60 patients on hemodialysis at Internal Medicine Department, Tanta University Hospital. All patients were subjected to laboratory investigations include (serum urea, creatinine, Calcium, Phosphorus, Parathyroid hormone and Magnesium), radiological assay include measurement of intima media thickness (IMT) of carotid, femoral and brachial arteries, measurement of peak systolic velocity (PSV) of the previous arteries and measurement of ankle brachial index (ABI). **Results:** Our study showed that a significant negative correlation was observed between serum Mg and carotid intima media thickness (CIMT). **Conclusion:** Serum Mg may considered as a modifiable risk factor of atherosclerosis in hemodialysis patients.

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1. Introduction

Chronic kidney disease is becoming more prevalent today and is associated with high costs and poor outcomes of treatments making it a worldwide public health threat.[1] CKD is defined as either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for at least 3 months.[2] CVD are the most important causes of mortality and morbidity in chronic renal patients mainly due to accelerated atherosclerosis. These patients have a risk of mortality 10-20 times higher than general population.[3]

Atherosclerosis (also known as Arteriosclerotic Vascular Disease or ASVD) is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol, chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells and promoted by low density (especially small particle).[4]The pathogenesis of atherosclerosis in CKD is somewhat different from general population and is also affected by other factors such as genetic factors, inflammation, hyperparathyroidism, malnutrition.[5]Early atherosclerosis can be evaluated by measurement of CIMT with ultrasonography, which is a simple, reliable, non-invasive method.[6]

Atherosclerosis is a well-known risk factor for CVD potentially triggering myocardial infarction and stroke. The pathogenesis of atherosclerosis is complex and like endothelial dysfunction and hyperlipidemia Some studies revealed that Mg may has a role in the pathogenesis of atherosclerosis.[7]Magnesium is one of the major intracellular cations. It is a vital element in human metabolism and general body function. Developments in methods to monitor this element have provided an improved understanding of its role in various diseases, particularly in CVD. [8]

The close association of high mortality and morbidity with CVD in HD patients is well documented. Although several factors have been proposed to explain the risk of CVD in maintenance hemodialysis patients, the causes of CVD in these patients remain controversial.[9]Recently, there is increasing evidence suggesting an association between low serum Mg levels and CVD in CKD as well as in general population.[10] Although, the mechanism of vascular calcification is multifactorial, it is now evident that Mg depletion may be involved in the pathogenesis of vascular calcification.[11] It seems that

Mg depletion may be the missing link between cardiovascular risk factors and atherosclerosis. Vascular calcification is an important factor for increased morbidity and mortality in CKD and dialysis patients.[8]There are unanswered questions about Mg balance and its effects in both CKD and dialysis patients and the development of atherosclerosis.

In our study we aimed to evaluate the relationship between serum Mg level and atherosclerotic changes in patients with CKD on hemodialysis.

Cases and Methods

This cross sectional study was conducted from April 2018 to April 2019, after obtaining cases informed written consent and within the approved protocol of Tanta University Ethical Committee. To maintain privacy, names of all cases were concealed and code numbers were used instead. Sixty patients with definite CKD by complete medical history, clinical examination, laboratory investigation selected from regular hemodialysis in Tanta University Hospital, Hemodialysis Units.

Exclusion criteria were cases with chronic liver disease, heart failure or unstable coronary artery disease, recent history of chronic diarrhea, malignancy and chronic infections, consumption of drugs affecting Mg within the past months like thiazide diuretics, PPI and aminoglycoside antibiotics.

All cases were subjected to the following

- History taking regarding age and sex, complete clinical examination: including, vital signs, chest, cardiac and abdominal examination.

- Laboratory investigations: Serum levels of urea, creatinine, serum magnesium. serum calcium, serum phosphorus and parathyroid hormone.

- Radiological assay: Measurement of the intima media thickness of the carotid, brachial and femoral arteries by superficial ultrasonography. Measurement of pulse wave velocities of the carotid, brachial and femoral arteries using a color Doppler ultrasonography. Measurement of Ankle Brachial index using blood pressure cuff and pulse volume recording Doppler ultrasound.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The following tests were used: Pearson coefficient, Kruskal Wallis test and Spearman coefficient.

3. Results

Laboratory investigations of the studied participants revealed that 21 patients (35%) showed normal calcium level, while 39 patients (65 %) showed hypocalcemia, 23 patients (38.3%) showed normal phosphorus level, while 37 patients (61.7 %) show hyperphosphatemia. Lastly 2 patients (3.3%) showed normal parathyroid hormone level, while 58 patients (96.7 %) showed high level of parathyroid hormone. (Table 1)

Table (1): laboratory data of the studied cases according to (N=60)

	Normal		Low		High		Mean ± SD
	No	*%*	*No*	*%*	*No*	*%*	
Calcium (mg/dl)	21	35%	39	65%	-	-	8.24 ± 1.01
Phosphorus (mg/dl)	23	38.3%	-	-	37	61.7%	5.24 ± 1.43
Parathyroid hormone (pg/ml)	2	3.3%	-	-	58	96.7%	221.6± 88.16

*: Statistically significant at $p \leq 0.05$

Table (2): Distribution of the studied cases according to serum Mg (N=60)

Serum Magnesium (mg/dl)	No.	%
Normal	12	20.0
Hypo	36	60.0
Hyper	12	20.0
Min – Max	1.30 – 2.80	
Mean ± SD	1.84 ± 0.49	
Median	1.65	

*: Statistically significant at $p \leq 0.05$

Magnesium level of study participant was normal in 12 patients (20%), low in 36 patients (60%), high in 12 patients (20%) and the mean value was 1.84 ± 0.49. (Table 2) Intima media thickness characters of study participants showed that, IMT for carotid artery ranged from 0.71 - 1.48 with a mean value of 1.06 ± 0.23, femoral artery IMT ranged from 0.52 - 1.35with a mean value of 0.73 ± 0.20 and brachial artery IMT ranged from 0.20 - 0.42 with a mean value of (0.27 ± 0.05).

Peak systolic velocity characters of study participants showed that, the mean value of PSV for carotid artery ranged from 51.10 - 97.75 with a mean

value of 76.0 ± 11.07, PSV femoral artery ranged from 53.45 - 91.80 with a mean value of 73.84 ± 10.38 and brachial artery PSV ranged from 45.90 - 107with a mean value of 73.16± 15.09. (Table 3 and Figure 1) No significant correlation was observed between serum magnesium and studied laboratory parameters including blood urea, serum creatinine, serum calcium, phosphorus, Parathyroid hormone and GFR in all participants. (Table 4)

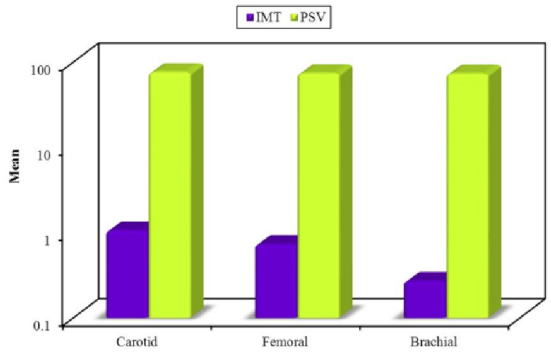

Figure (1): Descriptive analysis of the studied cases according to IMT and PSV.

Table (3): Analysis of the studied cases according to IMT and PSV (N=60)

	IMT (mm)	PSV (cm/sec.)
Carotid		
Min - Max	0.71 – 1.48	51.10 – 97.75
Mean ± SD	1.06 ± 0.23	76.0 ± 11.07
Median	1.02	76.80
Femoral		
Min - Max	0.52 – 1.35	53.45 – 91.80
Mean ± SD	0.73 ± 0.20	73.84 ± 10.38
Median	0.64	74.57
Brachial		
Min - Max	0.20 – 0.42	45.90 – 107.0
Mean ± SD	0.27 ± 0.05	73.16 ± 15.09
Median	0.27	69.30

IMT: Intima Media Thickness PSV: Peak systolic Velocity *: Statistically significant at $p \leq 0.05$

As regard CIMT, significant negative correlation was observed between serum Mg and CIMT. (Figure 2) Also, significant positive correlation was observed between serum creatinine and CIMT. On the other hand, no significant correlations were observed between CIMT and other laboratory parameters or duration of hemodialysis. No significant correlations were observed between BIMT, FIMT and laboratory parameters or duration of hemodialysis. As regard PSV, no significant correlation was observed between PSV of measured arteries (carotid, brachial, femoral) and different laboratory parameters or duration of hemodialysis. No significant correlation was observed between ABI and different laboratory parameters or duration of hemodialysis. (Table 5)

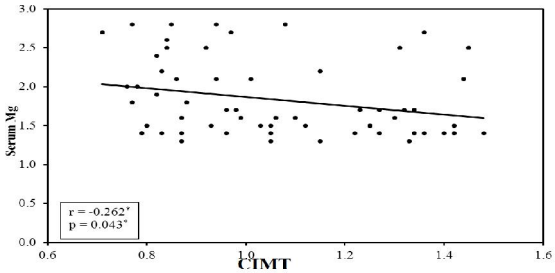

Figure (2): This figure shows significant negative correlation between serum magnesium and CIMT.

Table (4): Correlation between serum Magnesium with laboratory data.

	Serum Magnesium	
	r	P
Urea	-0.056	0.668
Creatinine	0.120	0.362
Calcium	-0.025	0.847
Phosphorus	0.179	0.170
Parathyroid hormone	-0.061	0.641
GFR	-0.249	0.065

r: Spearman coefficient *: Statistically significant at $p \leq 0.05$

Table (5): Correlation between IMT, PSV and ABI with different parameters (N= 60)

		IMT			PSV			ABI
		Carotid	*Femoral*	*Brachial*	*Carotid*	*Femoral*	*Brachial*	
Calcium	r	-0.033	0.138	0.130	-0.178	-0.031	0.079	-0.239
	P	0.803	0.293	0.323	0.173	0.817	0.547	0.066
Phosphorus	r	-0.150	-0.001	0.108	0.195	-0.102	0.049	0.210
	P	0.254	0.997	0.413	0.135	0.439	0.709	0.107
Parathyroid hormone	r	-0.036	-0.092	-0.056	0.057	-0.044	-0.047	-0.074
	P	0.787	0.484	0.673	0.666	0.740	0.724	0.575
Urea	r	-0.247	0.056	0.163	-0.123	0.077	0.040	-0.050
	P	0.057	0.669	0.213	0.347	0.556	0.764	0.704

		IMT			PSV			ABI
		Carotid	*Femoral*	*Brachial*	*Carotid*	*Femoral*	*Brachial*	
Creatinine	r	-0.281	-0.128	0.101	0.133	-0.021	0.113	0.015
	P	0.030*	0.331	0.442	0.310	0.874	0.391	0.907
GFR	r	0.178	-0.053	0.039	0.062	0.024	-0.272	-0.120
	P	0.175	0.686	0.768	0.638	0.857	0.065	0.361
Serum Mg	r	-0.262	0.075	-0.164	0.000	-0.175	0.151	-0.038
	P	0.043*	0.567	0.210	0.997	0.181	0.249	0.775
Duration of dialysis	r	-0.222	0.106	-0.008	0.018	-0.238	0.039	0.176
	P	0.088	0.418	0.950	0.891	0.067	0.768	0.178

r: Pearson coefficient *: Statistically significant at $p \leq 0.05$

4. Discussion:

The result of our study showing that CKD more common in males than females where males represent 58.3% and females represent 41.7 % of patients, this was in agreement with YORIFUJ M. et al. (2017) [9] who documented in their study that (69%) of the patients were male and (31%) were females. Liu F. et al. (2013) [12] also reported in their study that (53.06%) of patients were male and (46.94%) were female. In our study, the mean age in patients with ESRD was (45.90± 6.62years). Hsu et al. (2006) [13] proved that most previous studies of CKD and current recommendations for its management have not distinguished between patients of different ages, and efforts to identify risk factors for progression of CKD have generally focused on patient characteristics other than age.

The result of our study showed that patients with hypertension were (70%) and DM were (23.3%). This was in agreement with Parati G. et al. (2016) [14] who showed that hypertension is highly prevalent in CKD particularly in patients with ESRD receiving hemodialysis. Bakris G and Ritz E. (2009) [15] who found that the frequency of CKD continues to increase worldwide as does the prevalence of ESRD. The most common, but not the only, causes of CKD are hypertension and diabetes. As regard to serum urea the mean value in studied group was (175.8 ± 49.01mg/dl). There was a significant increase in serum urea in studied group and this was in accordance with those of Ali T. et al. (2014)[16] who reported that the mean of serum urea in the hemodialysis patients was (139.69 ± 27.59mg/dl) and in control group was (22.59 ± 6.30mg/dl) with statistical significance as (P <0.001).

As regard to serum creatinine the mean value in studied group was (7.79 ± 0.64 mg/dl). There was a significant increase in serum creatinine in studied group and this was in agreement with those of Sliem H. et al. (2011) [17] who reported that the mean of serum creatinine in the hemodialysis patients was (8.6 ± 2.2 mg/dl) and in control group was (0.7 ± 0.2mg/dl) with statistical significance as (P < 0.001). In our study, serum calcium levels were significantly lower than normal value. This was in agreement with Ali Y. et al. (2010) [18] who reported in their study that serum phosphate, alkaline phosphatase, and PTH, levels were significantly more elevated, whereas serum Ca levels were significantly lower in the study patients than the healthy controls.

Delucchi A. et al. (2008) [19] also reported the same findings in their studies. On the present study 96.7% of studied patients have higher PTH while 3.3% have normal PTH and the mean level of PTH was (221.6± 88.16 pg/ml). This was in agreement with Chutia H and Abraham A. (2013)[20] who found that 95.2% show hyperparathyroidism and 4.8% show normal PTH level. In our study, the mean value of serum phosphorus was (5.24 ± 1.43 mg/dl). There was a significant increase in serum phosphorus in our participants and this was in agreement with Warad P. et al. (2015) [21] who reported that the mean of phosphorus in the hemodialysis patients was (5.2 ± 0.68mg/dl) and in control group was (3.2 ± 0.28mg/dl) with statistical significance as (P < 0.001). In our study, the mean value of serum Mg was 1.84 ± 0.49 with 36(60%) patients had hypomagnesemia,12(20%) had hypermagnesemia and 12(20%) had normal Mg level and this was in agreement with Zaher M. et al. (2016) [22] who found a significant decrease in the serum Mg levels in children with CKD on regular HD than in the controls. Spiegel D. (2011) [10]showed that serum Mg of HD patients significantly decreases after hemodialysis sessions.

Alhosaini M. et al. (2014) [23] reported that both CKD and ESRD patients on dialysis have usually normal serum levels of Mg and sometimes even low serum Mg concentration (hypomagnesaemia). Van de Wal-Visscher E. et al. (2018) [24] reported that hypomagnesaemia is even more common (5–33%) when a 0.5 mEq/L dialysate Mg 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 absorption compared to healthy individuals, probably due to a deficiency of

active vitamin D. Also, use of Low-Mg dialysate (0.25 mmol/L or 0.5 mEq/L) is a risk factor for hypomagnesaemia in patients on both hemodialysis and peritoneal dialysis. [23]

It also might be a side effect of a number of different medications, such as thiazide diuretics, PPI, aminoglycoside antibiotics and calcineurin inhibitors.[24] Proton pump inhibitors are known to impair the adaptive increase in active intestinal Mg absorption in the face of Mg depletion and may therefore predispose to hypomagnesaemia in both CKD and ESRD patients.[23] Our study revealed no significant correlation between serum Mg and clinical characteristics of studied group (DM, Hypertension and duration of disease) and this was in agreement with Yorifog M. et al. (2017)[9] who reported no significant differences in the serum Mg levels between the males and females or between the patients with DM and without DM.

Also, our study revealed no significant correlation between serum Mg and laboratory data (Ca, P, PTH, urea and creatinine), and also this was in agreement with Yorifog M. et al. (2017) (9) who found in their study no significant differences in the PTH and vitamin D levels between the two categories of Mg levels: the lower and the higher. Khatami M. et al. (2013)[25] found no significant correlation between serum Mg levels and serum Ca, PTH and the other studied parameters. This may be attributed to small number of patients and short duration of CKD and dialysis.

In our study, serum Mg was negatively correlated with CIMT with statistical significance as ($P \leq 0.05$) and this was in agreement with Ortega O. et al. (2013)[26] 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 and the common CIMT has been observed and some recent observational studies have confirmed the superior survival of dialysis patients with serum Mg levels above the normal range, this survival advantage could be related to the inhibition of vascular calcification, phosphate-lowering effect, and to the reduction of the oxidative stress.

Liu F. et al. (2013)[12] reported that CIMT in patients with hypomagnesemia were higher than those in patients with hypermagnesemia. Salem S. et al. (2012)[27] found in their study on 36 patients on dialysis that Mg levels were inversely associated with the IMT of carotids and the PWV. Kanbay M. et al. (2010)[28] reported that multivariate analysis revealed that in HD patients, both serum Mg and intracellular Mg were negatively associated with common CIMT and demonstrated an inverse association between serum Mg and CIMT in HD patients. They found that, while the mean serum Ca and phosphorus did not change significantly, CIMT and PTH improved significantly after Mg supplementation within 2 months. The authors suggested that the beneficial effect of Mg on CIMT might be due to the decreased serum PTH level.

Tony E. et al. (2018) [29] reported that in HD patients, low Mg levels were reported to be associated with increased atherosclerosis of the common carotid artery. They also demonstrated an inverse association between serum Mg and IMT of common carotid artery in HD patients. Geiger H and Wanner C. (2012) [30] reported that various epidemiological studies demonstrated associations between low serum Mg levels and an increased risk for metabolic syndrome, type 2 diabetes mellitus, hypertension and atherosclerosis. Massy Z and Drüeke T. (2012)[31] told that Mg deficiency has also been reported to be related to the progression of atherosclerosis in several studies, including the observational Atherosclerosis Risk in Communities Study in middle-aged adults.

Ari E. et al. (2011)[32] founded that Mg may be negatively associated with CIMT, and a risk factor of CVD in HD patients. In another study, CIMT was decreased after Mg treatment supplements Mortazavi M. et al. (2013) [33] Turgut F. et al. (2008)[34]reported in their study that there was a significant inverse association between the absolute change in serum Mg concentrations and in right CIMT after 2 months of Mg treatment, therefore they concluded that Mg supplementation might be useful in reducing the progression of atherosclerosis in chronic dialysis patients. The role of Mg in atherosclerosis is not completely known, but it has been suggested that Mg possesses an anti-atherosclerotic effect, partly via its anti-inflammatory and antioxidant properties; conversely, by inhibiting endothelial proliferation, upregulating plasminogen activator inhibitor1 and vascular cell adhesion molecule-1, Mg deficiency promotes endothelial dysfunction and also promotes hydroxyapatite formation and calcification of vascular smooth muscle cells. [35] On the other hand, no significant correlation was found between serum Mg and BIMT or FIMT and PSV respectively and this was in agreement with Zaher M. et al. (2016) [22] showed that there was a significant increase in the CIMT and aortic IMT in the patients group compared to the controls but no relation was found in femoral IMT.

They also founded that there were no significant differences between the two studied groups regarding the PSV of the (carotid, aorta and femoral) arteries. Also, in our study no significant correlation was found between serum Mg and ABI and this agreed with Yorifog M. et al. (2017) [9] founded that there were no significant correlations between the serum Mg levels

and ABI. The present study showed no significant relation between other laboratory parameters and IMT, PSV and ABI and this was in agreement with Zaher M. et al. (2016) [22] showed no significant correlation among the CIMT, AIMT and FIMT and different parameters including (ca, P, PTH, cholesterol and triglycerides) in the patients group.

Liu F. et al. (2013) [12] reported in their study that partial and multiple linear regression analysis demonstrated that when all of these indicators Mg, CRP, P and PTH were incorporated as controlled variables, Mg might be negatively associated with CIMT independently. The results of our study revealed that low serum Mg level is significantly associated with increased risk of atherosclerosis in patients with CKD on HD. Finally, further studies are needed to investigate the long-term effects of Mg supplementation in CKD and whether improvement in calcification propensity is related to clinical endpoints.

Conclusion

Our study revealed that a low serum Mg level is significantly associated with increased risk of atherosclerosis in patients with chronic kidney diseases on hemodialysis.

Declaration of conflicting interest:

The authors declare that there is no conflict of interest.

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