Association Between Serum Magnesium and Risk Factors of Cardiovascular Disease in Hemodialysis Patients

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Introduction. There are associations between serum magnesium level and some risk factors of cardiovascular disease and atherosclerosis, such as lipid profile, serum albumin, C-reactive protein, serum phosphorus, parathyroid hormone, and diabetes mellitus in hemodialysis patients. The aim of this study was to examine these associations.

Materials and Methods. This study was conducted on 103 patients with end-stage renal disease on maintenance hemodialysis. Laboratory assessment was performed before hemodialysis session in a 12-hour fasting state. Patients were divided into two groups according to their serum magnesium concentration (< 2.6 mg/dL, n = 34 and ≥ 2.6 mg/dL, n = 69).

Results. The mean age of the patients was 57.4 ± 15.4 years. The mean serum magnesium was 2.80 ± 0.55 mg/dL (range, 1.7 mg/dL to 7 mg/dL). There were no significant differences in serum magnesium between patients with low and high values of high-density lipoprotein cholesterol, triglycerides, low-density lipoprotein cholesterol, and blood pressure. Of the 103 patients, 1 (1%) had hypomagnesemia, 41 (39.8%) had magnesium levels within normal range, and 61 (59.2%) had hypermagnesemia. Serum magnesium significantly correlated with plasma phosphorus level (r = 0.35, $P < .001$) and albumin (r = 0.24, $P = .01$). There were no correlations between serum magnesium level and age, body mass index, systolic blood pressure before dialysis, serum calcium, lipid profile, and apoprotein(a).

Conclusions. In our cohort of hemodialysis patients, there were no correlations between serum magnesium levels and atherogenic lipids, serum calcium, or parathyroid hormone.

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INTRODUCTION

Mortality rate of cardiovascular disease in dialysis patients is 20 to 40 times higher than in general population.[1,2] A number of population-based studies have indicated that there is an association between low serum magnesium concentration and risk factors of ischemic heart disease, such as diabetes mellitus,[3] metabolic syndrome,[4] and coronary artery disease and atherosclerosis risk.[5,6] A study of the national sample of US adults showed an inverse correlation between serum magnesium concentration and mortality of ischemic heart disease.[7] Maier and colleagues reported based on in vitro studies that low serum magnesium caused endothelial dysfunction by generating a pro-inflammatory, prothrombotic, and pro-atherogenic

environment that might lead to the development of cardiovascular disease.[8]

In dialysis patients, serum magnesium concentrations is expected to be higher than in the general population,[9] and is in parallel to magnesium levels in the dialysis solution.[10,11] Few studies have evaluated the association between serum magnesium concentration and risk factors of ischemic heart disease in hemodialysis patients. In Iran, there are few published data about this association. The aim of this study was to examine the relationship of serum magnesium and risk factors of ischemic heart disease, including lipid profile, serum albumin, C-reactive protein (CRP), serum phosphorus, and intact parathyroid hormone (PTH) for vascular calcification, diabetes mellitus, and other clinical characteristics in hemodialysis patients.

MATERIALS AND METHODS

Patients

This cross-sectional study was conducted on 103 patients with end-stage renal disease on maintenance hemodialysis after obtaining approval letter issued by the Ethic Committee of the Deputy Research of Tehran University of Medical Sciences. The conduct of this study was in adherence with the Declaration of Helsinki. Informed consent was obtained prior to participation in the study. Patients who had significant infection, malignancy, and history of parathyroidectomy were excluded.

The enrolled patients underwent regular hemodialysis using bicarbonate dialysis solution. Dialysis was performed using Fresenius 4008B machines. Low-flux polysulphone dialysis membranes were used. Individual ultrafiltration rates were held constant, from 500 mL/h to 800 mL/h to achieve dry weight. The dialysis solution temperature was maintained at 36.5°C. The concentrate of magnesium, sodium, calcium, and other electrolytes were fixed in the dialysis fluid.

The dialysis adequacy was evidenced by KT/V using the following formula:

$KT/V = -\ln(R-0.008 \times t) + (4-3.5 \times R) \times$ ultrafiltration/weight

where R is the ratio of postdialysis urea to predialysis urea.

The electrolyte concentration of the dialysis fluid was as follows: potassium, 2.0 mEq/L; chloride, 111.5 mEq/L; calcium, 1.25 mM/L (2.5 mEq/L or 5.0 mg/dL); magnesium, 1.0 mEq/L (1.2 mg/dL or 0.5 mM/L); and bicarbonate, 35 mEq/L.

History, Clinical and Biochemical Assessments

All patients were subjected to full history and clinical examination. History of smoking, diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, and the use of statins, sevelamer (at least 2 weeks before study), aluminum, calcium carbonate, and 1,25-hydroxyvitamin D were evaluated. Systolic and diastolic blood pressures were measured before dialysis. Hypertension was defined as a systolic blood pressure of 140 mm Hg and higher or a diastolic blood pressure of 90 mm Hg and higher predialysis or the current use of antihypertensive medication. Weight and height were measured for each participant, in order to calculate body mass index (BMI). A diagnosis of diabetes mellitus was made when as fasting blood glucose of 126 mg/dL and higher was detected or in the presence of a history of diabetes mellitus, previous use of oral hypoglycemic agents, or previous or current use of insulin. Patients were divided into two groups according to their serum magnesium concentration, as follows: a low-magnesium group (serum magnesium, < 2.6 mg/dL; n = 34) and a high-magnesium group (serum magnesium, ≥ 2.6 mg/dL; n = 69).

Laboratory assessment included blood urea nitrogen, serum creatinine, serum albumin, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), total cholesterol, triglyceride, magnesium, calcium, and phosphorus, quantitative CRP, and apoprotein(a). These parameters were measured at the start of the hemodialysis session, in a 12 hour-fasting state. Photometric method was used for the measurements by an auto-analyzer (BT-3500, Biotecnica Instruments, Rome, Italy) using Biosystem Kits (Barcelona, Spain). Serum 25-hydroxyvitamin D was measured using an enzyme-linked immunosorbent assay (Immunodiagnostic Systems, London, UK). Intact PTH was measured an enzyme-linked immunosorbent assay (Biomerica, Irvine, CA, USA).

Statistical Analyses

Data analysis was performed with the SPSS software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc, Chicago, Ill, USA). The distribution of variables was evaluated

by the 1-sample Kolmogorov-Smirnov test. For comparison of quantitative data, the independent *t* test or the Mann-Whitney test was used. The categorical outcome variables were compared using the chi-square test or the Fishers exact test, where appropriate. Stepwise multiple logistic regression analysis was used to identify predictors for hypermagnesemia (serum magnesium, ≥ 2.6 mg/dL). The independent variables entering the model were HDLC (reference group, < 40 in men and < 50 in women), LDLC, triglyceride, serum glucose, serum albumin, serum phosphorus, and sevelamer use. The Pearson correlation test was used for quantitative variables. Quantitative variables were presented as mean ± standard deviation, whereas percentages were used for categorical variables. Differences were considered significant when *P* value was less than .05.

Table 1. Characteristics of Patients*

Characteristic	Frequency (%)	Mean (Range)
Age, y	…	57.4 ± 15.4 (24 to 86)
Sex	…	…
Male	66 (64.1)	…
Female	34 (35.9)	…
Weight, kg	…	64.6 ± 11.1 (36 to 96)
Height, cm	…	162.9 ± 9.6 (139 to 190)
Body mass index, kg/m^2	…	24.2 ± 3.4 (16.8 to 33.9)
KT/V	…	1.3 ± 0.4 (0.4 to 2.1)
Dialysis duration, mo	…	68.2 ± 75.6 (1 to 309)
Systolic blood pressure, mm Hg	…	134.8 ± 21.6 (90 to 190)
Cause of ESRD		
Diabetes mellitus	38 (36.9)	…
Hypertension	21 (20.4)	…
Polycystic kidney disease	10 (9.7)	…
Glomerulonephritis	9 (8.7)	…
Urological causes	3 (2.9)	…
Unknown	22 (21.4)	…
Smoking	13 (12.6)	…
Diabetes mellitus	38 (36.9)	…
Hypertension	51 (49.5)	…
Cardiovascular Disease	29 (28.2)	…
Hyperlipidemia	26 (25.2)	…
Use of statin	31 (30.1)	…
Use of fibrate	1 (1.0)	…
Use of sevelamer	30 (29.1)	…
Use of aluminum	1 (1.0)	…
Use of calcium carbonate	49 (47.6)	…
Use of vitamin D	47 (45.6)	…
Serum magnesium, mg/dL	…	2.80 ± 0.55 (1.7 to 7)
Serum phosphorus, mg/dL	…	6.5 ± 2.4 (3 to 12.6)
Serum calcium, mg/dL	…	8.90 ± 1.26 (6.2 to 12.4)
Apoprotein(a), mg/dL	…	113.2 ± 33.4 (59 to 186)
LDLC, mg/dL	…	84.3 ± 25.1 (30 to 161)
HDLC, mg/dL	…	40.8 ± 16.2 (3.7 to 111)
Cholesterol, mg/dL	…	173.3 ± 49.8 (68 to 350)
Triglyceride, mg/dL	…	151.1 ± 99.6 (32 to 709)
Blood glucose, mg/dL	…	145.4 ± 106.4 (27 to 589)
Albumin, mg/dL	…	5.4 ± 0.97 (2.5 to 8.5)
CRP, mg/dL	…	7.06 ± 5.99 (0 to 59)
Parathyroid hormone, pg/mL	…	398.8 ± 290.2 (19 to 1000)
Serum vitamin D, mg/dL	…	24.6 ± 17.34 (0 to 95)

*ESRD indicates end-stage renal disease; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; and CRP, C-reactive protein.

RESULTS

Baseline characteristics of the population studied are shown in Table 1. The mean age was 57.4 ± 15.4 years, and 66 (64.1%) were men. The mean serum magnesium level was 2.80 ± 0.55 mg/dL (range, 1.7 mg/dL to 7 mg/dL). There was no significant differences in serum magnesium levels between patients with low and high HDLC cholesterol levels (2.78 ± 0.65 mg/dL versus 2.79 ± 0.35 mg/dL, P = .40), those with low and high triglyceride levels (2.69 ± 0.37 mg/dLversus 2.91 ± 0.73 mg/dL, P = .80), and those with and without a history of hypertension (2.76 ± 0.60 mg/dL versus 2.85 ± 0.39 mg/dL, P = .50).

Of the 103 patients, 1 (1%) had hypomagnesemia (serum magnesium level, 1.66 mg/dL), 41 (39.8%) had magnesium levels within normal range (1.8 mg/dL to 2.6 mg/dL), and 61 (59.2%) had magnesium levels higher than 2.6 mg/dL. There were no symptoms of hypermagnesemia in these patients. As shown in Table 2, there are no significant differences in serum magnesium levels in terms of sex, smoking, history of diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, statin administration, sevelamer administration, aluminum administration, and 1,25-hydroxyvitamin D, and low and high levels of HDLC, triglyceride, and LDLC. Serum magnesium was significantly higher in patients who were using calcium carbonate. Serum magnesium significantly correlated with plasma phosphorus level (P < .001) and serum albumin level (P = .01; Table 3). In logistic regression analysis, only the use of carbonate calcium was a significant predictor of hypermagnesemia (odds ratio, 2.96; 95% confidence interval, 1.06 to 8.25), when controlled for HDLC, LDLC, triglyceride, serum glucose, serum albumin, serum phosphorus, and sevelamer administration.

Comparing the two groups of patients with low and high magnesium concentrations, there were

Table 2. Comparison of Serum Magnesium Between Subgroups

Subgroup	n	Serum Magnesium, mg/dL	*P*
Sex			
Male	66	2.72 ± 0.36	
Female	37	2.90 ± 0.79	.10
Smoking			
Yes	13	2.63 ± 0.34	
No	90	2.80 ± 0.58	.20
History of diabetes mellitus			
Yes	38	2.71 ± 0.40	
No	65	2.82 ± 0.63	.30
History of hypertension			
Yes	51	2.76 ± 0.37	
No	52	2.81 ± 0.69	.60
History of cardiovascular disease			
Yes	29	2.81 ± 0.39	
No	74	2.77 ± 0.61	.70
History of hyperlipidemia			
Yes	26	2.85 ± 0.39	
No	77	2.76 ± 0.60	.50
Use of statin			
Yes	31	2.82 ± 0.38	
No	72	2.77 ± 0.62	.60
Use of sevelamer			
Yes	30	2.76 ± 0.43	
No	73	2.79 ± 0.60	.70

Table 3. Comparisons Between Patients With Low and High Serum Magnesium*

Characteristics	Low Serum Magnesium (n = 34)	High Serum Magnesium (n = 69)	*P*
Age, y	59.17 ± 14.67	56.59 ± 15.75	.40
Body mass index, kg/m^2	24.21 ± 3.19	24.26 ± 3.56	.90
KT/V	1.29 ± 0.40	1.35 ± 0.38	.40
Dialysis duration, mo	62.65 ± 75.37	70.91 ± 76.14	.60
Systolic blood pressure, mm Hg	138.82 ± 22.53	132.89 ± 21.08	.20
Serum phosphorus level, mg/dL	5.90 ± 2.26	6.87 ± 2.41	.05
Serum calcium level, mg/dL	8.76 ± 1.28	9.08 ± 1.25	.20
Apoprotein(a), mg/dL	108.44 ± 33.74	115.60 ± 33.26	.30
LDLC, mg/dL	77.94 ± 24.55	87.50 ± 25.01	.07
HDLC, mg/dL	39.69 ± 14.95	41.40 ± 16.88	.60
Cholesterol, mg/dL	158.41 ± 44.69	180.60 ± 50.84	.03
Triglyceride, mg/dL	121.88 ± 74.05	165.50 ± 107.64	.04
Blood glucose, mg/dL	141.56 ± 96.13	147.24 ± 111.73	.80
CRP, mg/dL	5.73 ± 3.02	7.73 ± 6.94	.10

*LDLC indicates low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; and CRP, C-reactive protein.

Table 4. Correlation of Serum Magnesium Level With Other Quantitative Variables*

Characteristic	Serum Magnesium	
	r	*P*
Age	-0.075	.40
Body mass index	0.165	.96
KT/V	0.096	.30
Dialysis duration	0.050	.60
Systolic blood pressure	0.018	.80
Serum phosphorus	0.356	< .001
Serum calcium	0.013	.90
Apoprotein (a)	-0.035	.70
LDLC	0.126	.20
HDLC	-0.034	.70
Cholesterol	0.168	.09
Triglyceride	0.137	.16
Blood glucose	0.077	.40
CRP	0.105	.20
Serum albumin	0.249	.01
Parathyroid hormone (n = 88)	0.030	.70
Serum vitamin D (n = 88)	-0.096	.30

*LDLC indicates low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; and CRP, C-reactive protein.

no significant differences in terms of sex, cause of end-stage renal disease, history of diabetes mellitus, history of hypertension, smoking, sevelamer administration, body mass index, systolic blood pressure, plasma glucose, serum calcium, LDLC, HDLC, PTH, and serum 1,25-hydroxyvitamin D. Serum albumin and cholesterol were significantly lower in patients with low magnesium concentrations as compared to those with high magnesium levels (P = .01 and P = .03, respectively). Also, plasma phosphorus level was marginally lower in those with a magnesium level lower than 2.6 mg/dL (P = .05). Serum albumin and serum phosphorus levels had a significant correlation with serum magnesium (r = 0.24, P = .01 and r = 0.35, P < .001, respectively; Table 4).

DISCUSSION

In our study, there were no significant differences in serum magnesium between patients with and without high levels of HDLC, LDLC, and triglyceride, and history of hypertension. The mean serum magnesium was 2.80 ± 0.55 mg/dL (range, 1.7 mg/dL to 7 mg/dL; Table 1). We did not find any correlation between serum magnesium level and age, body mass index, systolic blood pressure before dialysis, serum calcium, LDLC, HDLC, triglyceride, and apoprotein(a).

In Nasri and Kheiri's study,[12] there was a linear correlation between magnesium level and triglyceride and apoprotein(a) in hemodialysis patients, but we could not show this correlation (Table 4). Robles and colleagues suggested that magnesium might affect lipid metabolism in hemodialysis patients. Dyslipidemia may be worsened by increasing of serum magnesium levels in hemodialysis patients.[13]

Tzanakis and Oreopoulus reported that the use of magnesium salts as phosphate binders inhibited the development or progression of vascular calcification. Parathyroid hormone excretion is suppressed by serum magnesium, and high magnesium dialysis solution may stabilize intradialytic hemodynamic.[14] In our study, serum magnesium had no significant correlation with PTH and serum 1,25-hydroxyvitamin D levels; however, Baradaran and Nasri found a significant correlation between serum magnesium levels and serum 1,25-hydroxyvitamin D levels (r = 0.40, P = .009), while the correlation between serum magnesium levels and PTH (r = -0.30, P = .08) was not significant.[15] Navarro and colleagues showed serum magnesium concentrations was reversely correlated with PTH levels both in hemodialysis and peritoneal dialysis patients, independent of the main factors regulating parathyroid gland function (calcium, phosphorus, and vitamin D).[16]

In Ishimura and colleagues' study, mortality was significantly higher in the low-magnesium group (< 2.77 mg/dL) as compared to that in the high-magnesium group of maintenance hemodialysis patients.[17] According to their study,[17] patients with lower magnesium concentrations were significantly older than those with higher magnesium concentrations. However, there was no significant difference in age between our patient groups with low and high magnesium levels (cutoff level, 2.6 mg/dL).

In our study, serum albumin and phosphorus levels were significantly lower in patients with low magnesium concentrations compared to the high-magnesium group. There were no significant differences in other variables (Table 3). This is concordant with Ishimura and colleagues[17] and Katopodis and coworkers' studies.[18] The former group found that serum albumin, phosphate, and calcium levels were significantly lower as compared to those with higher serum magnesium. Lower magnesium concentration was a significant

predictor of mortality, with unknown underlying mechanis.[17] Katopodis and coworkers reported a weak correlation between serum pre-albumin level and serum magnesium concentration.[18]

CONCLUSIONS

In our study, there was no correlations between magnesium and atherogenic lipids like low HDLC and high apoprotein(a) levels. In line of inflammation, we could not find any relationship between serum magnesium and CRP, but we found a significant correlation between serum magnesium level and serum albumin. Magnesium did not significantly correlate with PTH and serum vitamin D levels, but had a relationship with phosphorus. The limitation of our study was low number of patients, so these results should be confirmed in future studies with more patients.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Collins AJ, Li S, Ma JZ, Herzog C. Cardiovascular disease in end-stage renal disease patients. Am J Kidney Dis. 2001;38:S26-9.
2. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;32:s112-9.
3. Kao W H L, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Arch Intern Med. 1999;159:2151-59.
4. He K, Liu K, Daviglus ML, et al. Magnesium intake and incidence of metabolic syndrome among young adults. Circulation. 2006;113:1675-82.
5. Gartside P, Glueck C. The important role of modifiable dietary and behavioral characteristics in the causation and prevention of coronary heart disease hospitalization and mortality: the prospective NHANES I follow-up study. J Am Coll Nutr. 1995;14:71-9.
6. Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 1998;136:480-90.
7. Ford ES. Serum magnesium and ischaemic heart disease: findings from a national sample of US adults. Int J Epidemiol. 1999;28:645-51.
8. Maier JAM, Malpuech-Brugere C, Zimowska W, Rayssiguier Y, Mazur A. Low magnesium promotes endothelial cell dysfunction: implications for atherosclerosis, inflammation and thrombosis. Biochim Biophys Acta. 2004;1689:13-21.
9. Navarro JF, Mora C, Jimenez A, Torres A, Macia M, Garcia J. Relationship between serum magnesium and parathyroid hormone levels in hemodialysis patients. Am J Kidney Dis. 1999;34:43-8.
10. Kelber J, Slatopolsky E, Delmez JA. Acute effects of different concentrations of dialysate magnesium during high-efficiency dialysis. Am J Kidney Dis. 1994;24:453-60.
11. Navarro-Gonzalez J. Magnesium in dialysis patients: serum levels and clinical implications. Clinical Nephrol. 1998;49:373-8.
12. Nasri H, Kheiri S. Effects of diabetes mellitus, age, and duration of dialysis on parathormone in chronic hemodialysis patients. Saudi J Kidney Dis Transpl. 2008;19:608-13.
13. Robles NR, Escola JM, Albarran L, Espada R, Cruz A. Correlation of serum magnesium and serum lipid levels in hemodialysis patients. Nephron. 1998;27:644-8.
14. Tzanakis IP, Oreopoulos DG. Beneficial effects of magnesium in chronic renal failure: a foe no longer. Int Urol Nephrol. 2009;41:363-71.
15. Baradaran A, Nasri H. Correlation of serum magnesium with serum parathormone levels in patients on regular hemodialysis. Saudi J Kidney Dis Transpl. 2006;17:344-50.
16. Navarro JF, Mora C, Garcia J. Serum magnesium and parathyroid hormone levels in dialysis patients. Kidney Int. 2000;57:2654.
17. 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.
18. Katopodis KP, Koliousi EL, Andrikos EK, Pappas MV, Elisaf MS, Siamopoulos KC. Magnesium homeostasis in patients undergoing continuous ambulatory peritoneal dialysis: role of the dialysate magnesium concentration. Artif Organs. 2003;27:853-7.

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