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Is low magnesium a clue to arteriovenous fistula complications in hemodialysis?

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Abstract
Purpose Magnesium insufficiency is a pro-atherogenic factor involved in endothelial dysfunction, atherosclerosis, and vascular calcification. Our aim was to examine the role of magnesium in the development of arteriovenous fistula complications in hemodialysis.
Methods This was a retrospective clinical investigation of data from 88 patients who were divided into two groups: those with and without arteriovenous fistula complications. We examined the influence of sex, demographics, and clinical and laboratory parameters. The existence of fistula stenosis was determined by measuring Doppler flow, while B-mode ultrasound was used to detect plaques and evaluate the carotid artery intima–media thickness.
Results Patients with arteriovenous fistula complications had significantly higher leukocyte counts ($p = 0.03$), platelet counts ($p = 0.03$), phosphate concentrations ($p = 0.044$), and alkaline phosphatase concentrations ($p = 0.04$). Patients without complications had significantly greater blood flow through the arteriovenous fistula ($p < 0.0005$), higher magnesium concentrations ($p = 0.004$), and a lower carotid artery intima–media thickness ($p = 0.037$). The magnesium level was inversely correlated with leukocyte ($p = 0.028$) and platelet ($p = 0.016$) counts. The magnesium concentration was significantly lower in patients with carotid artery plaques ($p = 0.03$). Multiple linear regression, using magnesium as the dependent variable in patients with arteriovenous fistula complications, indicated statistically significant correlations with platelet ($p = 0.005$) and leukocyte ($p = 0.027$) counts and carotid plaques ($p = 0.045$).
Conclusions Hypomagnesemia is a significant pro-atherogenic factor and an important predictor of arteriovenous fistula complications.

Keywords Magnesium · Complication · Arteriovenous fistula · Hemodialysis

Introduction

As with potassium, magnesium is a dominant intracellular cation that acts as a catalyst and activator of many intracellular enzymatic reactions, particularly those that are dependent on ATP [1]. Magnesium is also a natural calcium channel blocker and plays an important role in cardiovascular, neurologic, and metabolic functions [2]. Approximately 99 % of total magnesium is located in bone, muscles, and non-muscular soft tissue. Thus, extracellular magnesium accounts for approximately 1 % of the total and is found primarily in serum and red blood cells [3]. Hypomagnesemia is associated with increased cardiovascular morbidity, atherosclerosis, hypertension, and dyslipidemia [1, 4]. A small number of studies on circulating magnesium concentrations in patients undergoing dialysis have shown a clear association between low serum magnesium levels and the incidence of peripheral arterial calcification [5, 6].

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It is well known that patients with chronic renal failure have a two to five times more frequent incidence of vascular calcifications compared with the general population. The underlying pathogenesis is not clear, although it is assumed that several dynamic cell-mediated processes similar to the formation of normal bone tissue participate in producing these calcificates. Vascular smooth muscle cells that form the medial layer of the vessel wall play a central role in this process [7]. Progressive loss of renal function leads to elevation of fibroblast growth factor levels, reduced excretion of phosphate, and dysregulation of bone mineral metabolism, promoting vascular calcification [8]. There is also ample evidence that magnesium may affect vascular tone [9]. The most common fistula complications are thrombosis and stenosis, which are mainly the consequence of changes in the endothelium of blood vessels [10–12].

The aim of our study was to assess the potential role of magnesium in the occurrence of arteriovenous fistula complications.

Materials and methods

Design

This retrospective cross-sectional study was conducted at the Clinic for Urology and Nephrology, Clinical Center Kragujevac, Serbia. We included patients who were undergoing chronic hemodialysis, all of whom had an arteriovenous fistula for vascular access. Following the application of exclusion criteria regarding factors that could influence magnesium levels (magnesium-based phosphate binder therapy, use of diuretics or proton pump inhibitors, malnutrition, alcoholism, and diabetes mellitus), there were 128 participants. After a 2-year evaluation, 88 participants remained at the end of the monitoring period. They were divided into a group with arteriovenous fistula complications (52/88 patients, 59 %) and a group without complications (36/88 patients, 41 %). We registered thrombosis and stenosis as the most common arteriovenous fistula complications. The study was approved by the ethics committee of the Clinical Center Kragujevac and was performed in accordance with the Helsinki declaration for medical research.

Biochemical tests

Biochemical analyses were performed using flow cytometry (Beckman Coulter Inc., Fullerton, CA) or spectrophotometrically on an ILAB-600 instrument (Diamond Diagnostics, Holliston, MA, USA). For all patients, the concentration of magnesium in the dialysate corresponded with the target range for normal magnesium levels. Relevant laboratory parameters, including peripheral magnesium, parathormone, and C-reactive protein concentrations, were determined quarterly, and the mean values were recorded for each group of patients.

Clinical and demographic parameters

We also compared the patients' sex and demographics, duration of hemodialysis, systolic and diastolic arterial blood pressure, cigarette smoking, and type of hemodialysis (bicarbonate/hemodiafiltration) between the two groups.

Color Doppler ultrasound

The intima–media thickness and the presence of atherosclerotic plaques in the carotid artery are considered indicators of subclinical forms of arteriosclerosis. B-mode sonography is an efficient method to visualize hemodynamic flow and detect carotid artery plaques [13]. Using a Shimadzu SDU-2200 instrument (Tokyo, Japan), all sonographic scans were performed by one observer following the procedures described by Geroulakos et al. [14] and Wiese et al. [15]. The intima–media thickness was calculated as the mean value of six individual measurements at different points within the region of interest (three for the right and three for the left artery); i.e., the intima–media thickness was calculated for both sides. A plaque was defined as a distinct area with an intima–media thickness exceeding twice that of neighboring sites. Wall thickness was not determined at the plaque-containing sites [14, 15].

The existence of fistula stenosis was estimated from Doppler flow. Specific characteristics at the area of narrowing were a luminal diameter reduction of >50 %, peak systolic flow velocity of >400 cm/s, and a pronounced aliasing phenomenon. Indirect characteristics were obtained by ultrasound imaging of the feeding brachial artery in the middle of the upper arm with flow measurement and were seen as high-resistance Doppler waveforms and reduction in access flow volume. Fistula thrombosis was based on the presence of clinical signs and symptoms and on ultrasound examination findings [15].

Statistical analysis

Descriptive statistics, including the numbers and percentages of categorical data, means, standard deviation, median, and range of numerical data, were used to characterize the results. For parametric data, the independent samples *t* test was used to evaluate differences between groups. The Mann–Whitney test, Spearman's rank-order correlation, and multiple regression analyses were used when indicated. In all analyses, the probability (p) of statistical significance was set at 0.05. Statistical analyses were performed using SPSS for Windows, version 22 (IBM Corp., Armonk, NY, USA).

Table 1 Comparison of biochemical parameters between the two groups of patients

Biochemical parameters	Patients with AVF complications ($N = 52$)	Patients without AVF complications ($N = 36$)	p value
Leukocytes ($\times 10^{-9}$/L), mean ± SD	7.75 ± 2.68	6.9 ± 1.9	0.03*
Erythrocytes ($\times 10^{-12}$/L), mean ± SD	3.34 ± 0.49	3.37 ± 0.37	0.33
Hemoglobin (g/L), mean ± SD	101 ± 14	101 ± 10	0.37
Platelets ($\times 10^{-9}$), mean ± SD	188 ± 7.99	159 ± 11.39	0.03*
Glycemia (mmol/L), mean ± SD	6.05 ± 2.2	5.9 ± 2.18	0.36
Urea (mmol/L), mean ± SD	21.9 ± 7.37	26.4 ± 23.7	0.24
Creatinine (μmol/L), mean ± SD	855 ± 213	858 ± 203	0.36
Potassium (mmol/L), mean ± SD	5.17 ± 0.11	4.9 ± 0.11	0.17
Sodium (mmol/L), mean ± SD	136.8 ± 0.47	137.8 ± 0.42	0.133
Total calcium (mmol/L), mean ± SD	2.22 ± 0.18	2.21 ± 0.17	0.22
Inorganic phosphorus (mmol/L), mean ± SD	1.87 ± 0.079	1.63 ± 0.08	0.044*
Parathormone (pmol/L), mean ± SD	188 ± 455.8	260 ± 493.9	0.24
C-reactive protein (U/L), mean ± SD	15 ± 3.4	22.4 ± 6.34	0.27
Magnesium (mmol/L), mean ± SD	1.068 ± 0.03	1.193 ± 0.04	0.004*
Cholesterol (mmol/L), mean ± SD	3.65 ± 0.3	4.02 ± 0.47	0.52
LDL cholesterol (mmol/L), mean ± SD	2.9 ± 0.66	3.5 ± 0.97	0.63
HDL cholesterol (mmol/L), mean ± SD	0.95 ± 0.06	2.1 ± 1.35	0.13
Alkaline phosphatase (U/L), mean ± SD	127 ± 24.6	67.7 ± 5.59	0.04*

AVF arteriovenous fistula, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

* Statistically significant difference

Results

The arteriovenous fistula complication group had a significantly higher mean leukocyte count, platelet count, phosphate level, and alkaline phosphatase level and a significantly lower mean magnesium concentration (Table 1). Other laboratory variables did not vary significantly.

Regarding the demographic and clinical characteristics, the intima–media thickness of the carotid artery was significantly higher and the blood flow through the arteriovenous fistula was markedly lower in the arteriovenous fistula complication group than in the group without fistula complications (Table 2). Other clinical and demographic characteristics did not differ significantly between the two groups.

Using Spearman's rank-order test, statistically significant weakly negative correlations were found for all participants between the magnesium concentration and both the leukocyte ($r = -0.242$, $p = 0.028$) and platelet counts ($r = -0.258$, $p = 0.016$) (Table 3). Correlations between the magnesium concentration and clinical parameters showed that patients with higher magnesium levels had fewer plaques ($p = 0.03$) (Table 4).

Multiple linear regression results for the complication group, using peripheral magnesium concentration as the dependent variable, showed that magnesium levels were independently correlated with the leukocyte count ($B = 0.022$, $p = 0.027$), platelet count ($B = 0.001$, $p = 0.005$), and plaque formation ($B = 0.089$, $p = 0.045$) (Table 5).

Discussion

Magnesium may play a significant role in vascular calcification. The peripheral circulating magnesium concentration was significantly lower in the arteriovenous fistula complication group in our study. Several in vitro and in vivo studies [16, 17] have shown that a lack of magnesium causes vascular stenosis, platelet aggregation, inflammation, and oxidative stress, leading to dysfunction of the vascular endothelium and subsequent calcification. A cohort study by Kanbay et al. [18] showed that magnesium may be an independent predictor of future cardiovascular outcomes at different stages of kidney disease. However, regardless of accepted views on the connection between cardiovascular diseases and disorders of mineral metabolism in patients undergoing hemodialysis, the role of magnesium in this population is unclear [9]. Several studies have shown negative correlations between the magnesium concentration and carotid artery intima–media thickness, an early and reliable marker of atherosclerosis [1, 7, 19, 20] that significantly increases the risk of cardiovascular disease [21]. In fact, Turgut et al. [22] found that magnesium supplementation provides indirect supporting evidence for reduced vascular

Table 2 Patients' demographic and clinical characteristics

Investigated parameters	Patients with AVF complications ($N = 52$)	Patients without AVF complications ($N = 36$)	p value
Age (years), mean ± SD	61.5 ± 10	62 ± 8.7	0.182
Sex, *n* (%)			
Males	38 (73)	29 (81)	0.45
Females	14 (27)	7 (19)	
Intima–media thickness (mm), mean ± SD	1.099 ± 0.025	1.021 ± 0.026	0.037*
Plaques, *n* (%)			
Yes	32 (62)	21 (58)	0.82
No	20 (38)	15 (42)	
Duration of dialysis (months), mean ± SD	63 ± 64.3	60 ± 66.3	0.6
Type of HD, *n* (%)			
BD	39 (75)	22 (61)	0.24
HDF	13 (25)	14 (39)	
Smoking history, *n* (%)			
Yes	23 (44)	17 (47)	0.83
No	29 (56)	19 (53)	
Blood pressure (mmHg)			
Systolic, mean ± SD	132 ± 2.76	133 ± 3.15	0.88
Diastolic, mean ± SD	81 ± 1.45	80.7 ± 2.15	0.81
Blood flow of the arteriovenous fistula (mL), mean ± SD	572 ± 26	723 ± 50.8	0.005*

AVF arteriovenous fistula, *HD* hemodialysis, *BD* bicarbonate dialysis, *HDF* hemodiafiltration

calcification. However, some reports emphasize that magnesium might not improve endothelial function and that decreased carotid intima–media thickness as a marker of atherosclerosis may be the result of inhibition of calcification by parathormone, calcium, and phosphorus regulation [23]. In our study, we found significantly higher values for the intima–media thickness in the arteriovenous fistula complication group. Correlation and multiple regression analyses showed a marked association between the magnesium level and carotid artery plaque formation; specifically, low magnesium may have been a predictor of plaque formation in our patients. These results suggest that magnesium plays an important role in the development or acceleration of atherosclerosis and, eventually, in the development of vascular calcification in patients with arteriovenous fistula complications when undergoing hemodialysis.

The native arteriovenous fistula, compared with arteriovenous grafts and catheters, is the vascular access of choice for hemodialysis because of its longevity and lower complication and mortality rates. However, the development of significant stenosis secondary to intimal hyperplasia necessitates revision, while the occurrence of thrombosis remains an important clinical problem [24]. Ultrasound measurements of vessel diameter and time-averaged velocity allow for calculation of blood flow [15, 25]. As expected, there was a significant difference in blood flow through the arteriovenous fistula between our two groups of patients. However, no correlation between blood flow through the arteriovenous fistula and magnesium concentration was apparent. This finding is similar to that of Polkinghorne et al. [26], who reported that blood flow has only a modest effect on the development of significant arteriovenous fistula stenosis.

Our group of dialysis patients with arteriovenous fistula complications had low circulating magnesium and high phosphate concentrations. This confirms earlier data indicating that progressive loss of kidney function leads to disorders of bone mineral metabolism, which then promotes vascular calcification, primarily in response to elevated phosphate levels [8].

These findings support the therapeutic use of magnesium supplements as phosphate binders to improve the motility and tone of the arterial walls and prevent vascular calcification. In fact, it is important to emphasize the need for research that could provide information about the actual impact of magnesium carbonate as a phosphate binder on the development of arteriovenous fistula complications in patients undergoing hemodialysis.

Reduced intracellular and extracellular levels of magnesium may increase oxidative stress, promote inflammation,

Table 3 Correlations between the investigated parameters with magnesium concentration

Variable	Magnesium *r*
Age	0.041
Duration of dialysis	0.096
Intima–media thickness	−0.009
Systolic tension	0.073
Diastolic tension	−0.016
Erythrocyte count	0.046
Leukocyte count	−0.242*
Hemoglobin concentration	0.056
Platelet count	−0.258*
Total protein concentration	−0.033
Albumin concentration	0.101
Glycemia	−0.115
Urea	−0.111
Creatinine	0.003
Parathormone	−0.161
C-reactive protein	−0.107
Cholesterol	−0.377
LDL cholesterol	−0.181
HDL cholesterol	−0.132
Triglycerides	−0.139
Alkaline phosphatase	−0.012
Potassium	−0.133
Sodium	−0.052
Calcium	−0.074
Phosphorus	−0.179
Blood flow through the arteriovenous fistula	0.133

LDL low-density lipoprotein, *HDL* high-density lipoprotein

impair endothelial function, induce vasospasm, and accelerate atherogenesis [27]. Magnesium stimulates the synthesis of nitric oxide, causing vasodilation. In an animal model, magnesium deficiency induced inflammatory syndrome, which is characterized by leukocyte activation of macrophages, the release of proinflammatory cytokines, activation of the acute phase response, and enhanced production of free radicals [6, 25–30]. The mean leukocyte count in our arteriovenous fistula complication group was significantly higher than that of patients without complications. There was also a significant negative correlation between the leukocyte count and magnesium concentration. Specifically, a low magnesium concentration accompanied by a high leukocyte number may indicate an inflammatory state with decreased antioxidant capacity and possible atherogenic potential in these patients, confirming our previous research [31].

The role of platelets in stenosis and thrombosis of vascular access for hemodialysis is well known, and patients with arteriovenous fistula complications had significantly higher platelet counts in our study. Multiple regression analysis confirmed that a high platelet count is a probable predictor of the development of arteriovenous fistula complications.

Magnesium deficiency, especially combined with stress and catecholamine release, leads to an increased influx of calcium into vascular smooth muscle cells, which results in increased vascular tone. Thus, magnesium competes with calcium for binding sites on calcium channels in vascular smooth muscle cells. Magnesium decreases sensitivity to the effects of free radicals, improves endothelial function, and inhibits platelet aggregation. Reduced activity of calcium channels diminishes intracellular calcium levels, which induces relaxation and vasodilation. Magnesium also increases the synthesis of prostaglandin I2 in the endothelium, consequently reducing platelet aggregation [30]. We found significantly higher numbers of leukocytes and platelets in the arteriovenous fistula complication group. Also, both platelet and leukocyte counts correlated inversely with magnesium levels in our patients, so a low magnesium concentration clearly accompanied the increases in platelet and leukocyte numbers.

Hypomagnesemia is associated with high levels of alkaline phosphatase, which increases bone metabolism and promotes vascular calcification [16]. As a significant marker of bone metabolism and an important parameter in patients with kidney disease, alkaline phosphatase levels were significantly higher in patients with fistula complications.

Study limitations

The main limitation of this study is the relatively small sample size with consequent limited power of the statistical analyses. Also, as a cross-sectional investigation, we cannot infer a temporal relationship from our observations. We examined all conditions and lifestyle factors that could affect peripheral magnesium concentrations. However, as in any observational study, unknown confounding and residual factors and their effects on the magnitude or significance of our observations are difficult to estimate. Longitudinal studies followed by randomized trials will be necessary to confirm the relationship between magnesium, calcification, and arteriovenous fistula complications in patients undergoing hemodialysis. Our results are a preliminary step in a long-term project in which it will be necessary to organize research to confirm and present new important insights regarding the association of magnesium and arteriovenous fistulas complications in patients undergoing hemodialysis.

Table 4 Magnesium concentrations in relation to patients' qualitative characteristics

Variables	Magnesium (mmol/L)	
	Median (range)	*p* value
Sex		
Male	1.2 (0.7–1.6)	0.896
Female	1.2 (0.8–1.5)	
Plaques		
Yes	1.2 (0.7–1.6)	0.030*
No	1.3 (0.8–1.5)	
Type of HD		
BD	1.2 (0.8–1.5)	0.914
HDF	1.2 (0.7–1.6)	
Smoking history		
Yes	1.2 (0.7–1.6)	0.424
No	1.2 (0.8–1.5)	
Complications		
Yes	1.1 (0.7–1.4)	0.705
No	1.1 (0.7–1.7)	

HD hemodialysis, *BD* bicarbonate dialysis, *HDF* hemodiafiltration

Table 5 Multiple linear regression (magnesium as the dependent variable) of the independent factors associated with vascular calcification in patients with arteriovenous fistula complications

Coefficients[a]					
Model	Unstandardized coefficients		Standardized coefficients	*t*	Sig.
	B	Standard error	Beta		
1					
(Constant)	1.320	0.206		6.407	0.000
Platelet count	0.001	0.000	0.308	2.913	0.005
Plaques	0.089	0.044	0.216	2.037	0.045
Leukocyte count	0.022	0.010	0.240	2.259	0.027

[a] Dependent variable: magnesium

Conclusions

Hypomagnesemia is a significant pro-atherogenic and predictive factor for arteriovenous fistula complications in patients undergoing hemodialysis. Additional well-designed research is required to determine the possible benefit of magnesium supplements and their role in preventing vascular access complications.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study (retrospective study), formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

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