

Lower Serum Magnesium Is Associated with Cardiovascular Risk Factors and Mortality in Haemodialysis Patients

Patrícia João Matias^{a–d} Ana Azevedo^{a–c} Ivo Laranjinha^{b, c} David Navarro^{a, c}
Marco Mendes^{a–c} Carina Ferreira^{a–d} Tiago Amaral^{a–c} Cristina Jorge^{a–c}
Inês Aires^{a–d} Célia Gil^{a–c} Aníbal Ferreira^{a–d}

^aNephrocare – Vila Franca de Xira – Dialysis Unit, Vila Franca de Xira, ^bDialverca – Dialysis Unit, Forte da Casa, ^cNIDAN, and ^dFaculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisboa, Portugal

Key Words

Haemodialysis · Magnesium · Mortality · Vascular calcifications

Abstract

Background: Hypomagnesaemia is a cardiovascular (CV) risk factor in the general population. The aim of this study was to evaluate the relationship between pre-dialysis magnesium (Mg) and CV risk markers, [including pulse pressure (PP), left ventricular mass index (LVMI) and vascular calcifications (VC)], and mortality in haemodialysis (HD) patients.

Methods: We performed a 48-month prospective study in 206 patients under pre-dilution haemodiafiltration with a dialysate Mg concentration of 1 mmol/l. **Results:** Lower Mg concentrations were predictors of an increased PP (≥ 65 mm Hg) ($p = 0.002$) and LVMI (≥ 140 g/m²) ($p = 0.03$) and of a higher VC score (≥ 3) ($p = 0.01$). Patients with Mg < 1.15 mmol/l had a lower survival at the end of the study ($p = 0.01$). Serum Mg < 1.15 mmol/l was an independent predictor of all-cause ($p = 0.01$) and CV mortality ($p = 0.02$) when adjusted for multiple CV risk factors. **Conclusions:** Lower Mg levels seem to be associated with increased CV risk markers, like PP, LVMI and VC, and with higher mortality in HD patients.

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Introduction

Magnesium is the second most abundant intracellular cation that is involved in a large variety of biological functions, such as neuromuscular excitation, electrolyte balance and bone metabolism. Magnesium also plays a vital role in the regulation of vascular tone, heart rhythm, and platelet-activated thrombosis [1, 2]. In experimental models, magnesium deficiency has been associated with increased inflammatory response and increased production of cytokines and reactive oxygen species [3–5].

Serum magnesium concentration is maintained in a narrow range by the kidney and the digestive tract in healthy subjects. In dialysis patients, where the kidney function is abolished, serum magnesium concentrations are elevated and higher than in the general population [6], and its balance depends of the intake and most importantly of magnesium dialysate concentration [7, 8].

Studies from the general population have linked magnesium deficiency with endothelial dysfunction, insulin resistance, hyperaldosteronism and inflammation [9], all of which are associated with vascular calcifications. On the other hand, hypomagnesaemia is associated with traditional Framingham cardiovascular risk factors, such as diabetes, lipid disorders, and hypertension [10]. Low se-

rum magnesium was also a strong predictor of an increase in left ventricular mass in a large German cohort of patients, even after adjustment for many covariates including hypertension [11]. Hypomagnesaemia induces an atherogenic lipid profile through activation of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) next to a decrease of lecithin-cholesterol acetyltransferase and lipoprotein lipase activity [12].

Cardiovascular disease is the most common cause of death in chronic kidney disease (CKD) patients [13]. Few clinical studies have demonstrated that lower serum magnesium levels are associated with vascular calcification and mortality in CKD stage 5D patients [14–17]. Moreover, hypermagnesaemia inhibits parathyroid hormone (PTH) secretion [18, 19], which is considered an independent risk factor for vascular calcification [20], left ventricular hypertrophy [21] and mortality [22, 23] in CKD patients.

Animal models have also shown an association between lower magnesium levels and cardiovascular disease. In both uremic and non-uremic rats, a prolonged magnesium-deficient diet with subsequent hypomagnesaemia leads to increased aortic, cardiac, and renal calcium concentration [24], widespread tissue calcifications [25], increased large artery media thickness and collagen content and higher pulse pressure and mortality [26].

On the other hand, higher magnesium exposure inhibited calcification of both bovine and murine vascular smooth muscle cells (VSMC) [27, 28] while opposing their apoptosis and osteoblastic differentiation by downgrading transcription factors in a dose-dependent manner. Magnesium also stimulates the expression of anti-calcification proteins such as osteoprotegerin [29], matrix Gla protein (MGP) and osteopontin [27, 28].

The aim of this study was to evaluate the relationship between pre-dialysis magnesium levels and cardiovascular risk markers, [including pulse pressure (PP), left ventricular mass index (LVMI) and vascular calcifications], and mortality in CKD stage 5D patients.

Subjects and Methods

Study Design

This was an observational, 48-month prospective, single-centre study of a cohort of prevalent haemodialysis (HD) patients.

Population

The study included 206 patients, 113 (55%) males and 93 (45%) females, with mean age of 63.6 ± 14.3 years. All patients were under pre-dilution haemodiafiltration with a dialysate magnesium concentration of 1 mmol/l. High flux membranes (helixone-Fresenius)

and ultrapure water (evaluated monthly by kinetic chromogenic test) were used. The mean HD time was 42.3 ± 38.6 months.

Fifty-four patients (26%) were diabetics and seventy (34%) had hypertension. Coronary artery disease was diagnosed if the patient had a typical history of angina pectoris or had suffered a myocardial infarction, had a positive stress test or had undergone a percutaneous coronary intervention or coronary bypass surgery. According to these criteria, coronary artery disease was diagnosed in 58 (28%) patients.

At the beginning of the study, ninety-four (46%) patients were taking active forms of vitamin D: 12% ($n = 11$) oral calcitriol, with a mean dose of 1.1 ± 0.5 (0.25 – 1.75) $\mu\text{g}/\text{week}$, and 88% ($n = 83$) iv paricalcitol, with a mean dose of 7.0 ± 4.5 (2.5 – 30) $\mu\text{g}/\text{week}$. All patients were receiving 'native' vitamin D supplementation with cholecalciferol 2,400 UI three times per week after HD.

One hundred and forty eight patients (72%) were under therapy with phosphate binders: 13 (9%) were taking calcium carbonate with a mean dose of 1.5 ± 0.8 (1 – 4) g/day and 135 (91%) were taking sevelamer with a mean dose of 3.8 ± 1.7 (0.8 – 7.2) g/day. None of the patients was under magnesium carbonate treatment.

Only 8 patients (4%) were taking diuretics. On the other hand, the use of proton pump inhibitors (PPIs) was very common with 152 patients (74%) under that therapy. Unlike other studies [30], the use of PPIs was not correlated with magnesium levels.

Pulse pressure (PP) was evaluated at baseline in the mid-week HD session in which blood chemistry analysis were obtained, based on blood pressure (BP) measurement before HD. PP was calculated by the formula $\text{PP} = \text{SBP} - \text{DBP}$ (SBP, systolic blood pressure; DBP, diastolic blood pressure).

Biochemical Analysis

Serum magnesium was measured pre-dialysis in a mid-week HD session using a xylidyl blue colorimetric method on a Roche/Hitachi cobas c 701 analyser (Roche Diagnostics, Mannheim, Germany) and normal range of values is 0.67 to 1.07 mmol/l. Serum calcium (Ca), serum phosphorus (P), $\text{Ca} \times \text{P}$ product, total intact PTH (iPTH), haemoglobin, albumin and C-reactive protein (CRP) were measured simultaneously with magnesium. Albumin was evaluated using the colorimetric assay bromocresol purple (reference value >4.0 g/dl) and CRP (reference value <1 mg/dl) was measured by an immunoturbidimetric assay. Total iPTH was evaluated by an electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany) and normal range of values is 15–65 pg/ml.

Echocardiographic Evaluation

At the beginning of the study, each patient underwent an echocardiographic examination (M mode and 2-D) and LVMI was calculated using the Devereux formula [31] and indexed to body surface area. Presence of left ventricular hypertrophy was defined on the basis of an LVMI greater than $125 \text{ g}/\text{m}^2$ for both men and women [32].

Vascular Calcification Score

Vascular calcifications were evaluated at baseline, using a simple vascular calcification score (SVCS) developed by Adragão et al. [33]. This vascular calcification score is based on the analysis of plain radiographic films of pelvis and hands. These authors found that an SVCS ≥ 3 was associated with an increase of cardiovascular events and mortality [33].

Statistical Analysis

Variables are expressed as frequencies for categorical variables, mean values with SD for normally distributed variables and median values (interquartile ranges) for non-normally distributed variables. Comparison between groups was performed using t test for normally distributed variables and Wilcoxon test for non-normally distributed variables. Spearman correlation was used for univariate analysis and linear regression was used for multivariate analysis (confidence interval of 95%). Variables entered in multivariate analysis were age, diabetes, albumin, PP, LVMI and vascular calcification score. Survival curves were estimated by Kaplan-Meier analysis and compared by the log-rank test.

A Cox regression model was used to identify predictors of mortality. Magnesium cut-off value used in survival curves was determined via a receiver operating characteristic (ROC) curve.

Statistical analysis was performed with SPSS system 19.0 (SPSS Inc., Chicago, Ill., USA) and the Medcalc program version 6.0 (Medcalc software, Mariakerke, Belgium). For all comparisons, a $p < 0.05$ was considered statistically significant.

Results

The baseline demographic, clinical, biochemical and vascular characteristics are reported in table 1. Mean serum magnesium was 1.36 ± 0.18 (0.82–1.81) mmol/l and only 5 patients (4.5%) had normal values, with the remaining 95.5% ($n = 197$) showing hypermagnesaemia. None of the patients presented hypo (<0.7 mmol/l) or severe hypermagnesaemia (>2 mmol/l). Diabetics presented lower magnesium levels ($p = 0.03$), but patients with hypertension or coronary artery disease had similar values. Patients taking either active vitamin D or phosphate binders also presented similar magnesium levels.

Patients with higher PP (≥ 65 mm Hg) ($p = 0.01$), left ventricular hypertrophy ($LVMI \geq 125$ g/m²) ($p = 0.02$) and more vascular calcifications ($SVCS \geq 3$) ($p = 0.008$) had significantly lower serum magnesium concentrations (fig. 1).

In univariate analysis, magnesium levels were negatively correlated with age ($r = -0.44$; $p = 0.006$), diabetes mellitus ($r = -0.42$; $p = 0.007$), iPTH ($r = -0.33$; $p = 0.02$), PP ($r = -0.36$; $p = 0.01$), LVMI ($r = -0.37$; $p = 0.01$) and SVCS ($r = -0.40$; $p = 0.008$). Serum magnesium concentrations were positively correlated with albumin ($r = 0.57$; $p < 0.001$) (table 2). In patients with CRP ≤ 5 mg/dl ($n = 194$), there was a negative correlation ($r = -0.41$; $p = 0.007$) between magnesium and CRP serum levels.

In multivariate analysis, lower magnesium concentrations were independent predictors of an increased PP (≥ 65 mm Hg) ($p = 0.002$) and LVMI (≥ 140 g/m²) ($p = 0.03$) and of a higher SVCS score (≥ 3) ($p = 0.01$) (table 3).

Seventy-six (37%) patients died during the 48-month period of the study, forty-three (57%) from cardiovascu-

Table 1. Clinical, biochemical and vascular parameters of the studied population

Variable	Patients (n = 206)
Age, years	63.6 $\pm$ 14.3
Male gender	113 (55%)
HD duration, months	42.3 $\pm$ 38.6
Diabetes	54 (26%)
Hypertension	70 (34%)
Coronary disease	58 (28%)
Active vitamin D	94 (46%)
Phosphate binders	148 (72%)
Diuretics	8 (4%)
Proton pump inhibitors	152 (74%)
Calcium, mg/dl	8.4 $\pm$ 0.5 (7.3–10.5)
Phosphorus, mg/dl	4.6 $\pm$ 1.5 (1.8–9.7)
Calcium $\times$ phosphorus, mg/dl ²	48.5 $\pm$ 15.7 (16.6–83.4)
iPTH, pg/ml	289 $\pm$ 248 (3–1,873)
Magnesium, mmol/l	1.36 $\pm$ 0.18 (0.82–1.81)
Haemoglobin, g/dl	12.4 $\pm$ 1.3 (8.6–15.2)
C-reactive protein, mg/dl	0.8 $\pm$ 1.6 (0.1–16.2)
Albumin, g/dl	4.0 $\pm$ 0.3 (3.1–5.1)
eKt/V	1.5 $\pm$ 0.3 (0.9–2.6)
nPCR, g/kg/day	1.2 $\pm$ 0.3 (0.7–1.6)
PP, mm Hg	69 $\pm$ 19 (38–114)
LVMI, g/m ²	129 $\pm$ 34 (63–213)
SVCS >0	122 (59%)
SVCS ≥ 3	78 (38%)

nPCR = Normalized protein catabolic rate; PP = pulse pressure; LVMI = left ventricular mass index; SVCS = simple vascular calcification score.

lar causes. Patients who died from cardiovascular causes had lower levels of serum magnesium (1.32 ± 0.17 vs. 1.42 ± 0.14 ; $p = 0.008$). Also patients who died from overall causes had lower magnesium values (1.30 ± 0.19 vs. 1.45 ± 0.15 ; $p < 0.001$) (fig. 2).

The cut-off value of serum magnesium determined by ROC curve analysis was 1.15 mmol/l (AUC: 0.74; 95% CI: 0.66–0.83; 73% sensitivity; 71% specificity; 86% negative predictive value and 2.27 positive likelihood ratio). Kaplan-Meier analysis showed that all-cause (log rank = 15.37; $p < 0.001$) and CV mortality (log rank = 11.74; $p = 0.001$) were responsible for a significant lower 48-month survival in patients with mean magnesium levels ≤ 1.15 mmol/l (fig. 3).

Cox regression analysis showed that serum magnesium is an independent negative predictor of all-cause (HR = 0.87; $p = 0.01$) and cardiovascular mortality (HR = 0.82; $p = 0.02$), using models adjusted for age, diabetes mellitus, time on HD, CRP, PP, LVMI and SVCS (table 4).

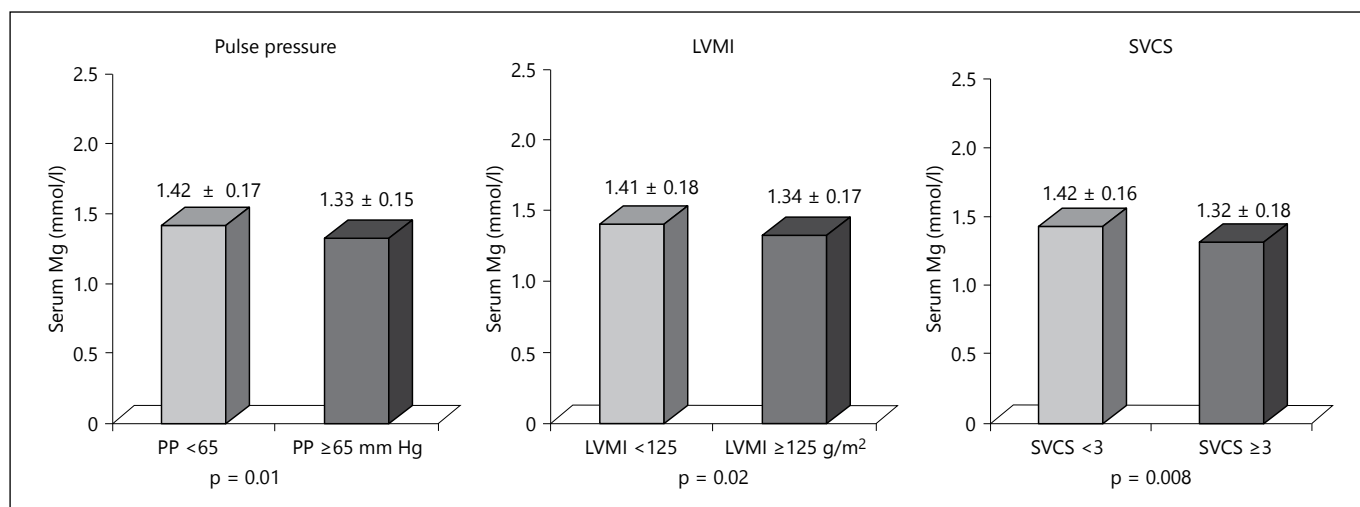


Fig. 1. Patients with higher pulse pressure (≥ 65 mm Hg), left ventricular hypertrophy ($\text{LVMI} \geq 125$ g/m²) and more vascular calcifications ($\text{SVCS} \geq 3$) had significantly lower serum Mg concentrations.

Discussion

In CKD patients, magnesium is important in regulating some aspects of mineral bone disorders associated with chronic renal failure, in cardiovascular health and also in survival [1, 9]. According to our results, from a large prevalent HD population, low magnesium levels are a good cardiovascular risk marker, associated with higher PP, LVMI and SVCS, and a good predictor of all-cause and cardiovascular mortality.

In this study, magnesium levels are negatively correlated with the presence of diabetes. In the general population, hypomagnesaemia has also been linked to the development of type 2 diabetes mellitus [34, 35]. It has been suggested that magnesium regulates cellular glucose metabolism directly because it serves as an important cofactor for various enzymes and acts as a second messenger for insulin [36]. It was also observed that insulin enhances intracellular magnesium uptake and this in turn mediates diverse effects ascribed to insulin [37]. Furthermore, hypomagnesaemia may induce altered cellular glucose transport, reduced pancreatic insulin secretion, defective post-receptor insulin signalling and/or altered insulin-insulin receptor interactions and thus aggravate insulin resistance [38].

Large population studies, performed in healthy individuals, showed that patients with the lowest magnesium level had the highest risk for coronary disease [39, 40]. However, in our study, patients with coronary artery disease did not present lower magnesium concentrations.

Table 2. Univariate associations between serum magnesium and other studied parameters (Spearman correlation)

	Magnesium	
	r	p
Age	-0.44	0.006
Diabetes mellitus	-0.42	0.007
Albumin	0.57	<0.001
iPTH	-0.33	0.02
PP	-0.36	0.01
LVMI	-0.37	0.01
SVCS	-0.40	0.008

PP = Pulse pressure; LVMI = left ventricular mass index; SVCS = simple vascular calcification score.

Table 3. Multivariate analysis (linear regression)

Dependent variable	Independent variables	β	95% CI	p	R ²
Magnesium	Age	0.19	0.05–0.33	<0.001	0.436
	Diabetes mellitus	0.16	0.09–0.29	0.006	
	Albumin	3.3	2.03–3.73	0.01	
	PP ≥ 65 mm Hg	0.18	0.07–0.29	0.002	
	LVMI ≥ 140 g/m ²	0.15	0.10–0.24	0.03	
	SVCS ≥ 3	0.17	0.08–0.30	0.01	

PP = Pulse pressure; LVMI = left ventricular mass index; SVCS = simple vascular calcification score.

Fig. 2. Patients who died from overall and cardiovascular causes had significantly lower magnesium levels.

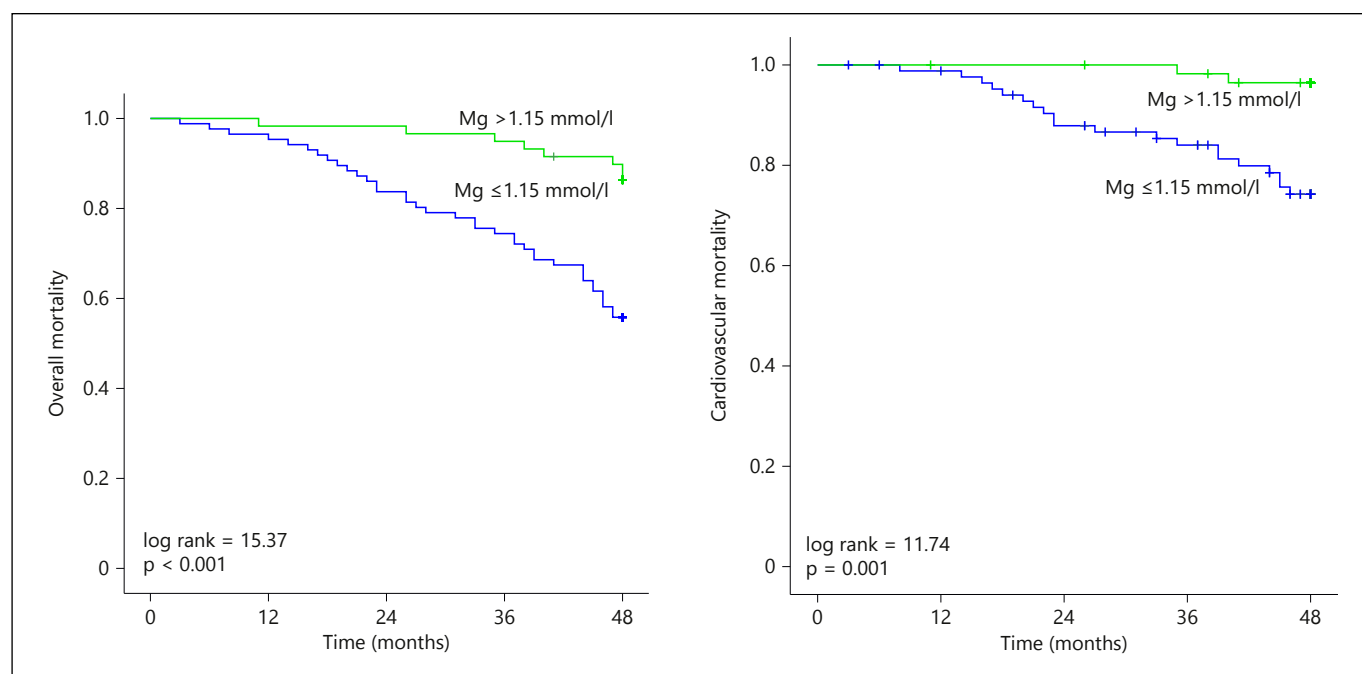
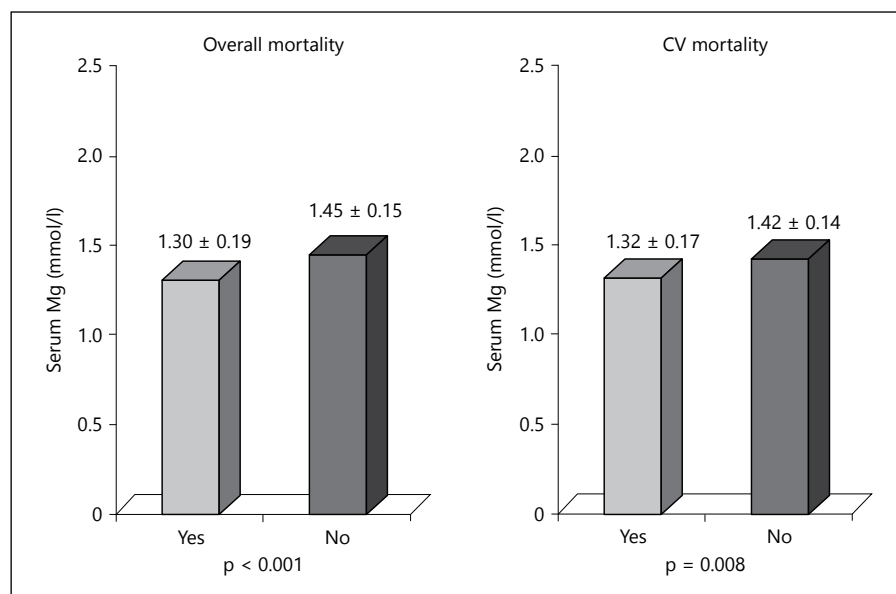


Fig. 3. A serum magnesium ≤ 1.15 mmol/l was associated with a lower overall and cardiovascular survival (Kaplan-Meier analysis).

Patients with lower serum magnesium had a significantly greater age and serum albumin was lower, compared with those with higher serum magnesium. These results are in accordance with others [17, 41] and may indicate that lower magnesium is related to malnutrition in these patients.

Hypomagnesaemia has also been linked to increased inflammation. Experimental magnesium deficiency induces an inflammatory syndrome in animal models, characterized by macrophage and white blood cell activation, release of proinflammatory cytokines, activation of an acute-phase response and excessive production of ox-

Table 4. Predictors of all-cause and cardiovascular mortality (Cox regression)

Dependent variable	Independent variables	HR	95% CI	p	R ²
Overall mortality	Age	1.42	1.08–1.53	0.02	0.473
	Time on HD	5.21	1.70–13.52	<0.001	
	Diabetes mellitus	7.34	2.81–18.83	<0.001	
	Albumin	0.81	0.82–0.97	0.01	
	C-reactive protein	1.93	1.07–3.16	0.007	
	Magnesium	0.87	0.88–0.99	0.01	
	PP ≥65 mm Hg	2.17	1.13–3.24	0.004	
	LVMI ≥140 g/m ²	1.98	1.09–3.20	0.003	
Cardiovascular mortality	SVCS ≥3	3.26	2.11–5.08	0.001	0.418
	Age	1.76	1.12–2.98	0.01	
	Time on HD	5.77	1.94–14.37	0.005	
	Diabetes mellitus	2.93	1.29–7.37	0.008	
	Coronary disease	1.87	1.23–2.34	0.02	
	C-reactive protein	1.90	1.25–2.87	0.01	
	Magnesium	0.82	0.72–0.95	0.02	
	PP ≥65 mm Hg	1.95	1.13–3.19	0.006	
	LVMI ≥140 g/m ²	2.19	1.16–3.22	0.004	
	SVCS ≥3	3.12	2.17–6.14	0.002	

PP = Pulse pressure; LVMI = left ventricular mass index; SVCS = simple vascular calcification score.

xygen-free radicals [42, 43]. In this study, in patients with CRP ≤5 mg/dl, there was a negative correlation between magnesium and inflammation (measured by CRP serum levels).

One other important role of magnesium is the effect on PTH lowering through the binding to the calcium-sensing receptor (CaSR) [44–46]. CaSR is expressed in both parathyroid and kidney, and it has distinct binding sites for both calcium and magnesium [44–46]. Furthermore, it seems that in parathyroid gland, sensitivity to magnesium is 2–3 times less than for calcium [46]. In situations of high serum magnesium, magnesium is thought to bind the CaSR in the parathyroid gland and might cause reduced PTH release [47, 48]. As in other studies, magnesium concentrations were inversely correlated with iPTH.

Over the years, studies have reported an inverse relationship between magnesium and blood pressure [35]. In spite of considerable research, the exact underlying causes for altered magnesium metabolism in hypertension remain unclear. It is assumed that inadequate dietary magnesium intake or a malfunction in magnesium metabolism can lead to vasospasm and endothelial damage [49, 50]. Magnesium deficiency, in particular when combined with stress and catecholamine secretion, might lead to enhanced entry of calcium into VSMC, which in turn can result in increased arteriolar tone and coronary spasm. Hypertension and its complications may also be the final

consequences of increased calcium influx and contraction of VSMC [1, 51]. Moreover, it was observed that magnesium acts on most types of calcium channels in VSMC exerting substantial arterial blood pressure-lowering properties, resulting in a reduction of peripheral and cerebral vascular resistance [37, 52]. In vivo and in vitro studies in animals (pregnant rats) have demonstrated magnesium-induced relaxation of smooth muscle. Such findings suggest the vasodilatory potential of magnesium in large arteries such as the aorta [53], in smaller resistance vessels as the mesenteric arteries and in the cerebral arteries [54]. These and similar data indicate that vascular tone can be modified by decreasing blood pressure via minor changes in magnesium levels [55]. Our study also showed an inverse association between magnesium concentrations and pulse pressure.

A large recent epidemiological study revealed that low magnesium levels, regardless of other cardiovascular risk factors, were associated with the long-term gain of left ventricular mass [11], a significant predictor of adverse cardiovascular events. In line with these results, we revealed that lower magnesium concentrations were predictors of an increased LVMI. One possible explanation for this association is the relationship between hypomagnesaemia and high aldosterone levels [1, 9], responsible for the development of left ventricular hypertrophy and myocardial fibrosis.

As well as in the general population [1, 36] and in CKD patients [14–16], our study shows that lower magnesium levels are associated with the presence of more vascular calcifications (as showed by a higher SVCS). Several *in vitro* studies have shown that magnesium can have an inhibitory effect on hydroxyapatite formation and precipitation, as well as on the calcification process. Posner's group demonstrated in the 1970s and 1980s that magnesium stabilized amorphous calcium phosphate and inhibited the formation of calcium-acidic phospholipid-phosphate complexes in metastable calcium phosphate solutions [56]. Bennett et al. [57] also found that magnesium was also able to inhibit calcium pyrophosphate dihydrate crystal formation *in vitro*. More recently, the effect of magnesium was examined on *in vitro* VSMC transformation into osteoblast-like cells and calcification [28]. The addition of 2.0–3.0 mM magnesium to a high-phosphate medium prevented osteogenic differentiation and calcification, in part via the restoration of the activity of the cation channel known as transient receptor potential melastatin 7 (TRPM7). Magnesium also increased the expression of anti-calcification proteins, including osteopontin and MGP [28]. Furthermore, it was shown that magnesium can stimulate the CaSR, which is expressed on VSMC [44]. Stimulation of the CaSR by calcimimetics reduced mineral deposition in VSMCs and delayed the progression of both aortic calcification and atherosclerosis in uraemic apolipoprotein E deficient mice [58]. The exact underlying mechanisms have not been resolved so far but this suggests that one of the ways of how magnesium influences VSMC calcification might be via the CaSR. Thus, magnesium can protect against vascular calcification via multiple molecular mechanisms.

Hypomagnesaemia has been associated in CKD [9, 17] and non-CKD [37] patients with overall mortality. Accordingly, we found that lower magnesium levels are an independent predictor of all-cause and cardiovascular mortality in dialysis patients. The reason for this association is still unknown, but may be due to the fact that lower magnesium concentrations are related to decreased immunity [3], increased inflammation [4, 5], higher susceptibility to malignant neoplasia [59] and cardiovascular disease [1, 37]. Magnesium can be related to cardiovascular disease by several mechanisms. Besides the association with vascular calcifications [14–16], magnesium exerts a direct modulatory action on cardiac excitability and both VSMC and cardiac contraction and relaxation [60]. Intradialytic changes in magnesium could be correlated with intradialytic hypotension in HD patients [7, 9]. Hypomagnesaemia has been shown to contribute to cardiac

morbidity and mortality, particularly in states associated with myocardial ischemia [61]. Magnesium deficiency induced coronary vasospasm, defective energy metabolism and excessive free radical generation [1, 61] may be important variables acting in concert, or independently, to affect myocardial function.

This study has some limitations due to the fact of being an observational study and serum magnesium levels were measured once at the beginning of the study. Nevertheless, this study shows a significant relationship between lower magnesium concentrations and cardiovascular risk markers, like PP, LVMI and SVCS, and with all-cause and cardiovascular mortality in a large HD population.

While the mean serum concentration of our HD patients (1.36 mmol/l) would be considered indicative of hypermagnesaemia in the healthy population, serum magnesium concentrations in HD patients may be optimal at a higher concentration, in view of a better survival under HD conditions, without causing severe and symptomatic hypermagnesaemia. Further, dialysate magnesium concentrations may be optimal at a concentration higher than the current concentration of 1 mmol/l in view of patient survival, since the serum magnesium concentration in HD patients parallels the magnesium level in the dialysate [62]. In haemodiafiltration, we must also consider the fact that convection generates a negative balance of this cation, which is independent of its concentration in the dialysate [63].

Alternatively, the use of magnesium carbonate as a phosphate binder could also amplify these protective effects of magnesium on cardiovascular dysfunction. More studies are required to establish an optimal level of magnesium in HD patients and an optimal concentration of magnesium in the dialysate.

Conclusions

Patients on dialysis have a mortality rate higher than the general population. Several mechanisms, not fully clarified, may be implicated. In this study, we hypothesized that lower serum magnesium is associated with cardiovascular risk markers, such as higher PP, LVMI and SVCS. Lower magnesium levels also seem to be independent predictors of overall and cardiovascular mortality in this population of prevalent HD patients. Randomized controlled trials examining the question of whether increased serum magnesium or higher magnesium intake is beneficial or not, in terms of outcomes, in CKD patients are needed.

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