Research Article

**Kidney
Diseases**

Kidney Dis 2020;6:109–118
DOI: 10.1159/000504601

Received: September 24, 2019
Accepted after revision: November 6, 2019
Published online: December 11, 2019

Hypomagnesemia and Short-Term Mortality in Elderly Maintenance Hemodialysis Patients

Caibao Lu Yiqin Wang Daihong Wang Ling Nie Ying Zhang Qiuyu Lei
Jiachuan Xiong Jinghong Zhao

Department of Nephrology, the Key Laboratory for the Prevention and Treatment of Chronic Kidney Disease of Chongqing, Kidney Center of PLA, Xinqiao Hospital, Army Medical University (Third Military Medical University), Chongqing, PR China

Keywords

Magnesium · Mortality · Hemodialysis · Risk factor

Abstract

Background: The relationship between magnesium and mortality in hemodialysis patients has been evaluated in several prospective studies, but few have assessed the risk of all-cause mortality in elderly hemodialysis patients. The aim of this study was to evaluate the association between magnesium levels and the risk of cardiovascular and overall mortality in elderly maintenance hemodialysis patients. **Methods:** This was a retrospective study, and patients undergoing maintenance hemodialysis were screened for eligibility at a single dialysis center between July and December 2016. Patients were divided into two groups based on their magnesium levels: a low magnesium level group and a high magnesium level group. Associations between magnesium level and risk of cardiovascular and all-cause mortality were analyzed with a Cox proportional hazards regression model. **Results:** In total, 413 patients were included with a median follow-up period of 12 months. We found that compared to patients with high magnesium levels, those with low magnesium levels had significantly lower levels of hemoglobin, urea, creatinine, uric acid, phosphate, potassium, chloride,

albumin, and spKt/V ($p < 0.05$ for each parameter). There was a strong correlation between the baseline mean serum magnesium concentration 1 year prior and the concentration 1 year later ($r^2 = 0.519$, $p < 0.001$). After adjustment for confounding factors, multivariate Cox proportional hazards analysis showed hypomagnesemia to be an independent predictor of all-cause and cardiovascular mortality in chronic hemodialysis patients. Furthermore, subgroup analysis was performed, revealing that serum magnesium levels were still strongly associated with all-cause mortality and cardiovascular mortality in patients older than 60 years, with HR values of 0.020 (95% CI 0.001–0.415) and 0.010 (95% CI 0.000–0.491), respectively. In addition, there were still significant associations between the serum magnesium level and all-cause mortality and cardiovascular mortality in elderly dialysis patients at the 6-month follow-up visit. **Conclusion:** Our study indicates that lower serum magnesium levels are strongly associated with cardiovascular and all-cause mortality in maintenance hemodialysis patients, especially in the short term and in those who are elderly. Factors affecting serum magnesium concentrations in hemodialysis patients should be investigated, and correcting hypomagnesemia may benefit elderly hemodialysis patients.

© 2019 The Author(s)
Published by S. Karger AG, Basel

KARGER

karger@karger.com
www.karger.com/kdd

© 2019 The Author(s)
Published by S. Karger AG, Basel

**Karger
Open access**

This article is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND) (<http://www.karger.com/Services/OpenAccessLicense>). Usage and distribution for commercial purposes as well as any distribution of modified material requires written permission.

Jinghong Zhao, MD, PhD, or Dr. Jiachuan Xiong
Department of Nephrology, Kidney Center of PLA, Xinqiao Hospital
Army Medical University (Third Military Medical University)
Chongqing, 400037 (PR China)
E-Mail zhaojh@tmmu.edu.cn or xiongjc@tmmu.edu.cn

Introduction

Magnesium (Mg) is the fourth most abundant cation in the body and the second most important intracellular cation [1]. In recent years, the importance of Mg has been increasingly recognized due to the growing awareness that it is required as a cofactor in multiple enzymatic reactions and that it plays an important role in neuromuscular processes [2]. Mg also functions in mineral bone metabolism, adenosine triphosphate metabolism, neurotransmitter release and regulation of vascular tone, heart rhythm, and platelet-activated thrombosis [3–5]. Changes in Mg homeostasis may occur in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [6]. Moreover, it has been reported that Mg deficiency is associated with vascular calcifications, atherosclerosis, and cardiovascular disease (CVD) and might increase the risk of sudden cardiac death [7]. Overall, an understanding of the physiology of Mg handling is important for CKD and ESRD patients. Recently, a growing body of literature is associating hypomagnesemia with critical clinical endpoints, such as an increased risk of CVD, arrhythmia, and mortality [8]. However, most of these studies have focused on general dialysis patients with a broad age range and long-term effects. Conversely, the association between hypomagnesemia and mortality in elderly maintenance hemodialysis (HD) patients, especially in the short term, has not been well documented. In this study, we investigated hypomagnesemia and the risk of mortality in elderly maintenance HD patients.

Materials and Methods

Patient Selection

This was a retrospective study. In total, 413 adult patients (mean age 50.4 ± 14.3 years) undergoing stable, regular HD at the purification center of the Department of Nephrology at Xinqiao Hospital between July and December 2016 were screened for eligibility. All data used in this study were collected from the database of the Blood Purification Center's Data Registry (BPCDR). Baseline data such as age, sex, body mass index (BMI), systolic blood pressure, and serum levels of urea nitrogen, creatinine, albumin, blood hemoglobin, and intact parathyroid hormone were collected. In addition, the medications, including anti-hypertension, glucose-lowering agent, calcium, antibiotics, proton pump inhibitor (PPI), and other commonly used drugs were analyzed. The patients received dialysis three times a week, and the blood flow rate ranged from 230 to 350 mL/min during the procedure. A GAM-BRO AK 95 HD machine (Baxter International Inc., Lund, Sweden) was used for HD, and the electrolyte concentration of the dialysate fluid was as follows: sodium 140 mmol/L, potassium 2.0 mmol/L, chloride 107 mmol/L, calcium 1.5 mmol/L, phosphate 0 mmol/L, Mg 0.5 mmol/L, and bicarbonate 35 mmol/L.

Biochemical Assays and Other Measurements

To measure serum albumin, calcium, phosphate, and Mg levels using routine laboratory methods, blood was collected just before the start of a dialysis session in a nonfasting state. Serum Mg was measured by the isocitrate dehydrogenase enzymatic method (Aqua-auto Kainos Mg Test Kit; Kainos Co. Ltd., Tokyo, Japan). The normal range of serum Mg concentrations in healthy subjects is 0.75–1.25 mmol/L. Mean values of measurements during the 6 months before January 2017 were used for analysis. To examine variability in serum Mg concentrations, levels in most patients who had survived 1 year after enrollment in the study (during October 2017 and March 2018, $n = 351$) were measured. Serum calcium concentrations were corrected by serum albumin concentrations, as follows: corrected calcium (mmol/L) = measured calcium (mmol/L) + $(40 - \text{albumin [g/L]})/40$.

Statistical Methods

Data are summarized as the mean $\pm$ SD. Differences in means between the two groups were evaluated by Student's *t* test. Categorical data were compared between groups by the χ^2 test. *p* values < 0.05 were considered statistically significant. All calculations, including Cox proportional hazards models and Kaplan-Meier analysis, were performed on a personal computer using statistical analysis software SPSS 24.0 (IBM Co., Armonk, NY, USA).

Results

Baseline Characteristics of the Included Patients

In total, 413 patients were involved in this study. The average age of the patients was 50.4 ± 14.3 years, and 57.4% were male. The HD duration was 43 months; 97% of the vascular access was via an arteriovenous fistula, and diabetes patients accounted for 14.4% of the study population. The mean BMI was 22.1 ± 3.3 kg/m². Mg concentrations were normally distributed, with a mean $\pm$ SD of 1.01 ± 0.15 mmol/L, as shown in Figure 1. Mg concentrations were also measured 1 year later to examine variability in serum Mg concentrations, and there was a strong correlation between the baseline mean serum Mg concentration and the Mg concentration 1 year later ($r^2 = 0.519$, $p < 0.0001$; Fig. 2). Patients were divided into two groups according to their baseline mean serum Mg concentration, as follows: a low Mg level group (serum Mg < 1.0 mmol/L, $n = 199$) and a high Mg level group (serum Mg ≥ 1.0 mmol/L, $n = 214$). Table 1 shows the baseline clinical characteristics of the HD patients in each of the two groups. The levels of hemoglobin, urea, creatinine, uric acid, phosphate, potassium, chloride, and albumin in addition to spKt/V were significantly lower in patients with low Mg concentrations than in those with high Mg concentrations ($p < 0.05$ for each parameter). There were no significant differences in sex, age, duration of HD, vascular access, or the presence of diabetes between the two

Fig. 1. Distribution of baseline serum Mg levels.

groups. In terms of laboratory parameters, there were no differences in white blood cell count, intact parathyroid hormone, or the levels of creatinine, corrected calcium, sodium, total protein, AST, ALT, and ALP between the groups. Moreover, there was no significant difference in medication, including insulin, calcium, antibiotics, PPI, anti-hypertension drugs, and statin, between the two groups.

Association of Baseline Serum Mg Categories with Mortality

During the follow-up period of 11.7 ± 1.5 months, 33 patients died; 25 of those patients were in the low Mg level group and 8 patients in the high Mg level group. Univariate analysis with Cox proportional hazards models was performed, and Table 2 presents the univariate associations between mortality and the other covariates. In addition to a lower Mg concentration, increased age, lower BMI, the presence of diabetes, lower serum albumin level, increased ALP level, lower creatinine level, lower uric acid level, lower potassium level, and lower spKt/V were significant univariate predictors of increased all-cause mortality. As shown in Table 3, Mg concentration was a significant independent predictor of mortality (HR 0.269, 95% CI 0.079–0.918, $p = 0.036$) in addition to age, BMI, the presence of diabetes, and spKt/V. Individuals with low Mg concentrations exhibited a significantly higher mortality rate than did those with high Mg concentrations ($p = 0.001$). Kaplan-Meier analysis was performed to examine the univariate association between the two groups and the outcomes of the cohort (Fig. 3a, b). The results showed that the rates of all-cause mortality

Fig. 2. Variability in serum Mg concentrations. There was a strong correlation between the baseline mean serum Mg concentration and the Mg concentration 1 year later.

(log-rank, $p = 0.001$) and cardiovascular mortality (log-rank, $p = 0.005$) were significantly higher in the low Mg level group than in the high Mg level group. Moreover, subgroup analysis showed that there was still a significant difference in all-cause mortality (log-rank, $p = 0.012$) and cardiovascular mortality (log-rank, $p = 0.037$) between the low Mg level group and the high Mg level group during the 6-month follow-up period (Fig. 3c, d).

Mg Categories and Mortality in Elderly HD Patients

We further analyzed the association between Mg and mortality risk in elderly patients (>60 years old). The basic information is listed in Table 4. There were 125 patients in total, and 46.4% were female. There was no difference in sex, age, HD duration, spKt/V, vascular access, or prevalence of diabetes between the low Mg level group and the high Mg level group. Compared with the high Mg level group, lower levels of hemoglobin, uric acid, phosphate, and albumin were observed in the low Mg level group. There was also no significant difference in medication, including insulin, calcium, antibiotics, PPI, anti-hypertension drugs, and statin between the two groups except for antibiotics and β -blocker. Cox proportional hazards regression analysis was performed and showed that the level of serum Mg was strongly associated with all-cause mortality and cardiovascular mortality, as shown in Table 3 and Figure 4; HRs were 0.020 (95% CI 0.001–0.415) and 0.010 (95% CI 0.000–0.491) for all-cause mortality and car-

Table 1. Baseline characteristics of the hemodialysis patients according to serum Mg concentration

Characteristics	Total (<i>n</i> = 413)	Lower Mg group (<i>n</i> = 199)	Higher Mg group (<i>n</i> = 214)	<i>p</i> value
Gender (male/female)	237/176	120/79	117/97	0.248
Age, years	50.4±14.3	51.1±14.7	49.7±13.8	0.324
Hemodialysis duration, months	43 (1–217)	43 (1–217)	43 (1–188)	0.883
Vascular access				0.932
Autogenous AVF	392	189	203	
Graft AVF	14	6	8	
Catheter	7	4	3	
BMI, kg/m ²	22.2±3.4	22.1±3.5	22.3±3.2	
Diabetes (diabetes/non-diabetes)				0.274
Diabetes	60	25	35	
Non-diabetes	353	174	179	
Hemoglobin, g/L	102.9±16.8	100.1±15.9	105.4±17.2	0.001
White blood cell, ×10 ⁹ /L	6.5±1.9	6.3±1.9	6.6±2.0	0.064
Platelet, ×10 ⁹ /L	169.9±62.7	164.9±59.2	174.6±65.4	0.115
iPTH, pg/mL	557.2 (24.75–3,000)	546.55 (43.5–3,000)	564.2 (24.75–3,000)	0.474
Urea, mmol/L	23.2±6.9	21.1±7.3	25.1±5.8	<0.001
Creatinine, μmol/L	923.5±279.1	845.2±754.4	996.3±226.6	<0.001
Uric acid, μmol/L	462.1±114.9	433.5±123.6	488.7±99.2	<0.001
Mg, mmol/L	1.01±0.15	0.89±0.08	1.12±0.11	<0.001
Phosphate, mmol/L	2.02±0.64	1.80±0.58	2.21±0.63	<0.001
Corrected calcium, mmol/L	2.15±0.26	2.14±0.27	2.17±0.25	0.318
Potassium, mmol/L	4.88±0.74	4.67±0.68	5.08±0.75	<0.001
Sodium, mmol/L	137.7±2.8	137.9±2.9	137.6±2.6	0.188
Chloride, mmol/L	100.0±4.1	100.0±4.1	99.9±4.1	0.820
Post-Mg, mmol/L	0.84±0.14	0.79±0.13	0.87±0.15	<0.001
Mg 1 year later, mmol/L	1.00±0.11	0.95±0.10	1.04±0.11	<0.001
Total protein, g/L	67.1±8.2	66.1±9.2	68.1±6.8	0.051
Albumin, g/L	40.6±5.5	39.4±6.3	41.7±4.4	0.001
AST, IU/L	18.4±14.9	19.5±18.5	17.3±10.3	0.237
ALT, IU/L	16.6±13.8	16.7±13.3	16.6±14.4	0.964
Total bilirubin, μmol/L	11.1±5.5	11.0±5.9	11.2±5.1	0.864
ALP, IU/L	116.1±169.1	125.1±203.3	107.1±126.5	0.389
spKt/V	1.4±0.5	1.3±0.4	1.4±0.5	0.024
Medications				
Insulin	58 (14.0)	27 (13.6)	31 (14.5)	0.788
Calcium	212 (51.3)	108 (54.3)	104 (48.6)	0.249
Antibiotics	21 (5.1)	14 (7.0)	7 (3.3)	0.082
PPI	13 (3.1)	7 (3.5)	6 (2.8)	0.678
CCB	386 (93.5)	187 (94.0)	199 (93.0)	0.687
ACEI or ARB	337 (81.6)	159 (79.9)	178 (83.2)	0.390
β-blocker	307 (74.3)	154 (77.4)	153 (71.5)	0.171
Clopidogrel	153 (37.0)	71 (35.7)	82 (38.3)	0.579
Statin	181 (43.8)	86 (43.2)	95 (44.4)	0.810

Data are presented as *n* (%), mean ± SD, or median (range) as appropriate. Lower Mg group = Mg <1 mmol/L; Higher Mg group = Mg ≥1 mmol/L. Mg, magnesium; AVF, arteriovenous fistula; BMI, body mass index; iPTH, intermittent parathyroid hormone; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PPI, proton pump inhibitor; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Univariate associations between mortality and other covariates

	HR	95% CI	<i>p</i> value
Age (per 1 year)	1.088	1.057–1.120	<0.001
Gender (male vs. female)	1.076	0.759–1.525	0.682
Hemodialysis duration (per 1 month)	1.003	0.995–1.010	0.494
BMI	0.859	0.761–0.971	0.015
Diabetes (diabetes vs. non-diabetes)	3.543	1.743–7.202	<0.001
Albumin (per 1 g/L)	0.939	0.884–0.997	0.040
Corrected calcium (per 1 mmol/L)	1.375	0.358–5.289	0.643
ALP	1.001	1.000–1.002	0.029
Mg group (to lower Mg group)	3.532	1.593–7.831	0.002
Hemoglobin	0.990	0.971–1.010	0.311
White blood cell	0.952	0.795–1.142	0.599
Platelet	0.994	0.987–1.000	0.054
iPTH, pg/mL	1.000	1.000–1.001	0.896
Urea	0.955	0.909–1.003	0.068
Creatinine	0.998	0.997–0.999	0.001
Uric acid, μ mol/L	0.996	0.994–0.999	0.014
Mg (per 1 mmol/L)	0.017	0.002–0.197	0.001
Phosphate, mmol/L	0.728	0.413–1.284	0.273
Potassium, mmol/L	0.555	0.344–0.896	0.016
Sodium, mmol/L	0.919	0.817–1.033	0.155
Chloride, mmol/L	0.964	0.885–1.049	0.395
spKt/V	0.140	0.046–0.427	0.001
Vascular access	5.191	0.124–217.7	0.388

HR, hazard ratio; BMI, body mass index; ALP, alkaline phosphatase; Mg, magnesium; iPTH, intermittent parathyroid hormone.

Table 3. Subgroup analysis of Mg and mortality in hemodialysis patients

	Overall mortality			Cardiovascular mortality		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
All patients						
Mg (per 1 mmol/L)	0.017	0.002–0.197	0.001	0.011	0.000–0.269	0.006
Mg group (low to high)	3.535	1.594–7.838	0.002	4.285	1.422–12.910	0.010
Age $\geq$ 60, 12-month follow-up						
Mg (per 1 mmol/L)	0.020	0.001–0.415	0.012	0.010	0.000–0.491	0.021
Mg group (low to high)	4.358	1.474–12.882	0.008	5.525	1.224–24.934	0.026
Age $\geq$ 60, 6-month follow-up						
Mg (per 1 mmol/L)	0.033	0.000–2.624	0.127	0.016	0.000–2.490	0.109
Mg group (low to high)	2.019	0.939–4.344	0.072	6.730	0.828–54.705	0.075

Mg, magnesium; HR, hazard ratio.

diovascular mortality, respectively. In addition, Kaplan-Meier analysis indicated significant differences in all-cause mortality (log-rank, $p = 0.003$) and cardiovascular mortality (log-rank, $p = 0.012$) between the two groups (Fig. 4a, b). Based on subgroup analysis, we also

found that significant associations between the serum level of Mg and all-cause mortality (log-rank, $p = 0.049$) and cardiovascular mortality (log-rank, $p = 0.038$) in elderly dialysis patients remained during the 6-month follow-up period (Fig. 4c, d).

Fig. 3. Kaplan-Meier analysis of Mg and mortality. **a** Overall mortality over a 12-month period. **b** Cardiovascular mortality over a 12-month period. **c** Overall mortality over a 6-month period. **d** Cardiovascular mortality over a 6-month period.

Discussion

In the present study, we found that a lower Mg concentration was a significant predictor of all-cause and cardiovascular mortality. Furthermore, these associations were most evident in elderly maintenance HD patients and during short-term follow-up. Moreover, there was a solid positive correlation between baseline mean serum Mg concentrations and serum Mg concentrations 1 year later.

Currently, there is a significant focus on serum calcium and phosphate concentrations in HD patients, and the relationship between serum calcium and phosphate and mortality in CKD and ESRD patients has been well documented [9]. In contrast, there has been relatively little focus on Mg concentrations. In the general population, the prevalence of hypomagnesemia is approximately 15%, though

the prevalence is much higher in intensive care units [10], and one study reported that approximately 70% of pediatric intensive care unit patients have hypomagnesemia [11]. Although the role of Mg in CKD and its impact on cardiovascular morbidity and mortality is not well understood, several previous studies have shown an association between serum Mg levels and higher all-cause mortality in patients undergoing maintenance HD [12–17]. Moreover, in peritoneal dialysis patients, hypomagnesemia is associated with increased all-cause and cardiovascular mortality [18–20]. In nondialysis patients with CKD, Kanbay et al. [8] demonstrated that compared with serum Mg levels higher than 2.05 mg/dL, serum Mg levels below 2.05 mg/dL can increase the cardiovascular mortality rate. In our study, we also demonstrated that the significance of a lower level of Mg as a predictor of mortality was independent of other known covariates, such as increased age and the

Table 4. The basic characteristic of patients over 60 years of age

Characteristics	Total (<i>n</i> = 125)	Lower Mg group (<i>n</i> = 67)	Higher Mg group (<i>n</i> = 58)	<i>p</i> value
Gender (male/female)	67/58	36/31	31/27	0.975
Age, years	67.6±6.1	67.6±5.9	67.6±6.2	0.997
Hemodialysis duration, months	43 (15–80)	55 (15–84)	41 (15–76)	0.425
Vascular access				0.647
Autogenous arteriovenous fistula	113	62	51	
Graft arteriovenous fistula	9	4	5	
Catheter	3	1	2	
BMI, kg/m ²	22.2±3.4	21.6±3.5	22.8±3.1	0.046
Diabetes (diabetes/non-diabetes)				0.907
Diabetes	36	19	17	
Non-diabetes	89	48	41	
Hemoglobin, g/L	104.5±15.5	99.7±14.5	110.0±14.8	<0.001
White blood cell, ×10 ⁹ /L	6.5±1.8	6.3±1.9	6.7±1.6	0.291
Platelet, ×10 ⁹ /L	162.9±64.8	156.5±59.0	170.4±70.8	0.231
iPTH, pg/mL	393.0 (271.0–707.4)	346.5 (205.1–625.0)	412.2 (293.2–840.3)	0.103
Urea, mmol/L	22.3±6.9	19.8±7.3	25.2±5.1	<0.001
Creatinine, μmol/L	787.0±245.8	695.8±246.9	892.4±199.4	<0.001
Uric acid, μmol/L	438.2±107.3	407.9±113.9	474.2±86.9	<0.001
Mg, mmol/L	0.98±0.14	0.88±0.08	1.10±0.08	<0.001
Phosphate, mmol/L	1.90±0.61	1.73±0.59	2.10±0.57	0.001
Corrected calcium, mmol/L	2.10±0.24	2.12±0.23	2.10±0.25	0.613
Potassium, mmol/L	4.76±0.80	4.57±0.74	4.98±0.83	0.003
Sodium, mmol/L	137.6±3.1	137.6±3.2	137.6±2.9	0.957
Chloride, mmol/L	100.4±4.3	100.2±4.5	100.6±4.0	0.657
Post-Mg, mmol/L	0.82±0.07	0.79±0.07	0.84±0.06	<0.001
Mg 1 year later, mmol/L	0.90±0.12	0.94±0.09	1.04±0.12	<0.001
Total protein, g/L	66.7±8.5	65.8±9.9	67.8±6.3	0.230
Albumin, g/L	38.7±5.2	36.9±5.6	40.9±3.6	<0.001
AST, IU/L	19.1±10.5	20.5±12.1	17.3±7.8	0.137
ALT, IU/L	18.3±16.8	16.9±12.5	20.0±21.1	0.372
Total bilirubin, μmol/L	10.9±5.0	11.6±6.1	10.0±2.8	0.134
ALP, IU/L	88.7 (65.1–133.8)	93.8 (67.0–160.5)	83.1 (61.1–119.2)	0.205
spKt/V	1.3±0.3	1.2±0.5	1.3±0.2	0.460
Medications				
Insulin	35 (28.0)	21 (31.3)	14 (24.1)	0.371
Calcium	71 (56.8)	41 (61.2)	30 (51.7)	0.286
Antibiotics	13 (10.4)	11 (16.4)	2 (3.4)	0.018
PPI	6 (4.8)	4 (6.0)	2 (3.4)	0.511
CCB	111 (88.8)	62 (92.5)	49 (84.5)	0.154
ACEI or ARB	96 (76.8)	54 (80.6)	42 (72.4)	0.280
β-blocker	75 (60.0)	47 (70.1)	28 (48.3)	0.013
Clopidogrel	54 (43.2)	31 (46.3)	23 (39.7)	0.457
Statin	65 (52.0)	38 (56.7)	27 (46.6)	0.257

Data are presented as *n* (%), mean ± SD, or median (range) as appropriate. Lower Mg group = Mg <1 mmol/L; Higher Mg group = Mg ≥1 mmol/L. Mg, magnesium; AVF, arteriovenous fistula; BMI, body mass index; iPTH, intermittent parathyroid hormone; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PPI, proton pump inhibitor; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Fig. 4. Kaplan-Meier analysis of Mg and mortality in elderly hemodialysis patients. **a** Overall mortality over a 12-month period. **b** Cardiovascular mortality over a 12-month period. **c** Overall mortality over a 6-month period. **d** Cardiovascular mortality over a 6-month period.

presence of diabetes, which is consistent with the findings of previous reports. However, we also observed that patients with low serum Mg levels were significantly older and had significantly lower serum levels of albumin, phosphate, and calcium than did those with high serum Mg levels. These results may indicate that lower serum Mg levels are related to malnourishment in these patients. Selim et al. [14] reported an observable association between Mg and mortality within a 5-year follow-up period, and Ago et al. [21] showed that the same association could be observed in a 1-year follow-up period. The results of our study indicate that at the time of patient enrollment, the mean serum Mg concentration over the previous 6 months can predict survival, especially in elderly patients. We found that lower serum Mg levels can increase all-cause and cardiovascular mortality in the short term. Other significant predictors were increased age, longer duration of HD, the presence of

diabetes, lower albumin level, and lower phosphate level. Furthermore, after adjustment for these confounders, a lower serum Mg level remained a significant predictor for increased mortality according to multivariate Cox proportional analysis. Our results support that a lower level of serum Mg is a significant predictor of mortality, independent of other parameters of malnourishment, including the presence of diabetes, lower albumin levels, and lower phosphate levels. Hypomagnesemia may be influenced by medications, such as insulin, calcium, antibiotics, PPI, and chemotherapeutic drugs. But in our study, there was no significant difference in medications between the two groups, which suggested that hypomagnesemia may be caused by the decreased intake or other reasons. This issue needs to be further addressed.

Previous experimental research suggested that Mg plays a crucial role in cardiovascular function [22], and

lower Mg intake and/or lower serum Mg levels have been reported to be related to CVD in nondialysis subjects [23–25]. Accordingly, we examined the predictive association between serum Mg levels and cardiovascular mortality and found a lower serum Mg level to be a significant predictor of cardiovascular mortality according to independent multivariate Cox proportional hazard analysis. Regarding the electrolyte concentration of the dialysate, much attention has been focused on calcium and phosphate, particularly in consideration of vascular calcification and renal osteodystrophy [26], but relatively little attention has been focused on Mg. Nonetheless, Mg has recently been shown to inhibit vascular calcification, both by direct effects on the vessel wall and by indirect, systemic effects [27, 28]. Zaher et al. [29] performed a study to assess the relationship between serum Mg levels and vascular stiffness in children on regular HD and found significantly lower serum Mg levels in these children, with these lower serum Mg levels being associated with increased vascular calcification. Taken together, we believe that the role of Mg in vascular calcification is as important as are the roles of serum calcium and phosphate.

The serum Mg concentration is linked to dietary Mg intake. Thus, in patients on maintenance HD, serum Mg levels are primarily determined by the Mg concentration of the dialysate [30]. At present, a dialysate Mg concentration of 0.50 mmol/L is routinely prescribed. In a pilot study, Schmaderer et al. [31] investigated the impact of a higher dialysate Mg concentration (0.75 mmol/L) on mortality, and Cox proportional hazards regression showed that a higher dialysate Mg concentration independently predicted a 65% reduction in the risk of all-cause mortality. Subsequently, these authors conducted a randomized controlled clinical trial to examine the effect of increasing the dialysate Mg concentration from 1.0 to 2.0 mEq/L for 28 days compared with maintaining the dialysate Mg concentration at 1.0 mEq/L on the propensity toward serum calcification in subjects undergoing HD. They concluded that increasing the dialysate Mg concentration indeed increased the propensity toward serum calcification in these subjects [32]. These results demonstrate that serum Mg concentrations in HD patients may be optimal at a higher concentration, in view of the observed improved survival under HD conditions, without causing severe and symptomatic hypermagnesemia. Regardless, further studies are required to establish the optimal level of serum Mg in HD patients and the optimal concentration of Mg in the dialysate.

There were some limitations to this study. First, at the start of the study, we could not obtain data on serum lip-

id levels, smoking history, or history of CVD or non-CVD, which may affect the survival of HD patients. Second, we could not include information on medications, such as lipid-lowering drugs, calcium carbonate or calcium acetate, and vitamin D, which have been reported to affect patient survival. Finally, this was a single-center study, and additional multicenter studies with large sample sizes are needed.

In conclusion, we demonstrate that a lower serum Mg concentration is associated with all-cause and cardiovascular mortality in maintenance HD patients, especially in the short term and in those older than 60 years. HD patients with hypomagnesemia should be carefully evaluated for mortality risk. In addition, further studies are needed to verify whether Mg supplementation or higher dialysate Mg concentrations have potential benefits for HD patients with hypomagnesemia.

Acknowledgments

We thank the medical staff at the Department of Nephrology, the Key Laboratory for the Prevention and Treatment of Chronic Kidney Disease of Chongqing, Kidney Center of PLA, Xinqiao Hospital, Army Medical University (Third Military Medical University).

Statement of Ethics

The study protocol was approved by the Medicine Ethics Committee of Xinqiao Hospital and was in adherence with the Declaration of Helsinki. All participating patients provided written informed consent.

Disclosure Statement

The authors declare that they have no competing interests.

Funding Sources

This work was supported by the National Key Research and Development Program of China (2018YFC1312700), National Natural Science Foundation of China (81873605, 81700379), Science and Technology Innovation Projects for Social Undertakings and Livelihood Security in Chongqing (cstc2017shmsA130106), and Clinical Research Foundation of Xinqiao Hospital (2016YLC38).

Author Contributions

C.L., Y.W., Q.L., and D.W. collected the data and reviewed the literature. C.L., J.X., and J.Z. provided valuable input in the study design and data collection and drafted the article and revised it critically. L.N. and Y.Z. provided the literature review. All authors read and approved the manuscript and met the criteria for authorship.

References

- Al Alawi AM, Majoni SW, Falhammar H. Magnesium and human health: perspectives and research directions. *Int J Endocrinol*. 2018 Apr;2018:9041694.
- Laires MJ, Monteiro CP, Bicho M. Role of cellular magnesium in health and human disease. *Front Biosci*. 2004 Jan;9(1-3):262–76.
- Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth*. 1999 Aug;83(2):302–20.
- Volpe SL. Magnesium in disease prevention and overall health. *Adv Nutr*. 2013 May;4(3):378S–83S.
- Shechter M. Magnesium and cardiovascular system. *Magnes Res*. 2010 Jun;23(2):60–72.
- Kanbay M, Goldsmith D, Uyar ME, Turgut F, Covic A. Magnesium in chronic kidney disease: challenges and opportunities. *Blood Purif*. 2010;29(3):280–92.
- Massy ZA, Drueke TB. Magnesium and outcomes in patients with chronic kidney disease: focus on vascular calcification, atherosclerosis and survival. *Clin Kidney*. 2012 Feb;5(Suppl 1):i52–i61.
- Kanbay M, Yilmaz MI, Apetrii M, Saglam M, Yaman H, Unal HU, et al. Relationship between serum magnesium levels and cardiovascular events in chronic kidney disease patients. *Am J Nephrol*. 2012;36(3):228–37.
- Da J, Xie X, Wolf M, Disthabanchong S, Wang J, Zha Y, et al. Serum Phosphorus and Progression of CKD and Mortality: A Meta-analysis of Cohort Studies. *Am J Kidney Dis*. 2015 Aug;66(2):258–65.
- Fairley J, Glassford NJ, Zhang L, Bellomo R. Magnesium status and magnesium therapy in critically ill patients: A systematic review. *J Crit Care*. 2015 Dec;30(6):1349–58.
- Deshmukh CT, Rane SA, Gurav MN. Hypomagnesaemia in paediatric population in an intensive care unit. *J Postgrad Med*. 2000 Jul-Sep;46(3):179–80.
- Lacson E Jr, Wang W, Ma L, Passlick-Deetjen J. Serum Magnesium and Mortality in Hemodialysis Patients in the United States: A Cohort Study. *Am J Kidney Dis*. 2015 Dec;66(6):1056–66.
- Li L, Streja E, Rhee CM, Mehrotra R, Soohoo M, Brunelli SM, et al. Hypomagnesemia and Mortality in Incident Hemodialysis Patients. *Am J Kidney Dis*. 2015 Dec;66(6):1047–55.
- Selim GN, Spasovski G, Tozija L, Georgievska-Ismail L, Zafirova-Ivanovska B, Masin-Spasovska J, et al. Hypomagnesemia and cause-specific mortality in hemodialysis patients: 5-year follow-up analysis. *Int J Artif Organs*. 2017 Oct;40(10):542–9.
- Yu L, Li H, Wang SX. Serum Magnesium and Mortality in Maintenance Hemodialysis Patients. *Blood Purif*. 2017;43(1-3):31–6.
- de Roij van Zijdewijn CL, Grooteman MP, Bots ML, Blankestijn PJ, Steppan S, Büchel J, et al. Serum Magnesium and Sudden Death in European Hemodialysis Patients. *PLoS One*. 2015 Nov;10(11):e0143104.
- João Matias P, Azevedo A, Laranjinha I, Navarro D, Mendes M, Ferreira C, et al. Lower serum magnesium is associated with cardiovascular risk factors and mortality in haemodialysis patients. *Blood Purif*. 2014;38(3-4):244–52.
- Cai K, Luo Q, Dai Z, Zhu B, Fei J, Xue C, et al. Hypomagnesemia Is Associated with Increased Mortality among Peritoneal Dialysis Patients. *PLoS One*. 2016 Mar;11(3):e0152488.
- Yang X, Soohoo M, Streja E, Rivara MB, Obi Y, Adams SV, et al. Serum Magnesium Levels and Hospitalization and Mortality in Incident Peritoneal Dialysis Patients: A Cohort Study. *Am J Kidney Dis*. 2016 Oct;68(4):619–27.
- Ye H, Cao P, Zhang X, Lin J, Guo Q, Mao H, et al. Serum magnesium and cardiovascular mortality in peritoneal dialysis patients: a 5-year prospective cohort study. *Br J Nutr*. 2018 Aug;120(4):415–23.
- Ago R, Shindo T, Banshodani M, Shintaku S, Moriishi M, Masaki T, et al. Hypomagnesemia as a predictor of mortality in hemodialysis patients and the role of proton pump inhibitors: A cross-sectional, 1-year, retrospective cohort study. *Hemodial Int*. 2016 Oct;20(4):580–8.
- Kolte D, Vijayaraghavan K, Khera S, Sica DA, Frishman WH. Role of magnesium in cardiovascular diseases. *Cardiol Rev*. 2014 Jul-Aug;22(4):182–92.
- Lutsey PL, Alonso A, Michos ED, Loefer LR, Astor BC, Coresh J, et al. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr*. 2014 Sep;100(3):756–64.
- Joosten MM, Gansevoort RT, Mukamal KJ, van der Harst P, Geleijnse JM, Feskens EJ, et al.; PREVENT Study Group. Urinary and plasma magnesium and risk of ischemic heart disease. *Am J Clin Nutr*. 2013 Jun;97(6):1299–306.
- Zhang W, Iso H, Ohira T, Date C, Takamashi A; JACC Study Group. Associations of dietary magnesium intake with mortality from cardiovascular disease: the JACC study. *Atherosclerosis*. 2012 Apr;221(2):587–95.
- Locatelli F, Cannata-Andía JB, Drüeke TB, Hörl WH, Fouque D, Heimbürger O, et al. Management of disturbances of calcium and phosphate metabolism in chronic renal insufficiency, with emphasis on the control of hyperphosphataemia. *Nephrol Dial Transplant*. 2002 May;17(5):723–31.
- Neven E, De Schutter TM, Dams G, Gundlach K, Steppan S, Büchel J, et al. A magnesium based phosphate binder reduces vascular calcification without affecting bone in chronic renal failure rats. *PLoS One*. 2014 Sep 17;9(9):e107067.
- Herencia C, Rodríguez-Ortiz ME, Muñoz-Castañeda JR, Martínez-Moreno JM, Canalejo R, Montes de Oca A, et al. Angiotensin II prevents calcification in vascular smooth muscle cells by enhancing magnesium influx. *Eur J Clin Invest*. 2015 Nov;45(11):1129–44.
- Zaher MM, Abdel-Salam M, Abdel-Salam R, Sabour R, Morsy AA, Gamal D. Serum magnesium level and vascular stiffness in children with chronic kidney disease on regular hemodialysis. *Saudi J Kidney Dis Transpl*. 2016 Mar;27(2):233–40.
- Rosanoff A, Weaver CM, Rude RK. Suboptimal magnesium status in the United States: are the health consequences underestimated? *Nutr Rev*. 2012 Mar;70(3):153–64.
- Schmaderer C, Braunisch MC, Suttman Y, Lorenz G, Pham D, Haller B, et al. Reduced Mortality in Maintenance Haemodialysis Patients on High versus Low Dialysate Magnesium: A Pilot Study. *Nutrients*. 2017 Aug;9(9):E926.
- Bressendorff I, Hansen D, Schou M, Pasch A, Brandt L. The Effect of Increasing Dialysate Magnesium on Serum Calcification Propensity in Subjects with End Stage Kidney Disease: A Randomized, Controlled Clinical Trial. *Clin J Am Soc Nephrol*. 2018 Sep;13(9):1373–80.