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Original Investigation

Hypomagnesemia and Mortality in Incident Hemodialysis Patients

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Background: In the general population, low serum magnesium levels are associated with poor outcomes and death. While limited data suggest that low baseline magnesium levels may be associated with higher mortality in hemodialysis (HD) patients, the impact of changes in magnesium levels over time is unknown.

Study Design: We examined the association of time-varying serum magnesium levels with all-cause mortality using multivariable time-varying survival models adjusted for clinical characteristics and other time-varying laboratory measures.

Setting & Participants: 9,359 maintenance HD patients treated in a large dialysis organization between 2007 and 2011.

Predictor: Time-varying serum magnesium levels across 5 magnesium increments (<1.8, 1.8-<2.0, 2.0-<2.2, 2.2-<2.4, and ≥2.4 mg/dL).

Outcome: All-cause mortality.

Results: 2,636 individuals died over 5 years. Time-varying serum magnesium levels < 2.0 mg/dL were associated with higher mortality after adjustment for demographics and comorbid conditions, including hypertension, diabetes, and malignancies (reference: magnesium, 2.2-<2.4 mg/dL): adjusted HRs for serum magnesium level < 1.8 and 1.8 to <2.0 mg/dL were 1.39 (95% CI, 1.23-1.58; $P < 0.001$) and 1.20 (95% CI, 1.06-1.36; $P = 0.004$), respectively. Some associations were attenuated to the null after incremental adjustment for laboratory test results, particularly serum albumin. However, among patients with serum albumin measurements, low albumin level (<3.5 g/dL) and magnesium level < 2.0 mg/dL were associated with an additional death risk (adjusted HR, 1.17; 95% CI, 1.05-1.31; $P = 0.004$), whereas patients with high serum albumin levels (≥3.5 g/dL) exhibited low death risk (adjusted HRs of 0.53 and 0.53 [$P \leq 0.001$] for magnesium < 2.0 and ≥2.0 mg/dL, respectively; reference: albumin < 3.5 g/dL and magnesium ≥ 2.0 mg/dL).

Limitations: Causality cannot be determined, and residual confounding cannot be excluded given the observational study design.

Conclusions: Lower serum magnesium levels are associated with higher mortality in HD patients, including those with hypoalbuminemia. Interventional studies are warranted to examine whether correction of hypomagnesemia ameliorates adverse outcomes in this population.

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INDEX WORDS: Magnesium; hypomagnesemia; time-varying serum magnesium; dialysis; serum albumin; death risk; all-cause mortality; cohort; end-stage renal disease (ESRD); incident hemodialysis patients.

Magnesium is the second most abundant intracellular cation in the body, and it is essential for the regulation of various enzymatic and cellular functions. Magnesium homeostasis is tightly regulated in the body, and in patients with preserved kidney function, normal magnesium levels are maintained by renal reabsorption and excretion.[1,2] In contrast, in dialysis patients, serum magnesium levels are largely dependent on dietary intake and dialysate magnesium concentrations.

In the general population, low serum magnesium levels have been associated with higher risk of type 2 diabetes mellitus,[3,4] hypertension,[5-7] cardiac arrhythmia,[8] cardiovascular disease (CVD), and mortality.[9-13] Recent data show that hypomagnesemia may be a risk factor for the development of chronic kidney disease, including end-stage renal disease (ESRD).[14-17] In patients with ESRD receiving hemodialysis (HD), limited data suggest that hypomagnesemia is associated with increased all-cause

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and cardiovascular mortality.[18,19] However, these studies were limited by short follow-up times and failure to account for changes in magnesium levels over time. Moreover, these studies were conducted outside the United States and thus may not be generalizable to the US dialysis population given the varying dialysate magnesium concentrations used in different countries. Therefore, we conducted what to our knowledge is the first observational study investigating the association between serum magnesium level and all-cause mortality in a large US cohort of maintenance HD patients. We hypothesized that lower serum magnesium levels are associated with higher death risk.

METHODS

Study Cohort

This was a retrospective study of patients with ESRD who were initiated on maintenance HD treatment in one of the outpatient dialysis facilities of a large US dialysis organization and were followed up over a period of 5 years (January 2007 to December 2011).[20] Patients were included provided that they were 18 years or older, underwent in-center HD for at least 60 days, and had serum magnesium measured at least once during their first 91-day period of HD. The study was approved by the University of California Irvine and DaVita Clinical Research.

Demographic and Clinical Measures

Age was estimated by using date of birth and date of study entry (date of dialysis therapy initiation). Body mass index was calculated at baseline from post-HD dry body weight in kilograms divided by height in meters squared. Race and ethnicity determinations were based on self-report and included the following: white, African American, Hispanic, Asian, and other. The following 9 comorbid conditions (ascertained from *International Classification of Diseases, Ninth Revision* codes) were considered: diabetes mellitus, hypertension, atherosclerotic disease, congestive heart failure, cerebrovascular disease, dyslipidemia, chronic obstructive pulmonary disease, liver disease, and malignancy.

Magnesium and Other Laboratory Values

Blood samples were drawn using standardized techniques in all dialysis clinics and were transported within 24 hours to a single laboratory center (DaVita Laboratory, Deland, FL), where the laboratory values were measured by automated and standardized methods. All blood samples were collected predialysis except for postdialysis serum urea nitrogen (SUN) for calculation of urea kinetics. Most laboratory values were measured monthly, including serum potassium, bicarbonate, SUN, calcium, phosphorus, albumin, alkaline phosphatase (ALP), normalized protein catabolic rate (nPCR), and white blood cells. Serum intact parathyroid hormone (iPTH) and ferritin were measured at least quarterly. Hemoglobin was measured weekly to biweekly in most patients. Delivered dialysis dose was estimated by single-pool Kt/V using the urea kinetic model.

All patients included in the study had serum magnesium measurements within the first 91 days of study entry (baseline quarter). The subsequent serum magnesium level was checked frequently, but not routinely. To minimize measurement variability, all repeat measurements for each 91-day interval from date of dialysis therapy initiation were averaged and used in all models. For iPTH, ALP, and ferritin, the distributions were skewed; thus, they were logarithmically transformed in the adjusted models. The exposure of interest was time-varying serum magnesium level. Serum magnesium levels per each patient quarter (91-day interval) were divided into 5 groups (<1.8, 1.8-<2.0, 2.0-<2.2, 2.2-<2.4, and ≥ 2.4 mg/dL). Serum magnesium category cutoffs were chosen according to a normal reference range of 1.8 to 2.4 mg/dL and a 0.2-mg/dL incremental change within this reference range. Time-varying serum magnesium measurements would account for changes in the exposure over time and allow for estimation of short-term exposure-mortality associations.

Outcome Ascertainment

The study outcome of interest was all-cause mortality, and patients were followed up over a 5-year period (January 2007 to December 2011) from initiation of HD therapy. Patients were censored for loss to follow-up, discontinuation of dialysis therapy, kidney transplantation, or transfer to a nonaffiliated dialysis clinic.

Statistical Methods

Patients' baseline demographics, clinical characteristics, and laboratory values across serum magnesium categories were summarized as proportion, mean $\pm$ standard deviation, or median with interquartile range (IQR) as dictated by data type and were compared using χ^2 test or analysis of variance for parametric variables (or Kruskal-Wallis test for nonparametric variables). Correlations between baseline continuous magnesium levels and other covariates were examined by Pearson correlation.

Associations between 5 levels of time-varying serum magnesium levels and mortality risk were determined using time-varying Cox proportional hazards regression models, which included repeat and time-updated measurements of covariates that were averaged over each 91-day interval from patients' date of dialysis therapy initiation. Time-varying models allow for the change in exposure and covariates and their association with the outcome over time in order to ascertain short-term exposure-mortality associations.[21] Time-varying serum magnesium–mortality associations were examined with unadjusted models and with 2 levels of multivariable adjustment: (1) case-mix models, which adjusted for baseline characteristics of age; sex; race/ethnicity (white, African American, Hispanic, Asian, or other); comorbid conditions, including diabetes mellitus, hypertension, and history of cancer; and dialysis dose as indicated by single-pool Kt/V; and (2) case-mix plus malnutrition-inflammation-cachexia syndrome (MICS) models, which included all covariates in the case-mix model plus baseline body mass index and 11 time-updated laboratory variables that bear associations with clinical outcomes in HD patients: serum albumin, potassium, ALP, predialysis SUN, nPCR, albumin-adjusted calcium, phosphorus, iPTH, hemoglobin, white blood cells, and ferritin. For sensitivity analyses, the association between time-varying serum magnesium level as a continuous variable and mortality was examined using nonparametric restricted cubic splines with best estimated knots defined at the 25th, 50th, and 75th percentiles of observed values (1.8, 2.05, and 2.3 mg/dL).

We also conducted magnesium-mortality association analyses across a priori defined subgroups to investigate potential effect modification by sociodemographics, comorbid conditions, and laboratory values. In addition, we examined the relationship between serum magnesium and albumin levels over time using linear mixed regression models with unstructured variance to account for intrasubject correlations in repeat measurements. Associations of combined time-varying magnesium and albumin levels and mortality were then examined, for which patients were divided into 4 (2×2) groups according to time-updated serum magnesium (<2.0 vs ≥ 2.0 mg/dL) and albumin levels (<3.5 vs ≥ 3.5 g/dL).

For patients with data for serum magnesium at baseline but missing for subsequent follow-up periods, the last available

magnesium level was assumed to be unchanged until the next measurement or occurrence of the event (death or censor). Missing quarterly laboratory values (<0.5% for all tests except nPCR, for which 3.8% were missing) were otherwise imputed by population means or medians of the existing values in the same patient quarter in multivariable models. All analyses were implemented using SAS, version 9.3 (SAS Institute Inc), and Stata, version 10.1 (Stata Corp LP).

RESULTS

Study Cohort Description

A total of 208,820 patients with ESRD who initiated dialysis therapy during January 2007 to December 2011 within one of the outpatient facilities of a large dialysis organization were identified. After excluding patients who received treatment for fewer than 60 days or those who underwent a dialysis modality other than thrice-weekly in-center HD at study entry, there were 112,017 remaining patients (Fig 1). Of these patients, 9,359 who had serum magnesium measured during the first 91-day period following initiation of dialysis therapy formed the final study cohort (Fig 1). Mean serum magnesium level of the cohort was 2.1 ± 0.4 (standard deviation) mg/dL, and median concentration was 2.1 (IQR, 1.8-2.3) mg/dL. Baseline clinical characteristics of these patients stratified according to 5 baseline serum magnesium categories are presented in Table 1. Patients with lower serum magnesium levels tended to be older and white; were more likely to have had prior malignancy but less likely to have had diabetes; had lower hemoglobin, serum albumin, nPCR, SUN, potassium, adjusted calcium, and phosphorus levels; and had higher ferritin and ALP levels. Serum magnesium level positively correlated with nutritional marker values, including albumin, SUN, and nPCR (Pearson correlation coefficients of 0.21, 0.27, and 0.21, respectively; $P < 0.001$ for all). However, correlations of serum magnesium levels with dialysis dose (ie, single-pool Kt/V) and iPTH level were weak and nonsignificant (Pearson correlation coefficients of −0.01 [$P = 0.2$] and 0.01 [$P = 0.4$], respectively).

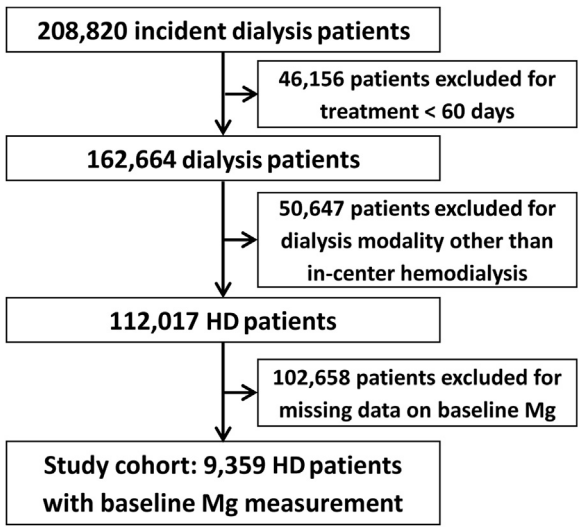

Figure 1. Algorithm (flow chart) of patient selection for the cohort. Abbreviations: HD, hemodialysis; Mg, magnesium.

Serum Magnesium Levels and All-Cause Mortality

During follow-up, 2,636 deaths occurred over a mean follow-up of 19 ± 15 (range, 2.0-59.9) months. To account for changes in serum magnesium levels over time and examine short-term serum magnesium–mortality associations, serum magnesium level and all-cause mortality associations were examined using time-varying Cox survival models, as shown in Fig 2. In unadjusted time-varying models, with the reference group as magnesium levels of 2.2 to <2.4 mg/dL, serum magnesium levels < 2.0 mg/dL were significantly associated with increased risk for death: hazard ratios (HRs) of 1.63 (95% confidence interval [CI], 1.44-1.85; $P < 0.001$) and 1.30 (95% CI, 1.15-1.47; $P < 0.001$), for magnesium levels <1.8 and 1.8 to <2.0 mg/dL, respectively. These associations were somewhat attenuated after case-mix adjustment but remained statistically significant: adjusted HRs were 1.39 (95% CI, 1.23-1.58; $P < 0.001$) and 1.20 (95% CI, 1.06-1.36; $P = 0.004$) for magnesium levels < 1.8 and 1.8 to <2.2 mg/dL, respectively. However, these associations were further attenuated to the null after additional adjustment for case-mix and MICS covariates, particularly serum albumin level.

Within these case-mix and MICS-adjusted models examining the association of serum magnesium level and mortality risk, higher serum albumin level had a strong association with improved survival. For every 1-g/dL increase in time-varying serum albumin levels, there was a 62% decreased risk of mortality (adjusted HR, 0.38; 95% CI, 0.35-0.42; $P < 0.001$). In associations examining time-varying continuous serum magnesium levels with all-cause mortality using nonparametric restricted cubic splines, we observed that both lower and higher serum magnesium levels exhibited a trend toward increased mortality risk, although high magnesium levels > 3 mg/dL were not statistically significant due to a small sample size (Fig S1, available as online supplementary material).

In case-mix–adjusted subgroup analyses (Table S1; Fig S2), we observed a consistent association between lower serum magnesium level and higher mortality across most subgroups, except in patients with high serum albumin levels.

Relationship Between Serum Magnesium and Albumin

Baseline serum magnesium and albumin levels were positively correlated in unadjusted Pearson correlation

Table 1. Baseline Characteristics of 9,359 Hemodialysis Patients According to Baseline Serum Magnesium Level

Characteristics	Total (N = 9,359)	<1.8 (n = 1,809)	1.8-<2.0 (n = 1,870)	2.0-<2.2 (n = 2,278)	2.2-<2.4 (n = 1,712)	≥2.4 (n = 1,690)
Age, y	63.3 ± 14.9	64.5 ± 14.4	64.4 ± 14.6	63.2 ± 14.9	62.8 ± 14.8	61.3 ± 15.8
Female sex	43.8	46.1	44.2	43.5	42.2	42.9
Race[a]						
White	53.4	56.3	53.0	54.8	52.2	50.1
African American	29.2	31.5	31.5	28.7	28.0	26.1
Hispanic	13.0	9.1	11.4	12.8	15.4	17.0
Asian	2.0	1.3	1.6	1.6	1.9	3.4
Other	2.4	1.7	2.5	2.1	3.3	4.0
Primary insurance						
Medicare	56.4	55.8	57.6	57.4	55.7	55.2
Medicaid	5.5	4.2	5.3	5.1	5.7	7.2
Other[a]	38.1	40.0	37.1	37.5	38.7	37.6
BMI, kg/m^2	28.4 ± 7.6	28.5 ± 7.8	28.8 ± 7.7	28.7 ± 7.7	28.3 ± 7.5	27.8 ± 7.3
Comorbid conditions						
Diabetes	59.1	54.2	60.5	58.9	61.9	60.2
Hypertension[a]	46.6	45.8	44.9	47.0	47.3	48.1
CVD	16.4	14.3	16.3	17.7	16.7	16.6
CHF	37.8	36.6	37.9	37.4	38.5	39.0
CVA	1.2	0.8	1.3	1.2	1.0	1.4
Dyslipidemia	26.1	25.5	26.6	24.0	26.5	28.4
COPD[a]	5.1	4.8	5.2	5.5	4.4	5.3
Liver disease[a]	1.5	2.1	1.7	1.5	1.3	1.2
Cancer	2.5	3.6	2.2	2.5	2.0	1.9
Baseline laboratory values						
Hb, g/dL	11.1 ± 1.2	10.8 ± 1.2	11.0 ± 1.2	11.1 ± 1.1	11.3 ± 1.2	11.4 ± 1.2
Hb < 10 g/dL, %	17.9	25.3	19.7	16.9	14.6	12.8
WBC, × 10^3/μL[a]	7.87 ± 2.90	7.91 ± 2.70	7.91 ± 2.87	7.99 ± 3.17	7.78 ± 3.05	7.84 ± 2.61
Ferritin, ng/mL[a,b]	302 [174-521]	382 [217-634]	316 [187-564]	306 [177-514]	271 [154-461]	256 [144-427]
Albumin, g/dL	3.50 ± 0.48	3.35 ± 0.52	3.42 ± 0.48	3.52 ± 0.45	3.59 ± 0.45	3.64 ± 0.44
Albumin < 3.5 g/dL, %	43.5	56.6	49.9	42.4	36.4	31.2
nPCR, g/kg/d	0.79 ± 0.22	0.72 ± 0.21	0.76 ± 0.21	0.79 ± 0.21	0.82 ± 0.22	0.86 ± 0.22
ALP, IU/L[a,b]	87 [69-116]	91 [70-120]	88 [71-118]	86 [68-115]	86 [68-115]	86 [67-111]
Cholesterol						
Total, mg/dL	150.8 ± 45.9	145.7 ± 45.3	150.5 ± 44.2	151.3 ± 47.2	151.7 ± 44.7	155.6 ± 47.1
HDL, mg/dL	40.2 ± 14.1	38.8 ± 13.7	40.0 ± 14.5	39.5 ± 13.6	40.9 ± 14.4	42.3 ± 14.5
LDL, mg/dL	78.6 ± 35.0	74.9 ± 34.3	78.5 ± 33.0	79.5 ± 35.8	79.2 ± 34.8	80.8 ± 36.5
TG, mg/dL[a]	159.0 ± 91.7	160.2 ± 92.5	161.6 ± 91.9	156.1 ± 86.7	155.8 ± 86.1	162.0 ± 102.6
Potassium, mEq/L	4.4 ± 0.5	4.3 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.5 ± 0.5	4.6 ± 0.5
Bicarbonate, mEq/L	23.7 ± 2.8	23.6 ± 2.9	23.8 ± 2.7	23.7 ± 2.6	23.7 ± 2.8	23.6 ± 2.9
SUN, mg/dL	48.1 ± 14.5	42.9 ± 13.9	45.5 ± 13.7	47.8 ± 13.5	50.5 ± 14.3	54.2 ± 14.8
Adj Ca, mg/dL	9.1 ± 0.6	8.9 ± 0.6	9.1 ± 0.5	9.1 ± 0.5	9.2 ± 0.6	9.2 ± 0.6
Phosphorus, mg/dL	4.9 ± 1.2	4.5 ± 1.1	4.7 ± 1.1	4.8 ± 1.1	5.0 ± 1.2	5.3 ± 1.2
iPTH, pg/mL[b]	303 [189-476]	306 [190-484]	313 [193-483]	302 [191-471]	299 [185-468]	296 [183-468]
iPTH < 150 pg/mL, %	16.7	16.8	15.3	16.5	16.1	18.7
Dialysis adequacy: spKt/V[a]	1.58 ± 0.33	1.48 ± 0.33	1.48 ± 0.34	1.49 ± 0.34	1.47 ± 0.32	1.48 ± 0.34

Note: Magnesium expressed in mg/dL. Unless otherwise indicated, values for categorical variables are given as percentage; values for continuous variables, as mean ± standard deviation or median [interquartile range]. Comparison across serum magnesium levels by analysis of variance or Kruskal-Wallis test for continuous variables, or χ^2 test for categorical variables. Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; cholesterol in mg/dL to mmol/L, ×0.02586; phosphorus in mg/dL to mmol/L, ×0.3229; TG in mg/dL to mmol/L, ×0.01129; SUN in mg/dL to mmol/L, ×0.357.

Abbreviations: Adj Ca, albumin-adjusted calcium; ALP, alkaline phosphatase; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; Hb, hemoglobin; HDL, high-density lipoprotein; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein; nPCR, normalized protein catabolic rate; spKt/V, single-pool Kt/V; SUN, serum urea nitrogen; TG, triglycerides; WBC, white blood cell.

[a] *P* value not significant.

[b] Skewed distribution, median [1st quartile, 3rd quartile], and Kruskal-Wallis test.

analysis. In addition, for every 1-g/dL higher albumin level, there was about a 0.2-mg/dL higher serum magnesium level ($P < 0.001$) after accounting for intrasubject correlations in repeat measurements over time. The association between serum magnesium level and mortality differed by serum albumin levels as evidenced by the subgroup analyses. The interaction between time-varying serum magnesium and serum albumin levels was close to statistical significance ($P = 0.07$) in the case-mix– and MICS-adjusted model. When examining associations of time-varying combined serum magnesium and serum albumin levels with mortality, compared with patients with low albumin (<3.5 g/dL) and high magnesium levels (≥2.0 mg/dL) as reference, patients with high albumin levels (≥3.5 g/dL) had lower mortality irrespective of magnesium levels in case-mix– and MICS-adjusted models: adjusted HRs of 0.53 (95% CI, 0.46-0.60; $P < 0.001$) and 0.53 (95% CI, 0.47-0.58; $P < 0.001$) for patients with high albumin/low magnesium and high albumin/high magnesium levels, respectively (Table 2; Fig 3). However, compared to the reference group comprised of patients with low albumin and high magnesium levels, membership in the low albumin and low magnesium group was associated with an additional 17% higher risk of mortality in case-mix– and MICS-adjusted models: adjusted HR, 1.17 (95% CI, 1.05-1.30; $P = 0.004$).

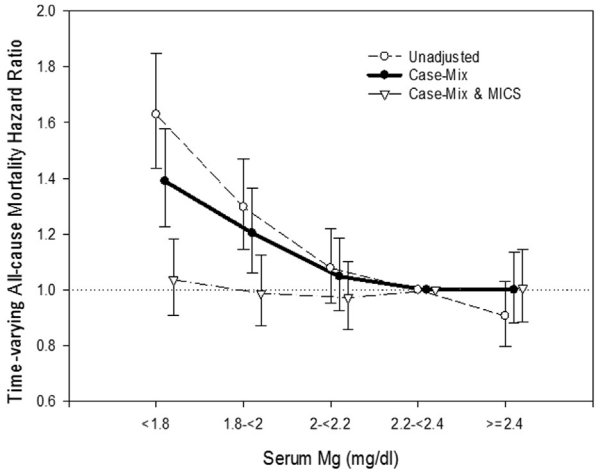

Figure 2. Time-varying all-cause mortality hazard ratios (and 95% confidence interval error bars) by quarterly serum magnesium (Mg) levels. Cox regression with 3 levels of adjustments: (1) unadjusted; (2) case-mix adjusted for age; sex; race/ethnicity (white, African American, Hispanic, Asian, or other); comorbid conditions including diabetes mellitus, hypertension, and history of cancer; and single-pool Kt/V; (3) case-mix and malnutrition-inflammation-cachexia syndrome (MICS) adjusted for all covariates in the case-mix model, plus body mass index and MICS surrogates markers (11 laboratory variables are described in text).

DISCUSSION

In this study, we found that lower serum magnesium levels were significantly associated with increased all-cause mortality in maintenance HD patients independent of sociodemographics and comorbid conditions using a time-varying model. However, we observed that the association was attenuated to the null when incrementally adjusted for inflammatory marker levels, especially with serum albumin. The association between time-varying serum magnesium levels and mortality was modified by time-varying serum albumin levels. Among hypoalbuminemic HD patients, hypomagnesemia contributed to an additional higher mortality risk.

To our knowledge, our study is the first to examine the relationship between time-varying serum magnesium levels and mortality in a large maintenance HD cohort in the United States over an extended follow-up. Our findings are consistent with previous studies of Japanese HD patients by Ishimura et al[18] that used an institutional registry and by Sakaguchi et al[19] that used national-registry HD data. However, both groups focused on baseline serum magnesium level alone, and Sakaguchi et al[19] limited their follow-up to 1 year.

Magnesium is an essential cation for vital cellular functions in the body. Under normal conditions, ~1% of total-body magnesium is found in extracellular fluid. In the general population, magnesium homeostasis is dependent on the balance between dietary intake and kidney reabsorption and excretion by the renal tubules, particularly in the thick ascending limb of the loop of Henle and distal nephrons.[1,2,22] Serum magnesium levels are tightly regulated, with a narrow normal range of 1.8 to 2.4 mg/dL. In anuric dialysis patients, there is loss of renal regulation of magnesium homeostasis, and magnesium levels are largely dependent on dietary intake and dialysate magnesium concentrations. In Japan and the United States, dialysate magnesium concentrations of 1.0 and 0.5 mEq/L, respectively, are typically used. Consequently, mean serum magnesium levels in the mentioned Japanese HD studies were much higher than in our cohort (2.77 ± 0.33[18] and 2.61 ± 0.52[19] vs 2.07 ± 0.36 mg/dL).

Despite their impaired capacity for magnesium renal excretion, low serum magnesium levels have commonly been reported in patients receiving HD or peritoneal dialysis.[23-25] Hypomagnesemia in this context has been attributed to decreased dietary intake,[26] protein-energy wasting,[18,19,27] and increased use of proton pump inhibitors.[21] In the present study, patients with lower serum magnesium levels at baseline had a much higher prevalence of malnutrition as assessed by protein-energy wasting markers, including lower serum albumin, SUN, and nPCR values. Malnutrition is common among dialysis

Table 2. Time-Varying All-Cause Mortality Hazard Ratios, by Serum Magnesium and Albumin Concentration Categories

		Unadjusted		Case-Mix		Case-Mix + MICS	
Alb,[a] g/dL	Mg,[a] mg/dL	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
<3.5	<2.0	1.28 (1.15-1.42)	<0.001	1.17 (1.05-1.30)	0.004	1.17 (1.05-1.31)	0.004
	≥2.0	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
≥3.5	<2.0	0.40 (0.35-0.45)	<0.001	0.40 (0.35-0.45)	<0.001	0.53 (0.46-0.60)	<0.001
	≥2.0	0.36 (0.33-0.40)	<0.001	0.41 (0.37-0.45)	<0.001	0.53 (0.46-0.58)	<0.001

Note: Case-mix analyses adjusted for age (years), sex (male, female), race (white, African American, Hispanic, Asian, or other), diabetes (yes, no), hypertension (yes, no), cancer (yes, no), and single-pool Kt/V. Case-Mix + MICS: case-mix + body mass index (kg/m^2), hemoglobin (g/dL), white blood cell count ($\times 10^3/\mu$L), ferritin (log ng/mL), alkaline phosphatase (log IU/L), potassium (mEq/L), Alb-adjusted calcium (mg/dL), phosphorus (mg/dL), intact parathyroid hormone (log pg/mL), Alb (g/dL), urea nitrogen (mg/dL), and nPCR (g/kg/d).

Abbreviations and definitions: Alb, albumin; CI, confidence interval; HR, all-cause mortality hazard ratio; Mg, magnesium; MICS, malnutrition-inflammation-cachexia syndrome.

[a]Values are quarterly measurements. Reference group: serum Mg ≥ 2.0 mg/dL and Alb < 3.5 g/dL.

patients.[28] Low serum albumin level, which was attributed to low protein intake and a high state of inflammation,[29] is one of the strongest predictors of all-cause and CVD mortality in dialysis patients.[30-32] In our study, serum albumin level was a dominant independent predictor of mortality after fully adjusting for all available potential comorbid and sociodemographic confounders ($P < 0.001$). After adjusting for serum albumin level, associations between magnesium level and mortality were attenuated to the null in case-mix– and MICS-adjusted survival models. However, among patients with low albumin levels, we found that low magnesium level was associated with an additional 17% higher death risk compared with those with high serum magnesium levels. These findings suggest that serum albumin level is not only a confounder but also a modifier of the association of serum magnesium level with all-cause mortality, and that additional pathogenic factors beyond protein-energy wasting may account for the link between lower serum magnesium level and death.

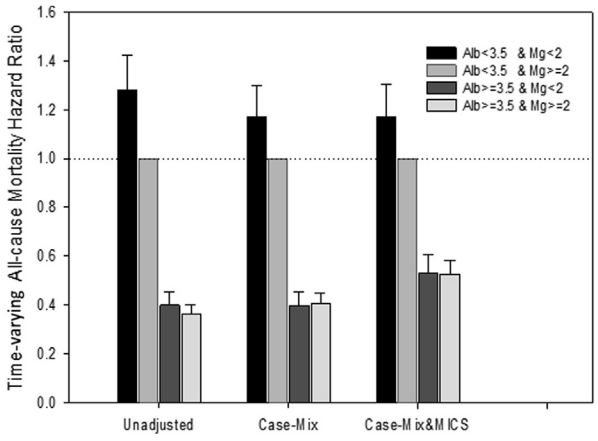

Figure 3. Time-varying all-cause mortality hazard ratios (and 95% confidence interval error bars) across 4 groups of serum magnesium (Mg; < 2 or ≥2 mg/dL) and albumin (Alb; < 3.5 or ≥3.5 g/dL) combination, with Mg ≥ 2 mg/dL and Alb < 3.5 g/dL as reference. Cox regression with 3 levels of adjustments: (1) unadjusted; (2) case-mix adjusted for age; sex; race/ethnicity (white, African American, Hispanic, Asian, or other); comorbid conditions including diabetes mellitus, hypertension, and history of cancer; and single-pool Kt/V; (3) case-mix and malnutrition-inflammation-cachexia syndrome (MICS) adjusted for all covariates in the case-mix model, plus body mass index and MICS surrogates markers (11 laboratory variables are described in text).

Hypomagnesemia may be associated with adverse outcomes by several mechanistic pathways. First, magnesium deficiency has been shown to induce endothelial dysfunction and promote atherosclerosis in both in vitro[33] and in vivo studies.[34] Second, low magnesium level promotes vascular calcification and vascular stiffness in studies of both animals[35,36] and humans,[37,38] including patients undergoing maintenance dialysis.[39,40] Third, magnesium possesses anti-inflammatory and antioxidant properties. Lower serum magnesium level is associated with increased inflammation in both nondialyzed[41,42] and dialyzed individuals.[18,19] In our study, patients with lower magnesium levels had higher ferritin and lower albumin levels, an indication of increased inflammation. Fourth, magnesium deficiency is associated with insulin resistance and metabolic syndrome,[43,44] including higher incidences of hypertension and dyslipidemia.[45,46] Furthermore, data from the general population suggest that magnesium supplementation is associated with a lower incidence of diabetes,[47] better control of diabetes[48] and hypertension,[6] and less inflammation and endothelial dysfunction.[49,50] In dialysis patients, long-term magnesium supplementation has been reported to reduce carotid intima-medial thickness.[40] However, further studies are needed to examine whether correction of hypomagnesemia by either oral supplement or higher magnesium concentration in dialysate would reduce the risk for death in patients

undergoing maintenance HD, especially those with hypoalbuminemia.

In this study, we observed an L-shaped association between serum magnesium levels and mortality, such that mortality risk reached a nadir at serum magnesium level of 2.2 mg/dL. When examined as a continuous variable, we found there was a trend toward higher death risk with levels > 3 mg/dL, although not statistically significant. Prior data suggest that hypermagnesemia may inhibit PTH secretion, leading to low bone turnover and vascular calcification[51,52] as potential risk factors for CVD and death. However, our study did not show a significant correlation between baseline serum magnesium and iPTH levels. Further studies are needed to confirm the association between moderate to severe hypermagnesemia and mortality risk, and to explore underlying mechanisms.

Strengths of our study include a large sample size of more than 9,000 maintenance HD patients, follow-up for up to 5 years, and serial magnesium measurements that enabled the time-varying survival analysis to account for short-term effects of serum magnesium levels.

There are several limitations to this present study. First, a large proportion of patients was excluded due to lack of serum magnesium measurements, increasing the risk of selection bias. However, a comparison of included versus excluded patients in the cohort showed similarity in baseline characteristics (Table S2). A comparison of patients receiving one versus more than one magnesium measurement showed that patients who only had a baseline serum magnesium measurement had shorter follow-up and were more likely to have diabetes, congestive heart failure, CVD, and dyslipidemia at baseline (Table S3). Second, because there was no information for specific cause of death in this cohort, we could not investigate the association between serum magnesium level and cardiovascular mortality. Third, ionized serum magnesium was not measured in this cohort. Approximately 30% of serum magnesium is bound to protein, primarily albumin, and therefore total measured magnesium levels may be affected by hypoalbuminemia.[53] A currently accepted equation correcting magnesium measurements for hypoalbuminemia has not been established, as it has for calcium. Additional studies that include analysis for ionized magnesium are warranted. Fourth, although we rigorously adjusted for various plausible confounders, given the observational study design, we are unable to determine whether associations were causal.

In conclusion, to our knowledge, this is the first study to examine the association between time-varying serum magnesium levels and mortality risk in a large national maintenance HD cohort. We observed that lower serum magnesium level was significantly associated with increased all-cause mortality when adjusted for comorbid and sociodemographic variables. We also found that there was a differential association between serum magnesium level and mortality across serum albumin levels such that hypomagnesemia had a particularly stronger association with death among patients with low albumin levels. Future studies are needed to determine the mechanisms underlying the association of hypomagnesemia with mortality, as well as the impact of correcting low magnesium levels with magnesium supplementation on survival among hypomagnesemic dialysis patients.

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Contributions: Study concept and design: LL, ES, CMR, KK-Z; data analyses: LL, ES, MS, CMR. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KK-Z takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Time-varying all-cause mortality HRs by Mg level across prespecified subgroups using case-mix model.

Table S2: Baseline characteristics of patients included in final cohort vs those excluded due to missing Mg.

Table S3: Baseline characteristics of patients with baseline measurement only vs baseline and another measurement.

Figure S1: Association of time-varying continuous levels of serum Mg with all-cause mortality HRs.

Figure S2: Time-varying all-cause mortality HRs across prespecified subgroups.

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REFERENCES

1. Konrad M, Schlingmann KP. Inherited disorders of renal hypomagnesaemia. *Nephrol Dial Transplant*. 2014;29(suppl 4):iv63-iv71.

2. Schlingmann KP, Konrad M, Seyberth HW. Genetics of hereditary disorders of magnesium homeostasis. *Pediatr Nephrol*. 2004;19(1):13-25.

3. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. *Clin J Am Soc Nephrol*. 2007;2(2):366-373.

4. Schulze MB, Schulz M, Heidemann C, Schienkiewitz A, Hoffmann K, Boeing H. Fiber and magnesium intake and incidence of type 2 diabetes: a prospective study and meta-analysis. *Arch Intern Med*. 2007;167(9):956-965.

5. Dickinson HO, Nicolson DJ, Campbell F, et al. Magnesium supplementation for the management of essential hypertension in adults. *Cochrane Database Syst Rev*. 2006;3:CD004640.

6. Jee SH, Miller ER 3rd, Guallar E, Singh VK, Appel LJ, Klag MJ. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. *Am J Hypertens*. 2002;15(8):691-696.

7. Peacock JM, Folsom AR, Arnett DK, Eckfeldt JH, Szklo M. Relationship of serum and dietary magnesium to incident hypertension: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol*. 1999;9(3):159-165.

8. Altura BM, Altura BT. New perspectives on the role of magnesium in the pathophysiology of the cardiovascular system. I. Clinical aspects. *Magnesium*. 1985;4(5-6):226-244.

9. Del Gobbo LC, Imamura F, Wu JH, de Oliveira Otto MC, Chiuve SE, Mozaffarian D. Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2013;98(1):160-173.

10. Larsson SC, Orsini N, Wolk A. Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. *Am J Clin Nutr*. 2012;95(2):362-366.

11. 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(3):480-490.

12. Reffelmann T, Ittermann T, Dorr M, et al. Low serum magnesium concentrations predict cardiovascular and all-cause mortality. *Atherosclerosis*. 2011;219(1):280-284.

13. Xu T, Sun Y, Xu T, Zhang Y. Magnesium intake and cardiovascular disease mortality: a meta-analysis of prospective cohort studies. *Int J Cardiol*. 2013;167(6):3044-3047.

14. Pham PC, Pham PM, Pham PT, Pham SV, Pham PA, Pham PT. The link between lower serum magnesium and kidney function in patients with diabetes mellitus type 2 deserves a closer look. *Clin Nephrol*. 2009;71(4):375-379.

15. Sakaguchi Y, Shoji T, Hayashi T, et al. Hypomagnesemia in type 2 diabetic nephropathy: a novel predictor of end-stage renal disease. *Diabetes Care*. 2012;35(7):1591-1597.

16. Tin A, Grams ME, Maruthur NM, et al. Results from the Atherosclerosis Risk in Communities study suggest that low serum magnesium is associated with incident kidney disease. *Kidney Int*. 2015;87(4):820-827.

17. Van Laecke S, Nagler EV, Verbeke F, Van Biesen W, Vanholder R. Hypomagnesemia and the risk of death and GFR decline in chronic kidney disease. *Am J Med*. 2013;126(9):825-831.

18. 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(4):237-244.

19. Sakaguchi Y, Fujii N, Shoji T, Hayashi T, Rakugi H, Isaka Y. Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis. *Kidney Int*. 2014;85(1):174-181.

20. Kuttykrishnan S, Kalantar-Zadeh K, Arah OA, et al. Predictors of treatment with dialysis modalities in observational studies for comparative effectiveness research. *Nephrol Dial Transplant*. 2015;30(7):1208-1217.

21. Dekker FW, de Mutsert R, van Dijk PC, Zoccali C, Jager KJ. Survival analysis: time-dependent effects and time-varying risk factors. *Kidney Int*. 2008;74(8):994-997.

22. Musso CG. Magnesium metabolism in health and disease. *Int Urol Nephrol*. 2009;41(2):357-362.

23. Eisenman K, Holley JL. A higher magnesium dialysate concentration treats hypomagnesemia. *Perit Dial Int*. 2005;25(6):604-605.

24. Ejaz AA, McShane AP, Gandhi VC, Leehey DJ, Ing TS. Hypomagnesemia in continuous ambulatory peritoneal dialysis patients dialyzed with a low-magnesium peritoneal dialysis solution. *Perit Dial Int*. 1995;15(1):61-64.

25. Markell MS, Altura BT, Sarn Y, et al. Deficiency of serum ionized magnesium in patients receiving hemodialysis or peritoneal dialysis. *ASAIO J*. 1993;39(3):M801-M804.

26. Wyskida K, Witkowicz J, Chudek J, Wiecek A. Daily magnesium intake and hypermagnesemia in hemodialysis patients with chronic kidney disease. *J Ren Nutr*. 2012;22(1):19-26.

27. Fein P, Suda V, Borawsky C, et al. Relationship of serum magnesium to body composition and inflammation in peritoneal dialysis patients. *Adv Perit Dial*. 2010;26:112-115.

28. Mehrotra R, Kopple JD. Nutritional management of maintenance dialysis patients: why aren't we doing better? *Ann Rev Nutr*. 2001;21:343-379.

29. Kim Y, Molnar MZ, Rattanasompattikul M, et al. Relative contributions of inflammation and inadequate protein intake to hypoalbuminemia in patients on maintenance hemodialysis. *Int Urol Nephrol*. 2013;45(1):215-227.

30. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, et al. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. *Nephrol Dial Transplant*. 2005;20(9):1880-1888.

31. Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis*. 2011;58(3):418-428.

32. Rambod M, Bross R, Zitterkoph J, et al. Association of malnutrition-inflammation score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. *Am J Kidney Dis*. 2009;53(2):298-309.

33. Maier JA. Endothelial cells and magnesium: implications in atherosclerosis. *Clin Sci*. 2012;122(9):397-407.

34. Adrian M, Chanut E, Laurant P, Gaume V, Berthelot A. A long-term moderate magnesium-deficient diet aggravates cardiovascular risks associated with aging and increases mortality in rats. *J Hypertens*. 2008;26(1):44-52.

35. Inagaki O, Syono T, Nakagawa K, Nishian Y, Takenaka Y, Takamitsu Y. Influence of magnesium deficiency on concentration of calcium in soft tissue of uremic rats. *Ren Fail*. 1996;18(6):847-854.

36. Planells E, Llopis J, Peran F, Aranda P. Changes in tissue calcium and phosphorus content and plasma concentrations of parathyroid hormone and calcitonin after long-term magnesium deficiency in rats. *J Am Coll Nutr*. 1995;14(3):292-298.

37. Hashimoto T, Hara A, Ohkubo T, et al. Serum magnesium, ambulatory blood pressure, and carotid artery alteration: the Ohasama study. *Am J Hypertens*. 2010;23(12):1292-1298.

38. Van Laecke S, Marechal C, Verbeke F, et al. The relation between hypomagnesaemia and vascular stiffness in renal transplant recipients. *Nephrol Dial Transplant*. 2011;26(7):2362-2369.

39. Meema HE, Oreopoulos DG, Rapoport A. Serum magnesium level and arterial calcification in end-stage renal disease. *Kidney Int*. 1987;32(3):388-394.

40. Turgut F, Kanbay M, Metin MR, Uz E, Akcay A, Covic A. Magnesium supplementation helps to improve carotid intima media thickness in patients on hemodialysis. *Int Urol Nephrol*. 2008;40(4):1075-1082.

41. Guerrero-Romero F, Rodriguez-Moran M. Hypomagnesemia, oxidative stress, inflammation, and metabolic syndrome. *Diabetes Metab Res Rev*. 2006;22(6):471-476.

42. King DE. Inflammation and elevation of C-reactive protein: does magnesium play a key role? *Magnes Res*. 2009;22(2):57-59.

43. Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. *Arch Biochem Biophys*. 2007;458(1):40-47.

44. Belin RJ, He K. Magnesium physiology and pathogenic mechanisms that contribute to the development of the metabolic syndrome. *Magnes Res*. 2007;20(2):107-129.

45. Corica F, Corsonello A, Ientile R, et al. Serum ionized magnesium levels in relation to metabolic syndrome in type 2 diabetic patients. *J Am Coll Nutr*. 2006;25(3):210-215.

46. Ma J, Folsom AR, Melnick SL, et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. *J Clin Epidemiol*. 1995;48(7):927-940.

47. Larsson SC, Wolk A. Magnesium intake and risk of type 2 diabetes: a meta-analysis. *J Intern Med*. 2007;262(2):208-214.

48. Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. *Diabet Med*. 2006;23(10):1050-1056.

49. King DE, Mainous AG 3rd, Geesey ME, Woolson RF. Dietary magnesium and C-reactive protein levels. *J Am Coll Nutr*. 2005;24(3):166-171.

50. Song Y, Li TY, van Dam RM, Manson JE, Hu FB. Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women. *Am J Clin Nutr*. 2007;85(4):1068-1074.

51. Courivaud C, Davenport A. Magnesium and the risk of all-cause and cardiac mortality in hemodialysis patients: agent provocateur or innocent bystander? *Kidney Int*. 2014;85(1):17-20.

52. Naves-Diaz M, Passlick-Deetjen J, Guinsburg A, et al. Calcium, phosphorus, PTH and death rates in a large sample of dialysis patients from Latin America. The CORES Study. *Nephrol Dial Transplant*. 2011;26(6):1938-1947.

53. Kroll MH, Elin RJ. Relationships between magnesium and protein concentrations in serum. *Clin Chem*. 1985;31(2):244-246.