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Original Investigation

Serum Magnesium Levels and Hospitalization and Mortality in Incident Peritoneal Dialysis Patients: A Cohort Study

Xiao Yang, MD, PhD,[1] Melissa Soohoo, MPH,[2] Elani Streja, PhD,[2] Matthew B. Rivara, MD,[3] Yoshitsugu Obi, MD, PhD,[2] Scott V. Adams, PhD,[3] Kamyar Kalantar-Zadeh, MD, PhD,[2] and Rajnish Mehrotra, MD, MS[3]

Background: Prior studies have shown the association of low serum magnesium levels with adverse health outcomes in patients undergoing hemodialysis. There is a paucity of such studies in patients undergoing peritoneal dialysis (PD).

Study Design: Cohort study.

Setting & Participants: 10,692 patients treated with PD from January 1, 2007, through December 31, 2011, in facilities operated by a single large dialysis organization in the United States.

Predictor: Baseline serum magnesium levels, examined as 5 categories (<1.8, 1.8-<2.0, 2.0-<2.2 [reference], 2.2-<2.4, and ≥2.4 mg/dL).

Outcomes: Time to first hospitalization and time to death using competing-risks regression models.

Results: The distribution of baseline serum magnesium levels in the cohort was <1.8 mg/dL, 1,928 (18%); 1.8 to <2.0 mg/dL, 2,204 (21%); 2.0 to <2.2 mg/dL, 2,765 (26%); 2.2 to <2.4 mg/dL, 1,765 (16%); and ≥2.4 mg/dL, 2,030 (19%). Of 10,692 patients, 6,465 (60%) were hospitalized at least once and 1,392 (13%) died during follow-up (median, 13; IQR, 7-23 months). Baseline serum magnesium level < 1.8 mg/dL was associated with higher risk for hospitalization and all-cause mortality after adjustment for demographic and clinical characteristics (adjusted HRs of 1.23 [95% CI, 1.14-1.33] and 1.21 [95% CI, 1.03-1.42], respectively). The higher risk for hospitalization persisted upon adjustment for laboratory variables, whereas that for all-cause mortality was attenuated to a nonsignificant level. The greatest risk for hospitalization was in patients with low serum albumin levels (<3.5 g/dL; *P* for interaction < 0.001).

Limitations: Possibility of residual confounding by unmeasured variables cannot be excluded.

Conclusions: Lower serum magnesium levels may be associated with higher risk for hospitalization in incident PD patients, particularly those with hypoalbuminemia. Additional studies are needed to confirm these findings and investigate whether correction of hypomagnesemia reduces these risks.

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INDEX WORDS: Magnesium; hypomagnesemia; end-stage renal disease (ESRD); peritoneal dialysis (PD); incident PD patients; hospitalization; all-cause mortality.

Magnesium, the fourth most abundant cation in the body, is the second most plentiful intracellular cation (after potassium). As much as 70% of serum magnesium is in the free ionized form, which has a crucial function in maintaining internal homeostasis by actions in the endocrine, musculoskeletal, nervous, and cellular messenger systems.[1] The reference range for total serum magnesium levels in adults is 1.7 to 2.4 mg/dL (0.7-1.0 mmol/L or 1.4-2.0 mEq/L).[2,3] In patients undergoing maintenance dialysis, magnesium homeostasis depends on dietary intake, intestinal absorption, and removal by kidneys and with dialysis. In turn, serum magnesium levels can be influenced by significant changes in dietary intake; residual kidney function; dialysis dose; losses through the gastrointestinal tract, kidneys, or with dialysis; or redistribution from the extracellular to intracellular space.

The relatively high prevalence of abnormal serum magnesium levels in patients with kidney disease has long been known, but until recently, little has been reported regarding adverse effects on health outcomes.[3] Studies have shown a strong inverse association of serum magnesium level with insulin resistance, new-onset diabetes mellitus, oxidative stress, endothelial dysfunction, hypertension, atherosclerosis, and systemic inflammation.[4] Observational studies have also shown a significant association between hypomagnesemia and higher all-cause mortality in patients with chronic kidney disease not undergoing dialysis or in those with end-stage renal disease (ESRD) treated with maintenance hemodialysis.[5-7]

From the [1]Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [2]University of California Irvine, Orange, CA; and [3]Kidney Research Institute and Harborview Medical Center, Division of Nephrology, University of Washington, Seattle, WA.

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Address correspondence to Rajnish Mehrotra, MD, MS, 325 Ninth Ave, Box 359606, Seattle, WA 98104. E-mail: rmehrotr@uw.edu

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Commercially available peritoneal dialysate contains 0.25 mmol/L of magnesium, resulting in daily net magnesium removal, and higher ultrafiltration with hypertonic solutions further increases magnesium losses into the dialysate.[8-10] However, to date, data for the effect of serum magnesium levels on health outcomes of patients undergoing peritoneal dialysis (PD) are sparse. We performed this study to test the hypothesis that in patients with ESRD undergoing PD, low serum magnesium levels are associated with higher risk for hospitalization and all-cause mortality.

METHODS

Study Population and Data Source

The study cohort comprised patients with ESRD who initiated treatment with PD from January 1, 2007, through December 31, 2011, and received care in one of the facilities operated by DaVita Inc, a large dialysis organization in the United States. Included patients were 18 years or older, underwent PD for at least 60 days, and had at least one serum magnesium measurement during the first 91-day period of treatment with PD. Patients were followed up for up to 5 years through December 2011 (median follow-up, 13 [IQR, 7-23] months). Institutional review boards at the University of Washington and University of California Irvine approved the study and waived the requirement for informed consent because only deidentified data were received.

All data were obtained from electronic medical records of the dialysis facilities. Age was estimated by using date of birth and date of first dialysis treatment, and 5 race/ethnicity categories were used for analyses (white, black, Hispanic, Asian, and other). Data for comorbid conditions were obtained from electronic medical records of the dialysis organization as provided by the treating health care providers and included diabetes mellitus, hypertension, congestive heart failure, atherosclerotic heart disease, and other cardiovascular diseases. Blood samples were drawn in dialysis facilities and shipped to a central laboratory (DaVita Laboratory, Deland, FL) within 24 hours, where measurements were made using automated and standardized methods. All clinical and laboratory data and doses of parenteral medications were summarized for the first 91-day period of PD.

The exposure of interest was baseline serum magnesium level, defined as an average of all measurements in the first 91 days of PD therapy. Patients were grouped into 5 magnesium categories ($<$1.8, 1.8-$<$2.0, 2.0-$<$2.2 [reference], 2.2-$<$2.4, and $\geq$2.4 mg/dL), chosen with recognition of a reference range of 1.8 to 2.4 mg/dL and a 0.2-mg/dL incremental change within this range.[6]

Outcomes

The 2 coprimary outcomes were time to (1) first hospitalization and (2) death from any cause. Data for each of these 2 outcomes were obtained from electronic medical records of the dialysis organization. The follow-up period comprised the interval from the date of the first PD treatment through the occurrence of one of the following events: a primary outcome (death or hospitalization for the respective analyses), kidney transplantation, transfer to another dialysis modality or a facility operated by another dialysis provider, or end of administrative follow-up. Patients were considered to have transferred to another dialysis modality only if they were treated with an alternative therapy for 60 continuous days; as such, all events (death or hospitalization) within 60 days of transfer were attributed to the PD.

Statistical Analyses

Data are presented as mean $\pm$ standard deviation, median with IQR, or proportions, when appropriate. Data for sex, race/ethnicity, geographic location, serum albumin, phosphorus, calcium, potassium, and bicarbonate were missing for $<$1%; serum iron saturation, ferritin, and parathyroid hormone values, for 1% to 5%; weekly Kt/V and residual kidney function, for 12%; and 4-hour dialysate to plasma creatinine ratio, for 27%. Five sets of imputations were done using a joint multivariable multiple imputation model to account for missing laboratory variables, including exposure, covariates (age, sex, race/ethnicity, primary medical insurance, cause of ESRD, history of transplantation, interval from initiation of dialysis therapy to initiation of PD therapy, diabetes, hypertension, atherosclerotic heart disease, congestive heart failure, other cardiovascular disease, blood hemoglobin level, serum albumin level, calcium level, phosphorus level, parathyroid hormone level, iron saturation, ferritin level, bicarbonate level, magnesium level, total weekly Kt/V, residual kidney function, and 4-hour dialysate to plasma creatinine ratio), 4 interaction terms selected a priori (serum albumin, phosphorus, and parathyroid hormone levels and residual kidney function with outcome), an indicator for the outcome of interest (present or not), and the Nelson-Aalen estimator.

Two separate time-to-event analyses were undertaken using competing-risks regression models to determine the association of baseline serum magnesium levels with first hospitalization and all-cause mortality.[11] For the analysis of all-cause mortality, competing events were kidney transplantation and transfer to in-center hemodialysis therapy. For analysis of hospitalization, competing events were all-cause mortality, kidney transplantation, and transfer to in-center hemodialysis therapy. Subhazard ratios (HRs) were obtained for the outcome of interest and combined using Rubin's rules.

Data were analyzed using the following levels of adjustment: (1) unadjusted; (2) case mix-adjusted for demographic and clinical characteristics, including age, sex, race/ethnicity, primary insurance, geographic location of dialysis facility (Northeast, South, Midwest, or West), year of incidence, cause of ESRD, prior kidney transplantation, comorbid conditions (diabetes mellitus, hypertension, congestive heart failure, atherosclerotic heart disease, and other cardiovascular diseases), and interval from initiation of dialysis therapy to initiation of PD therapy; (3) case-mix plus laboratory variables that included all mentioned covariates and values for hemoglobin, serum albumin, uncorrected calcium, phosphorus, intact parathyroid hormone, ferritin, iron saturation, bicarbonate, potassium, total weekly Kt/V, residual kidney function, 4-hour dialysate to plasma creatinine ratio from the peritoneal equilibration test, and treatment with automated PD within the first 91-day period of PD therapy.

Two different sensitivity analyses were done. First, associations of baseline serum magnesium level as a continuous variable were examined with HRs expressed for risk associated with every 0.2-mg/dL lower serum levels. Second, analyses were repeated by imputing the value for serum magnesium for 7,152 patients with missing values for the first 91 days of initiation of PD therapy.

Effect modification of the association of serum magnesium level ($<$1.8 compared to $\geq$1.8 mg/dL) with time to first hospitalization and all-cause mortality was examined for 4 a priori covariates (serum albumin $<$ 3.5 and $\geq$3.5 g/dL, parathyroid hormone $<$ 300 and $\geq$300 pg/mL, phosphorus $<$ 5 and $\geq$5 mg/dL, and residual kidney function $<$ 55 and $\geq$55 L/wk/1.73 m^2). Subgroup analyses were performed for covariates with P for the interaction term $<$ 0.05. The same demographic, clinical, and laboratory covariates were used for these subgroup analyses as mentioned, except the variable used to stratify the population for the particular analyses.

All analyses were performed using SAS, version 9.4 (SAS Institute Inc) and Stata, version 13.1 (StataCorp LP).