AJKD

Original Investigation

Serum Magnesium and Mortality in Hemodialysis Patients in the United States: A Cohort Study

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Background: Low serum magnesium levels in patients with kidney disease have been linked to increased mortality. This study investigated whether similar associations existed in maintenance hemodialysis (HD) patients.

Study Design: Cohort study.

Setting & Participants: All Fresenius Medical Care North America in-center HD patients with available serum magnesium measurements were studied. The initial exploratory study in 21,534 HD patients evaluated associations among serum magnesium level, dialysate magnesium concentration, and mortality from April 2007 through June 2008. The follow-up study in 27,544 HD patients evaluated associations between serum magnesium levels and mortality over 1 year (January through December 2008).

Predictors: The primary predictor was serum magnesium level, with adjustment for case-mix (age, sex, race, diabetes, and dialysis vintage and additionally for follow-up study: body surface area and vascular access) and laboratory variables (albumin, hemoglobin, phosphorus, equilibrated Kt/V, potassium, calcium, and intact parathyroid hormone values).

Outcome: Primary outcome variable was 1-year mortality risk, evaluated using Cox proportional hazards models.

Results: Among 21,534 HD patients in the exploratory study, there were 3,682 deaths. Higher dialysate magnesium level was associated with higher serum magnesium level ($R = 0.22$; $P < 0.001$). Patients with the lowest serum magnesium levels (<1.30 mEq/L) were at highest risk for death (HR, 1.63; 95% CI, 1.30-1.96; reference serum magnesium, 1.60-<1.90 mEq/L). Among 27,544 HD patients in the follow-up study, there were 4,531 deaths. In Cox proportional hazards models, there was a linear decline in death risk from the lowest to the highest serum magnesium category, with the best survival at serum magnesium levels ≥ 2.50 mEq/L (HR, 0.68; 95% CI, 0.56-0.82). However, risk estimates were attenuated with case-mix and lab adjustment. This pattern was consistent within diabetes subgroups and for cardiovascular or noncardiovascular causes of death.

Limitations: Observational study with cross-sectional serum magnesium measurements and no information for oral magnesium intake.

Conclusions: Elevated serum magnesium levels > 2.10 mEq/L were associated with better survival than low serum magnesium levels < 1.30 mEq/L in HD patients. Prospective studies may determine whether manipulation of low serum magnesium levels affects survival.

Am J Kidney Dis. ■(■):■-■.

INDEX WORDS: Serum magnesium concentration; dialysate magnesium prescription; hypomagnesemia; hypermagnesemia; hemodialysis (HD); end-stage renal disease (ESRD); mortality risk.

Based on observational studies in hemodialysis (HD) patients, it has been suggested that low serum magnesium levels are associated with cardiovascular (CV) morbidity (eg, mitral annular calcification, peripheral arterial calcification, and increased carotid intima-media thickness [cIMT]).[1-3] Moreover, magnesium may have a myocardial protective role.[4] In 1 Portuguese and 2 Japanese studies, higher mortality rates were observed in maintenance HD patients with low serum magnesium levels.[5-7] The current study investigated whether similar associations existed in a large national US cohort.

This observational study of patients from Fresenius Medical Care North America (FMCNA) outpatient dialysis facilities was conducted in 2 stages. The first stage was a retrospective exploratory evaluation into the distribution of serum magnesium levels and dialysate magnesium concentrations in a convenience sample of period-prevalent HD patients. We evaluated both the correlation between serum magnesium level and dialysate magnesium prescription and the potential association with 1-year mortality risk, with further consideration for serum potassium, calcium, and intact parathyroid hormone (iPTH) levels.

The second stage involved a follow-up study with a hypothesis that, unlike borderline hypermagnesemia, extremely high serum magnesium levels may associate

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Received March 6, 2015. Accepted in revised form June 4, 2015.

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0272-6386

http://dx.doi.org/10.1053/j.ajkd.2015.06.014

with higher death risk. This study was nested within a prospective observational evaluation of potentially actionable factors associated with mortality risk in a larger prevalent cohort of FMCNA HD patients.[8] This stage investigated a wider range of serum magnesium levels, with greater focus on serum magnesium levels above the normal range because elevated levels are not uncommon in HD patients. Furthermore, we determined whether serum magnesium levels have similar associations in patients with diabetes and those without and evaluated non-CV causes of death and CV death, as well as the subset of sudden cardiac death within all CV deaths, each investigated as distinct outcomes among patients who had a documented cause of death.

METHODS

Initial Exploratory Study

The source population (n = 83,744) included all FMCNA in-center HD patients who were actively treated as of July 1, 2007, and with serum magnesium results (n = 21,534) for the prior 3-month baseline period (April 1 to June 30, 2007) from all facilities reporting data to the Knowledge Center data warehouse.[9] Patients were followed up for 1 year (up to June 30, 2008) with the combination of death or withdrawal from dialysis therapy leading to death as the primary outcome.

Almost all (95%) patients were consistently treated by thrice-weekly HD, with the rest having additional fourth treatments intermittently for fluid overload and other indications and very few patients treated 2 times weekly, with proportions comparable within serum magnesium subgroups. Patients were treated almost exclusively using Fresenius polysulfone dialyzers. Median treatment time was 225 (interquartile range, 210-240) minutes and was similarly distributed within serum magnesium subgroups. No hemodiafiltration was performed.

Case-mix variables at baseline included patient age, sex, race, with or without diabetes mellitus, and duration of dialysis therapy prior to study entry (dialysis vintage). Prescribed dialysate magnesium concentration was obtained from physician orders. If patients had their dialysate magnesium concentration changed during the baseline period, a weighted mean of different dialysate magnesium prescriptions was calculated in proportion to the time that each order was in effect. Prescribed dialysate magnesium concentration was stratified into 5 categories: <0.75, 0.75 to 0.99, exactly 1.0 (reference), 1.01 to 1.49, and ≥1.50 mEq/L. In general, dialysate magnesium prescriptions were not based on an individual level, but determined at a facility level. For models involving dialysate magnesium concentration, an additional model was constructed that included an adjustment for serum magnesium level only, with serum magnesium input as a continuous variable. Dialysate prescriptions for calcium, sodium, and bicarbonate/acetate concentrations were not systematically linked to dialysate magnesium concentrations.

All laboratory examinations were performed by a single laboratory (Spectra Laboratories). A photometric color test for quantitative magnesium determination (Beckman Coulter; Olympus America, Inc) was used, which has a normal range of 1.30 to 2.10 mEq/L and coefficient of variation of about 1.3% to 1.6% (though the latter has been observed to be as low as ~1.2%). The test is linear within a concentration range of 0.5 to 8.0 mEq/L for serum and plasma samples. Change in serum magnesium concentrations over about 6 months was analyzed and stability was confirmed in a subset of more than 16,768 study patients (~78%) with available repeat test results (Table S1, available as online supplementary material). In addition to recording the mean value of all available serum magnesium levels and equilibrated Kt/V for patients during the baseline period, mean predialysis values were obtained for albumin, hemoglobin, phosphorus, potassium, calcium, and iPTH.

Correlation coefficients were obtained between serum magnesium and dialysate magnesium values, as well as to each of 3 laboratory variables selected a priori: potassium, calcium, and iPTH. Cox proportional hazard models produced hazard ratios (HRs) for mortality from unadjusted, case-mix–adjusted, and case-mix plus laboratory variable–adjusted models (ie, albumin, hemoglobin, phosphorus, equilibrated Kt/V, potassium, calcium, and iPTH), with higher serum magnesium level associating with lower mortality risk. The proportionality assumption was tested using visual inspection of survival curves and the SAS Proc PHREG Proportionality Test; all variables satisfied proportionality assumptions with the exception of albumin and hemoglobin, but this was mitigated by the large sample size.

With >80% of patients in the study cohort having baseline serum magnesium levels within the normal range (1.30-2.10 mEq/L),[10] categorization into equal patient numbers in the form of quartiles and sextiles would have not allowed for differentiating clinically meaningful serum magnesium levels. Thus, the categories chosen were based on clinical criteria: hypomagnesemia: magnesium < 1.30 mEq/L; low, mid, and high-normal magnesium levels: 1.30 to <1.60, 1.60 to <1.90, and 1.90 to 2.10 mEq/L, respectively; and hypermagnesemia: >2.10 mEq/L. The mid-normal range (1.60-<1.90 mEq/L) was used as the reference group.

Follow-up Analyses

Follow-up analyses were conducted according to the same methodology, with the following exceptions. The baseline period required serum magnesium levels obtained October 1 through December 31, 2007. Similarly, mortality was tracked for 1 year (up to December 31, 2008). Both CV disease (CVD)-related death (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes: 390.xx-447.xx) and the subset with sudden death (*ICD-9* codes: 427, 427.4x-427.5x, 427.8x, and 427.9) were identified. Case-mix variables included all prior exploratory variables with the addition of body surface area and vascular access type. Laboratory data were the same except for the omission of potassium level. This analysis of higher serum magnesium level categories was made possible by the larger sample size of the analytical file, which was primarily intended for another study designed to determine the top 5 potentially actionable variables associated with hospitalization and death.[8]

Survival analyses were conducted as described in a previous section. A stratified analysis was also performed to elicit potential effect modification by diabetes. Cox models were similarly constructed using the subgroup of patients with cause-of-death data to determine the association between serum magnesium level and non-CV deaths, serum magnesium level and CV deaths, and (separately) serum magnesium level and the smaller group with sudden cardiac deaths. The follow-up cohort maintained the first 4 categories and the reference category, but further broke down the hypermagnesemic categories into 3 more: >2.10 to <2.30, 2.30 to <2.50, and ≥2.50 mEq/L. Therefore, the exploratory and follow-up cohorts had differing categories of serum magnesium. Post hoc, follow-up for all-cause mortality was extended to 3 years to determine whether the findings were maintained (Fig S1). All statistical analyses were performed using SAS, version 9.2/9.3 (SAS Institute Inc).

RESULTS

Baseline Demographic Characteristics of Both Studies

The initial exploratory study cohort represented 21,534 of 83,744 (26%) of all FMCNA maintenance