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# Contribution of dysregulated serum magnesium to mortality in hemodialysis patients with secondary hyperparathyroidism: a 3-year cohort study

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## Abstract

**Background:** The extent of contribution of disturbed magnesium balance to mortality remains unclear among hemodialysis patients.

**Methods:** This was a cohort study involving 3276 patients on maintenance hemodialysis at 86 facilities in Japan from 2008 to 2010 who had secondary hyperparathyroidism (SHPT). Baseline serum magnesium (sMg) values were categorized into quintiles (≤2.3, >2.3–2.5, >2.5–2.7, >2.7–3.0 and >3.0 mg/dL), and the middle quintile was set as the reference. Outcome was all-cause death. Independent contribution to all-cause death was assessed via Cox regression to generate population-attributable fractions (PAFs).

**Results:** A total of 2165 patients from 68 facilities were analyzed. The lowest quintile of sMg was positively associated with lower serum potassium and albumin levels, higher C-reactive protein (CRP) levels and prevalence of atrial fibrillation and cerebrovascular disease than the other quintiles. The highest sMg quintile was positively associated with higher potassium levels, and negatively associated with lower serum albumin levels and higher intact parathyroid hormone and CRP levels and prevalence of cerebrovascular disease than the other quintiles. During a median follow-up of 3 years, the lowest and the second lowest quintiles of sMg were associated with all-cause death [adjusted hazard ratio (HR) 1.737, 95% confidence interval (95% CI) 1.200–2.512 and HR 1.675, 95% CI 1.254–2.238, respectively). Point estimates of adjusted HRs of the highest and the second highest sMg quintiles were higher than those of the middle quintile for all-cause death. Adjusted PAFs of lower sMg and of higher and lower sMg for all-cause death were 24.0% (95% CI 13.0–35.0%) and 30.7% (95% CI 14.5–46.8%), respectively.

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**Conclusion:** In hemodialysis patients with SHPT, dysregulated sMg is an important contributor to all-cause death. Further studies are warranted to examine whether or not correction of sMg improves survival.

**Key words:** cohort study, magnesium, mortality, population-attributable fraction

## Introduction

Magnesium (Mg) is an essential element in a number of biological processes [1, 2]; however, in patients with chronic kidney disease who require dialysis, balance in serum and total body Mg can be easily disturbed by poor dietary intake [3] or impaired regulation of Mg in the kidney, leading to a number of adverse conditions. For example, low levels of serum magnesium (sMg) have been shown to be associated with inflammation [4], vascular calcification [5] and cardiovascular disease [6], whereas high sMg has been associated with muscle weakness and cardiac rhythm abnormalities [7]. While these findings implicate dysregulated sMg in risk of death from a number of causes, previous studies investigating the effects of disturbed sMg on mortality among dialysis patients have failed to produce definitive results.

One hospital cohort study suggested that low sMg levels (<2.77 mg/dL) were associated with non-cardiovascular mortality but not with cardiovascular mortality [8]. However, as low sMg levels are associated with poor health conditions, such as inflammation and cardiovascular comorbidities [4, 6], which were not adjusted for, the association presented in this previous study might be confounded. A recently published nationwide cohort study suggested that relatively low (<2.7 mg/dL) and relatively high (>3.1 mg/dL) sMg levels are associated with all-cause mortality and cardiovascular mortality among hemodialysis patients [9]. However, as its follow-up period was limited to only 1 year, that relationship might have been susceptible to reverse causality; longer follow-up is therefore necessary to confirm the cause-and-effect relationship between dysregulated sMg levels and future cardiovascular disease. Of further note, these previous studies also failed to examine the extent to which disturbed sMg levels contribute to all-cause mortality and cardiovascular mortality. Clarification of this potential influence of disturbed sMg levels on deaths may help health policy makers and physicians decide how much attention to grant sMg levels in efforts to prevent death among dialysis patients.

Here, we investigated the relationship between dysregulated sMg and all-cause death over a 3-year period using the cohort study 'Mineral and Bone Disorders Outcomes Study for Japanese CKD Stage 5D Patients' (MBD-5D). We also assessed the extent of contribution of dysregulated sMg to deaths in this population.

## Materials and methods

The MBD-5D was a 3-year prospective cohort study. The study was approved by a central ethics committee (Kobe University's School of Medicine), and its design has been reported previously [10].

### Study population

The target population was hemodialysis patients with secondary hyperparathyroidism (SHPT). Eligibility criteria were those receiving hemodialysis at a participating facility as of 1 January 2008 and who either had intact parathyroid hormone (iPTH) concentration ≥180 pg/mL or were receiving an intravenous vitamin D receptor activator (VDRA) (calcitriol or maxacalcitol) or oral active VDRA (falecalcitriol, the only oral VDRA approved in Japan for SHPT treatment). Patients on dialysis for <3 months were excluded. From 86 facilities across Japan, 8229 patients were registered. The patients were followed up until January 2011. The MBD-5D study had two cohorts: the 'whole cohort' and the 'subcohort'. The whole cohort comprised all registrants ($n = 8229$), and the subcohort ($n = 3276$) was chosen from the whole cohort by random sampling to obtain detailed data. In the present study, we chose subcohort data with measured sMg and covariate values to estimate population-attributable fractions (PAFs).

### Outcomes, exposures and covariates

The primary outcome in this study was all-cause death, and the exposure of interest was sMg measured at baseline. To examine long-term effects of exposure to unbalanced Mg levels on death, we studied sMg as a fixed risk factor at baseline [11]. In primary analyses, sMg was categorized into quintiles (≤2.3, >2.3–2.5, >2.5–2.7, >2.7–3.0 and >3.0 mg/dL), with the middle quintiles used as reference. This categorization was defined *a priori*, as five groups is the required minimum to adequately analyze a non-linear relationship should both lower and higher sMg cause adverse events from a pathophysiological perspective [12].

Covariates used in the analyses included baseline patient characteristics [age, gender, vintage, primary renal disease, body mass index, cardiovascular diseases (coronary artery disease, atrial fibrillation, other arrhythmia, pacemaker, congestive heart failure, cerebrovascular disease, peripheral vascular disease, aortic disease and others), lung disease, liver disease, malignancy and history of parathyroidectomy] and levels of mineral and bone disorders (MBD)-related serum markers (calcium, phosphorus and iPTH) and other potential confounders [Kt/V, albumin, hemoglobin, serum potassium, serum iron, serum ferritin and serum C-reactive protein (CRP)].

Baseline data were collected at the time of enrollment for the subcohort patients and retrospectively for cases outside the subcohort. Serum whole parathyroid hormone (PTH) levels measured using a third-generation PTH assay were converted to iPTH levels using the following equation [13]:

$$\text{iPTH} = \text{whole PTH} \times 1.7$$

Serum calcium levels were corrected for albumin concentration using the modified Payne method, which is commonly used in Japanese dialysis settings [13].

### Statistical analysis

All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC, USA) and Stata version 12.1 (Stata Corp., College Station, TX, USA). Baseline characteristics were described for subcohort patients and stratified based on sMg quintile. Distribution of sMg among subcohort patients was displayed using a histogram (see Figure 1).

Associations between baseline characteristics and categorization to the lowest or the highest sMg quintile among subcohort patients were analyzed using generalized estimating equations with robust variance to account for facility clustering effects [14]. Crude mortality rate was estimated using the subcohort

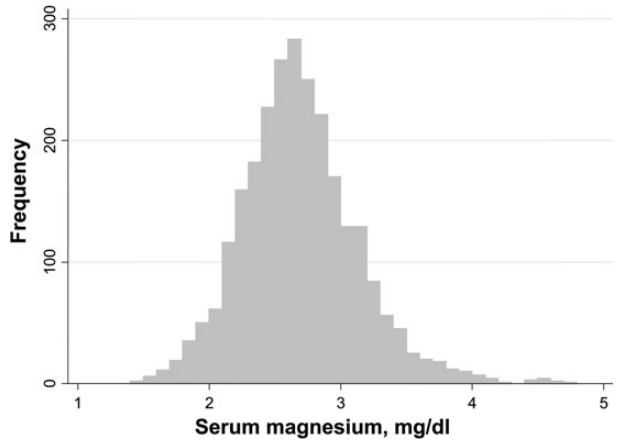


**Fig. 1.** Distribution of baseline sMg.

patients, and the crude rates for mortality stratified by sMg quintiles were calculated.

Associations between sMg and all-cause death were analyzed using Cox models. To estimate adjusted hazard ratios (HRs), all of the covariates described above were forced into multivariate analyses. Facility clustering effects of these analyses were addressed using a robust variance estimator [15].

To estimate the potential contribution of dysregulated sMg to all-cause death, we computed PAFs. In general, the PAF is the fraction of outcomes that would be prevented if a certain exposure were removed. For this study, the outcome used was all-cause death, and the main exposure was sMg. Of note, one assumption with this computation is the presence of an unconfounded, causal relationship between exposure and the outcome [16]. PAFs were computed using Cox models and the user-written command 'punafcc' in Stata version 12.1 [17, 18].

Data missing at baseline were replaced by their mean or median values or by predicted values from linear regression models. We felt comfortable using these simple imputation methods because very few MBD-related markers of interest had missing values (<0.2% at baseline, except for 6% of iPTH values). For serum levels of iron, ferritin and CRP, ~20% of values were missing. These values were imputed using a multiple imputation using the aregImpute function from the Hmisc library in R, using additive regression, bootstrapping and predictive mean matching [19].

We also conducted several sensitivity analyses. First, to assess the shape of sMg and mortality associations, we evaluated the association of sMg level with all-cause death using restricted cubic splines with knots at the 10th, 50th and 90th percentiles of sMg. We then repeated Cox models with more covariates (VDRA and phosphate binder use in addition to serum MBD markers, in accordance with another study [9]; cinacalcet was not marketed at baseline, and magnesium-containing phosphate binder is unavailable in Japan). We then examined the association between sMg quintile and death from cardiovascular disease. Finally, we conducted *ad hoc* analyses to estimate PAFs of lower sMg levels for all-cause deaths in two ways: (i) a PAF with assumption that the lower two sMg quintiles (≤2.3 and >2.3–2.5 mg/dL) would have been corrected to the middle quintile (>2.5–2.7 mg/dL), and (ii) a PAF with assumption that the combined category of the lower two sMg quintiles (≤2.5 mg/dL) would have been corrected to the combined category of the higher three sMg quintiles (>2.5 mg/dL). $P < 0.05$ was considered statistically significant.

## Results

Of the 3276 patients in the subcohort, 2185 from 68 facilities had baseline sMg values and were therefore entered into primary analyses (66.7% of the subcohort). The histogram for sMg showed a median value of 2.6 mg/dL (1st–99th percentiles, 1.7–4.4 mg/dL; Figure 1).

Baseline characteristics of the subcohort patients are presented in Table 1. Mean patient age was 61.7 years, and median dialysis vintage was 8.3 years. The lower the sMg quintile, the older patients tended to be, with shorter duration of dialysis; higher likelihood of diabetic nephropathy, atrial fibrillation, congestive heart failure and cerebrovascular disease; and greater likelihood of having low serum phosphorus, potassium and albumin levels and high serum ferritin and CRP levels. Baseline characteristics were similar between the subcohort patients with and without missing sMg values (Supplementary data, Table S1) except for other arrhythmia, peripheral vascular disease, and serum iron and ferritin levels. As a group, age, vintage, body mass index, sMg levels, and most comorbidities and laboratory values were similar among subcohort patients with and without missing sMg values.

Correlations between baseline characteristics and placement in the lowest or the highest sMg quintiles are presented in Table 2. Older age, atrial fibrillation, cerebrovascular disease, parathyroidectomy and lower potassium, albumin and phosphorus levels and higher ferritin and CRP levels were positively associated with being in the lowest sMg quintile, while longer dialysis vintage was negatively associated. In contrast, longer dialysis vintage and higher hemoglobin and potassium levels were positively associated with being in the highest sMg quintile, while older age, cerebrovascular disease and lower serum albumin levels and higher serum iPTH and CRP levels were negatively associated with being in this sMg quintile.

Over a median 3 years of follow-up, 334 deaths were observed, giving an incidence rate (IR) of 5.60 per 100 patient-years for all-cause mortality (Table 3).

Lower sMg quintiles corresponded to higher IRs for all-cause mortality were higher (Table 3). In covariate-adjusted Cox models, the lowest and the second lowest sMg quintiles were more closely associated with all-cause death than the middle quintile [HR 1.737, 95% confidence interval (95% CI) 1.200–2.512 and HR 1.675, 95% CI 1.254–2.238, respectively]. However, in contrast to findings for crude IRs, adjusted HRs of the highest and the second highest sMg quintiles were higher for all-cause death than the middle quintile, albeit not to a statistically significant degree (HR 1.330, 95% CI 0.882–2.003 and HR 1.334, 95% CI 0.901–1.974, respectively). Consistent with these findings, restricted cubic spline analysis showed the shape of the continuous association between sMg and all-cause death to be U shaped (P for non-linearity: 0.017) (Figure 2).

PAF analyses indicated that if both lower (the first and the second quintiles) and higher (the fourth and the fifth quintiles) sMg categories had been corrected to the middle quintile, a sizeable proportion of all-cause death could potentially have been prevented [30.8% (95% CI 14.8–46.8%)] (Table 4). *Ad hoc* analyses indicated that the contribution of lower sMg levels to deaths was modest: if lower sMg categories (the first and the second quintiles) could have been corrected to the middle quintile (with all other parameters remaining the same), the estimated PAF was 24.2% (95% CI 13.3–35.1%) (Table 4). Additional *ad hoc* analysis showed that if the combined category of the lower two sMg quintiles (≤2.5 mg/dL) could have been corrected to the combined category of the higher three sMg quintiles (>2.5 mg/dL), the

**Table 1.** Baseline characteristics of subcohort patients by sMg categories and overall[a]

| Characteristics | Baseline serum magnesium, mg/dL | | | | | Total |
|---|---|---|---|---|---|---|
| | ≤2.3 | >2.3–2.5 | >2.5–2.7 | >2.7–3.0 | >3.0 | |
| | *n* = 502 | *n* = 407 | *n* = 438 | *n* = 450 | *n* = 388 | *n* = 2185 |
| Demographics | | | | | | |
| Age, years | 65.8 (12.3) | 63.8 (12.3) | 61.8 (11.8) | 58.9 (12.3) | 57.3 (11.5) | 61.7 (12.5) |
| Gender | | | | | | |
| Women (%) | 36 | 38 | 37 | 39 | 39 | 38 |
| Men (%) | 64 | 62 | 63 | 61 | 61 | 62 |
| Renal disease | | | | | | |
| Glomerulonephritis (%) | 38 | 43 | 43 | 49 | 53 | 45 |
| Diabetic nephropathy (%) | 31 | 26 | 29 | 22 | 19 | 26 |
| Other diseases (%) | 31 | 31 | 27 | 29 | 28 | 29 |
| Vintage, years | 5.7 (0.9, 23.0) | 8.0 (1.7, 22.7) | 7.7 (1.5, 23.0) | 9.2 (2.1, 21.9) | 10.3 (2.7, 21.9) | 8.3 (1.5, 22.3) |
| Body mass index, kg/m$^2$ | 21.3 (3.7) | 21.4 (3.8) | 21.4 (3.4) | 21.4 (3.5) | 21.2 (3.3) | 21.3 (3.6) |
| Comorbidities | | | | | | |
| Cardiovascular disease | | | | | | |
| Coronary artery disease (%) | 27 | 26 | 25 | 24 | 25 | 25 |
| Atrial fibrillation (%) | 10 | 6 | 5 | 6 | 6 | 7 |
| Other arrhythmia (%) | 19 | 15 | 13 | 13 | 11 | 15 |
| Pacemaker (%) | 2 | 2 | 1 | 1 | 2 | 2 |
| Congestive heart failure (%) | 11 | 7 | 7 | 7 | 7 | 8 |
| Cerebrovascular disease (%) | 15 | 12 | 13 | 9 | 6 | 11 |
| Peripheral vascular disease (%) | 25 | 26 | 19 | 18 | 18 | 21 |
| Aortic disease (%) | 7 | 7 | 6 | 7 | 7 | 7 |
| Others (%) | 15 | 14 | 12 | 11 | 13 | 13 |
| Lung disease (%) | 8 | 7 | 8 | 8 | 7 | 7 |
| Liver disease (%) | 15 | 15 | 12 | 16 | 13 | 14 |
| Malignancy (%) | 5 | 5 | 5 | 4 | 4 | 5 |
| History of parathyroidectomy (%) | 6 | 8 | 5 | 6 | 7 | 6 |
| Laboratory measurements and treatment variables | | | | | | |
| Serum calcium,[b] mg/dL | 9.3 (0.9) | 9.4 (0.9) | 9.4 (0.9) | 9.6 (0.8) | 9.7 (0.9) | 9.5 (0.9) |
| Serum phosphorus, mg/dL | 5.2 (1.4) | 5.5 (1.4) | 5.6 (1.3) | 5.8 (1.4) | 5.9 (1.3) | 5.6 (1.4) |
| Serum iPTH, pg/mL | 272 (121, 557) | 263 (139, 585) | 276 (125, 679) | 262 (114, 618) | 263 (114, 652) | 268 (123, 607) |
| VDRA | | | | | | |
| Intravenous (%) | 41 | 45 | 46 | 51 | 54 | 47 |
| Oral (%) | 33 | 32 | 30 | 24 | 26 | 29 |
| None (%) | 26 | 23 | 23 | 24 | 20 | 24 |
| Phosphate binder | | | | | | |
| Both (%) | 13 | 20 | 26 | 30 | 32 | 24 |
| Calcium based (%) | 46 | 49 | 45 | 44 | 35 | 44 |
| Not calcium based (%) | 11 | 15 | 16 | 19 | 24 | 17 |
| None (%) | 30 | 16 | 12 | 7 | 9 | 15 |
| Kt/V | 1.39 (0.3) | 1.43 (0.3) | 1.41 (0.3) | 1.42 (0.3) | 1.44 (0.2) | 1.42 (0.3) |
| Hemoglobin, g/dL | 10.4 (1.2) | 10.5 (1.2) | 10.6 (1.1) | 10.5 (1.1) | 10.8 (1.2) | 10.5 (1.2) |
| Serum potassium, mEq/L | | | | | | |
| ≤3.5 µg/dL (%) | 5 | 3 | 3 | 1 | 1 | 3 |
| >3.5–6.0 µg/dL (%) | 91 | 93 | 87 | 90 | 82 | 89 |
| >6 µg/dL (%) | 3 | 5 | 11 | 9 | 17 | 8 |
| Serum albumin, g/dL | | | | | | |
| ≤3.5 mg/dL (%) | 42 | 29 | 28 | 18 | 13 | 27 |
| >3.5–3.8 mg/dL (%) | 29 | 33 | 33 | 32 | 32 | 32 |
| >3.8 mg/dL (%) | 29 | 37 | 39 | 50 | 54 | 41 |
| Serum iron, µg/dL | | | | | | |
| ≤60 µg/dL (%) | 60 | 58 | 54 | 54 | 55 | 56 |
| >60–100 µg/dL (%) | 33 | 35 | 37 | 37 | 37 | 36 |
| >100 µg/dL (%) | 7 | 7 | 8 | 9 | 7 | 8 |
| Serum ferritin, ng/dL | | | | | | |
| ≤100 ng/dL (%) | 39 | 43 | 48 | 50 | 53 | 46 |
| >100–200 ng/dL (%) | 29 | 29 | 30 | 25 | 24 | 27 |
| >200–500 ng/dL (%) | 25 | 23 | 19 | 21 | 18 | 21 |
| >500 ng/dL (%) | 7 | 5 | 4 | 4 | 4 | 5 |

Continued

**Table 1.** Continued

| Characteristics | Baseline serum magnesium, mg/dL | | | | | Total |
|---|---|---|---|---|---|---|
| | ≤2.3 | >2.3–2.5 | >2.5–2.7 | >2.7–3.0 | >3.0 | |
| | *n* = 502 | *n* = 407 | *n* = 438 | *n* = 450 | *n* = 388 | *n* = 2185 |
| Serum CRP, mg/L | | | | | | |
| ≤0.3 mg/dL (%) | 64 | 70 | 77 | 76 | 84 | 74 |
| >0.3–0.5 mg/dL (%) | 9 | 10 | 8 | 11 | 6 | 9 |
| >0.5–1.0 mg/dL (%) | 10 | 8 | 6 | 6 | 6 | 8 |
| >1.0 mg/dL (%) | 17 | 12 | 8 | 7 | 4 | 10 |

[a]Mean (SD) are presented for normally distributed data; otherwise, median (p10, p90) are presented for non-normally distributed data.
[b]Corrected for albumin concentration using the modified Payne method.

estimated PAF was 17.8% (95% CI 7.0–28.6%) (Supplementary data, Table S2; adjusted HRs for the recategorized sMg in the model are shown in Supplementary data, Table S3). Given that the number of patients with SHPT is ∼99 000 [proportion of patients with SHPT (serum iPTH > 180 pg/mL according to Japanese guidelines) was ∼32%, and the number of prevalent dialysis patients was 309 946 at the end of 2012 [20]] and crude annual mortality rate in this study is 5.6%, the estimated annual number of deaths among patients with SHPT is ∼5500. If association between dysregulated sMg and mortality is indeed causal, 990 (PAF 17.8%) to 1700 (PAF 30.8%) annual deaths could have been prevented among these patients by correcting the underlying conditions associated with dysregulated sMg.

In sensitivity analyses with more covariates, associations between sMg quintiles and mortality were similar to those noted in the primary analysis (Supplementary data, Table S4), with similar estimated proportions of all-cause death that could potentially have been prevented (Supplementary data, Table S5). When cardiovascular deaths were analyzed as outcome, point estimates of the associations between sMg quintiles and cardiovascular deaths were similar to those of the associations between sMg quintiles and all-cause death (Supplementary data, Table S6).

## Discussion

In this prospective study of Japanese hemodialysis patients with SHPT, relatively low sMg levels were found to be associated with all-cause death. In addition, PAF estimates suggest that sMg potentially has an unignorable impact on all-cause death. These findings may encourage health policy makers and physicians to pay more attention to dysregulated sMg than they do at present in an effort to reduce the number of preventable deaths among dialysis patients with SHPT.

Our findings here agree well with those of a previous study which found that both relatively low and relatively high sMg levels were associated with all-cause death and cardiovascular death [9]. However, the present and previous studies differed in several respects. First, nationwide questionnaire surveillance hampered determination of detailed biological measures and comorbidities assessed in the previous study, such as serum potassium, congestive heart failure and atrial fibrillation, which are potentially confounding variables that should be considered in the accurate assessment of the relationship between dysregulated sMg and deaths [21, 22]. Hypomagnesemia is frequently linked with hypokalemia [22], and indeed, we noted that sMg levels were positively correlated with serum potassium levels among hemodialysis patients in the present study (Table 2). We also noted an association between relatively low sMg levels and the presence of atrial fibrillation, and patients in lower sMg quintiles tended to have congestive heart failure. These findings suggest that the previous studies might have been confounded by these cardiovascular comorbidities [8, 9, 23]. Second, the previous study examined the association between sMg levels and 1-year deaths [9]. A study with such a short follow-up period is more susceptible to reverse causation; the observed lower sMg levels may have simply been a consequence of disease along with reduced serum albumin and elevated serum CRP levels. The follow-up period in the present study, however, was 3 years—a more biologically plausible duration than 1 year for examining effects on future all-cause deaths and cardiovascular deaths after long-term dysregulated Mg exposure. Third, the previous studies did not estimate PAFs [8, 9, 23]. Our use of PAFs in the present study suggested the magnitude of reduction in potential deaths in a hemodialysis population such as the one examined here.

We feel that the present findings will influence activities of physicians and medical researchers for several reasons. First, sMg is a potentially modifiable risk factor for deaths, able to be managed in part simply by customizing dialysate Mg levels. In Japan, the typical dialysate Mg concentration is 1 mEq/L (∼1.22 mg/dL). A previous study showed that lowering dialysate Mg levels subsequently resulted in decreased sMg levels [24]. In contrast, increasing dialysate Mg levels resulted in a decrease in serum iPTH, calcium and phosphorus levels and an increase in sMg levels [24], an effect that may prove particularly beneficial in hemodialysis patients suffering from SHPT. Further study is warranted to determine whether or not correction of sMg does indeed improve survival among hemodialysis patients. Second, our finding of an association between low sMg levels and cardiovascular comorbidities (atrial fibrillation and cerebrovascular disease) may stimulate research on the role of Mg in cardiovascular health. Our observed association between lower sMg levels and cerebrovascular diseases supports a previous finding that showed inverse correlation between sMg levels and carotid intima-media thickness, which is a predictor of cerebrovascular disease [25]. The relationship between reduced sMg levels and atrial fibrillation suggests that low sMg status may play a role in arrhythmogenesis, a notion consistent with previous research showing an association between hypomagnesemia and development of atrial fibrillation in the general population [21]. Third, other than its potential arrhythmogenic or atherogenic roles, low sMg status may be a marker for malnutrition, as reduced sMg levels have been associated with reduced serum albumin and elevated serum CRP levels. Further study is required to clarify the mechanism underlying the relatively high rates of death related to dysregulated sMg. Fourth, given the large PAF values

**Table 2.** Baseline characteristics associated with the lowest and the highest sMg categories[a]

| | For sMg ≤2.3 mg/dL | | | | For sMg >3.0 mg/dL | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | AOR | 95% CI | | P-value | AOR | 95% CI | | P-value |
| Age | | | | | | | | |
| Per 10 years | 1.244 | 1.112 | 1.393 | <0.001 | 0.795 | 0.707 | 0.894 | <0.001 |
| Gender | | | | | | | | |
| Men | | | | | | | | |
| Women | 0.734 | 0.511 | 1.055 | 0.095 | 1.305 | 0.981 | 1.737 | 0.068 |
| Vintage | | | | | | | | |
| ≤2 years | Ref. | | | | Ref. | | | |
| >2–5 years | 0.493 | 0.354 | 0.685 | <0.001 | 1.713 | 0.977 | 3.005 | 0.060 |
| >5–10 years | 0.390 | 0.272 | 0.559 | <0.001 | 2.786 | 1.686 | 4.603 | <0.001 |
| >10 years | 0.386 | 0.273 | 0.545 | <0.001 | 3.354 | 1.950 | 5.768 | <0.001 |
| Renal disease | | | | | | | | |
| Glomerulonephritis | Ref. | | | | Ref. | | | |
| Diabetic nephropathy | 1.144 | 0.800 | 1.636 | 0.460 | 0.892 | 0.635 | 1.252 | 0.508 |
| Other diseases | 1.065 | 0.816 | 1.390 | 0.642 | 0.949 | 0.694 | 1.298 | 0.744 |
| Cardiovascular diseases | | | | | | | | |
| Coronary artery disease | 0.936 | 0.662 | 1.325 | 0.710 | 1.139 | 0.827 | 1.570 | 0.425 |
| Atrial fibrillation | 1.711 | 1.209 | 2.421 | 0.002 | 0.934 | 0.540 | 1.614 | 0.806 |
| Other arrhythmia | 1.314 | 1.027 | 1.681 | 0.030 | 0.793 | 0.559 | 1.125 | 0.194 |
| Pacemaker | 0.680 | 0.329 | 1.405 | 0.297 | 2.666 | 0.816 | 8.710 | 0.104 |
| Congestive heart failure | 1.385 | 0.991 | 1.935 | 0.056 | 0.987 | 0.622 | 1.565 | 0.955 |
| Cerebrovascular disease | 1.336 | 1.035 | 1.725 | 0.026 | 0.527 | 0.351 | 0.790 | 0.002 |
| Peripheral vascular disease | 1.073 | 0.816 | 1.411 | 0.613 | 0.913 | 0.653 | 1.275 | 0.592 |
| Aortic disease | 0.821 | 0.470 | 1.434 | 0.488 | 1.442 | 0.942 | 2.208 | 0.092 |
| Others | 1.088 | 0.742 | 1.593 | 0.666 | 1.104 | 0.773 | 1.579 | 0.586 |
| Lung disease | 0.804 | 0.442 | 1.460 | 0.473 | 1.203 | 0.792 | 1.826 | 0.387 |
| Liver disease | 1.004 | 0.704 | 1.430 | 0.985 | 0.897 | 0.653 | 1.234 | 0.505 |
| Malignancy | 0.744 | 0.459 | 1.206 | 0.231 | 1.545 | 0.813 | 2.938 | 0.184 |
| History of parathyroidectomy | 1.636 | 1.063 | 2.516 | 0.025 | 0.781 | 0.464 | 1.316 | 0.353 |
| Body mass index | | | | | | | | |
| Per 5 kg/m$^2$ | 1.113 | 0.910 | 1.360 | 0.297 | 0.902 | 0.755 | 1.077 | 0.255 |
| Hemoglobin | | | | | | | | |
| Per 1 g/dL | 0.923 | 0.832 | 1.023 | 0.128 | 1.149 | 1.029 | 1.283 | 0.014 |
| Kt/V | | | | | | | | |
| Per 1 | 1.146 | 0.575 | 2.286 | 0.698 | 0.709 | 0.387 | 1.298 | 0.265 |
| Serum potassium | | | | | | | | |
| ≤3.5 mEq/L | 2.070 | 1.349 | 3.175 | 0.001 | 0.717 | 0.300 | 1.716 | 0.455 |
| >3.5–6.0 mEq/L | Ref. | | | | Ref. | | | |
| >6.0 mEq/L | 0.393 | 0.214 | 0.722 | 0.003 | 2.526 | 1.907 | 3.347 | <0.001 |
| Serum albumin | | | | | | | | |
| ≤3.5 g/dL | 2.183 | 1.494 | 3.189 | <0.001 | 0.392 | 0.248 | 0.619 | <0.001 |
| >3.5–3.8 g/dL | 1.210 | 0.941 | 1.556 | 0.137 | 0.823 | 0.636 | 1.064 | 0.137 |
| >3.8 g/dL | Ref. | | | | Ref. | | | |
| Serum calcium[b] | | | | | | | | |
| ≤8.4 mg/dL | 1.263 | 0.883 | 1.806 | 0.201 | 0.685 | 0.469 | 1.000 | 0.050 |
| >8.4–10 mg/dL | Ref. | | | | Ref. | | | |
| >10 mg/dL | 0.795 | 0.588 | 1.075 | 0.137 | 1.214 | 0.921 | 1.600 | 0.169 |
| Serum phosphorus | | | | | | | | |
| ≤3.5 mg/dL | 1.682 | 1.124 | 2.516 | 0.011 | 0.590 | 0.302 | 1.155 | 0.123 |
| >3.5–6.0 mg/dL | Ref. | | | | Ref. | | | |
| >6.0 mg/dL | 0.742 | 0.559 | 0.985 | 0.039 | 1.315 | 0.992 | 1.743 | 0.057 |
| Serum iPTH | | | | | | | | |
| ≤180 pg/mL | 1.009 | 0.759 | 1.342 | 0.949 | 1.012 | 0.690 | 1.485 | 0.950 |
| >180–300 pg/mL | Ref. | | | | Ref. | | | |
| >300–500 pg/mL | 1.262 | 1.000 | 1.593 | 0.050 | 0.726 | 0.552 | 0.953 | 0.021 |
| >500 pg/mL | 1.401 | 0.951 | 2.065 | 0.088 | 0.625 | 0.421 | 0.929 | 0.020 |
| Serum iron | | | | | | | | |
| ≤60 µg/dL | Ref. | | | | Ref. | | | |
| >60–100 µg/dL | 0.986 | 0.767 | 1.267 | 0.912 | 0.869 | 0.667 | 1.130 | 0.294 |
| >100 µg/dL | 0.949 | 0.614 | 1.467 | 0.814 | 0.699 | 0.399 | 1.223 | 0.209 |

Continued

**Table 2.** Continued

| Characteristics | For sMg ≤2.3 mg/dL | | | | For sMg >3.0 mg/dL | | | |
|---|---|---|---|---|---|---|---|---|
| | AOR | 95% CI | | P-value | AOR | 95% CI | | P-value |
| Serum ferritin | | | | | | | | |
| ≤100 ng/dL | Ref. | | | | Ref. | | | |
| >100–200 ng/dL | 1.142 | 0.774 | 1.686 | 0.502 | 0.808 | 0.590 | 1.108 | 0.186 |
| >200–500 ng/dL | 1.512 | 1.114 | 2.052 | 0.008 | 0.696 | 0.471 | 1.029 | 0.069 |
| >500 ng/dL | 2.049 | 1.119 | 3.751 | 0.020 | 0.769 | 0.387 | 1.525 | 0.452 |
| Serum CRP | | | | | | | | |
| ≤0.3 mg/dL | Ref. | | | | Ref. | | | |
| >0.3–0.5 mg/dL | 0.953 | 0.581 | 1.562 | 0.848 | 0.666 | 0.421 | 1.055 | 0.083 |
| >0.5–1.0 mg/dL | 1.322 | 0.877 | 1.993 | 0.183 | 0.809 | 0.454 | 1.441 | 0.472 |
| >1.0 mg/dL | 1.766 | 1.201 | 2.598 | 0.004 | 0.459 | 0.231 | 0.913 | 0.027 |

AOR, adjusted odds ratio.
[a]Estimated from logistic generalized estimating equations considering cluster effects by facilities with adjustment for all variables listed in the table.
[b]Corrected for albumin concentration using the modified Payne method.

**Table 3.** Associations between sMg levels and all-cause death

| Baseline Mg, mg/dL | Person-years | IR | Crude | | | Adjusted[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | 95% CI | P-value | HR | 95% CI | P-value |
| ≤2.3 | 1299 | 9.32 | 2.378 | 1.709–3.309 | <0.001 | 1.734 | 1.204–2.497 | 0.003 |
| >2.3–2.5 | 1099 | 6.82 | 1.735 | 1.285–2.345 | <0.001 | 1.649 | 1.231–2.209 | 0.001 |
| >2.5–2.7 | 1215 | 3.95 | 1 (Ref.) | | | 1 (Ref.) | | |
| >2.7–3.0 | 1261 | 3.96 | 1.002 | 0.718–1.399 | 0.988 | 1.305 | 0.869–1.961 | 0.200 |
| ≥3.0 | 1086 | 3.68 | 0.932 | 0.652–1.331 | 0.698 | 1.354 | 0.925–1.983 | 0.119 |

IR, incidence rate per 100 person-years.
[a]Estimated from Cox regression models considering cluster effects by facilities with adjustment for age, sex, vintage, primary renal disease, coronary artery disease, atrial fibrillation, other arrhythmia, pacemaker, heart failure, cerebrovascular disease, peripheral vascular disease, aortic disease, other cardiovascular disease, lung disease, liver disease, malignancy, history of parathyroidectomy, serum calcium, serum phosphorus, serum iPTH, Kt/V, serum potassium, serum albumin, body mass index, hemoglobin, serum iron, serum ferritin and serum CRP.

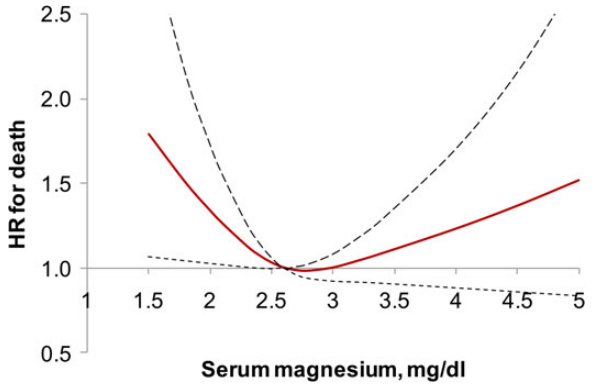


**Fig. 2.** Continuous associations between sMg levels and all-cause death using restricted cubic spline analyses. Solid line indicates point estimate. Dashed lines indicate 95% CI. Estimated from Cox regression models considering cluster effects by facilities with adjustment for age, sex, vintage, primary renal disease, coronary artery disease, atrial fibrillation, other arrhythmia, pacemaker, heart failure, cerebrovascular disease, peripheral vascular disease, aortic disease, other cardiovascular disease, lung disease, liver disease, malignancy, history of parathyroidectomy, serum calcium, serum phosphorus, serum iPTH, Kt/V, serum potassium, serum albumin, body mass index, hemoglobin, serum iron, serum ferritin and serum CRP.

for dysregulated sMg for deaths in our study, health policy makers and physicians should consider dysregulated sMg levels to be not merely an adjunct mineral abnormality but a potentially important contributor to deaths among hemodialysis patients. As such, assessment and management of dysregulated sMg levels should be incorporated into future guidelines for mineral abnormalities among dialysis patients.

The strength of the present study was that we demonstrated the relationship between dysregulated sMg levels and deaths in a relatively large hemodialysis population, adjusting for confounding variables such as malnutrition–inflammation markers (albumin, body mass index and CRP), serum potassium levels and

**Table 4.** PAFs for all-cause death among the study population[a]

| | Estimates (%) | 95% CI (%) |
|---|---|---|
| Higher and lower sMg levels[b] | 30.8 | 14.8–46.8 |
| Lower sMg levels[c] | 24.2 | 13.3–35.1 |

[a]Estimated from Cox regression models considering cluster effects by facilities with adjustment for age, sex, vintage, primary renal disease, coronary artery disease, atrial fibrillation, other arrhythmia, pacemaker, heart failure, cerebrovascular disease, peripheral vascular disease, aortic disease, other cardiovascular disease, lung disease, liver disease, malignancy, history of parathyroidectomy, serum calcium, serum phosphorus, serum iPTH, Kt/V, serum potassium, serum albumin, body mass index, hemoglobin, serum iron, serum ferritin and serum CRP.
[b]Estimates if higher (>2.7–3.0 and >3.0 mg/dL) and lower (≤2.3 and >2.3–2.5 mg/dL) categories could have been corrected to the middle sMg quintile (>2.5–2.7 mg/dL).
[c]Estimates if lower (>2.7–3.0 and >3.0 mg/dL) categories could have been corrected to the middle sMg quintile (>2.5–2.7 mg/dL).

many cardiovascular comorbidities, which are potentially related to both sMg levels and deaths [22, 26]. However, several limitations to the present study also warrant mention. First, we were unable to account for Mg-containing medication in our analyses. Use of Mg-containing laxatives might be associated with elevated sMg levels, and proton pump inhibitors are associated with reduced sMg levels [27]. However, these drugs *per se* are not predictors for deaths. We, therefore, believe it unlikely that effects of dysregulated sMg levels on deaths are confounded by these medications. Second, we noted a high rate of missing data for sMg values in our analyses. However, baseline characteristics among those with and without sMg values were similar in many aspects, and we therefore believe it unlikely that findings in a complete data set would be starkly different from those in the target population. Third, our analysis population was restricted to patients with SHPT. However, with regard to the relative risks between sMg levels and deaths, our results were similar to those from the nationwide hemodialysis population [9], suggesting that our findings may be generalizable to the entire hemodialysis population.

In conclusion, in Japanese hemodialysis patients with SHPT, dysregulated sMg was found to be associated with all-cause death. Furthermore, dysregulated sMg was found to have a potentially substantial contribution to all-cause death according to PAF estimates. Further study is warranted to clarify whether or not correction of sMg improves survival.

## Supplementary data

Supplementary data are available online at http://ckj.oxfordjournals.org.

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## Conflict of interest statement

The results presented in this article have not been published previously in whole or part, except in abstract format. T.A. has acted as a consultant for and received grants (research support) from Kyowa Hakko Kirin and is a member of the speakers' bureau of Kyowa Hakko Kirin. S.F. has acted as a scientific advisor for and received grants (research support) from Kyowa Hakko Kirin. M. F. has acted as a consultant for and received honoraria and received grants (research support) from Kyowa Hakko Kirin. The other authors have no conflicts of interest to disclose.

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## Appendix

The following investigators also participated in this study: Nobuo Hashimoto (H.N.MEDIC), Mari Ishida (Kitasaito Hospital), Toshiyuki Date (Date Clinic), Kiyotaka Yabuki (Yabuki Hospital), Hideki Tanida (Tendo Onsen Yabuki Clinic), Fumitoshi Yamauchi (San-ai Hospital), Mikihiko Fujishima (Yahaba Clinic), Tomohito Matsunaga (Eijinkai Hospital), Jun Urae (Ishinomaki Clinic), Hiroshi Kawaguchi (Iwaki Urological Hospital), Ikuo Takahashi (Kisen Hospital), Yoshiko Tanaka (Shinjuku-Koshin Clinic), Hideo Kobayashi (Suda Clinic), Maki Takahashi (Suda Naika Clinic), Tatsuya Nonaka (Seishokai Memorial Hospital), Hideto Emoto (Tokai Hospital), Kyosuke Nishio (Shinkoiwa Clinic), Atsushi Hayama (Moriyama Rehabilitation Hospital), Toshio Shinoda (Kawakita General Hospital Dialysis Center), Takashi Kono (Mihama Narita Clinic), Takahiro Mochizuki (Kameda Medical Center), Yasuo Kimura (Shin-Kashiwa Clinic), Noriyoshi Murotani (Chiba Social Insurance Hospital), Satoshi Yamaguchi (Asahi Hospital), Taichi Nakanishi (Kurihama Clinic), Kiyoshi Ozawa (Yokosuka Clinic), Takashi Nagaoka (Sagamihara Clinic), Takao Suga (Bousei Hiratsuka Clinic), Masakazu Suda (Suda Medical Clinic), Yoshikazu Goto (Saiyu Soka Hospital), Michio Kuwahara (Shuwa General Hospital Hemodialysis Clinic), Hiromi Shimoyama (Yuai Clinic), Kimihiko Matsuyama (Misato Kenwa Clinic), Kazue Ueki (Toho Hospital), Kyoko Ito (Heisei Hidaka Clinic), Katsuhiko Miyamoto (Seseragi Hospital), Takashi Ishizu (Tukuba Central Hospital), Shuichi Kikuchi (Ohba Renal Clinic), Masaki Kobayashi (Tokyo Medical University Ibaraki Medical Center), Mitsuyoshi Furuhashi (Maruyama Hospital), Masanori Wakabayashi (Bousei Daiichi Clinic), Kazuyoshi Nakamura (Fujidaiichi Clinic), Hirotake Kasuga (Kaikoukai Central Clinic), Itsuo Yokoyama (Nagoya Memorial Foundation Narumi Clinic), Chikao Yamazaki (Masuko Clinic SUBARU), Kijun Nagata (Sawada Hospital), Yasumasa Kawade (Suzuka Kidney Clinic), Toshiaki Kawanaka (Ishikiriseiki Hospital), Yoshihiro Tsujimoto (Inoue Hospital), Mikio Okamura (Ohno Memorial Hospital), Shigeki Okada (Okada Clinic), Senji Okuno (Kidney Center Shirasagi Clinic), Harumi Nagayama (Nagayama Hemodialysis Clinic), Shuji Okazaki (Nagayama Hospital), Yoshinori Tone (Fujii Clinic), Ibuki Yajima (Ibuki Clinic), Kouji Shibuya (Sumiyoshigawa Hospital), Kunihiko Yoshiya (Hara Genitourinary Hospital), Morihiro Kondou (Otowa Kinen Hospital), Satoru Yamazaki (Tojinkai Hospital), Ryoichi Miyazaki (Fujita Memorial Hospital), Katsuhiko Arimoto (Shigei Medical Research Hospital), Misaki Moriishi (Nakajima Tsuchiya Clinic), Takahito Nasu (Tokuyama Central Hospital), Seiichi Obayashi (Kinashi Obayashi Hospital), Yuzuru Sato (Sato Junkankika Naika), Takao Tanaka (Ohji Hospital), Hidetoshi Nakamura (Kokura Daiichi Hospital), Nobuhiko Koga (Shin-Koga Clinic), Harumichi Higashi (St Mary's Hospital), Kougi Yuu (Takahashi Naika Clinic), Asako Kitamura (Chikuho Social Insurance Hospital), Tomoji Matsumae (Murakami Memorial Hospital), Katsushige Abe (Jinikai Hospital), Masahiro Kawatomi (Kawatomi Internal Medicine Clinic), Motoko Tanaka (Akebono Clinic), Chisa Nogami (Kumamoto Urological Hospital), Etsuo Yoshidome (Ikeda Hospital), Shinyu Miyagi (Okinawa Daiichi Hospital), Satoshi Nakazato (Chibana Clinic), Yoshiki Shiohira (Tomishiro Central Hospital) and Kiyoyuki Tokuyama (Tokuyama Clinic).

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