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Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis

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Although previous studies in the general population showed that hypomagnesemia is a risk for cardiovascular diseases (CVD), the impact of magnesium on the prognosis of patients on hemodialysis has been poorly investigated. To gain information on this we conducted a nationwide registry-based cohort study of 142,555 hemodialysis patients to determine whether hypomagnesemia is an independent risk for increased mortality in this population. Study outcomes were 1-year all-cause and cause-specific mortality with baseline serum magnesium levels categorized into sextiles. During follow-up, a total of 11,454 deaths occurred, of which 4774 had a CVD cause. In a fully adjusted model, there was a J-shaped association between serum magnesium and the odds ratio of all-cause mortality from the lowest to highest sextile, with significantly higher mortality in sextiles 1–3 and 6. Similar associations were found between magnesium and both CVD and non-CVD mortality. The proportion of patients with a baseline intact parathyroid hormone level under 50 pg/ml was significantly higher in the highest sextile; however, after excluding these patients, the CVD mortality risk in the highest sextile was attenuated. Thus, hypomagnesemia was significantly associated with an increased risk of mortality in hemodialysis patients. Interventional studies are needed to clarify whether magnesium supplementation is beneficial for improving patient prognosis.

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Despite increasing knowledge and technical advances in the field of dialysis therapy, the risk of death is still unacceptably high among patients undergoing hemodialysis. The 5-year survival rate is 35% in the United States and 60% in Japan, far below that in the general population.[1,2] Cardiovascular diseases (CVD) account for nearly 40% of all deaths in patients with end-stage renal disease (ESRD).[1–4] Traditional CVD risk factors such as hypertension, dyslipidemia, insulin resistance, and obesity do not fully explain the increased risk observed in hemodialysis patients, while the elevation of several nontraditional risk factors such as inflammation, oxidative stress, malnutrition, anemia, and uremia has been considered to play a more important role.[5] In particular, much attention has been focused on mineral and bone disorder (MBD) in ESRD as a prominent contributor to the development of atherosclerosis and vascular calcification, in which phosphate retention is considered a key component.[6,7]

Magnesium (Mg), the fourth most abundant cation in the human body, plays an essential role in numerous biological processes. The importance of this mineral has been particularly recognized due to its antiatherosclerotic effect.[8] In the general population, a lower serum Mg level and/or lower dietary Mg intake is associated with an increased incidence of hypertension,[9] type 2 diabetes mellitus (DM),[10] metabolic syndrome,[11] and CVD, including myocardial infarction, stroke, atrial fibrillation, and sudden cardiac death.[12–17] A significant association between hypomagnesemia and increased risk for fatal and non-fatal CVD events was also reported in patients with pre-dialysis chronic kidney disease.[18] An interventional study in patients with coronary artery disease demonstrated that oral Mg supplementation could improve endothelial cell dysfunction.[19] Several *in vitro* studies have shown that Mg deficiency causes vascular constriction, platelet aggregation, inflammation, and oxidative stress, resulting in endothelial cell dysfunction and vascular calcification.[20] The direct protective effects of Mg on vascular calcification have also been demonstrated via multiple pathways, including inhibition of hydroxyapatite

formation[21] and suppression of transdifferentiation of vascular smooth muscle cells into osteoblast-like cells.[22,23]

Despite the well-accepted associations of CVD and mineral disturbances with hemodialysis, the role of Mg in this population is nearly unexplored. Previous cross-sectional studies in ESRD have reported that hypomagnesemia was significantly associated with an increased prevalence of mitral annular calcification,[24] peripheral arterial calcification,[25] and an increased carotid intima-media thickness.[26] Moreover, 2 months of oral Mg supplementation significantly decreased intima-media thickness.[27] However, very few studies have examined whether the serum Mg level is independently associated with mortality in this population. One previous small retrospective cohort study[28] could not demonstrate a significant association between the serum Mg level and CVD mortality, likely due to insufficient statistical power. Therefore, we conducted this cohort study using a nationwide registry of patients with ESRD in Japan to clarify the relationship between serum Mg levels and mortality.

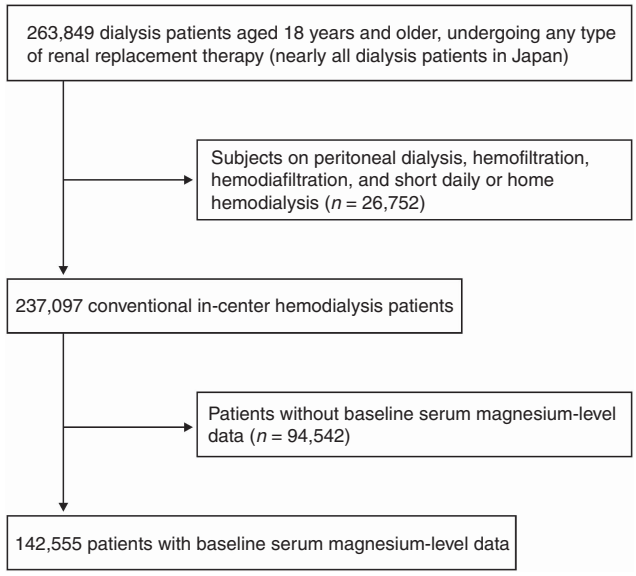

Figure 1 | Flowchart of the study enrollment process.

RESULTS

The study enrollment process is summarized in Figure 1. Of the total number of 263,849 dialysis patients, those on renal replacement therapy other than facility hemodialysis ($n = 26,752$) were excluded. Of 237,097 hemodialysis patients, baseline serum Mg level data were available for 142,555 subjects. We compared all baseline characteristics between the subjects with and without serum Mg level data and found no meaningful difference between groups (Supplementary Table 1 online). The mean (standard deviation (s.d.)) serum Mg level of the subjects was 2.61 (0.52) mg/dl. The baseline characteristics according to serum Mg sextiles are summarized in Table 1. A lower serum Mg level was significantly associated with older age, lower albumin, calcium, phosphate, and hemoglobin level, higher C-reactive protein (CRP) and alkaline phosphatase (ALP) level, and increased prevalence of DM, prior history of CVD, and hip fracture. To better understand the relationship between serum Mg and intact parathyroid hormone (iPTH) levels, which is strongly influenced by other MBD-related factors, univariate and multivariate restricted cubic spline functions were fitted with four knots (Figure 2). As shown, the iPTH level was almost at a plateau in the unadjusted model; however, after adjustment for age, sex, serum calcium, and phosphate level, and prescription of active vitamin D analogues and cinacalcet, an overall negative association was observed.

During follow-up, a total of 11,454 deaths occurred, in which 4774 (41.7%) were attributed to CVD and 6680 (58.3%) to non-CVD. Only a small proportion of the patients ($n = 367$ (0.3%)) received renal transplantation during follow-up. In a crude analysis, there was a significant J-shaped relationship between the Mg sextiles and outcomes (Table 2). Their associations were somewhat attenuated after additional adjustment for the relevant clinical factors of demographics, MBD– and malnutrition-inflammation atherosclerosis (MIA) complex–related factors, yet they remained statistically significant (fully adjusted odds ratio (OR) [95% confidence interval (CI)] of the lowest sextile was 1.28 [1.17, 1.41] ($P < 0.001$) for all-cause mortality, 1.24 [1.08, 1.42] ($P = 0.002$) for CVD mortality, and 1.32 [1.17, 1.49] ($P < 0.001$) for non-CVD mortality; Table 2). The continuous, fully adjusted association between the serum Mg level and all-cause mortality showed a similar relationship (Figure 3). The results of the subgroup analysis are shown in Table 3; the lowest sextile was significantly associated with a higher risk of all-cause mortality in all prespecified subgroups.

As the proportion of subjects with a baseline iPTH level < 50 pg/ml was significantly higher in the highest sextile (Table 1), we assumed that this low iPTH level increased the mortality risk of this group. Therefore, we performed the same multivariate analysis after excluding subjects with an iPTH level < 50 pg/ml. In this subgroup, CVD mortality risk in the highest sextile was attenuated and lost statistical significance (Table 2).

We further explored the associations between Mg levels and specific causes of non-CVD deaths. Of all the non-CVD deaths, infection ($n = 2156$; 32.3%) and cancer ($n = 1084$; 16.2%) were the two major causes. In the fully adjusted multivariate model, the ORs [95% CI] for infection-related deaths were 1.49 [1.20, 1.85] ($P < 0.001$), 1.33 [1.06, 1.67] ($P = 0.01$), 1.36 [1.08, 1.71] ($P = 0.008$), 1.33 [1.00, 1.76] ($P = 0.05$), 1.00 (Ref.), and 1.21 [0.93, 1.58] ($P = 0.15$) from the lowest to highest sextile, respectively. Because the inclusion of patients suffering from severe infections (and, consequently, of hypomagnesemia due to cachexia) at baseline would allow the possibility of reverse causality between hypomagnesemia and death from infection, an additional analysis excluding patients with high baseline CRP levels ($\geqslant 3.0$ mg/dl) was conducted. This analysis slightly attenuated the risk; the ORs [95% CI] were 1.44 [1.14, 1.81]