Association between Serum Magnesium Levels and Mortality in a Community-Based Population: The Yamagata (Takahata) Study

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Summary The element magnesium (Mg) is involved in various metabolic reactions within the human body, and its deficiency is considered a risk factor for several diseases. In this study, we investigated the relationship between serum Mg levels and mortality in a community-based population. We prospectively assessed the association between serum Mg levels at enrollment and all-cause mortality in 1,314 participants who underwent a community health examination. The mean serum Mg level was 2.4 (±0.2) mg/dL. Patients with serum Mg levels ≤2.3 mg/dL constituted the low Mg group, while those with serum Mg ≥2.4 mg/dL constituted the high Mg group. Ninety-three (7.1%) patients died during the 10-y follow-up period. Kaplan-Meier analysis revealed that all-cause mortality was significantly higher in the low Mg group (log-rank $p<0.05$). Cox proportional hazards analysis revealed a significant association in the unadjusted model (hazard ratio [HR] 1.72, 95% confidence intervals [CI] 1.14–2.58, $p<0.01$) and in the fully adjusted model (HR 1.73, 95% CI 1.09–2.76, $p<0.05$). This association was particularly strong in males (HR 2.08, 95% CI 1.19–3.63, $p<0.05$). Low serum Mg levels were significantly associated with the risk of all-cause mortality among males in a community-based Japanese population.

Key Words magnesium, mortality, population, cohort, risk factor

Magnesium (Mg) is the fourth-most abundant cation and an essential element in the human body. Most of it is located in the bones and muscles. Mg is a coenzyme involved in glucose metabolism, and protein and nucleic acid synthesis (*1*). It must be taken regularly and in sufficient quantities of Mg, and its metabolism is regulated in tissues such as the gastrointestinal tract, kidneys, and bones. Serum Mg is widely used as a biomarker of Mg intake because it can be easily measured, and serum Mg concentrations are maintained in the range of 0.75–0.955 mmol/L (*2*). In reality, however, there is a lack of evidence that serum Mg and dietary Mg intake are closely related, and potential Mg deficiency may occur even when serum Mg is within the normal range (*3*). It should also be noted that various diseases and drugs can also affect serum Mg concentrations (*4*, *5*).

Hypomagnesemia is most common clinical problem most commonly associated with abnormal Mg metabolism. The estimated prevalence of hypomagnesemia in the general population ranges from 2.5–15% (*6*, *7*). Hypomagnesemia is often caused by inadequate Mg intake and its excretion from the gastrointestinal tract and kidneys (*8*). Hypomagnesemia has been associated with various disease, including chronic obstructive pulmonary disease (*9*), type 2 diabetes mellitus (*10*), Alzheimer's disease (*11*), and cardiovascular disease (CVD) (*12*). A meta-analysis of 19 studies on Mg and CVD found an association between hypomagnesemia or inadequate Mg intake and the risk of developing CVD (*13*). Furthermore, it has been suggested that Mg is associated with life expectancy. Reports have indicated that mortality risk decreases with an increase Mg intake (*10*) and serum Mg concentration in maintenance hemodialysis patients (*14*). However, it has been reported that hypomagnesemia is not a risk factor for all-cause mortality or CVD (*15*). Therefore, the association between Mg levels and mortality remains debatable.

Most previous studies using serum Mg levels as an indicator of mortality have been conducted in Western populations, whereas no such studies have been conducted in the Japanese population. A previous study has indicated that inadequate Mg intake is associated with cardiovascular mortality in women (*16*). We conducted a prospective study to assess the effect of serum Mg levels on all-cause mortality in a community-based Japanese population.

MATERIALS AND METHODS

Participants in the Yamagata (Takahata) Study were registered at an annual community health check-up. Of

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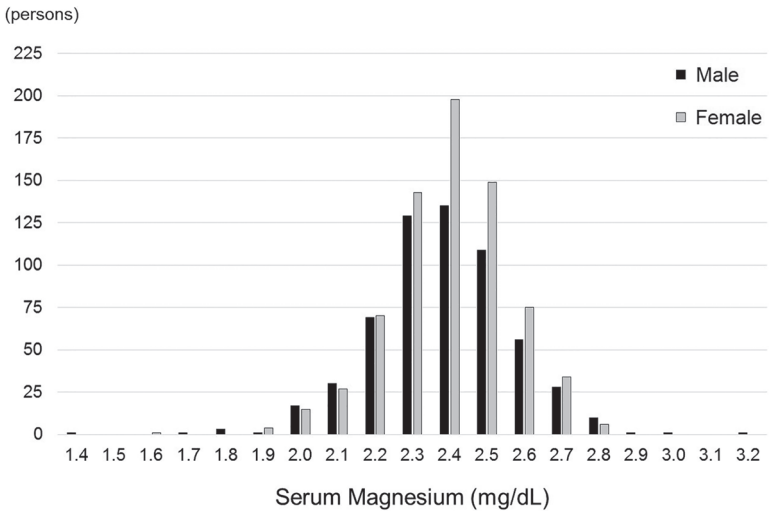

Fig. 1. Distribution of serum magnesium levels among the study subjects.

the 3,523 people who participated in the study between 2004 and 2006, 1,314 people whose serum Mg concentrations were measured were included in the study. The participants were followed-up for 10 y, and the relationship between serum Mg levels and all-cause mortality was examined. This study was approved by the Ethical Review Committee of Yamagata University School of Medicine (No. 2020-101). Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki. The study design, recruitment methods, and information about the study participants have been previously reported (*17*).

Measurements. In the baseline survey, the participants' clinical laboratory data and medical history-associated information were obtained using a self-report questionnaire. We confirmed the death based on the death certificate. Systolic and diastolic blood pressures were measured using a mercury sphygmomanometer after a participant remained in a resting and sitting position for at least 5 min. Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dL, hemoglobinA1c (HbA1c) level ≥6.5%, or the use of hypoglycemic agents. Dyslipidemia was defined as a serum total cholesterol level ≥220 mg/dL or the use of dyslipidemia medications. Participants who reported a daily or occasional alcohol consumption were classified as having alcohol consumption.

Participants who had a smoking habit were defined as smokers. Serum Mg levels were measured using the xylidine blue method. Estimated glomerular filtration rate (eGFR) values were calculated using Matsuo's equation (*18*).

Statistical analysis. Data were presented as the mean±standard deviation unless otherwise indicated. A Student's *t*-test was performed to evaluate differences in mean values while a Chi squared test was utilized to evaluate differences in propotions. Kaplan-Meier analysis with log-rank test and Cox proportional hazards model analysis were performed to examine the association between hypomagnesemia and all-cause mortality. We used the age- and sex-adjusted model and the fully adjusted model (adjusted for age, sex, body mass index (BMI), hypertension, diabetes, eGFR, alcohol consumption, smoking status, serum sodium, potassium, chlorine, calcium, phosphorus levels, aspartate aminotransferase (AST) and alanine aminotransferase (ALT)). We confirmed the proportional hazard assumption that the graph of the log(-log(survival)) versus log of survival time graph resulted in parallel lines. A p-value <0.05 indicated a statistically significant difference. All statistical analyses were performed using the JMP version 14 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

The distribution of serum Mg levels in the subjects is shown in Fig. 1. The mean serum Mg level was 2.4 (±0.2) mg/dL. We divided the participants into two groups: those with serum Mg levels ≤2.3 mg/dL (low Mg group) and those with serum Mg levels ≥2.4 mg/dL (high Mg group). The clinical characteristics of the study participants at the baseline are shown in Table 1. The total number of participants was 1,314 (592 males and 722 females), of which 511 (38.9%) were in the low Mg group. We compared the background factors of the 1,314 analyzed subjects with those of the other 2,209 subjects and found no significant differences. The low Mg group had a significantly higher prevalence of hypertension and diabetes compared to the high Mg group. In the low Mg group, serum sodium, potassium, chlorine, calcium, and phosphorus levels were significantly low, while eGFR, AST, ALT, gamma-glutamyl transpeptidase, and HbA1c levels were significantly high. Stratified comparisons between males and females revealed significant differences in alcohol consumption, AST, and gamma-glutamyl transpeptidase only in males. BMI, eGFR, and HbA1c were significantly differ-

Table 1. Baseline characteristics of study subjects.

	Total			Male			Female		
	Mg≦2.3	Mg≧2.4	*p* value	Mg≦2.3	Mg≧2.4	*p* value	Mg≦2.3	Mg≧2.4	*p* value
Number	511	803		251	341		260	462	
Age (y)	63.5±9.7	64.1±9.9	0.32	64.0±9.7	65.0±9.7	0.19	63.1±9.7	63.4±10.0	0.71
Body mass index (kg/m^2)	23.9±3.4	23.2±3.1	<0.01	23.6±3.1	23.4±2.8	0.30	24.2±3.6	23.2±3.3	<0.01
Alcohol consumption (%)	46.6	37.1	<0.01	78.9	68.3	<0.01	15.4	14.1	0.66
Smoking status (%)	33.1	29.5	0.18	59.8	58.7	0.80	7.3	8.0	0.77
Hypertension (%)	44.6	42.1	0.39	51.0	46.9	0.36	38.5	38.5	1.00
Diabetes (%)	9.0	3.4	<0.01	11.3	3.9	<0.01	6.8	3.1	0.03
Serum Na (mEq/L)	149.2±3.1	151.0±3.6	<0.01	149.0±3.2	150.5±3.7	<0.01	149.5±3.0	151.4±3.5	<0.01
Serum K (mEq/L)	4.2±0.4	4.4±0.4	<0.01	4.3±0.4	4.4±0.4	<0.01	4.2±0.4	4.3±0.4	<0.01
Serum Cl (mEq/L)	109.4±3.3	110.4±3.5	<0.01	109.0±3.4	109.9±3.6	<0.01	109.8±3.1	110.9±3.4	<0.01
Serum Ca (mg/dL)	9.8±0.4	9.9±0.4	<0.01	9.7±0.4	9.9±0.4	<0.01	9.8±0.4	9.9±0.4	<0.01
Serum P (mg/dL)	3.7±0.5	3.8±0.5	<0.01	3.4±0.5	3.5±0.5	0.04	3.9±0.5	4.0±0.5	<0.01
Serum total cholesterol (mg/dL)	198.3±31.1	200.4±30.5	0.23	190.1±30.0	193.4±29.5	0.18	206.2±30.2	205.5±30.2	0.76
Triglycerides (mg/dL)	104.9±57.6	105.1±53.6	0.96	113.1±68.6	112.5±60.2	0.90	97.0±43.1	99.7±47.4	0.46
eGFR (mL/min/1.73 m^2)	83.2±18.5	80.3±15.9	<0.01	82.4±16.9	80.8±16.4	0.26	84.0±19.9	79.9±15.5	<0.01
AST (IU/L)	25.7±11.2	23.7±7.1	<0.01	28.3±13.6	25.1±7.2	<0.01	23.2±7.4	22.7±6.9	0.32
ALT (IU/L)	23.3±12.8	21.7±10.6	0.01	25.5±14.4	23.6±11.7	0.08	21.2±10.7	20.2±9.6	0.20
γ-GTP (IU/L)	39.8±59.9	30.2±27.0	<0.01	54.9±80.5	39.3±33.5	<0.01	25.2±19.5	23.5±18.2	0.25
HbA1c (%)	5.3±0.7	5.2±0.6	0.01	5.3±0.8	5.2±0.6	0.29	5.3±0.7	5.2±0.5	<0.01
Mg (mg/dL)	2.2±0.1	2.5±0.1	<0.01	2.2±0.1	2.5±0.1	<0.01	2.2±0.1	2.5±0.1	<0.01

Parametric variables are expressed as mean±SD.
eGFR: estimated glomerular filtration rate.

ent only among females, and ALT was not significantly different between males and females.

The total number of deaths during the follow-up period was 93 (7.1%), of which 48 were in the low Mg group and 45 in the high Mg group. Kaplan-Meier analysis was performed to examine the relationship between serum Mg levels and mortality. The results indicated that the low Mg group had a significantly lower survival rate (log-rank $p<0.01$) (Fig. 2).

Cox proportional hazards analysis was performed to investigate the independent association between serum Mg levels and all-cause mortality (Table 2). In the unadjusted model, a significant association was observed between serum Mg levels and all-cause mortality (hazard ratio [HR] 1.72, 95% confidence intervals [CI] 1.14–2.58, $p<0.01$). The age- and sex-adjusted model revealed a significant association of serum Mg levels with all-cause mortality (HR 1.75, 95% CI 1.16–2.63, $p<0.01$). Furthermore, in the fully adjusted model, a significant association was found between serum Mg levels and all-cause mortality (HR 1.73, 95% CI 1.09–2.76, $p=0.02$). When the participants were examined based on sex, the association between serum Mg levels and all-cause mortality was observed only in males in the unadjusted, age-, and sex-adjusted, and fully adjusted models (unadjusted model: HR 1.83, 95% CI 1.13–2.98, $p=0.01$; age- and sex-adjusted model: HR 2.03, 95% CI 1.25–3.29, $p<0.01$; fully adjusted model: HR 2.08, 95%CI 1.19–3.63, $p=0.01$).

In the analysis pertaining to the cause of death, the HR of low Mg group for cardiovascular mortality was 2.61 (95% CI 1.09–6.30, $p=0.03$) in the unadjusted model and 1.69 (95% CI 0.62–4.63, $p=0.31$) in the fully adjusted model. The HR of low Mg group for non-cardiovascular mortality was 1.52 (95% CI 0.96–2.42, $p=0.07$) in the unadjusted model and 1.74 (95% CI 1.03–2.95, $p=0.04$) in the fully adjusted model.

DISCUSSION

In this study, Kaplan-Meier analysis showed that the low Mg group had a significantly lower survival rate than the high Mg group in the overall population. Cox proportional hazards analysis also showed a significantly increased hazard of total mortality in the low Mg group, an association that held even after adjusting for various confounders. When analyzed by sex, the increased hazard ratio was significant only in males. These results suggest that low serum Mg is associated with all-cause mortality independently of confounders and that the association is particularly strong in men.

Previous cohort studies have examined the association of dietary Mg intake with various diseases and mortality. A meta-analysis of 40 studies involving more than 1 million participants found no association between increased Mg intake (100 mg/d) and the risk of developing cardiovascular or coronary artery disease; however, the risk of heart failure and stroke reduced by 22% and 7%, respectively. The relative risk (RR) of total mortality was 0.90 (95% CI, 0.81–0.99) (*10*). A cohort study of 58,615 general community residents in Japan

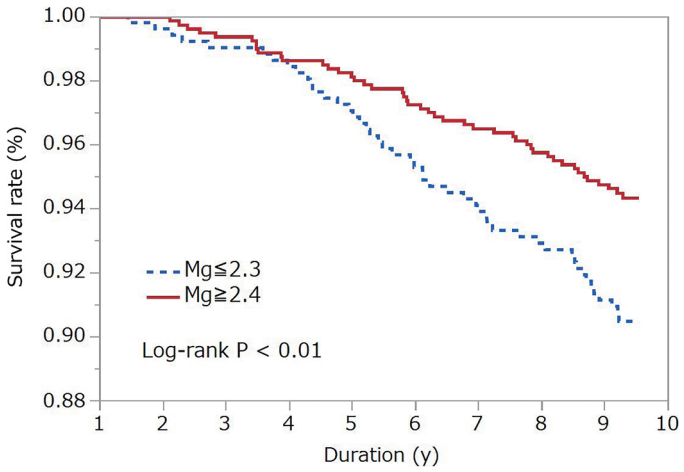

Fig. 2. Ten-year all-cause mortality rates according to serum magnesium levels.

found that Mg intake was inversely associated with cardiovascular mortality, especially among women (*16*). Few studies have examined the relationship between serum Mg levels and disease. A study of 9,820 community residents reported that hypomagnesemia was associated with an increased risk of total cardiovascular death and sudden cardiac death (*19*). A meta-analysis of 19 studies involving a total of 530,000 subjects examined the association of Mg intake and serum Mg levels with the risk of developing CVD. The RRs of the highest group versus the lowest group were 0.85 (95% CI, 0.78–0.92) for Mg intake and 0.77 (95% CI, 0.66–0.87) for serum Mg levels (*13*). However, some studies reported that serum Mg level were not associated with the risk of hypertension or CVD (*15*).

Although previous studies evaluating serum Mg levels in Japanese dialysis patients have been conducted (*20*), this study is the first to examine serum Mg levels in a community-based population. The results of this study revealed that serum Mg levels were associated with the risk of all-cause mortality in the Japanese population.

Various mechanisms have been suggested for the association between serum Mg levels and mortality risk. The Framingham Heart Study conducted in cohort participants without CVD reported that a 50 mg/d increase in Mg intake was associated with a 22% reduction in coronary artery calcification score and a 12% reduction in abdominal aortic calcification scores (*21*). Mg inhibits intracellular calcium deposition, transformation into osteoblast-like cells and apoptosis in vascular smooth muscle cells (VSMCs) (*22*), and also inhibits the hydroxyapatite formation outside the VSMCs (*23*). In addition, studies have confirmed that Mg suppresses various calcification-related factors and increases the expression of calcification inhibitory factors (*24*). Serum Mg levels reportedly affect vascular endothelial function (*25*).

Mg is also associated with inflammation as its deficiency causes the activation of leukocytes and macrophages, production of pro-inflammatory cytokines, acute-phase proteins, and free radicals (*26*). In a study involving menopausal women, Mg intake reduced the levels of inflammatory markers such as high-sensitive C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α receptor 2 (*27*). A meta-analysis of 11 studies reported that the administration of Mg helped significantly decrease CRP levels in groups with elevated CRP lvels of more than 3 mg/dL (*28*).

In the present study, the reason the association between hypomagnesemia and all-cause mortality was observed only in males is unclear. However, hypomagnesemia may be associated with malnutrition, which increase mortality rates (*29*). As heavy drinkers, who are more commonly males, are more likely to develop these conditions, malnutrition associated with hypomagnesemia may have affected mortality, especially among males. Analysis by cause of death revealed an association between hypomagnesemia and non-cardiovascular mortality in the fully adjusted model. An association between inadequate Mg intake and immune response, infection (*30*), and malignancy (*31*) has also been reported, and the results of this study may reflect this. Racial differences between Japanese and Westerners may influence the correlation between serum Mg levels and healthy life expectancy. But it is difficult to make a simple comparison because of the differences in physique, diet, and causes of death between Japanese and Westerners.

Although this study was a prospective cohort study involving the general population and was based on a standardized questionnaire and protocol, it had several limitations. First, serum Mg levels were available only for the baseline survey. Second, no information was available on the use of Mg-containing drugs and data of the presence of dehydration and thyroid function, which may affect serum Mg levels. The third limitation was the sample size. Although this study included more than 1,314 participants, the number of deaths was insufficient for a detailed examination in terms of the cause of death, including a multivariate analysis of cardiovascular death. The fourth limitation was the adoption of a unique serum Mg cutoff value. It may not be possible to simply compare with previous reports.

Table 2. The hazard ratios of low serum magnesium (≦2.3 mg/dL) for all-cause mortality.

	Person-year	Number of deaths	Incident rate (/1,000 person-year)	Unadjusted		Age, sex-adjusted		Fully adjusted[1]	
				HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value[1]
Total participants									
High Mg group	7,353	45	6.1	reference		reference		reference	
Low Mg group	4,601	48	10.4	1.72 (1.14–2.58)	<0.01	1.75 (1.16–2.63)	<0.01	1.73 (1.09–2.76)	0.02
Males									
High Mg group	3,077	29	9.4	reference		reference		reference	
Low Mg group	2,214	38	17.2	1.83 (1.13–2.98)	0.01	2.03 (1.25–3.29)	<0.01	2.08 (1.19–3.63)	0.01
Females									
High Mg group	4,276	16	3.7	reference		reference		reference	
Low Mg group	2,386	10	4.2	1.12 (0.51–2.47)	0.78	1.16 (0.52–2.55)	0.72	1.27 (0.51–3.18)	0.61

HR: hazard ratio, CI: confidence interval, Mg: magnesium.
[1] Adjusted for age, sex, body mass index, smoking status, alcohol intake, diabetes mellitus, hypertension, estimated glomerular filtration rate, serum sodium, serum potassium, serum chlorine, serum calcium, and serum phosphorus, aspartate aminotransferase, alanine aminotransferase.

In the present study, serum Mg levels were associated with the risk of all-cause mortality in males. Although it is difficult to determine a causal relationship because this is an observational study, the results suggest that Mg supplementation for patients presenting with hypomagnesemia may improve life expectancy. As high serum Mg levels cause adverse events (*32*), further studies are required to determine the optimal Mg levels and the interventions required for people with hypomagnesemia.

Authorship

Y.A and T.K conceived and designed the study, analyzed data, and drafted the manuscript. F.M, M.W, T.K, and U.Y reviewed the manuscript. All authors read and approval the final manuscript.

Disclosure of state of COI

None of the authors has any conflicts of interest to disclosure relevant to this study.

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