Hypomagnesemia in Type 2 Diabetic Nephropathy

A novel predictor of end-stage renal disease

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OBJECTIVE—There is now growing evidence that magnesium (Mg) deficiency is implicated in type 2 diabetes and its complications. However, it has not been fully elucidated whether hypomagnesemia is a predictor of end-stage renal disease (ESRD) in type 2 diabetic nephropathy.

RESEARCH DESIGN AND METHODS—This retrospective cohort study included 455 chronic kidney disease (CKD) patients (144 with type 2 diabetic nephropathy and 311 with nondiabetic CKD) who were hospitalized at Osaka General Medical Center for a CKD educational program between April 2001 and December 2007. The primary outcome was progression to renal replacement therapy. Participants were categorized based on serum Mg level into Low-Mg (serum Mg level ≤1.8 mg/dL) and High-Mg (serum Mg level >1.8 mg/dL) groups with the previously published normal lower limit chosen as the cutoff point.

RESULTS—Of the subjects with type 2 diabetic nephropathy, 102 progressed to ESRD during follow-up (median, 23 months). A multivariate Cox proportional hazards model showed that after adjustment for various demographic factors and laboratory data, the Low-Mg group had a 2.12-fold higher risk of ESRD than the High-Mg group (95% CI 1.28–3.51; $P = 0.004$). In contrast, 135 of the nondiabetic CKD subjects progressed to ESRD during follow-up (median, 44 months). No significant difference in outcome was found between the Low- and High-Mg groups of this population (adjusted hazard ratio, 1.15; 95% CI 0.70–1.90; $P = 0.57$).

CONCLUSIONS—Hypomagnesemia is a novel predictor of ESRD in patients with type 2 diabetic nephropathy.

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Magnesium (Mg) is the fourth most abundant cation in the human body and plays a key role in many fundamental biological processes, including energy metabolism and DNA synthesis. Mg deficiency has been shown to cause endothelial cell dysfunction, inflammation, and oxidative stress, which are major contributors to atherosclerosis (1–3). Some epidemiologic studies have reported associations between low Mg intake or serum Mg level and hypertension, coronary artery disease, and ischemic stroke (4–6).

Mg and type 2 diabetes have a close relationship. Approximately one-third of patients with type 2 diabetes have hypomagnesemia, mainly caused by enhanced renal excretion (7). Mg deficiency is associated with poor glycemic control, and Mg supplementation improves insulin sensitivity (8). Moreover, there is substantial evidence of associations between hypomagnesemia and various complications of type 2 diabetes, including neuropathy, retinopathy, foot ulcers, and albuminuria (9–12). The relationship between Mg deficiency and advanced type 2 diabetic nephropathy, however, remains to be fully elucidated. Pham et al. (13) reported that serum Mg level was significantly associated with the slope of inverse serum creatinine (SCr) in type 2 diabetes with near-normal renal function. However, they failed to show a significant association between hypomagnesemia and hard renal outcome (doubling of SCr and initiation of renal replacement therapy [RRT]), probably due to low statistical power (14). Therefore, the aim of the current study was to determine whether hypomagnesemia is a predictor of end-stage renal disease (ESRD) in patients with advanced type 2 diabetic nephropathy. We also compared the impact of hypomagnesemia on renal outcome in type 2 diabetic nephropathy with that in nondiabetic chronic kidney disease (CKD).

RESEARCH DESIGN AND METHODS

Subjects

In this cohort study, the medical records of all patients hospitalized at Osaka General Medical Center for a CKD educational program between April 2001 and December 2007 were retrospectively analyzed. The patients were followed from the day of hospitalization until either the time of the outcome or the end of the study's observational period (1 April 2011). We excluded patients with either <3 months of follow-up data or type 1 diabetes.

The study protocol was approved by the Faculty of Medicine Ethics Committee of Osaka General Medical Center.

CKD educational program

The CKD educational program was a 1-week program in which nephrologists, nurses, and nutritionists educated patients with CKD about their renal disease and provided individualized nutritional therapy and treatment options for ESRD. Patients who already received RRT, presented with acute kidney injury, or had severe acute complications such as acute heart failure, stroke, or systemic infection were excluded from the study. In accordance with the National Kidney Foundation

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definition, CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL · min^{-1} · 1.73 m^{-2} and/or proteinuria lasting for at least 3 months. The eGFR was calculated using an equation for estimating GFR for Japanese individuals: eGFR = $194 \times \text{SCr}^{1.094} \times \text{age}^{-0.287} \times 0.739$ (if female), where SCr is in mg/dL (15). Proteinuria was defined as protein excretion >300 mg in a 24-h urine sample. After the program, the patients were followed up by nephrologists in the outpatient department of Osaka General Medical Center.

Outcomes

The primary outcome was progression to ESRD defined as the initiation of RRT. The secondary outcome was a composite of time-to-first-event of progression to ESRD or death from any cause. All outcomes were ascertained from the medical records.

Predictors

The main predictor was serum Mg level measured using the xylidyl blue method. Participants were categorized by serum Mg level with a cutoff value of 1.8 mg/dL (Low-Mg group, serum Mg level ≤1.8 mg/dL; High-Mg group, serum Mg level >1.8 mg/dL). This cutoff value was chosen based on the previously published normal lower limit (16). Serum Mg level was also treated as a continuous variable to model the nonlinear effect of serum Mg level on the outcome.

Baseline characteristics

Demographic data including age, sex, CKD etiology, presence or absence of diabetes, hypertension, dyslipidemia, pre-existing cardiovascular disease (CVD) or stroke, and medication (angiotensin-converting enzyme inhibitors [ACEIs], angiotensin II receptor blockers [ARBs], statins, loop and thiazide diuretics, and Mg oxide [MgO]) were obtained from the patients' medical records. The principal indication for prescribing MgO in Japan is constipation, and there was no off-label use in any study subject.

Laboratory data including SCr, calcium (Ca), phosphorus (P), Mg, albumin, and hemoglobin A_{1c} (HbA_{1c}) levels were measured from the first blood samples, which were obtained from most participants soon after admission. If these were not available, the most recent measurement within 1 month of admission was used. Because HbA_{1c} levels were measured using high-pressure liquid chromatography (MBC Laboratories Inc., Tokyo, Japan), the estimated National Glycohemoglobin Standardization Program (NGSP) equivalent values for HbA_{1c} were calculated using the following formula: HbA_{1c} (NGSP) = HbA_{1c} (Japanese Diabetes Society) + 0.4 (17). When serum albumin level was <4.0 g/dL, the serum Ca level was adjusted as follows: corrected serum Ca level (mg/dL) = measured serum Ca level (mg/dL) + (4.0 − serum albumin [g/dL]) (18). A 24-h urine sample was obtained after admission to measure creatinine clearance (CCr) and urine protein (UP). All parameters were measured in the clinical chemistry laboratory of Osaka General Medical Center using standard techniques.

Definitions of hypertension, diabetes, and dyslipidemia

Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg as measured by automatic devices with the patient in a sitting position and/or a previous diagnosis of hypertension. Diabetes was defined as a fasting glucose concentration ≥126 mg/dL, nonfasting glucose concentration ≥200 mg/dL, HbA_{1c} (NGSP) value ≥6.5%, and/or a previous diagnosis of diabetes. Dyslipidemia was defined as a triglyceride level ≥150 mg/dL, LDL cholesterol ≥140 mg/dL, and/or previous diagnosis of dyslipidemia (19). Pre-existing CVD was defined as a history of coronary artery disease, hypertensive heart disease, valvular heart disease, cardiomyopathy, or arrhythmia. Pre-existing stroke was defined as a history of cerebral infarction, cerebral hemorrhage, or subarachnoid hemorrhage.

Statistical analysis

Continuous variables were expressed as median (interquartile range) and categorical variables as number (percent). The two groups were compared using the Mann-Whitney *U* test or χ^2 test as appropriate.

Spearman rank correlation analysis was used to evaluate the correlations between serum Mg level as a continuous variable and serum Ca and P levels and CCr.

Survival analyses were performed using Kaplan-Meier survival curves (log-rank test) and Cox proportional hazards models. First, univariate Cox models were constructed for all baseline characteristics. All variables for which $P < 0.1$ in the univariate Cox models and/or in the baseline comparisons between the Low- and High-Mg groups were further entered into multivariate Cox models. The proportionality assumption was checked by introducing time-dependent variables of each baseline characteristic into the model. The linearity of the log hazard ratio (HR) was verified for each continuous variable except for age and CCr; we therefore treated age and CCr as categorical variables (age, ≤65 and >65 years; CCr, ≤30 and >30 mL/min). Finally, a multivariate Cox model with a restricted cubic spline graph was used to examine the association between serum Mg level as a continuous variable and log-adjusted relative HR. Data were missing for only one (HbA_{1c}) of the type 2 diabetic nephropathy subjects and five (both CCr and UP) of the nondiabetic CKD subjects. Given the very small proportion of missing data, we did not employ a data imputation method, as doing so would not have affected the direction or magnitude of our results.

All reported *P* values were two-sided, and values of $P < 0.05$ were considered statistically significant. Statistical analyses were performed using R statistical software (version 2.7.1; R Foundation for Statistical Computing), SPSS 11.0J (SPSS Japan Inc.), and JMP 8 (SAS Institute).

RESULTS

Study population and baseline characteristics

Of the 547 CKD patients admitted to the CKD educational program, 26 were excluded from the analyses (17 were followed up for <3 months, 1 was diagnosed with type 1 diabetes, and the medical records of 8 patients had been discarded). Of the remaining 521 patients, baseline serum Mg level data were not available for 66. We compared all baseline characteristics between the patients with and without serum Mg level data and found no significant differences between groups (data not shown), except in the proportion of MgO users ($P = 0.03$); among 35 MgO users, only 1 did not have serum Mg level data. Those patients with available serum Mg level data ($n = 455$) were eligible for further analyses. The median serum Mg level was 2.1 mg/dL (interquartile range, 1.9–2.3 mg/dL) and not normally distributed. The baseline characteristics stratified by Mg group are summarized in Table 1. Among the subjects with type 2 diabetic nephropathy, the Low-Mg group had significantly higher UP levels, lower serum albumin levels, and a lower proportion of MgO users. Among the nondiabetic CKD patients, the Low-Mg group had significantly lower serum albumin levels and a higher proportion of

Table 1—*Baseline characteristics stratified by Mg group in subjects with type 2 diabetic nephropathy and nondiabetic CKD*

	Type 2 diabetic nephropathy (*n* = 144)			Nondiabetic CKD (*n* = 311)		
Characteristics	Low-Mg (*n* = 35)	High-Mg (*n* = 109)	*P* value	Low-Mg (*n* = 44)	High-Mg (*n* = 267)	*P* value
Age (years)	62 (51–67)	65 (58–72)	0.05	66 (56–72)	68 (58–74)	0.42
Sex, male (%)	25 (71.4)	72 (66.1)	0.55	30 (68.2)	157 (58.8)	0.23
CCr (mL/min)	20.7 (13.2–33.0)	27.9 (17.7–40.3)	0.14	30.5 (17.9–42.4)	28.8 (16.6–42.6)	0.41
UP (g/24 h)	3.8 (2.5–6.6)	3.1 (1.3–5.6)	0.04	0.7 (0.1–2.8)	0.5 (0.1–1.4)	0.20
HbA_{1c} (NGSP) (%)	6.9 (6.3–7.6)	7.4 (6.6–8.2)	0.07	—	—	—
Ca (mg/dL)	9.2 (8.8–9.4)	9.1 (8.8–9.4)	0.69	9.1 (8.8–9.3)	9.1 (8.8–9.4)	0.66
P (mg/dL)	3.9 (3.3–4.3)	3.9 (3.5–4.5)	0.33	3.4 (3.1–3.7)	3.6 (3.2–4.2)	0.06
Albumin (g/dL)	3.1 (2.5–3.4)	3.4 (2.9–3.8)	0.04	3.6 (3.3–3.9)	3.8 (3.6–4.1)	<0.001
Hypertension (%)	34 (97.1)	103 (94.5)	0.50	37 (84.1)	222 (83.2)	0.88
Dyslipidemia (%)	33 (94.3)	97 (89.0)	0.33	36 (81.8)	238 (89.1)	0.19
Pre-existing stroke (%)	8 (22.9)	18 (16.5)	0.41	4 (9.1)	35 (13.1)	0.44
Pre-existing CVD (%)	10 (28.6)	18 (16.5)	0.13	6 (13.6)	55 (20.6)	0.26
ACEI/ARB (%)	24 (68.6)	86 (78.9)	0.22	33 (75.0)	145 (54.3)	0.008
Statin (%)	11 (31.4)	41 (37.6)	0.50	9 (20.5)	84 (31.5)	0.13
Loop (%)	24 (68.6)	61 (56.0)	0.18	10 (22.7)	70 (26.2)	0.62
Thiazide (%)	3 (8.6)	10 (9.2)	0.91	5 (11.4)	9 (3.4)	0.04
MgO (%)	0 (0)	9 (8.2)	0.02	1 (2.3)	24 (9.0)	0.08

Data are presented as number (%) or median (interquartile range).

ACEI/ARB and thiazide diuretic users. The causes of kidney failure in the subjects with nondiabetic CKD included chronic glomerulonephritis (*n* = 172), benign nephrosclerosis (*n* = 102), rheumatoid arthritis (*n* = 6), amyloidosis (*n* = 5), polycystic kidney disease (*n* = 4), gouty nephropathy (*n* = 3), hydronephritis (*n* = 2), others (*n* = 10), and unknown (*n* = 7).

Associations between serum Mg level as a continuous variable and Ca, P, and Ccr

There was no significant correlation between serum Mg level as a continuous variable and serum Ca level (Spearman $\rho = -0.06$; $P = 0.25$). In contrast, a significant positive correlation was found between serum Mg and P levels (Spearman $\rho = 0.14$; $P = 0.003$).

Because the relationship between Mg and renal function may vary with the presence of diabetes (20), we tested the correlation between serum Mg level and CCr after stratifying the subjects by the presence or absence of type 2 diabetes. A significant negative correlation between serum Mg level and CCr was noted in patients with non–type 2 diabetes (Spearman $\rho = -0.22$; $P = 0.004$) but not in those with type 2 diabetes (Spearman $\rho = -0.006$; $P = 0.91$).

Survival analysis

Of the subjects with type 2 diabetic nephropathy, 102 progressed to ESRD, and 5 died during follow-up (median, 23 months). Kaplan-Meier analysis (Fig. 1) showed that the Low-Mg group had significantly worse primary outcome than the High-Mg group ($P = 0.001$). Except for the Mg group, those variables for which $P < 0.10$ in the univariate Cox models were age ($P = 0.07$), CCr ($P < 0.001$), UP ($P < 0.001$), serum P and albumin levels ($P < 0.001$ and 0.003, respectively), ACEI/ARB ($P = 0.09$), loop and thiazide diuretics ($P = 0.02$ and

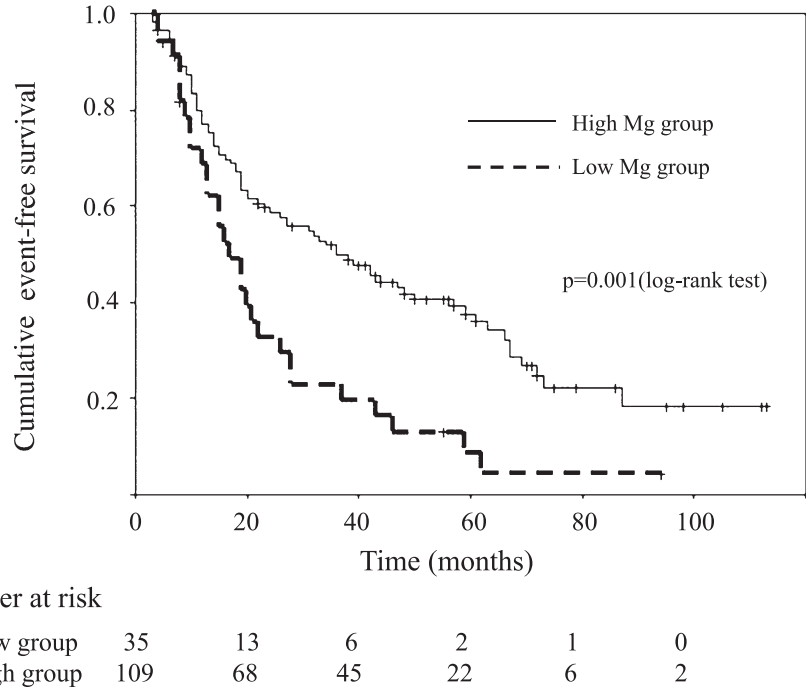

Figure 1—*Kaplan-Meier estimation of cumulative event-free survival for the primary outcome in type 2 diabetic nephropathy.*

0.07, respectively), and MgO ($P = 0.07$). Above these variables, HbA_{1c} for which $P < 0.10$ in the baseline comparisons between the Low- and High-Mg groups (Table 1) were further entered into the multivariate Cox models, which showed that patients in the Low-Mg group were at a 2.12-fold higher risk of developing ESRD than were those in the High-Mg group (95% CI 1.28–3.51; $P = 0.004$) (Table 2). Similar results were obtained for the secondary outcome (adjusted HR [95% CI]: 2.19 [1.34–3.59]; $P = 0.002$). A cubic spline curve of serum Mg level as a continuous variable against the predicted log-adjusted relative HR for the primary outcome (Fig. 2) showed that the relative hazard appeared to increase as serum Mg level decreased to <2.0 mg/dL but almost plateaued above this value. In this analysis, serum Mg level was still significantly associated with the outcome ($P = 0.003$).

In contrast, 135 of the patients with nondiabetic CKD progressed to ESRD, and 13 died during follow-up (median, 44 months). Cox models showed that patients in the Low- and High-Mg groups did not differ significantly in both primary and secondary outcomes (Table 2).

Additional analysis in type 2 diabetic nephropathy

We performed additional analyses in the subjects with type 2 diabetic nephropathy. As MgO strongly affects the serum Mg level, Cox models excluding the MgO users were constructed; however, this exclusion did not change the main results (Table 2).

We repeated the analyses after excluding patients with CCr <15 mL/min because these patients had already reached the predialysis period and were, therefore, unsuitable candidates for estimating the influence of Mg on renal outcome. Low-mg level remained a significant predictor of poor outcome under these conditions (Table 2).

When serum Mg levels were corrected by serum albumin level by using the formula proposed by Kroll et al. (21) (albumin-corrected serum Mg [mmol/L] = measured serum Mg [mmol/L] + 0.05 (4.0 − serum albumin [mg/dL] [if serum albumin ≤4.0 mg/dL]), low-Mg level remained a significant predictor of outcome (Table 2).

Because of the possibility of incomplete 24-h urine collection, we substituted eGFR (as a continuous variable) for CCr; this did not change the results (adjusted HR [95% CI]: primary outcome, 2.27 [1.38–3.73]; $P = 0.001$; secondary outcome, 2.32 [1.42–3.78]; $P = 0.001$).

Given the strong physiological association between Ca and Mg, we added the serum Ca level as an explanatory variable to the original multivariate Cox models, after which the prognosis was still significantly worse for patients in the Low-Mg group than for those in the High-Mg group (adjusted HR [95% CI]: primary outcome, 2.27 [1.37–3.74]; $P = 0.001$; secondary outcome, 2.34 [1.43–3.82]; $P = 0.001$). Similarly, as hypertension is an established risk factor for the progression of type 2 diabetic nephropathy, we

Table 2—*Survival analysis by Cox proportional hazards models*

		Univariate			Multivariate		
	Number of events	HR[a]	95% CI	*P* value	HR[a]	95% CI	*P* value
Subjects with type 2 diabetic nephropathy							
Total cohort ($n = 144$)[b]							
Primary	102	2.01	1.28–3.08	0.003	2.12	1.28–3.51	0.004
Secondary	107	1.98	1.27–3.01	0.003	2.19	1.34–3.59	0.002
After excluding MgO users ($n = 135$)[b]							
Primary	97	1.93	1.23–2.96	0.005	2.13	1.28–3.54	0.004
Secondary	101	1.92	1.23–2.92	0.005	2.20	1.34–3.63	0.002
After excluding those with CCr <15 mL/min ($n = 112$)[b]							
Primary	76	2.24	1.35–3.72	0.002	2.33	1.28–4.26	0.006
Secondary	80	2.22	1.35–3.64	0.002	2.41	1.34–4.33	0.003
After serum Mg level was corrected by serum albumin level ($n = 144$)[b]							
Primary	102	1.70	1.04–2.78	0.04	2.40	1.40–4.14	0.002
Secondary	107	1.71	1.06–2.76	0.03	2.46	1.45–4.19	0.001
Subjects with serum P level <3.9 mg/dL ($n = 71$)[c]							
Primary	41	2.31	1.19–4.50	0.01	2.35	1.11–4.96	0.03
Secondary	44	2.09	1.09–4.02	0.03	2.13	1.03–4.39	0.04
Subjects with serum P level ≥3.9 mg/dL ($n = 72$)[c]							
Primary	61	2.00	1.11–3.61	0.02	1.94	1.03–3.65	0.04
Secondary	63	2.08	1.17–3.70	0.01	2.04	1.10–3.80	0.02
Subjects with nondiabetic CKD ($n = 311$)[d]							
Primary	135	1.13	0.71–1.81	0.60	1.16	0.70–1.90	0.57
Secondary	148	1.08	0.60–1.50	0.74	1.05	0.65–1.70	0.78

[a]With reference to the High-Mg group. [b]The models were adjusted for age, CCr, UP, HbA_{1c} (NGSP), serum P level, serum albumin level, ACEI/ARB use, loop diuretic use, thiazide diuretic use, and MgO use. [c]The models were adjusted for CCr, UP, and serum P. [d]The model was adjusted for CCr, UP, serum Ca level, serum P level, serum albumin level, ACEI/ARB use, thiazide diuretic use, and MgO use.

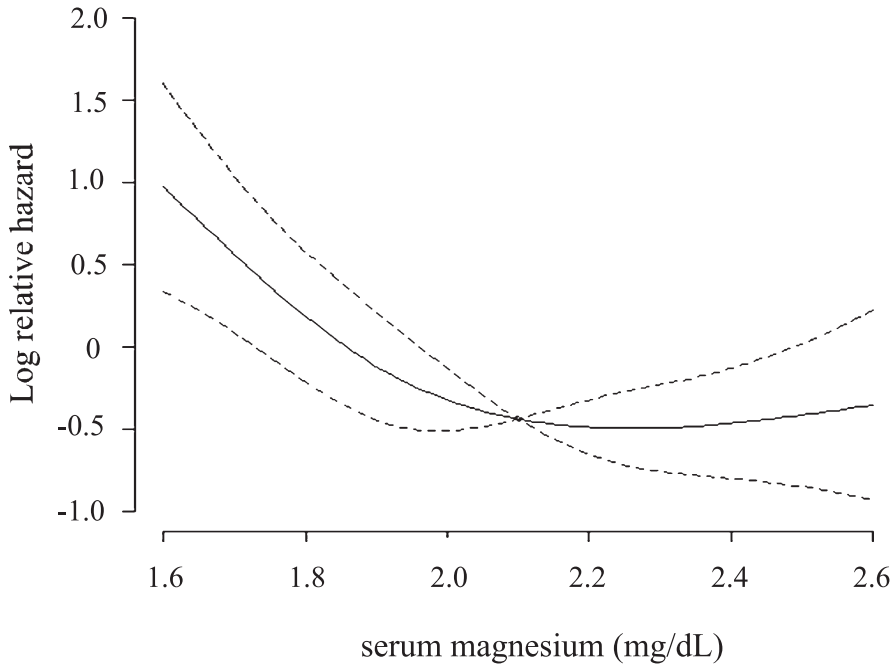

Figure 2—*Estimated log-relative hazards for the primary outcome in a multivariate regression spline model in type 2 diabetic nephropathy subjects. The model was adjusted for age, CCr, UP, HbA_{1c}, serum P and albumin levels, ACEI/ARB use, loop or thiazide diuretic use, and MgO use. The solid line represents the estimated log-relative HR, and the dashed line represents the 95% CI.*

added hypertension to the original models, but it did not significantly alter the results (adjusted HR [95% CI]: primary outcome, 2.07 [1.25–3.45]; $P = 0.005$; secondary outcome, 2.14 [1.30–3.52]; $P = 0.003$).

To minimize confounding due to the strong correlation between serum Mg and P levels, we performed a subgroup analysis stratified by median serum P level. Because the number of events in each subgroup could not accommodate all baseline characteristics into multivariate models as explanatory variables, we chose those variables that were significant in the multivariate Cox model in the total cohort (i.e., CCr [$P < 0.001$], UP [$P < 0.001$], and serum P level [$P < 0.001$]) as well as Mg group. The Low-Mg group had a significantly poor outcome in both subgroups, and the adjusted HRs for the outcomes in each subgroup were comparable (Table 2). The interaction between serum P level and Mg group in the total cohort was not statistically significant ($P = 0.16$). These results suggest that the effect of Mg group on outcome was independent of P status.

CONCLUSIONS—In this observational study, we found that hypomagnesemia was significantly associated with progression to ESRD in patients with type 2 diabetic nephropathy but not in those with nondiabetic CKD.

To the best of our knowledge, this is the first study to demonstrate the influence of hypomagnesemia on hard renal outcome in patients with advanced type 2 diabetic nephropathy. Pham et al. (13) investigated type 2 diabetic patients with near-normal renal function and found a significant association between serum Mg level and the slope of the inverse SCr. However, that study was limited by its use of a surrogate renal outcome. The same authors later re-evaluated the long-term outcomes of the cohort but found no significant association between Mg level and hard renal outcome (14), probably because the small number of events had low statistical power. That study had several other drawbacks, including no adjustment for confounding factors and selection bias due to missing SCr data for ~40% of the subjects. In comparison, the current study was more robust because of the use of hard renal outcome (ESRD), good data availability, and a relatively small proportion of subjects lost to follow-up (7.6% of the subjects with type 2 diabetic nephropathy). Moreover, the results were adjusted for potential confounding factors, and their robustness was confirmed by several additional sensitivity analyses. Taken together, our findings showed that hypomagnesemia in patients with type 2 diabetic nephropathy is a novel independent predictor of ESRD.

An important clinical implication of our findings is that Mg supplementation may be renoprotective in type 2 diabetic nephropathy. It was reported that higher Mg intake is significantly associated with a lower risk of type 2 diabetes (22). $MgCl_2$ supplementation improves the insulin resistance index and lowers HbA_{1c} in patients with type 2 diabetes (8). The effect of Mg on renal function has also been investigated in a few animal experiments. For example, rats fed an Mg-deficient diet have been shown to have higher urine *N*-acetyl-β-D-glucosaminidase levels, indicating that Mg deficiency induces renal interstitial tubular injury (23). In a rat model of acute ischemic kidney injury, Mg supplementation has been shown to have a renoprotective effect (24). To date, however, the effect of Mg supplementation on type 2 diabetic nephropathy has not been studied directly.

It is unclear why the impact of hypomagnesemia on renal outcome differed between type 2 diabetic nephropathy and nondiabetic CKD. It was reported that Mg deficiency may promote the development of diabetes complications via cell membrane transport disruption and subsequent intracellular depletion of *myo*-inositol (25). Mg deficiency is, in fact, associated with various type 2 diabetes complications including albuminuria (9–12). Therefore, it is plausible that Mg deficiency has specific pathogenic significance in type 2 diabetic nephropathy; however, the exact role of Mg deficiency in type 2 diabetic nephropathy warrants further investigation.

Investigation of the association between hypomagnesemia and renal outcome requires particular attention on potential confounding factors. First, Mg deficiency in the general population has been implicated in hypertension (4), dyslipidemia (26), coronary artery disease (5), and ischemic stroke (6), which are the major causes and complications of CKD. Unlike this evidence, however, there were no significant differences in terms of the prevalence of hypertension, dyslipidemia, pre-existing CVD, and pre-existing stroke between the Low- and High-Mg groups in patients with type 2 diabetic nephropathy. This difference is probably due to the different nature of the studied populations. We also confirmed that a significant association between

hypomagnesemia and poor renal outcome in type 2 diabetic nephropathy was independent of hypertension, an established risk factor of the progression of type 2 diabetic nephropathy.

Another potential confounder is Ca and P because Mg homeostasis is closely linked to these minerals. In general, hypomagnesemia causes hypocalcemia via peripheral parathyroid hormone (PTH) resistance, inhibition of PTH secretion, and impaired conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (27–29). However, we found no significant correlation between serum Mg and Ca levels. One possible explanation for this is that PTH and 1,25-dihydroxyvitamin D are more strongly influenced by reduced renal function in patients with CKD, thereby attenuating the relationship between Mg and Ca. The relationship between Mg and P is not fully understood, but P depletion reduced Mg ion reabsorption in the distal convoluted tubule in an in vitro study (30). We also observed a significant positive correlation between serum Mg and P levels. Schwarz et al. (31) reported that high serum P levels were significantly associated with CKD progression. They also showed that low serum Ca tended to be associated with increased risk of CKD progression. We showed that the significant association between hypomagnesemia and poor renal outcome in patients with type 2 diabetic nephropathy was independent of serum Ca and P levels. This result suggests that serum Mg level should be considered when evaluating the influence of CKD mineral and bone disease on renal outcome, especially in patients with type 2 diabetic nephropathy.

Finally, renal function is the major regulator of the serum Mg level. Dewitte et al. (20) reported a significant negative correlation between CCr and serum total and ionized Mg levels in patients without diabetes but no significant correlation in those with diabetes, which is in agreement with our findings. Although the reason for this difference is uncertain, insulin enhances Mg reabsorption at the thick ascending limb of the loop of Henle, where ~55% of the filtered Mg is reabsorbed (32). Therefore, in patients with diabetes, insulin resistance or deficiency can promote Mg loss at the thick ascending limb (33), which might compensate for the reduced glomerular filtration (34). Given the lack of a significant correlation between CCr and serum Mg level in type 2 diabetic nephropathy, CCr may not be a potent confounder of hypomagnesemia for poor renal outcome in this population.

The current study has some limitations. First, the observational nature of the study design precluded proving a causative relationship between hypomagnesemia and poor renal outcome. Although we tried to correct for the major confounding factors known to be associated with serum Mg level and CKD progression, we cannot rule out residual confounding effects. Unfortunately, the number of MgO users in type 2 diabetic nephropathy subjects was too small to estimate accurately the influence of MgO use as Mg supplementation on renal outcome. Second, the total serum Mg level was used to evaluate Mg status. Although the serum Mg level correlates fairly well with the intracellular free Mg level (35), only 1% of the total body Mg exists extracellularly; therefore, serum Mg level may be an insensitive marker for intracellular Mg deficiency (36). Because hypoalbuminemia decreases serum total Mg level but not ionized Mg level, we corrected serum Mg level for serum albumin level in additional analysis after which hypomagnesemia remained significantly associated with poor renal outcome in type 2 diabetic nephropathy. Finally, our study was conducted at a single hospital, and the study subjects were patients who had attended a CKD educational program, which could have created a selection bias toward compliant patients. Our findings, therefore, require further external validation.

We showed that hypomagnesemia independently predicts the progression to ESRD in patients with advanced type 2 diabetic nephropathy. Our findings suggest that Mg supplementation may be renoprotective in this population. The precise pathogenesis of Mg deficiency in type 2 diabetic nephropathy should be further investigated.

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Y.S. researched data and wrote the manuscript. H.K. and K.N. researched data. T.S., T.H., Y.I., H.R., and Y.T. reviewed and edited the manuscript. Y.S., H.K., T.S., K.N., T.H., N.O., A.S., Y.I., M.S., H.R., K.M.T., and Y.T. contributed to discussion. Y.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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