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Serum Magnesium Level Is Associated with Type 2 Diabetes in Women with a History of Gestational Diabetes Mellitus: The Korea National Diabetes Program Study

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Gestational diabetes mellitus (GDM) is a strong predictor of postpartum prediabetes and transition to overt type 2 diabetes (T2DM). Although many reports indicate that low magnesium is correlated with deteriorated glucose tolerance, the association between postpartum serum magnesium level and the risk for T2DM in women with a history of GDM has not been evaluated. We analyzed postpartum serum magnesium levels and development of prediabetes and T2DM in women with prior GDM according to American Diabetes Association (ADA) criteria using the Korean National Diabetes Program (KNDP) GDM cohort. During a mean follow-up of 15.6 ± 2.0 months after screening, 116 women were divided into three groups according to glucose tolerance status. Ultimately, eight patients (6.9%) were diagnosed with T2DM, 59 patients (50.9%) with prediabetes, and 49 patients (42.2%) with normal glucose tolerance (NGT) after follow-up. The T2DM group had the lowest serum magnesium level (0.65 [0.63-0.68] mM/L) in the postpartum period, but there was no significant difference between the prediabetes group (0.70 [0.65-0.70] mM/L) and the NGT group (0.70 [0.65-0.70] mM/L) (P = 0.073) Multiple logistic regression analysis showed that postpartum HOMA-IR was a significant predictor of both prediabetes and T2DM. Moreover, we found that postpartum serum magnesium level was also a possible predictor for T2DM development. Serum magnesium level in the postpartum period may be a possible predictor for T2DM development in women with a history of GDM.

Keywords: Diabetes, Gestational; Serum Magnesium; Hypomagnesaemia; Prediabetes; Diabetes Mellitus; Type 2

INTRODUCTION

Gestational diabetes mellitus (GDM), defined as glucose intolerance during pregnancy, is a risk factor not only for adverse perinatal outcome, but also for postpartum prediabetes and development of type 2 diabetes mellitus (T2DM). The Diabetes Prevention Program study results showed that women with self-reported GDM and impaired glucose tolerance (IGT) had a 74% increased risk of developing T2DM compared to women with no GDM history and normal glucose tolerance (1).

GDM is similar to T2DM in terms of pathophysiology in that insulin resistance is a cardinal factor. Therefore, the pathophysiology of GDM plays an important role in the understanding of T2DM and the assessment of its risk factors. Until recently, obesity, sedentary life style and genetics were known risk factors for the development of type 2 diabetes. However, recent reports have revealed that there are many other possible risk factors, such as magnesium deficiency.

Magnesium is the fourth most abundant cation in the body and plays an important physiological role. It is a cofactor in enzymatic reactions involving energy metabolism and carbohydrate oxidation, as well as insulin secretion, receptor binding, and physiologic activity. Decreased blood and tissue levels of magnesium are related to the incidence of high blood pressure, kidney stones, heart disease, coronary artery spasms,

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systemic inflammation, insulin resistance, and T2DM (2-5).

Moreover, a previous report showed that a low serum magnesium level was a strong, independent predictor of incident type 2 diabetes in a cohort of non-diabetic middle-aged adults (6), and the Health Professionals Follow-up Study and the Nurses' Health Study also demonstrated that subjects in the highest quintile of oral magnesium intake had a lower risk of developing type 2 diabetes than those in the lowest quintile of magnesium intake (7).

Furthermore, a-10 yr follow-up study in Mexico also showed hypomagnesemia was independently associated with the development of abnormal glucose tolerance status including type 2 diabetes (8). And recently, Song et al. reported that magnesium intake from the diet is modestly and inversely associated with some, but not all, markers of systematic inflammation and endothelial dysfunction in apparently healthy women (9). Moreover, Federici et al. reported that not only the presence of type 2 diabetes, but also the degree of metabolic control in obese individuals who had undergone bariatric surgery were essential in accounting for the lower levels of serum magnesium (10). However, there is some controversy regarding whether magnesium supplementation could improve insulin sensitivity and metabolic control (11-13).

On this basis, we conducted a prospective cohort study to investigate postpartum serum magnesium level and the development of T2DM in women with a history of GDM.

MATERIALS AND METHODS

Study subjects

The Korean National Diabetes Program (KNDP) study is an ongoing, multicenter, prospective cohort study investigating the course of T2DM and diabetic risk in patients who have been previously diagnosed with gestational diabetes mellitus (GDM) using the Carpenter and Coustan criteria. This cohort is composed of 13 KNDP-affiliated hospitals, as described previously (14).

Our study population was derived from the KNDP GDM cohort, which is followed annually at the Endocrinology Department of Cheil General Hospital after having been diagnosed by a universal two-step GDM screening program at 24-28 weeks of gestation. The first step was a 50-g glucose challenge test, and women with a positive result underwent a 3-hr 100-g oral glucose tolerance test (OGTT).

Women with GDM were advised to return to the hospital for a postpartum 75-g OGTT at 6-12 weeks after delivery. Routine annual follow-up was conducted with a 75-g OGTT and a metabolic assessment, including measurements of blood pressure, waist and hip circumferences, and biochemical assessments according to the KNDP GDM cohort protocol. The postpartum and follow-up 75-g OGTT results were interpreted using ADA criteria. We excluded patients with history of overt diabetes or type 1 diabetes. No participants had history of cardiovascular disease, stage 2 hypertension, malignancy, or severe renal or hepatic disease. As the exact time of diabetes onset was not ascertainable due to the irregularity of follow-up, the date of diagnosis was estimated as the date of the 75-g OGTT test.

Anthropometric and laboratory measurements

Baseline anthropometric measurements, including pre-pregnancy weight and anthropometric measurements were recorded at the postpartum visit and every follow-up visit. The body mass index (BMI) of each study subject after pregnancy was calculated as weight/height^2 (kg/m^2), and waist circumference was also measured at the postpartum visit and follow-up visit using the midpoint between the lower border of the rib cage and the iliac crest.

All blood samples were drawn after a 12-hr overnight fast and were stored at -80°C until analysis. The glucose oxidase method (YSI 2300-STAT; Yellow Springs Instrument Co., Yellow Springs, OH, USA) was used to determine plasma glucose, and a radioimmunoassay kit (Linco Research Inc, St. Louis, MO, USA) was used to measure insulin level. Insulin resistance was determined by HOMA-IR (Homeostasis model assessment = serum insulin [mU/L] × serum glucose [mM/L]/22.5]. Serum magnesium level was measured using the ADVIA 1650 chemistry system (Siemens, Tarrytown, NY, USA). The mean intra- and inter-assay coefficients of variation for serum magnesium were 2.8% and 4.2%, respectively.

Statistical analysis

Data are expressed as mean ± SD, median (inter-quartile ranges), or percentage (%). Differences between groups were assessed using a one-way analysis of variance or the Kruskal-Wallis test for continuous variables. Tukey's multiple comparison test and the Wilcoxon rank-sum test were used for multiple comparisons. Bonferroni's correction was used to adjust for multiple comparisons.

We used multiple logistic regression analysis to investigate the risk factors for T2DM and prediabetes. Variables with a P value < 0.2 in the univariate analysis were selected for multiple logistic analysis. We estimated the odds ratio and 95% confidence interval when serum magnesium level was 0.1 mM/L decreased, because serum magnesium level was relatively small and very narrow range. We also excluded variables that correlated too highly with the other covariates. Data were analyzed using SPSS for Windows version 12.0 (SPSS Inc, Chicago, IL, USA). A P value < 0.05 was considered statistically significant.

Ethics statement

The institutional review board of Cheil General Hospital approved this study protocol (CGH-IRB-2006-22), and informed

consent was obtained from each subject.

RESULTS

A total of 451 patients were enrolled in the KNDP gestational diabetes cohort between August 2005 and March 2010. Among these patients, 180 women were followed for more than one year. However, we regrettably did not have follow-up serum magnesium data for 62 women. Ultimately, 116 women had their serum magnesium status assessed in the postpartum period, and the prospective analysis was based on information from the first year after delivery.

Retrospectively, mean age at delivery was 33.9 yr, and the mean follow-up duration was 15.6 ± 2.0 months. The mean postpartum serum magnesium level was 0.69 mM/L (reference range: 0.7-1.05 mM/L).

Table 1 shows that after follow-up, eight patients (6.9%) were diagnosed with T2DM; 59 patients (50.9%) with prediabetes, including impaired fasting glucose, impaired glucose tolerance, or both; and 49 patients (42.2%) with NGT using the ADA criteria (15). The T2DM group had the lowest serum magnesium level (0.65 [0.63-0.68] mM/L) at the postpartum visit, whereas the prediabetes group (0.70 [0.65-0.70] mM/L) and NGT group (0.70 [0.65-0.70] mM/L) were not significantly different (Fig. 1).

Multiple logistic regression analysis showed that postpartum HOMA-IR was a significant predictor of both prediabetes and T2DM (prediabetes, odds ratio [OR] 2.367, 95% confidence interval [CI] 1.348-4.155 (data not shown); T2DM, OR 2.321; 95% CI 1.101-4.891, Table 2). Moreover, we also founded that postpartum hypomagnesemia is a possible risk factor for T2DM since the corresponding odds ratio for a 0.1 mM/L decrease in the serum magnesium level was 12.956 (95% CI, 1.104-152.011).

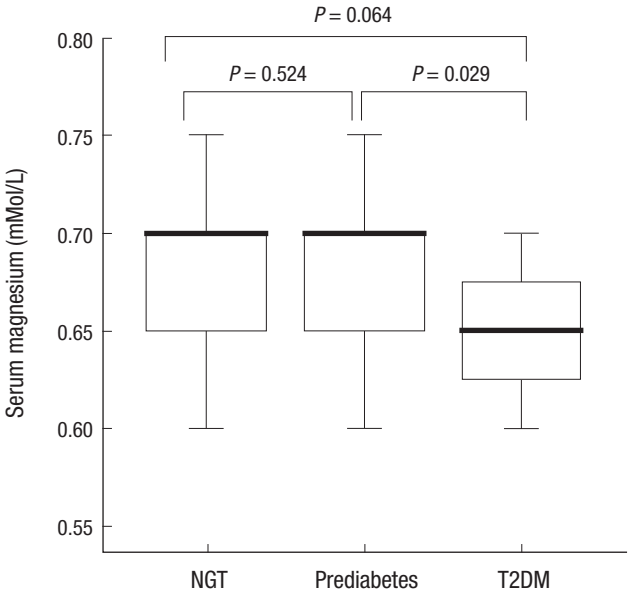

Fig. 1. Postpartum serum magnesium level according to glucose tolerance status during the follow-up period (NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus).

Table 1. Clinical and laboratory characteristics of the study subjects after follow-up glucose tolerance status.

Characteristics	NGT	Prediabetes	T2DM	*P*
No. of patients	49	59	8	
Age at delivery (yr)	34.0 (31.0-37.0)	34.0 (31.0-37.0)	33.5 (31-35.5)	0.884
Follow-up duration (months)*	15.0 (14.0-16.0)	15.0 (14.0-16.0)	16.0 (13.5-17.0)	0.857
Weight gain during pregnancy (kg)	9.6 (7.7-12.9)	9.5 (7.0-13.0)	10.0 (7.5-12.5)	0.938
Antepartum values				
Fasting plasma glucose (mM/L)*	4.5 (4.3-4.7)[a]	4.8 (4.6-5.3)[b]	5.7 (5.3-6.2)[c]	< 0.001
3-hr post-100 g OGTTplasma glucose (mM/L)*	8.2 (7.9-8.7)[a]	8.1 (7.5-8.7)[a]	9.7 (9.3-10.9)[b]	0.003
Apgar score at 1 min*	8.0 (8.0-9.0)[a]	8.0 (8.0-9.0)[a]	8.0 (6.5-8.0)[b]	0.038
Apgar score at 5 min*	9.0 (9.0-9.0)	9.0 (8.0-9.0)	9.0 (8.0-9.0)	0.258
Birth weight of baby (g)*	3,230.0 (2,930.0-3,405.0)	3,230.0 (3,000.0-3,590.0)	3,195.0 (2,997.5-3,640.0)	0.713
Postpartum values				
Serum magnesium postpartum (mM/L)	0.70 (0.65-0.70)	0.70 (0.65-0.70)	0.65 (0.63-0.68)	0.073
Body mass index postpartum (kg/m^2)*	22.2 (20.6-23.2)[a]	22.9 (21-24.7)[a]	25.4 (23.5-28.4)[b]	0.005
Follow-up values				
Body mass index at follow-up (kg/m^2)*	21.1 (19.9-22.2)[a]	22.2 (19.8-24.5)[b]	27.7 (23.4-29.8)[c]	< 0.001
Waist circumference at follow-up (cm)*	71.0 (67.0-75.0)[a]	73.0 (68.0-80.0)[a]	88.0 (78.0-88.0)[b]	0.001
SBP at follow-up (mmHg)*	110.0 (100.0-116.0)	110.0 (100.0-120.0)	112.0 (109.0-120.0)	0.138
DBP at follow-up (mmHg)	70.0 (60.0-76.0)	70.0 (64.0-78.0)	70.0 (60.0-75.0)	0.561
Fasting plasma glucose (mM/L)*	5.1 (4.8-5.3)[a]	5.4 (5.0-5.9)[b]	6.7 (6.2-7.8)[c]	< 0.001
2-hr post-75 g OGTT plasma glucose* (mM/L)	5.9 (5.2-6.8)[a]	7.9 (6.7-8.8)[b]	12.2 (11.2-13.2)[c]	< 0.001
HOMA-IR at follow-up*	2.0 (1.5-2.6)[a]	2.5 (1.8-3.1)[a]	4.1 (3.8-5.9)[b]	< 0.001
HbA1c at follow-up (%)*	5.3 (5.1-5.5)[a]	5.7 (5.4-5.8)[b]	6.5 (6.1-6.7)[c]	< 0.001
HbA1c at follow-up (mM/L)*	58 (56-60)	62 (59-63)	71 (67-73)	< 0.001

Data are presented as mean ± SD or median (inter-quartile range). *P* values represent overall differences across groups as determined by one-way analysis of variance (ANOVA) or Kruskal-Wallis' H-test* for continuous variables. [a,b,c]Same letters indicate no statistical significance based on Tukey's post-hoc analysis or Wilcoxon's rank-sum test. SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment insulin resistance.

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Table 2. Odds ratios (and 95% confidence intervals) from a logistic regression analysis with the development of type 2 diabetes as a dependent variable

Variables	B	SE	Sig.	Odds ratio	95% CI for Exp (B)	
					Lower	Upper
Age	-0.036	0.106	0.736	0.965	0.785	1.187
HOMA IR	0.842	0.380	0.027	2.321	1.101	4.891
BMI	0.303	0.172	0.078	1.354	0.966	1.897
Serum magnesium	-25.615	12.564	0.041	12.956*	1.104*	152.011*

*Odds ratio and 95% CI when serum magnesium level was 0.1 mM/L decreased). BMI, Body mass index; HOMA-IR, homeostasis model assessment insulin resistance.

DISCUSSION

This is the first study to demonstrate an association between postpartum serum magnesium level and development of T2DM. The results suggest that low postpartum serum magnesium is a potent risk factor for future T2DM.

Magnesium plays a key role in carbohydrate metabolism. Magnesium may influence the release and activity of hormones that help control blood glucose level via tyrosine kinase. Additionally, insulin partially regulates intracellular magnesium accumulation (16, 17). In humans, nearly all magnesium is supplied from vegetables, seafood, nuts, or seeds. However, meals high in protein or fat, a diet high in phosphorus or calcium or alcohol use may decrease magnesium absorption. In fact, the magnesium level in the human body is tightly regulated and depends on the balance between intestinal absorption and renal excretion. Therefore, in most normal adults, serum magnesium ranges from 0.70 to 1.10 mM/L. In Korea, there was a few report about magnesium status of normal population or pregnant women, Song et al. reported that the magnesium levels of these subjects including type 2 diabetes patients are 0.85± 0.07 mM/L, respectively (18). However, the National Academy of Science and the Institute of Medicine have reported that an estimated 50%-85% of the US population has subclinical or severe magnesium deficiency (19).

Although extracellular magnesium accounts for 1% of total body magnesium, serum magnesium is considered a good indicator of magnesium deficiency. Therefore, most studies have analyzed magnesium status by magnesium intake until recently. Magnesium intake assessed by a food diary is associated with various disorders, such as insulin resistance, T2DM, atherosclerosis, hypertension, osteoporosis, and cancer (2, 20-22).

However, Lopez-Ridaura et al. (7) found that low blood level of magnesium is frequently observed in patients with T2DM and is associated with increased insulin resistance. In addition, serum magnesium is regarded as an additional risk factor for cardiovascular disease in type 2 diabetes and is also associated with both increased diabetic complications and all-cause mortality in type 2 diabetic patients (23, 24). Previous studies have reported that the first change appearing during experimentally-induced magnesium deficiency in humans and experimental animals is a decrease in serum magnesium concentration (25). Moreover, other researchers have reported that the serum magnesium concentration is sufficient to confirm a deficient status in the body (26, 27).

However, there are ongoing debates about whether magnesium supplementation has beneficial effects on metabolic parameters. Recent reports have shown that oral magnesium supplementation reduces insulin resistance even in non-diabetics (28), and improves borderline hypertension (29). Randomized controlled trials are warranted to provide additional evidence to settle this debate.

Gestational diabetes is a precursor of T2DM and prediabetes. Although magnesium deficiency in pregnant women is frequently observed due to inadequate or low magnesium intake, there are some disagreements about magnesium depletion in patients with gestational diabetes. Decreased serum magnesium is a known risk factor for intrauterine growth restriction (30), but no significant differences were observed in the fetal weights in our study. Meanwhile, our study showed that 1-min Apgar scores decreased slightly in the T2DM group (the lowest magnesium status group), but no significant relationship was observed between serum magnesium level and 1-min Apgar score by simple correlation analysis (r = 0.101, P = 0.328). In our study, serum magnesium level was obtained after delivery, and we did not observe a clear relationship between fetal weight and serum magnesium in this report.

This study showed that postpartum serum magnesium level influenced postpartum glucose tolerance and also demonstrated that the T2DM group with previous gestational diabetes had the lowest serum magnesium level in the postpartum period.

However, our study had some limitations. First, serum magnesium is influenced by creatinine clearance, but we could not estimate creatinine clearance because we did not measure serum creatinine during the postpartum period. Second, although this study was planned as a prospective design, the follow-up duration was relatively short, and the number of subjects was small. Third, dietary magnesium intake and supplementation of multi-vitamins and minerals were also important, but we did not include a food intake diary in this report. Fourth, it is not serum magnesium but intracellular magnesium that is an appropriate marker of magnesium status, and we could not evaluate intracellular magnesium status in this study. However, serum magnesium has been shown to be proportional to intracellular magnesium in many previous reports, and serum magnesium is an easily measured potential marker of intracellular magnesium status. Fifth, there were no data about preterm serum magnesium level. Maybe it brings about many confounding factor to our result, but lower serum magnesium level in preterm gestational women is known risk factor of preterm delivery. Our cohort data showed that birth weight of baby was within nor-

mal range, and serum magnesium level after delivery is within lower normal range.

In conclusion, low serum magnesium level was shown to be a potent risk factor for T2DM in patients with a history of gestational diabetes. This result is in agreement with those of several previous reports showing a relationship between serum magnesium level or magnesium intake and various inflammatory disorders, such as T2DM. The role of serum magnesium in the pathophysiology of T2DM and other chronic inflammatory disorders warrants further investigation.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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