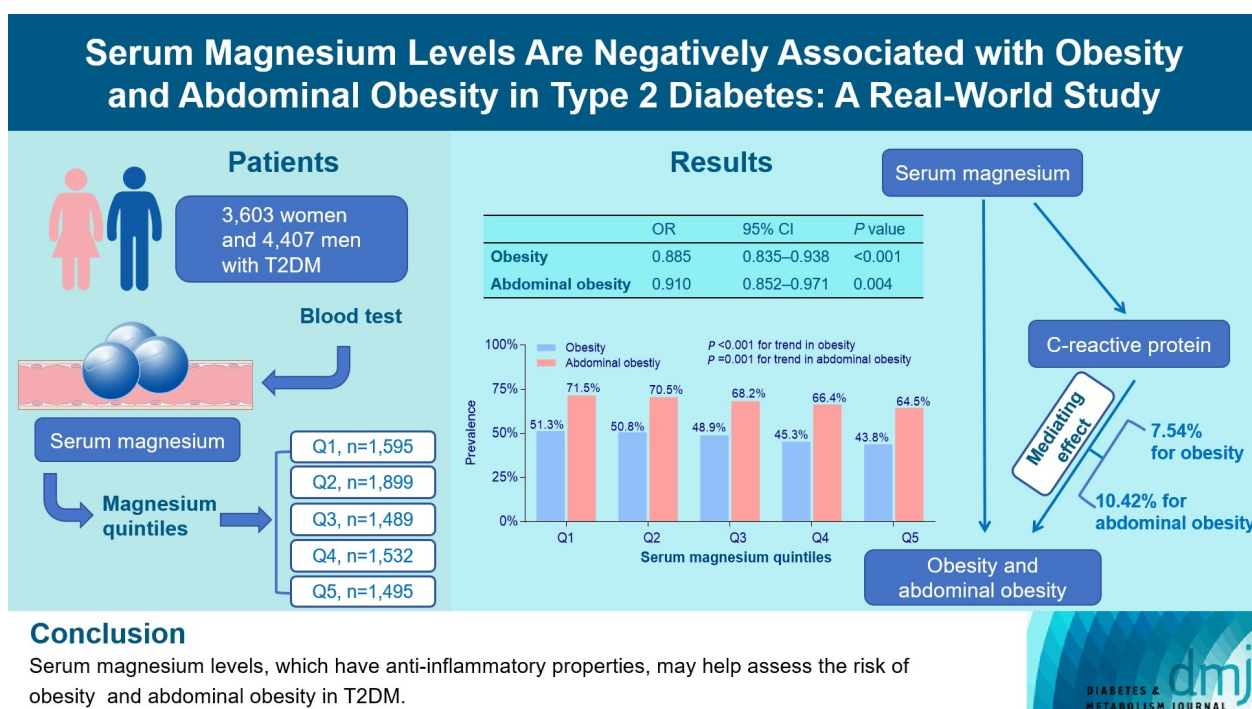


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Diabetes Metab J 2024;48:1147-1159 | <https://doi.org/10.4093/dmj.2023.0401>



Highlights

- Low serum magnesium levels increased the risk of obesity and abdominal obesity in T2DM.
- The negative link between serum magnesium and obesity may be due to its anti-inflammatory effects.
- Serum magnesium levels can help assess the risk of obesity and abdominal obesity in T2DM.

How to cite this article:

Xu MR, Wang AP, Wang YJ, Lu JX, Shen L, Li LX. Serum Magnesium Levels Are Negatively Associated with Obesity and Abdominal Obesity in Type 2 Diabetes Mellitus: A Real-World Study. *Diabetes Metab J* 2024;48:1147-1159. <https://doi.org/10.4093/dmj.2023.0401>

Serum Magnesium Levels Are Negatively Associated with Obesity and Abdominal Obesity in Type 2 Diabetes Mellitus: A Real-World Study

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Background: There remains controversy over the relationship between serum magnesium levels and obesity in type 2 diabetes mellitus (T2DM). Therefore, the aim of this study was to assess whether there is any association of serum magnesium levels with obesity and abdominal obesity in T2DM.

Methods: This cross-sectional, real-world study was conducted in 8,010 patients with T2DM, which were stratified into quintiles according to serum magnesium levels. The clinical characteristics and the prevalence of obesity and abdominal obesity were compared across serum magnesium quintiles in T2DM. Regression analyses were used to evaluate the relationship of serum magnesium with obesity and abdominal obesity in T2DM (clinical trial registration number: ChiCTR1800015893).

Results: After adjustment for age, sex, and duration of diabetes, the prevalence of obesity and abdominal obesity was significantly declined across magnesium quintiles (obesity: 51.3%, 50.8%, 48.9%, 45.3%, and 43.8%, respectively, $P < 0.001$ for trend; abdominal obesity: 71.5%, 70.5%, 68.2%, 66.4%, and 64.5%, respectively, $P = 0.001$ for trend). After controlling for confounders, there were clearly negative associations of serum magnesium levels and quintiles with obesity and abdominal obesity in T2DM. Moreover, C-reactive protein partly mediates the effect of serum magnesium on obesity and abdominal obesity ($P = 0.016$ and $P = 0.004$, respectively).

Conclusion: The significantly negative relationship between serum magnesium and the risk of obesity and abdominal obesity was observed in T2DM. Furthermore, the independently negative association of serum magnesium with obesity may be explained by its anti-inflammatory functions. Serum magnesium levels may be applied to assess the risk of obesity and abdominal obesity in T2DM.

Keywords: Diabetes mellitus, type 2; Magnesium; Obesity; Obesity, abdominal

INTRODUCTION

Magnesium ions have been identified as essential cofactors in more than 600 enzymatic reactions in the body, which regulate a variety of physiological activities such as protein synthesis,

glycolysis, and energy metabolism [1]. In addition, increasing number of studies have shown that the decrease in extracellular magnesium ions leads to the increase in intracellular calcium and iron ions, which induce increased production and decreased clearance of peroxides and trigger inflammatory path-

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Received: Nov. 8, 2023; Accepted: Mar. 6, 2024

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ways [2-4]. Therefore, the change of magnesium ions can lead to pathological changes such as endothelial cell destruction and insulin resistance, and is also associated with chronic inflammatory diseases such as atherosclerosis and chronic kidney disease (CKD) [2,4,5]. Interestingly, in a rat model with metabolic syndrome (MetS) combined with CKD, supplementation with dietary magnesium significantly reduces oxidative stress and inflammatory responses, thereby acting as an intravascular protector [6].

Due to the vital physiological role of magnesium ions, multiple clinical studies have observed a significant correlation between serum magnesium levels and a range of metabolic diseases such as diabetes and cardiovascular disease [7-10]. For example, Zhang et al. [11] recently reported that low serum magnesium not only was a risk factor for the development of diabetes, but also significantly and positively correlated with diabetes-related indicators such as fasting plasma glucose (FPG), postprandial blood glucose, and glycosylated hemoglobin (HbA1c), suggesting that hypomagnesemia (serum magnesium <0.75 mmol/L) can lead to insulin resistance and poor glycemic control.

As one of the metabolic disorders, obesity is also a key risk factor for other metabolic diseases such as diabetes, non-alcoholic fatty liver disease, and cardiovascular disease [12,13]. Furthermore, there have been increasing evidences that abdominal obesity may have more serious detrimental effects on metabolic homeostasis [14]. Given the close association of serum magnesium levels with metabolic diseases, a wide variety of studies have observed a strong relationship between serum magnesium and obesity. For example, Hassan et al. [15] revealed that serum magnesium levels were significantly higher in overweight and obese children than in children with normal weight, and negatively associated with body mass index (BMI).

However, another previous study conducted with a large sample of South Asians and white Canadians found that there was no difference in serum magnesium levels among different BMI groups in men [16]. Similarly, Alasfar et al. [17] also observed no obvious differences in serum magnesium levels between non-obese and morbidly obese women. Therefore, the association between serum magnesium and obesity in different populations is controversial and needs further clarification.

Furthermore, the correlation between serum magnesium and obesity also remains a controversy in type 2 diabetes mellitus (T2DM) population [17-19]. Chu et al. [18] found that BMI decreased significantly with increasing serum magnesium tertiles in patients with T2DM. Additionally, another study in-

volving 210 elderly patients with T2DM demonstrated that high magnesium intake reduced the incidence of centripetal obesity, high body fat ratio and high BMI, but no correlation was observed between serum magnesium and metabolic parameters [20]. In contrast, no significant relationship between serum magnesium and BMI was observed in an investigation with 2,222 patients with T2DM [19]. Moreover, relevant studies about the relationship between serum magnesium and obesity as well as abdominal obesity remains sparse in Chinese patients with T2DM. Therefore, the aim of our study was to explore the actual association of serum magnesium with obesity, as well as abdominal obesity in Chinese T2DM patients with relatively large samples in a real-world setting, respectively.

METHODS

Study population

A total of 11,805 patients with T2DM were enrolled in the present cross-sectional, real-world study. These participants were consecutively recruited from the Department of Endocrinology and Metabolism, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from January 2003 to December 2012. Among them, these subjects were excluded as follows: (1) age below 18 years old; (2) incomplete physical examination and laboratory test data; (3) acute diabetic complications such as diabetic ketoacidosis; (4) taking magnesium supplements or taking drugs that influences serum magnesium levels; (5) systemic inflammatory disease; and (6) progressive malignancy. Ultimately, 8,010 T2DM subjects were included in the final analysis.

All participants were interviewed to obtain their information on the duration of diabetes (DD), smoking habits, alcohol consumption, history of hypertension (HTN), and use of medications, including sulfonylureas (SUs), metformin, and insulin or insulin analogues (IIAs). This study was guided by the principles of the Declaration of Helsinki and approved by the Ethics Committee of the Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (approval number: 2018-KY-018(K)). Each subject signed a written consent form.

Physical examination and laboratory measurements

The physical examination data were obtained according to the standard protocol, including systolic blood pressure (SBP), diastolic blood pressure (DBP), body weight, height, waist cir-

cumference (WC), and hip circumference. BMI, waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) were calculated according to our previous method [21–24]. Venous blood samples were collected from all subjects after an overnight fast and 2 hours after breakfast. Laboratory measurements included FPG, 2-hour postprandial plasma glucose (2hr PPG), fasting C-peptide (FCP), 2-hour postprandial C-peptide (2hr CP), HbA1c, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), creatinine (Cr), serum uric acid (SUA), urinary albumin excretion (UAE), and C-reactive protein (CRP). Serum magnesium levels were determined using the xylydyl blue method by the Hitachi 7600 analyzer (Hitachi, Tokyo, Japan) [18]. The 24-hour UAE, estimated glomerular filtration rate (eGFR), and the updated homoeostasis model assessment of insulin sensitivity/insulin resistance were calculated, as described in our previous study [21].

Diagnostic criteria

Normal serum magnesium levels were defined as 0.65 to 1.05 $\mu\text{mol/L}$ according to the normal reference range of serum magnesium in our hospital. Based on normal serum magnesium levels, low serum magnesium was defined as serum magnesium levels $<0.65 \mu\text{mol/L}$ and high serum magnesium as $>1.05 \mu\text{mol/L}$. The definitions of smoking, alcohol consumption, and HTN were consistent with our previous studies [25]. With reference to our previous studies [26], T2DM was diagnosed based on the 1999 World Health Organization criteria. According to our previous description, obesity was defined as a BMI $\geq 25 \text{ kg/m}^2$, and the diagnostic criteria for the severity of obesity was defined as BMI 25 to 30 kg/m^2 for mild obesity, 30 to 35 kg/m^2 for moderate obesity, and over 35 kg/m^2 for severe obesity [27]. According to the Chinese criteria proposed by the Chinese Obesity Task Force and our previous study, abdominal obesity was defined as a WC $\geq 90 \text{ cm}$ in men and $\geq 80 \text{ cm}$ in women [13]. In addition, mild abdominal obesity was specified as a WC of 90 to 100 cm for men and 80 to 90 cm for women, moderate abdominal obesity 100 to 110 cm for men and 90 to 100 cm for women, severe abdominal obesity $\geq 110 \text{ cm}$ for men and $\geq 100 \text{ cm}$ for women, respectively [13].

Statistical analyses

We analyzed all data using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA) and R version 4.0.2 software (R Foun-

dation for Statistical Computing, Vienna, Austria). Normally and non-normally distributed data were expressed as mean $\pm$ standard deviation and median with interquartile range, respectively. One-way analysis of variance (ANOVA) with least significant difference was carried out to determine group differences in normally distributed variables, whereas the Kruskal-Wallis test was performed to compare non-normally distributed variables. Prevalence data and frequency differences were compared using chi-square tests. When controlling for confounding factors, binary logistic regression and general linear regression were conducted to assess the differences between groups.

Restricted cubic splines were used with three knots at the 10th, 50th, and 90th centiles to flexibly model the relationship between serum magnesium and obesity/abnormal obesity after adjusting covariates in model 6. Moreover, we conducted a causal mediation analysis to assess whether CRP could be a potential mediator linking serum magnesium to obesity/abnormal obesity, using the R “mediation” package. $P < 0.05$ was considered statistically significant.

To assess the associations of serum magnesium levels and quintiles with obesity and abdominal obesity in T2DM, six logistic regression models were constructed: model 1 was unadjusted; model 2 was adjusted for age, gender, and DD; model 3 was additional adjusted for medical history, including HTN, smoking, and alcohol drinking; model 4 was additional adjusted for the use of drugs, including the use of IIAs, metformin, and SUs; model 5 included additional adjustments for physical examination data, including SBP and DBP; and model 6 included further adjustments for laboratory results, including ALT, TC, HDL-C, LDL-C, TG, eGFR, Cr, SUA, UAE, FPG, 2hr PPG, HbA1C, FCP, 2hr CP, and CRP.

RESULTS

Characteristics of the subjects according to serum magnesium quintiles

Table 1 shows the clinical characteristics of the T2DM patients. According to serum magnesium levels, the T2DM patients were divided into serum magnesium quintiles with cut-offs of <0.82 , $0.82\text{--}0.87$, $0.88\text{--}0.91$, $0.92\text{--}0.96$, and $>0.96 \text{ mmol/L}$. Marked differences were observed for sex and age across serum magnesium quintiles ($P < 0.05$). After controlling for age and sex, significantly elevated trends in 2hr CP and Cr were observed with increasing quintiles of serum magnesium (all

Table 1. Characteristics of the subjects according to serum magnesium quintiles

Variable	Q1 (n=1,595)	Q2 (n=1,899)	Q3 (n=1,489)	Q4 (n=1,532)	Q5 (n=1,495)	P value ^a	P value ^b
Serum magnesium, mmol/L	<0.82	0.82–0.87	0.88–0.91	0.92–0.96	>0.97	-	-
Male sex	782 (49.0)	1,046 (55.1)	858 (57.6)	873 (57.0)	848 (56.7)	<0.001	<0.001
Age, yr	58±13	59±13	59±12	61±12	62±12	<0.001	<0.001
DD, mo ^c	108 (48–156)	96 (36–156)	96 (36–156)	96 (36–156)	84 (36–144)	0.003	0.011
Smoking	458 (28.7)	570 (30.0)	468 (31.4)	467 (30.5)	436 (29.2)	0.498	0.468
Drinking	253 (15.9)	305 (16.1)	276 (18.5)	250 (16.3)	256 (17.1)	0.257	0.451
HTN	889 (55.7)	1,014 (53.4)	828 (55.6)	812 (53.0)	833 (55.7)	0.300	0.001
IAs	1,226 (76.9)	1,428 (75.2)	1,032 (69.3)	969 (63.3)	896 (59.9)	<0.001	<0.001
SUs	1,026 (64.3)	1,245 (65.6)	962 (64.6)	1,017 (66.4)	989 (66.2)	0.685	0.954
Metformin	1,058 (66.3)	1,170 (61.6)	900 (60.4)	849 (55.4)	774 (51.8)	<0.001	<0.001
SBP, mm Hg	133±17	132±17	132±17	132±17	132±18	0.759	0.051
DBP, mm Hg	81±9	80±9	80±9	79±9	80±9	0.006	0.850
BMI, kg/m ²	25.37±3.84	25.19±3.46	25.07±3.33	24.81±3.38	24.67±3.28	0.752	0.871
WC, cm	90.41±10.95	90.51±10.40	89.84±10.05	89.21±10.07	88.97±10.33	<0.001	0.630
WHtR	0.55±0.07	0.55±0.06	0.54±0.06	0.54±0.06	0.54±0.06	<0.001	0.370
WHR	0.92±0.07	0.92±0.07	0.92±0.06	0.92±0.06	0.91±0.06	<0.001	0.820
FPG, mmol/L ^c	8.4 (6.7–10.7)	8.0 (6.4–10.1)	7.7 (6.2–9.5)	7.3 (5.9–9.2)	7.0 (5.8–8.5)	<0.001	<0.001
2hr PPG, mmol/L ^c	13.9 (11.1–17.3)	13.9 (10.7–17.2)	13.2 (9.9–16.6)	12.4 (9.5–15.9)	12.1 (9.3–15.3)	<0.001	<0.001
HbA1c, %	9.50±2.29	9.14±2.18	8.79±2.07	8.38±2.01	8.12±2.04	<0.001	<0.001
FCP, ng/mL ^c	1.81 (1.09–2.56)	1.71 (1.11–2.49)	1.82 (1.15–2.57)	1.83 (1.24–2.61)	1.95 (1.24–2.76)	<0.001	0.087
2hr CP, ng/mL ^c	3.45 (2.05–5.58)	3.85 (2.21–5.80)	4.08 (2.41–6.03)	4.44 (2.75–6.25)	4.56 (2.78–6.42)	<0.001	<0.001
HOMA2-IR	1.59 (0.95–2.30)	1.49 (0.96–2.17)	1.53 (0.95–2.22)	1.57 (1.00–2.20)	1.61 (1.03–2.27)	0.078	0.807
TG, mmol/L ^c	1.52 (1.04–2.33)	1.44 (1.00–2.15)	1.39 (0.99–2.14)	1.39 (0.98–2.02)	1.38 (0.99–1.97)	<0.001	0.699
TC, mmol/L	4.78±1.20	4.75±1.22	4.74±1.11	4.72±1.03	4.73±1.14	0.648	0.400
HDL-C, mmol/L	1.10±0.31	1.12±0.32	1.13±0.30	1.14±0.30	1.15±0.33	<0.001	0.901
LDL-C, mmol/L	2.96±0.95	3.01±0.94	3.05±0.94	3.05±0.89	3.07±0.97	0.007	0.502
ALT, U/L ^c	17 (12–26)	18 (13–28)	19 (13–29)	19 (14–30)	21 (15–33)	0.534	0.252
Cr, µmol/L ^c	62 (50–75)	65 (54–78)	66 (55–78)	68 (58–81)	71 (60–85)	<0.001	0.008
SUA, µmol/L ^c	317 (260–384)	314 (261–374)	310 (258–372)	311 (263–372)	319 (266–377)	0.067	0.953
UAE, mg/day ^c	15 (8–53)	12 (7–37)	11 (7–28)	11 (6–26)	10 (6–26)	<0.001	0.003
eGFR, mL/min/1.73 m ^{2c}	121 (96–146)	123 (93–136)	110 (92–131)	106 (88–126)	101 (83–120)	<0.001	<0.001

Values are presented as number (%), mean ± standard deviation, or median (interquartile range).

DD, duration of diabetes; HTN, hypertension; IIA, insulin or insulin analogue; SU, sulfonylurea; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio; FPG, fasting plasma glucose; 2hr PPG, 2-hour postprandial plasma glucose; HbA1c, glycosylated hemoglobin; FCP, fasting C-peptide; 2hr CP, 2-hour postprandial C-peptide; HOMA2-IR, updated homoeostasis model assessment of insulin sensitivity/insulin resistance; TG, total triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; Cr, creatinine; SUA, serum uric acid; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate.

^aThe *P* values were not adjusted for sex for the trend, ^bThe *P* values were adjusted for sex for the trend, ^cThe Mann-Whitney *U* test was applied.

P<0.05). Conversely, the use of IIAs and metformin, DD, FPG, 2hr PPG, HbA1c, UAE, and eGFR were markedly declined across serum magnesium quintiles (all *P*<0.05). Additionally,

after adjustment for age and sex, the prevalence of HTN differed significantly among the serum magnesium quintiles, but without a trend towards an increase or decrease (*P*<0.05).

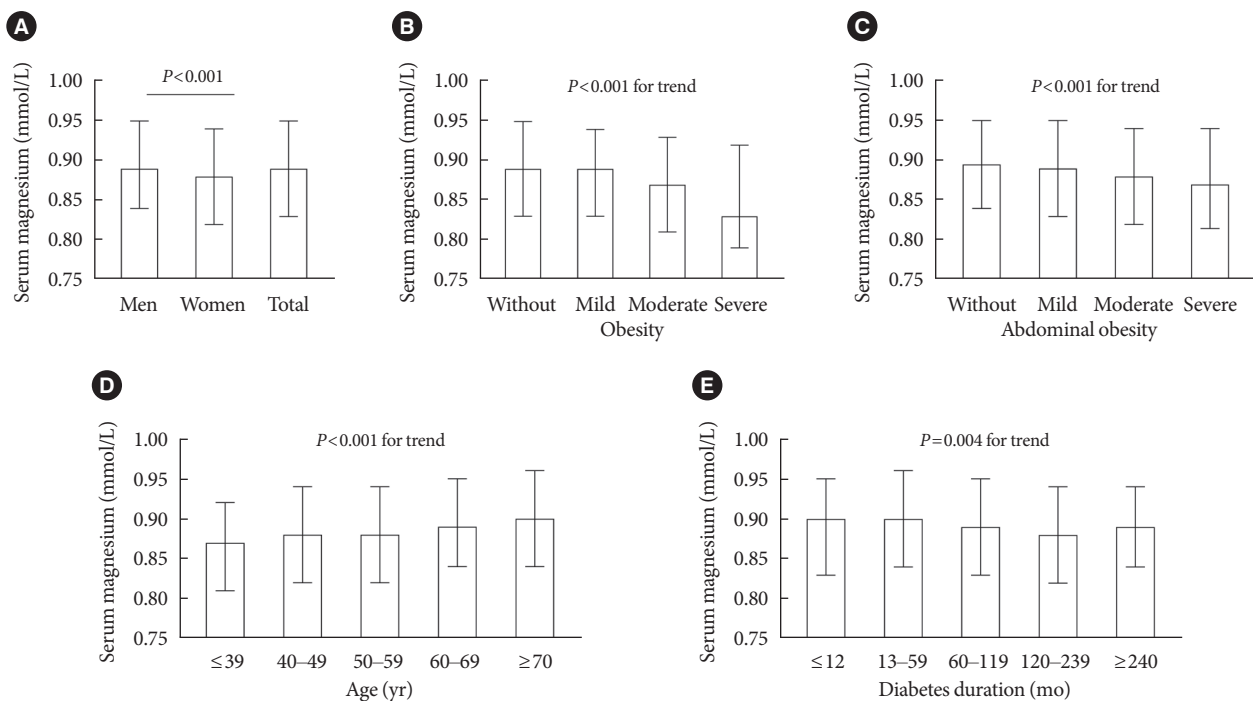


Fig. 1. Comparisons of serum magnesium levels in different groups. (A) Comparison of serum magnesium levels between men and women with type 2 diabetes mellitus after adjusting for age and duration of diabetes (DD) ($P < 0.001$). (B) Comparison of serum magnesium levels stratified by the degree of obesity after adjusting for age, sex, and DD ($P < 0.001$ for trend). (C) Comparison of serum magnesium levels stratified by the degree of abdominal obesity after adjusting for age, sex, and DD ($P < 0.001$ for trend). (D) Comparison of serum magnesium levels stratified by age after adjusting for DD and sex ($P < 0.001$ for trend). (E) Comparison of serum magnesium levels stratified by DD after adjusting for age and sex ($P < 0.001$ for trend).

Comparisons of serum magnesium levels in different groups

Fig. 1 compares serum magnesium levels in different groups in T2DM subjects. Serum magnesium levels were significantly lower in men than in women after controlling for age and DD ($P < 0.001$, Fig. 1A). Furthermore, there was a noticeably increasing trend in serum magnesium levels with advancing age, while an inverse trend was observed with prolonged DD ($P < 0.001$ for trend, Fig. 1D; $P = 0.004$, Fig. 1E). Additionally, serum magnesium levels demonstrated a clear decline with increasing severity of obesity and abdominal obesity. Notably, the patients with obesity or abdominal obesity exhibited substantially lower serum magnesium levels compared to those without ($P < 0.001$ for trend, Fig. 1B and C).

Comparisons of the prevalence of obesity and abdominal obesity stratified by sex, age, and DD

Supplementary Fig. 1 compares the prevalence of obesity and abdominal obesity stratified by sex, age, and DD in T2DM patients. There was no significant difference in the prevalence of

obesity between genders (48.8% in men and 47.4% in women, $P = 0.509$, Supplementary Fig. 1A) after adjustment for age and DD; however, the prevalence of abdominal obesity was markedly higher in women (81.8%) than in men (57.4%) ($P < 0.001$, Supplementary Fig. 1A). In addition, the prevalence of obesity significantly decreased with increasing age, while the prevalence of abdominal obesity obviously increased with advancing age ($P < 0.001$ for trend in obesity and $P = 0.002$ for trend in abdominal obesity, respectively; Supplementary Fig. 1B). Furthermore, statistically significant differences were found in the prevalence of obesity and abdominal obesity among different DD groups ($P = 0.013$ for trend in obesity and $P = 0.019$ for trend in abdominal obesity, respectively; Supplementary Fig. 1C).

Comparisons of the prevalence of obesity and abdominal obesity among serum magnesium quintiles

Fig. 2 compares the prevalence of obesity and abdominal obesity among serum magnesium quintiles in patients with T2DM. After controlling for age, sex, and DD, a clear downward trend

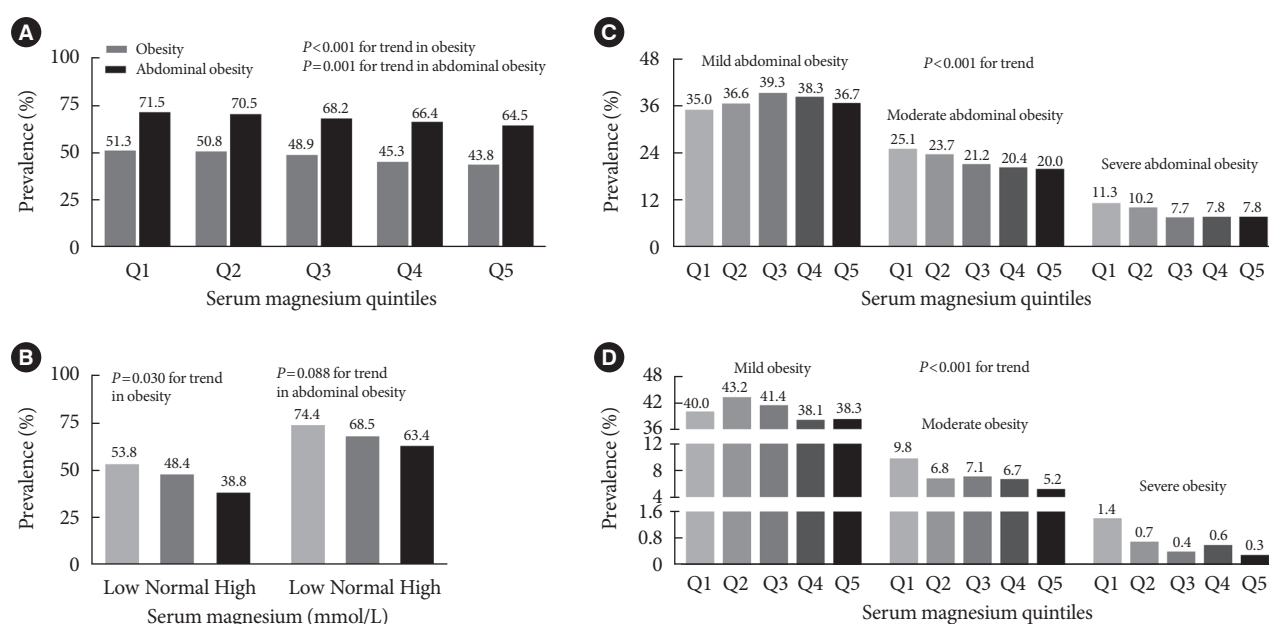


Fig. 2. Comparisons of the prevalence of obesity and abdominal obesity among serum magnesium quintiles. (A) Comparison of the prevalence of obesity and abdominal obesity stratified by serum magnesium quintiles after adjusting for age, sex, and duration of diabetes (DD) ($P < 0.001$ for trend in obesity, $P = 0.001$ for trend in abdominal obesity). (B) Comparison of the prevalence of obesity and abdominal obesity in low, normal, high serum magnesium group after adjusting for age, sex, and DD ($P = 0.030$ for trend in obesity, $P = 0.088$ for trend in abdominal obesity). (C) Comparison of the prevalence of mild, moderate, and severe obesity across serum magnesium quintiles after adjusting for age, sex, and DD ($P < 0.001$ for trend). (D) Comparison of the prevalence of mild, moderate, and severe abdominal obesity across serum magnesium quintiles after adjusting for age, sex, and DD ($P < 0.001$ for trend).

in the prevalence of obesity and abdominal obesity was observed with increasing quintiles of serum magnesium (51.3%, 50.8%, 48.9%, 45.3%, 43.8% for each quintile in obesity, respectively, $P < 0.001$ for trend; and 71.5%, 70.5%, 68.2%, 66.4%, 64.5% for each quintile in abdominal obesity, respectively, $P = 0.001$ for trend) (Fig. 2A). Interestingly, the prevalence of obesity and abdominal obesity gradually declined from low to high serum magnesium group ($P = 0.030$ for trend in obesity, and $P = 0.088$ for trend in abdominal obesity, respectively; Fig. 2B). Additionally, the prevalence of severe obesity and abdominal obesity significantly increased with the decreased serum magnesium quintile ($P < 0.001$ for trend in obesity, Fig. 2C; $P < 0.001$ for trend in abdominal obesity, Fig. 2D).

Linear relationship between serum magnesium levels and BMI, WC, WHR, and WHtR

In Supplementary Fig. 2, correlation analysis displays the linear relationship between serum magnesium concentration and anthropometric measures including BMI, WC, WHR, and WHtR. After controlling for age, sex, DD, a weakly but signifi-

cantly negative correlation was found between serum magnesium levels and BMI ($R = -0.077$, $P < 0.001$, Supplementary Fig. 2A), WC ($R = -0.074$, $P < 0.001$, Supplementary Fig. 2B), WHR ($R = -0.089$, $P < 0.001$, Supplementary Fig. 2C), and WHtR ($R = -0.078$, $P < 0.001$, Supplementary Fig. 2D) in T2DM patients.

Association of serum magnesium levels with obesity and abdominal obesity

Table 2 analyses the associations of serum magnesium levels with obesity and abdominal obesity in T2DM subjects. The obviously negative associations of serum magnesium levels with obesity and abdominal obesity were observed (model 1) (odds ratio [OR], 0.879; 95% confidence interval [CI], 0.841 to 0.919; $P < 0.001$ for trend in obesity, and OR, 0.881; 95% CI, 0.840 to 0.923; $P < 0.001$ for trend in abdominal obesity, respectively). Furthermore, significant correlations between serum magnesium levels and obesity/abdominal obesity remained even after further adjustment for various confounding factors in models 2–6 ($P < 0.001$ for trend in obesity in models 2–4 and model 6 respectively; $P = 0.001$ for trend in obesity in model 5; $P < 0.001$

Table 2. The association of serum magnesium levels with obesity and abdominal obesity

Variable	OR	95% CI	P value
Obesity			
Model 1	0.879	0.841–0.919	<0.001
Model 2	0.888	0.849–0.928	<0.001
Model 3	0.899	0.859–0.940	<0.001
Model 4	0.919	0.877–0.963	<0.001
Model 5	0.922	0.881–0.966	0.001
Model 6	0.885	0.835–0.938	<0.001
Abdominal obesity			
Model 1	0.881	0.840–0.923	<0.001
Model 2	0.886	0.843–0.932	<0.001
Model 3	0.895	0.851–0.942	<0.001
Model 4	0.925	0.878–0.975	0.004
Model 5	0.927	0.880–0.977	0.004
Model 6	0.910	0.852–0.971	0.004

Model 1: unadjusted; Model 2: adjusted for age, gender, and duration of diabetes; Model 3: additionally adjusted for hypertension, smoking, and alcohol drinking; Model 4: additionally adjusted for the use of insulin or insulin analogues, metformin, and sulfonylurea; Model 5: additionally adjusted for systolic blood pressure and diastolic blood pressure; Model 6: further adjusted for alanine aminotransferase, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total triglyceride, estimated glomerular filtration rate, creatinine, serum uric acid, urinary albumin excretion, fasting plasma glucose, 2-hour postprandial plasma glucose, glycosylated hemoglobin, fasting C-peptide, 2-hour postprandial C-peptide, and C-reactive protein.

OR, odds ratio; CI, confidence interval.

for trend in abdominal obesity in models 2–3; $P=0.004$ for trend in abdominal obesity in models 4–6).

Association of serum magnesium with obesity and abdominal obesity analyzed by restrictive cubic spline

Supplementary Fig. 3 shows the association of serum magnesium with obesity and abdominal obesity analyzed by restrictive cubic spline (RCS). In RCS, after adequate correction for confounders according to model 6, the OR for obesity were significantly decreased with increasing serum magnesium ($P=0.001$, Supplementary Fig. 3A). Additionally, when serum magnesium >0.89 mmol/L, the patients had an obviously lower OR value (<1.00) in obesity ($P=0.001$, Supplementary Fig. 3A). Moreover, significantly lower OR (<1.00) was also observed when serum magnesium levels were higher than 0.89 mmol/L in abdominal obesity ($P=0.045$, Supplementary Fig. 3B).

Association of serum magnesium quintiles with obesity and abdominal obesity

Table 3 exhibits the associations of serum magnesium quintiles with obesity and abdominal obesity in T2DM subjects. After controlling for multiple confounders, as shown in models 1–6, the prevalence of obesity significantly decreased with increasing serum magnesium quintiles ($P<0.001$ in models 1 and 2, $P=0.001$ in model 3, $P=0.020$ in model 4, $P=0.023$ in model 5, and $P=0.001$ in model 6 for trend in obesity, respectively). Furthermore, the prevalence of abdominal obesity also noticeably decreased across the serum magnesium quintiles in patients with T2DM after fully controlling for confounding variables in model 6 ($P=0.031$ in model 6 for trend in abdominal obesity).

Role of CRP in the relationship between serum magnesium and obesity/abdominal obesity

Fig. 3 illustrates the comparisons of serum CRP levels in different groups and the mediation effect of CRP in the association of serum magnesium with obesity and abdominal obesity in patients with T2DM. Classical acute inflammation leads to a marked increase in serum CRP levels. In contrast, the hallmark of low-grade chronic inflammation is a slight rise in CRP being a range of concentrations of 3 to 10 mg/L [28]. Therefore, to eliminate the effect of acute inflammation such as infection, we excluded the patients with CRP >10 mg/L when analyzing the effect of CRP on the association between serum magnesium and obesity as well as abdominal obesity.

We found that CRP was significantly higher in the T2DM patients with obesity/abdominal obesity than in those without obesity/abdominal obesity ($P<0.001$ for all trend, Fig. 3A). In addition, CRP levels were obviously increased with the degree of severity of obesity and abdominal obesity ($P=0.025$ for all trends in obesity, $P<0.001$ for trend in abdominal obesity, Fig. 3B). Moreover, CRP levels showed a significantly negative correlation with serum magnesium quintiles ($P=0.046$ for trend, Fig. 3C). Additionally, mediation analysis indicated that the average direct effects (ADE) of serum magnesium on obesity was -0.312 ($P<0.001$), where the average causal mediation effects (ACMEs) of CRP as a mediator was -0.026 ($P=0.016$), and 7.54% of the total effect of serum magnesium on obesity could be explained by the ACME of CRP (Fig. 3D). Similarly, serum magnesium on abdominal obesity had an ADE= -0.203 ($P<0.001$), where the ACME of CRP was -0.024 ($P=0.004$), accounting for 10.42% of the total effect of serum magnesium on abdominal obesity (Fig. 3E).

Table 3. Association of serum magnesium quintiles with obesity and abdominal obesity

Variable	OR (95% CI)					P values for trend
	Q1	Q2	Q3	Q4	Q5	
Obesity						
Model 1	1	0.979 (0.857–1.119)	0.909 (0.789–1.047)	0.788 (0.684–0.906)	0.740 (0.642–0.852)	<0.001
Model 2	1	0.990 (0.866–1.131)	0.921 (0.799–1.061)	0.805 (0.699–0.927)	0.761 (0.660–0.877)	<0.001
Model 3	1	1.023 (0.893–1.171)	0.937 (0.812–1.082)	0.843 (0.730–0.973)	0.786 (0.680–0.908)	0.001
Model 4	1	1.049 (0.914–1.204)	0.962 (0.831–1.113)	0.889 (0.768–1.029)	0.844 (0.728–0.978)	0.020
Model 5	1	1.057 (0.920–1.214)	0.963 (0.831–1.115)	0.887 (0.766–1.028)	0.854 (0.736–0.990)	0.023
Model 6	1	1.093 (0.923–1.294)	0.947 (0.791–1.134)	0.870 (0.727–1.042)	0.768 (0.639–0.923)	0.001
Abdominal obesity						
Model 1	1	0.952 (0.822–1.102)	0.855 (0.733–0.997)	0.790 (0.678–0.919)	0.727 (0.625–0.847)	<0.001
Model 2	1	1.007 (0.865–1.173)	0.921 (0.785–1.081)	0.832 (0.710–0.975)	0.753 (0.643–0.882)	0.001
Model 3	1	1.043 (0.894–1.217)	0.932 (0.792–1.095)	0.872 (0.743–1.024)	0.774 (0.660–0.908)	0.001
Model 4	1	1.077 (0.921–1.261)	0.968 (0.821–1.142)	0.938 (0.796–1.106)	0.850 (0.720–1.002)	0.053
Model 5	1	1.082 (0.925–1.267)	0.970 (0.822–1.144)	0.934 (0.793–1.101)	0.859 (0.728–1.014)	0.063
Model 6	1	1.125 (0.925–1.367)	0.961 (0.784–1.178)	1.000 (0.817–1.225)	0.823 (0.671–1.010)	0.031

Model 1: unadjusted; Model 2: adjusted for age, gender, and duration of diabetes; Model 3: additionally adjusted for hypertension, smoking and alcohol drinking; Model 4: additionally adjusted for the use of insulin or insulin analogues, metformin, and sulfonylurea; Model 5: additionally adjusted for systolic blood pressure and diastolic blood pressure; Model 6: further adjusted for alanine aminotransferase, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, estimated glomerular filtration rate, creatinine, serum uric acid, urinary albumin excretion, fasting plasma glucose, 2-hour postprandial plasma glucose, glycosylated hemoglobin, fasting C-peptide, 2-hour postprandial C-peptide, and C-reactive protein.
OR, odds ratio; CI, confidence interval.

DISCUSSION

In this real-world study with relatively large samples, a significantly negative associations of serum magnesium levels with obesity and abdominal obesity were observed in patients with T2DM. Therefore, our findings suggested that low levels of serum magnesium may be an independent risk factor for the occurrence of obesity and abdominal obesity in patients with T2DM.

The present study revealed that serum magnesium levels in patients with T2DM were noticeably higher in men than in women; increased with age and decreased with DD. Consistent with our findings A previous study demonstrated that serum magnesium levels are negatively correlated with estrogen in women [29], which might explain the significantly lower serum magnesium levels in women compared to men in our present study. However, Masood et al. [30] found no significant differences in serum magnesium levels stratified by gender, age, and DD in patients with T2DM. Variations in serum

magnesium levels across different study based on age, sex, and DD may be attributed to sample size, ethnicity, and geographical region.

More importantly, previous studies have demonstrated that serum magnesium plays a crucial protective role in metabolic diseases including obesity [15,31,32]. For example, as serum magnesium quartiles ranged from high to low, Shi and Masood [31] observed an increased prevalence of obesity, diabetes, HTN, and hyperlipidemia in a general population. However, the relationship between serum magnesium and obesity in diabetic populations has been scarcely investigated and remains controversial. For example, similar to our findings, a study involving 119 adults with T2DM aged 25 to 65 years showed that the subjects with hypomagnesemia had significantly higher BMI than those with normal serum magnesium [33]. Babikr et al. [34] also reported a strongly negative correlation between serum magnesium and BMI in diabetic patients ($r=-0.234$, $P<0.0001$), which was also consistent with our findings.

However, in contrast to our findings and the studies men-

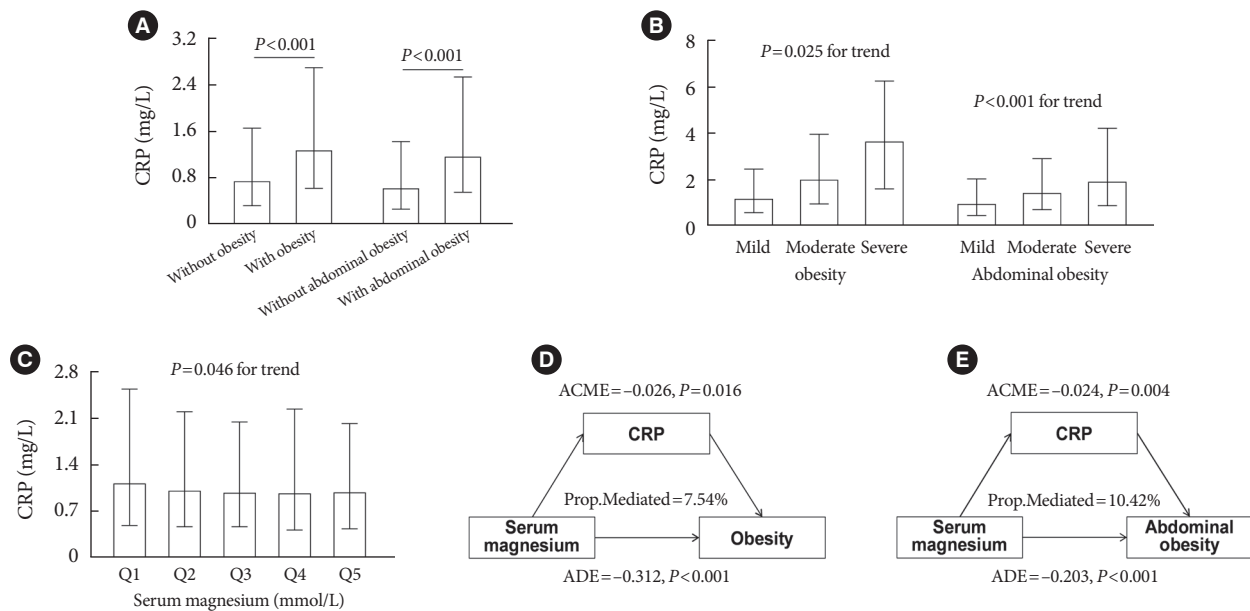


Fig. 3. Role of C-reactive protein (CRP) in the relationship between serum magnesium and obesity/abdominal obesity. (A) Comparison of serum CRP levels between the patients with and without obesity/abdominal obesity after controlling for gender, age, and duration of diabetes (DD) ($P < 0.001$ for trend in obesity and abdominal obesity). (B) Comparison of serum CRP levels in mild, moderate, and severe obesity/abdominal obesity after controlling for gender, age, and DD ($P = 0.025$ for trend in obesity, $P < 0.001$ for trend in abdominal obesity). (C) Comparison of serum CRP levels across serum magnesium quintiles after adjusting for gender, age, and DD ($P = 0.046$ for trend). (D) The mediation effects of CRP on the association between serum magnesium and obesity ($P = 0.016$). (E) The mediation effects of CRP on the association between serum magnesium and abdominal obesity ($P = 0.004$). ACME, average causal mediation effect; ADE, average direct effects.

tioned above [33,34], Pokharel et al. [35] found no significant association between serum magnesium and the development of obesity in patients with T2DM. Additionally, in a study of 65 patients with newly diagnosed T2DM, no significant differences were observed in BMI, WC, and WHR values between those with and without magnesium deficiency [36]. Therefore, we conducted the current study in T2DM population to investigate the real relationship between serum magnesium and obesity as well as abdominal obesity. In fact, we observed a strong association of decreased serum magnesium with obesity and abdominal obesity in T2DM subjects. Moreover, the RCS plot also provided a significant non-linear negative correlation between serum magnesium and obesity as well as abdominal obesity, especially when serum magnesium levels were higher than 0.89 mmol/L.

Furthermore, in addition to BMI, our data showed that an increase in serum magnesium levels was also significantly associated with a decrease in WC, WHR, and WHtR values, which are well-known indicators of abdominal obesity. Similar to our results, Hirschler et al. [37] also found a significantly

negative correlation between serum magnesium and WC, and a strong association of hypomagnesemia with central obesity in indigenous Argentinean children living at high altitude. Similar results were observed in another study including 428 adult patients with T2DM, in which a significant correlation between serum magnesium levels and WHR was found [38]. Since abdominal obesity is strongly linked to metabolic diseases [14], the significant correlation between serum magnesium levels and abdominal obesity suggests that serum magnesium may play an important role in metabolic regulation.

Interestingly, a remarkable decrease in the prevalence of severe obesity and abdominal obesity was found in the higher quintiles of serum magnesium, which suggested that low levels of serum magnesium may be a predictor of the progression to severe obesity and abdominal obesity in T2DM. Similar to our study, an investigation in Brazil found that serum magnesium levels significantly decreased with advancing obesity [39]. Moreover, Zaakouk et al. [40] also observed a significantly negative association between serum magnesium levels and the degree of obesity severity in children and adolescents. Further-

more, in a 30-year prospective cohort study, the most significantly negative correlation between magnesium intake and BMI was found in the highest quintile of magnesium intake [41]. Therefore, these studies including our study confirmed that high levels of serum magnesium have a notably ameliorative effect on the severity of obesity in different populations including T2DM population.

In addition, our study further revealed that serum CRP levels not only noticeably increased in T2DM subjects with obesity and abdominal obesity, but also obviously and positively associated with the severity of obesity and abdominal obesity. Furthermore, serum CRP in patients with T2DM was observed to be significantly and negatively correlated with serum magnesium. Additionally, 7.54% and 10.42% of the effect of serum magnesium on obesity and abdominal obesity was attributed to CRP-mediated effects. Thus, the protective role of serum magnesium in obesity is in part due to its anti-inflammatory effects. CRP, a well-known and reliable indicator of systemic inflammation, has been shown to remarkably correlate with obesity [42]. Furthermore, a previous study demonstrated that abdominal obesity exhibited the strongest remarkable correlation with CRP levels compared to other MetS components [43].

Obesity has been considered to be a disease characterized by chronic low-grade inflammation, and oxidative stress has been shown to be a crucial pathological mechanism in the development of obesity [44]. In a 20-year follow-up study, Kim et al. [45] observed a significantly negative correlation between serum magnesium and CRP levels in population without diabetes at baseline, which further corroborated our findings in patients with T2DM. Meanwhile, basic researches have also demonstrated the anti-oxidative stress and anti-inflammatory effects of magnesium by acting as a physiological inhibitor of xanthine oxidase and nicotinamide adenine dinucleotide phosphate oxidase and as a cofactor of adenosine triphosphate to inhibit the production of reactive oxygen species [46,47]. Therefore, we speculated that serum magnesium protects against the onset and progression of obesity and abdominal obesity in T2DM patients, mainly through its anti-inflammatory role.

Moreover, a significant decline in FPG, 2hr PPG, TG, and HbA1c levels with increasing quintiles of serum magnesium was identified in the present study. Additionally, as serum magnesium quintiles increased, 2hr CP levels were elevated considerably, indicating that serum magnesium probably plays an important role in preserving insulin function. In fact, various studies have demonstrated that magnesium ion, serving as a

cofactor for rate-limiting enzymes such as tyrosine kinase and glucokinase, plays a key role in the regulation of insulin secretion and function, and glycolysis [48]. Accordingly, it has been reported that FPG and PPG levels were significantly high in T2DM with hypomagnesemia [38]. In addition, a randomized controlled trial revealed that magnesium supplementation dramatically increased the levels of FCP and fasting insulin in overweight participants [49]. Therefore, high levels of serum magnesium may influence the regulation of energy metabolism, particularly glucose metabolism, to alleviate the development of obesity and abdominal obesity.

There were several limitations in the current study. Firstly, it was a single-center, cross-sectional study, thus the causal relationship between serum magnesium and obesity and abdominal obesity could not be established and needed to be further validated in future prospective studies. Additionally, dietary intake and exercise habits can influence obesity and abdominal obesity, whereas data on the specific diets and exercise patterns of our study participants were not available. In addition, we did not measure more direct parameters of oxidative stress to investigate their association with the occurrence and development of obesity and abdominal obesity. Finally, only hospitalized patients with T2DM were included in our study, which limited the generalizability of our findings to other populations such as diabetic patients from the community.

In conclusion, this real-world study with a large sample provided clear clinical evidence that serum magnesium not only significantly and negatively associated with obesity and abdominal obesity, but also linked with the severity of obesity and abdominal obesity in patients with T2DM, which probably attributed to its metabolic modulation, anti-oxidative stress, and anti-inflammatory effects. Serum magnesium may be used to assess the risk of obesity and abdominal obesity in T2DM subjects.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at <https://doi.org/10.4093/dmj.2023.0401>.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: L.X.L.

Acquisition, analysis, or interpretation of data: M.R.X., A.P.W., Y.J.W., J.X.L.

Drafting the work or revising: L.X.L., M.R.X., Y.J.W., J.X.L.

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FUNDING

This work was supported by the National Natural Science Foundation of China (81170759, 81770813, and 82070866), the National Key Research and Development Plan (2018YFC1314900 and 2018YFC1314905), the Shanghai Research Center for Endocrine and Metabolic Diseases (2022ZZ01002), and Shanghai Municipal Key Clinical Specialty.

ACKNOWLEDGMENTS

We thank the other investigators, the staff and all the patients of the present study for their invaluable contributions.

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