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Association between serum magnesium concentration and metabolic syndrome, diabetes, hypertension and hyperuricaemia in knee osteoarthritis: a cross-sectional study in Hunan Province, China

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ABSTRACT

Objectives To examine the associations between serum magnesium (Mg) concentration with the prevalence of metabolic syndrome (MetS), diabetes mellitus (DM), hypertension (HP) and hyperuricaemia (HU) in patients with radiographic knee osteoarthritis (OA).

Methods The present study was conducted at the Health Management Center of Xiangya Hospital. Radiographic OA was evaluated for patients aged over 40 years with basic characteristics and blood biochemical assessment. Serum Mg concentration was measured using the chemiluminescence method. MetS, DM, HP and HU were diagnosed based on standard protocols. The associations between serum Mg concentration with MetS, DM, HP and HU were evaluated by conducting multivariable adjusted logistic regression.

Results A total of 962 patients with radiographic knee OA were included. Compared with the lowest quintile, the multivariable adjusted ORs and related 95% CIs of DM were 0.40 (95% CI 0.23 to 0.70, p=0.001), 0.33 (95% CI 0.18 to 0.60, p<0.001), 0.27 (95% CI 0.14 to 0.52, p<0.001) and 0.22 (95% CI 0.11 to 0.44, p<0.001) in the second, third, fourth and highest quintiles of serum Mg, respectively (p for trend <0.001); the multivariable adjusted ORs of HU were 0.33 (95% CI 0.19 to 0.59, p<0.001), 0.52 (95% CI 0.30 to 0.91, p=0.022) and 0.39 (95% CI 0.22 to 0.70, p=0.001) in the third, fourth and highest quintiles of serum Mg, respectively (p for trend <0.001); and the multivariable adjusted ORs of MetS were 0.59 (95% CI 0.36 to 0.94, p=0.027) in the second and 0.56 (95% CI 0.34 to 0.93, p=0.024) in the highest quintiles of serum Mg. However, the inverse association between serum Mg and the prevalence of MetS was non-linear (p for trend=0.067). There was no significant association between serum Mg and HP in patients with OA.

Conclusions The serum Mg concentration was inversely associated with the prevalence of MetS, DM and HU in patients with radiographic knee OA.

Level of evidence Level III, cross-sectional study.

Strengths and limitations of this study

- This is the first study examining the associations between serum magnesium (Mg) and the prevalence of metabolic syndrome, diabetes mellitus, hypertension and hyperuricaemia in patients with radiographic knee osteoarthritis.
- The multivariable logistical regression models in this study were adjusted for a considerable number of potential confounding factors, which greatly improved the reliability of the results.
- The kidney is the key organ in maintaining Mg homoeostasis. This study conducted a sensitivity analysis by adding estimated glomerular filtration rate into the multivariable logistic regression models, and the reverse associations remained significant.
- This study adopted cross-sectional design, which precluded causal correlations.
- Serum Mg concentration was adopted as the indicator of body Mg content in this study, which may not be the best indicator of body status.

INTRODUCTION

The association between osteoarthritis (OA) and metabolic diseases, especially metabolic syndrome (MetS)[1 2] and diabetes mellitus (DM),[3–5] has drawn increasing attention in the past few years. OA includes three specific phenotypes: metabolic OA, age-related OA and injury-related OA.[6] A large number of studies have indicated that the prevalence of MetS,[7–9] DM[10–18] and hypertension (HP)[7 9–13 19 20] is either higher in patients with OA or associated with OA. In addition, some other studies reported that MetS,[21 22] DM[23 24] and HP[21 22] are risk factors of OA progression. Thus, it appears necessary to pay more attention and adopt appropriate measures

to reduce the high prevalence of metabolic diseases in patients with OA, which also seems to be beneficial in delaying OA progression.

Serum magnesium (Mg), one of the most important micronutrients for human health, has been reported to be negatively associated with MetS,[25–29] DM[30–38] and HP[30 39–41] by lots of studies. Meanwhile, our previous study showed an inverse association between serum Mg and hyperuricaemia (HU).[42] However, to the best knowledge of the authors, there is not yet a study examining the association between the serum Mg concentration and the aforementioned metabolic diseases (MetS, DM, HP and HU) in patients with OA. On the other hand, we have previously shown that the serum Mg concentration may be inversely associated with radiographic knee OA.[43] Therefore, we speculate that the prevalence of MetS, DM, HP and HU in patients with OA may be reduced by elevating the level of serum Mg, which can in turn delay OA progression. Thus, the objective of the present study was to examine the associations between the serum Mg concentration with the prevalence of MetS, DM, HP and HU in patients with radiographic knee OA. It was hypothesised that serum Mg concentration was inversely associated with these diseases.

METHODS

Study population

The present study was conducted at the Health Management Center of Xiangya Hospital between October 2013 and November 2014. The study design has been published previously.[42–46] Registered nurses were engaged to interview all participants during the examination using a standard questionnaire, with the purpose to collect information on demographic characteristics and health-related habits. Participants were selected based on the following inclusion criteria: (1) 40 years old or above; (2) undergoing weight-bearing bilateral anteroposterior radiography of the knee, and diagnosed with knee OA according to the Kellgren-Lawrence (K-L) radiographic atlas (knee joint was graded K-L 2 or above); (3) availability of all basic characteristics, including age, gender, Body Mass Index (BMI) and blood pressure; (4) availability of biochemical test results, including serum Mg concentration; (5) availability of information related to the living habits, including education background, activity level, smoking, drinking and medication status. Initially, the present cross-sectional study retrieved 1820 patients with radiographic knee OA aged over 40 years who exhibited sound basic characteristics and required blood biochemical assessment (including serum Mg concentration). Among them, 962 patients offered demographic characteristics and health-related habits and were finally included in this study.

Blood biochemistry

All blood samples were drawn after a 12-hour overnight fast and were kept at 4°C until analysis. Blood tests were undertaken using the Beckman Coulter AU 5800 (Beckman Coulter, Brea, California, USA). The inter-assay and intra-assay coefficients of variation were tested at both low concentrations (2.5 mmol/L for glucose, 118 µmol/L for uric acid and 0.60 mmol/L for serum Mg) and high concentrations (6.7 mmol/L for glucose, 472 µmol/L for uric acid and 1.00 mmol/L for serum Mg) of standard human samples. The intra-assay coefficients of variation were 0.98% (2.5 mmol/L) and 1.72% (6.7 mmol/L) for glucose, 1.39% (118 µmol/L) and 0.41% (472 µmol/L) for uric acid, and 1.86% (0.60 mmol/L) and 1.65% (1.00 mmol/L) for serum Mg, respectively. The inter-assay coefficients of variation were 2.45% (2.5 mmol/L) and 1.46% (6.7 mmol/L) for glucose, 1.40% (118 µmol/L) and 1.23% (472 µmol/L) for uric acid, and 1.87% (0.60 mmol/L) and 1.70% (1.00 mmol/L) for serum Mg, respectively.

Assessment of other exposures

Blood pressure was measured by an electronic sphygmomanometer. The weight and height of each subject were measured respectively to calculate the BMI. Information on the average frequency of physical activity (never, one to two times per week, three to four times per week, five times and above per week) and average duration of physical activity (less than half an hour, half an hour to 1 hour, 1 to 2 hours, more than 2 hours) were collected through survey questionnaire. The smoking, alcohol drinking and medication status were collected during the face-to-face interview.

Assessment of MetS, DM, HP and HU

MetS was diagnosed based on the Chinese Diabetes Society criteria,[47–49] which requires meeting at least three of the following four items: (1) BMI ≥25 kg/m^2; (2) fasting plasma glucose ≥6.1 mmol/L or diagnosed DM; (3) systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg, or treatment of previously diagnosed HP; (4) triglycerides ≥1.7 mmol/L and/or high-density lipoprotein (HDL) cholesterol <0.9 mmol/L in men or <1.0 mmol/L in women, or treatment for this lipid abnormality. Subjects with fasting glucose ≥7.0 mmol/L or currently undergoing drug treatment for blood glucose control were regarded as patients with DM, and subjects with systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or currently undertaking antihypertensive medication were regarded as patients with HP. HU was defined as uric acid ≥416 µmol/L for men and ≥360 µmol/L for women or currently undergoing drug treatment for uric acid control.

Statistical analysis

The continuous data were expressed as mean with SD, and the category data were expressed in percentage. Differences in continuous data were evaluated by one-way classification analysis of variance (normally distributed data) or Kruskal-Wallis H test (non-normally distributed data), while differences in category data were assessed by

the χ^2 test. The serum Mg was classified into five categories based on the quintile distribution: ≤0.85, 0.86–0.89, 0.90–0.92, 0.93–0.96 and ≥0.97 mmol/L. The prevalence of MetS, DM, HP and HU in each quintile of serum Mg in patients with OA was assessed by scatter plots.

Logistic regression was conducted to calculate the ORs with 95% CIs for the associations between serum Mg and MetS, DM, HP and HU. Specifically, model 1 was adjusted by covariates of age (continuous data) and gender (male, female). Then, model 2 was adjusted by additional covariates of BMI (continuous data), educational level (high school or above, lower than high school), smoking status (yes, no), activity level (continuous data), alcohol drinking status (yes, no), HP (yes, no), DM (yes, no) and dyslipidemia (yes, no) on the basis of model 1. Dyslipidemia was defined as triglycerides ≥1.7 mmol/L and/or HDL cholesterol <0.9 mmol/L in men or <1.0 mmol/L in women, or treatment for this lipid abnormality. Notably, the selection of covariates in model 2 varied slightly for examining different associations (between serum Mg and MetS, DM, HP or HU). For example, BMI, HP and dyslipidemia were adjusted for the association between serum Mg and DM, but not for the association between serum Mg and MetS, simply because MetS was diagnosed based on BMI, HP and dyslipidemia status. Model 3 was established based on model 2, with adjustment of an additional covariate, estimated glomerular filtration rate (eGFR). eGFR (continuous data) was calculated from the Chronic Kidney Disease Epidemiology Collaboration equation.[50] All covariates in the present study were chosen referring to some of the previous similar studies.[27 33 51 52] Tests for linear trends were conducted based on logistic regression using a median variable of Mg concentration in each category.

Scatter plots were plotted using R V.3.4.4.[53] Other data analyses were performed using SPSS V.17.0; p value ≤0.05 was considered to be statistically significant. All tests were two tailed.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of the study. There were no plans to disseminate the results of the research to study participants.

RESULTS

A total of 962 subjects (377 women, accounting for 39.2%) were included in the present cross-sectional study. The characteristics of the study population according to quintiles of serum Mg are presented in table 1. The mean age of the subjects was 54.9±7.6 years. The overall prevalence of MetS, DM, HP and HU in patients with OA were 21.4%, 12.0%, 38.5% and 18.3%, respectively. Significant differences were observed across the quintiles of serum Mg for fasting glucose, as well as the prevalence of DM and HU.

The prevalence of MetS in each quintile of serum Mg in patients with OA is shown in figure 1A. The outcomes of multivariable adjusted associations between MetS and serum Mg concentration are shown in table 2. Compared with the lowest quintile, the age–gender adjusted ORs (model 1) suggested significant decreased prevalence of MetS in the second (OR 0.61, 95% CI 0.38 to 0.97, p=0.038) and the highest (OR 0.59, 95% CI 0.36 to 0.96, p=0.035) quintiles of serum Mg; the multivariable adjusted ORs (model 2) also suggested significant decreased prevalence of MetS in the second (OR 0.60, 95% CI 0.37 to 0.96, p=0.035) and the highest (OR 0.61, 95% CI 0.37 to 0.99, p=0.047) quintiles. The sensitivity analysis, by adding eGFR into model 2, also reached similar results—significant lower prevalence of MetS in the second (OR 0.59, 95% CI 0.36 to 0.94, p=0.027) and the highest quintiles (OR 0.56, 95% CI 0.34 to 0.93, p=0.024) compared with the reference quintile of serum Mg. No clear trend was evident in the third and fourth quintiles of serum Mg. The p values for trend were 0.090 (model 1), 0.120 (model 2) and 0.067 (model 3), respectively.

Figure 1B shows the prevalence of DM in each category of serum Mg in patients with OA. Table 3 illustrates the multivariable adjusted relations between serum Mg and DM in patients with OA. Both the age–gender adjusted OR values (model 1) and the multivariable adjusted OR values (model 2) suggested a strong inverse association between serum Mg and DM. The age–gender adjusted ORs for the prevalence of DM were 0.38 (95% CI 0.22 to 0.66, p=0.001), 0.34 (95% CI 0.19 to 0.61, p<0.001), 0.29 (95% CI 0.15 to 0.55, p<0.001) and 0.20 (95% CI 0.10 to 0.40, p<0.001) in the second, third, fourth and fifth quintiles of serum Mg, respectively, and the p value for trend was <0.001. The multivariable adjusted ORs for the prevalence of DM were 0.40 (95% CI 0.23 to 0.70, p=0.001), 0.32 (95% CI 0.18 to 0.59, p<0.001), 0.26 (95% CI 0.13 to 0.50, p<0.001) and 0.21 (95% CI 0.11 to 0.42, p<0.001) in the second, third, fourth and fifth quintiles of serum Mg, respectively, and the p value for trend was <0.001. The sensitivity analysis, by adding eGFR into model 2, showed similar results—significant lower prevalence of DM in the second (OR 0.40, 95% CI 0.23 to 0.70, p=0.001), third (OR 0.33, 95% CI 0.18 to 0.60, p<0.001), fourth (OR 0.27, 95% CI 0.14 to 0.52, p<0.001) and highest quintiles (OR 0.22, 95% CI 0.11 to 0.44, p<0.001) compared with the reference quintile of serum Mg, and the p value for trend was <0.001.

The prevalence of HP in each quintile of serum Mg in patients with OA is depicted in figure 1C. The multivariable adjusted relations between serum Mg and HP in patients with OA are illustrated in table 4. According to both the age–gender adjusted ORs (model 1) and the multivariable adjusted ORs (model 2), there was no significant association between serum Mg and HP, and the p values for trend were 0.929 and 0.377, respectively. The sensitivity analysis, by adding eGFR into model 2, reached the same results.

The prevalence of HU in each category of serum Mg in patients with OA is shown in figure 1D. The multivariable adjusted relations between serum Mg and

Table 1 Basic characteristics of included subjects according to quintiles of serum Mg (n=962)

	Quintiles of serum Mg					
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	P values
Median Mg concentration (mmol/L)	0.82	0.87	0.91	0.94	0.99	–
Participants (n)	200	215	190	168	189	–
Age (years)	53.8 (7.3)	54.6 (7.6)	55.2 (7.9)	55.3 (7.1)	56.1 (8.0)	0.062
BMI (kg/m^2)	25.2 (3.2)	24.9 (3.2)	25.0 (3.7)	25.2 (3.4)	24.6 (3.2)	0.464
Female (%)	37.5	42.3	36.8	42.3	37.0	0.627
Smoking (%)	27.5	27.4	21.6	24.4	21.7	0.457
Alcohol drinking (%)	34.5	36.3	40.5	41.1	38.1	0.645
High school diploma (%)	45.0	47.4	45.3	56.5	48.1	0.184
Activity level (hour/week)	2.0 (3.5)	2.0 (3.3)	2.3 (3.5)	2.1 (3.1)	2.4 (3.5)	0.457
Fasting glucose (mmol/L)	6.6 (3.0)	5.7 (1.7)	5.7 (1.4)	5.5 (0.9)	5.5 (1.6)	0.009
Systolic pressure (mm Hg)	129.2 (16.9)	128.3 (17.9)	130.4 (16.2)	128.8 (16.3)	129.6 (17.7)	0.837
Diastolic pressure (mm Hg)	81.2 (11.8)	79.8 (12.1)	80.7 (11.0)	80.7 (10.7)	80.3 (10.5)	0.654
HDL cholesterol (mmol/L)	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)	1.5 (0.3)	1.5 (0.4)	0.374
Triglyceride (mmol/L)	2.1 (1.9)	1.8 (1.5)	2.0 (2.1)	1.8 (1.0)	2.3 (2.9)	0.620
Uric acid (μmol/L)	337.3 (101.7)	329.0 (80.7)	321.3 (86.3)	331.5 (78.0)	329.4 (81.7)	0.590
eGFR (mL/min/1.73 m^2)	80.2 (14.4)	77.7 (10.7)	76.0 (10.6)	75.8 (10.7)	74.3 (12.0)	<0.001
MetS (%)	26.5	17.7	25.8	19.6	17.5	0.059
DM (%)	23.5	10.7	10.0	8.3	6.3	<0.001
HP (%)	40.0	33.5	37.4	42.3	40.2	0.432
HU (%)	25.5	19.1	13.2	18.5	14.8	0.018

Data are mean (SD), unless otherwise indicated. P values are for test of difference across all quintiles of serum Mg.
BMI, Body Mass Index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HP, hypertension; HU, hyperuricaemia; MetS, metabolic syndrome; Mg, magnesium.

HU in patients with OA are illustrated in table 5. Both the age–gender adjusted OR values (model 1) and the multivariable adjusted OR values (model 2) suggested significant decreased prevalence of HU in the third quintile (age–gender adjusted OR 0.44, 95% CI 0.26 to 0.75, p=0.002; multivariable adjusted OR 0.38, 95% CI 0.22 to 0.67, p=0.001) and fifth quintile (age–gender adjusted OR 0.51, 95% CI 0.30 to 0.85, p=0.010; multivariable adjusted OR 0.50, 95% CI 0.29 to 0.87, p=0.013) compared with the lowest quintile of serum Mg, and the p values for trend were 0.008 and 0.006, respectively. The sensitivity analysis, by adding eGFR into model 2, showed similar outcomes—significant lower prevalence of HU in the third (OR 0.33, 95% CI 0.19 to 0.59, p<0.001), fourth (OR 0.52, 95% CI 0.30 to 0.91, p=0.022) and highest quintiles (OR 0.39, 95% CI 0.22 to 0.70, p=0.001) compared with the reference quintile of serum Mg, and the p value for trend was <0.001.

DISCUSSION

The results of this study suggested that the serum Mg concentration was negatively associated with the prevalence of MetS, DM and HU in subjects with radiographic knee OA. To control potential confounders, several covariates including characteristics, living habits and underlying diseases were selected, and even the eGFR was added into the multivariable logistic regression models to eliminate the influence of renal function on Mg excretion. The reverse associations mentioned above remained significant after adjustments of these confounders. However, the association between serum Mg and the prevalence of MetS was non-linear, with no clear trend in the third and fourth quintiles of serum Mg. Moreover, the negative association between serum Mg and the prevalence of HP was not observed in patients with radiographic knee OA.

Mg, the fourth most abundant cation in the human body and the second most profuse intracellular cation, is a metallic cofactor for over 300 enzymatic reactions. It appears to play an important role in glucose metabolism and insulin homoeostasis, which are both highly correlated with metabolic diseases, especially MetS and DM. The mechanisms involved in Mg deficiency in patients with MetS, DM and HU are probably multifactorial. The most important factor may be insulin resistance, as Mg is essential for insulin action and is a critical cofactor for several enzymes in carbohydrate metabolism, which is important for the phosphorylation reactions of

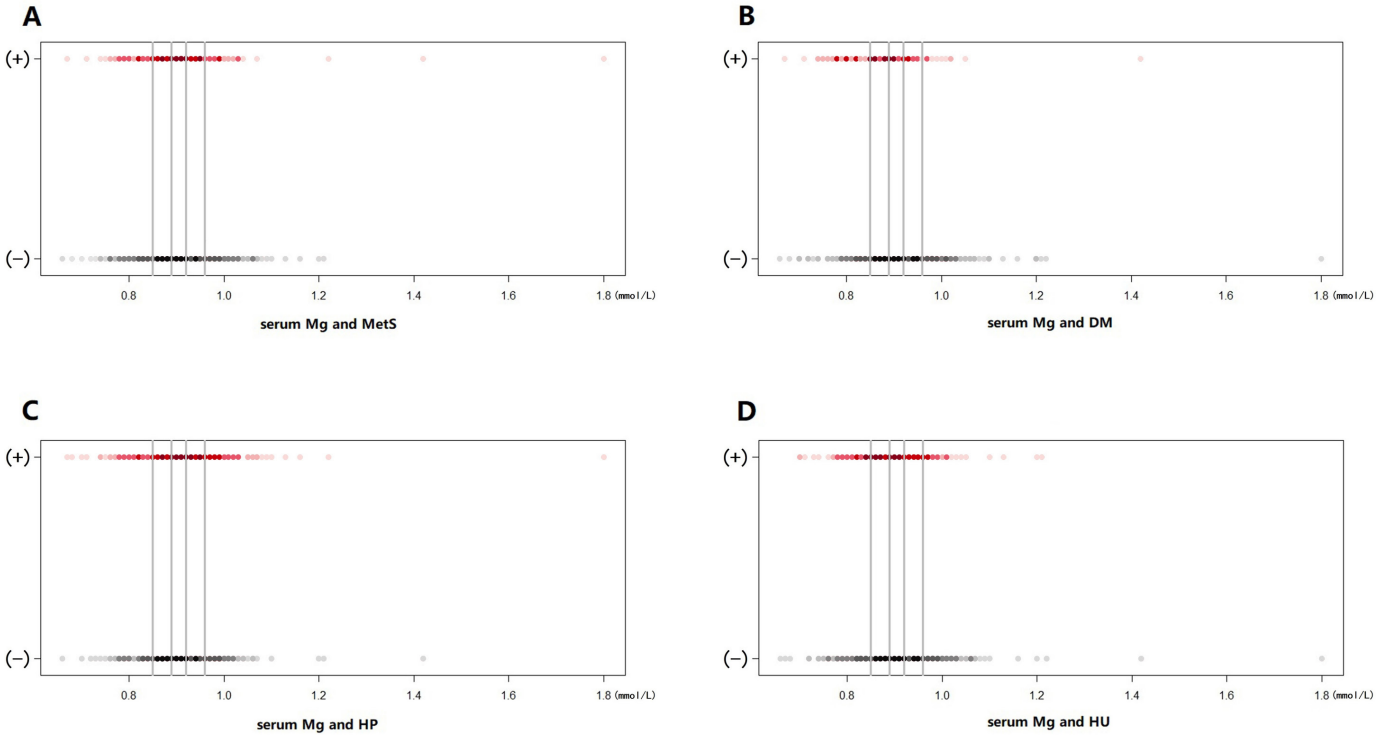

Figure 1 Prevalence of metabolic syndrome (MetS) (A), diabetes mellitus (DM) (B), hypertension (HP) (C) and hyperuricaemia (HU) (D) in each quintile of serum Mg in patients with radiographic knee OA. The figures above present the prevalence of MetS (A), DM (B), HP (C) and HU (D) among the 962 patients with OA under different quintiles of serum Mg levels. The horizontal axis denotes the serum Mg level, and the vertical axis indicates whether a subject is diagnosed with the specific disease: (+), disease; (–), no disease. The solid grey lines represent the boundaries in between the five quintiles of serum Mg levels. The red and black spots represent the prevalence of diseases and no diseases at each serum Mg level, respectively. The darker the colour of a spot, the more patients with OA there are at the corresponding concentration.

tyrosine kinase in the insulin receptor.[31 54–58] Of course, it is necessary to highlight the fact that insulin can also induce Mg excretion[59] and produce a significant decline of plasma Mg through ion exchange.[60] Thus, there seems to be a vicious circle between Mg deficiency and insulin resistance.

Other potential mechanisms include glucose transportation,[57] oxidative stress[57] and inflammatory cytokines,[61–63]

Table 2 Multivariable adjusted relations of serum Mg and MetS in patients with OA (n=962)

	Quintiles of serum Mg					P for trend
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
Median Mg concentration (mmol/L)	0.82	0.87	0.91	0.94	0.99	–
Participants (n)	200	215	190	168	189	–
MetS (%)	26.5	17.7	25.8	19.6	17.5	–
Model 1*	1.00 (reference)	0.61 (0.38 to 0.97)	0.97 (0.61 to 1.52)	0.69 (0.42 to 1.14)	0.59 (0.36 to 0.96)	0.090
P values	–	0.038	0.881	0.150	0.035	–
Model 2*	1.00 (reference)	0.60 (0.37 to 0.96)	1.00 (0.63 to 1.57)	0.70 (0.42 to 1.15)	0.61 (0.37 to 0.99)	0.120
P values	–	0.035	0.985	0.160	0.047	–
Model 3*	1.00 (reference)	0.59 (0.36 to 0.94)	0.95 (0.60 to 1.51)	0.67 (0.40 to 1.10)	0.56 (0.34 to 0.93)	0.067
P values	–	0.027	0.830	0.114	0.024	–

Data are adjusted OR (95% CI), unless otherwise indicated.
*Model 1 was adjusted for age (continuous data) and gender (male, female); model 2 was adjusted for age (continuous data), gender (male, female), educational level (high school or above, lower than high school), smoking status (yes, no), activity level (continuous data) and alcohol drinking status (yes, no); model 3 was adjusted based on model 2, with additional factor of estimated glomerular filtration rate (continuous data).
MetS, metabolic syndrome; Mg, magnesium; n, number; OA, osteoarthritis.

Table 3 Multivariable adjusted relations of serum Mg and DM in patients with OA (n=962)

	Quintiles of serum Mg					P for trend
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
Median Mg concentration (mmol/L)	0.82	0.87	0.91	0.94	0.99	–
Participants (n)	200	215	190	168	189	–
DM (%)	23.5	10.7	10.0	8.3	6.3	–
Model 1*	1.00 (reference)	0.38 (0.22 to 0.66)	0.34 (0.19 to 0.61)	0.29 (0.15 to 0.55)	0.20 (0.10 to 0.40)	<0.001
P values	–	0.001	<0.001	<0.001	<0.001	–
Model 2*	1.00 (reference)	0.40 (0.23 to 0.70)	0.32 (0.18 to 0.59)	0.26 (0.13 to 0.50)	0.21 (0.11 to 0.42)	<0.001
P values	–	0.001	<0.001	<0.001	<0.001	–
Model 3*	1.00 (reference)	0.40 (0.23 to 0.70)	0.33 (0.18 to 0.60)	0.27 (0.14 to 0.52)	0.22 (0.11 to 0.44)	<0.001
P values	–	0.001	<0.001	<0.001	<0.001	–

Data are adjusted OR (95% CI), unless otherwise indicated.
*Model 1 was adjusted for age (continuous data) and gender (male, female); model 2 was adjusted for age (continuous data), Body Mass Index (continuous data), gender (male, female), educational level (high school or above, lower than high school), smoking status (yes, no), activity level (continuous data), alcohol drinking status (yes, no), hypertension (yes, no) and dyslipidemia (yes, no); model 3 was adjusted based on model 2, with additional factor of estimated glomerular filtration rate (continuous data).
DM, diabetes mellitus; Mg, magnesium; n, number; OA, osteoarthritis.

and cellular calcium homoeostasis.[55] Mg is an essential cofactor of the high-energy phosphate-bound enzymatic pathways involved in the modulation of glucose transport across cell membranes.[57] It also plays a role in the mechanisms of cellular antioxidant defence.[64] The oxidative stress, defined as a persistent imbalance between the excessive production of reactive oxygen species and/or defects in antioxidant defence, has been implicated in the pathogenesis of diabetic complications.[57] Moreover, low serum Mg levels are strongly related to elevated serum concentrations of both tumour necrosis factor alpha and C reactive protein (CRP),[65] suggesting that Mg deficiency may contribute to the development of low-grade chronic inflammation syndrome and the development of glucose metabolic disorders through the former pathway. In addition, lower Mg concentration can enhance calcium-mediated vasoconstriction, blunt cardiac and smooth muscle relaxation, and thus contribute to BP elevation.[55] However, the decreased serum calcium concentration in patients with radiographic knee OA may weaken the association between Mg and HP.[66]

MetS[21 22] and DM[4 23 24] were reported to be the risk factors of OA progression. Moreover, serum Mg level has been proven to be significantly associated with CRP concentration,[27 67–69] and higher CRP might serve as a prediction factor for OA progression.[70 71] Thus, OA

Table 4 Multivariable adjusted relations of serum Mg and HP in patients with OA (n=962)

	Quintiles of serum Mg					P for trend
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
Median Mg concentration (mmol/L)	0.82	0.87	0.91	0.94	0.99	–
Participants (n)	200	215	190	168	189	–
HP (%)	40.0	33.5	37.4	42.3	40.2	–
Model 1*	1.00 (reference)	0.71 (0.47 to 1.06)	0.83 (0.54 to 1.25)	1.00 (0.66 to 1.54)	0.89 (0.59 to 1.35)	0.929
P values	–	0.095	0.368	0.987	0.582	–
Model 2*	1.00 (reference)	0.77 (0.50 to 1.19)	0.89 (0.57 to 1.39)	1.10 (0.70 to 1.74)	1.08 (0.69 to 1.68)	0.377
P values	–	0.245	0.608	0.686	0.744	–
Model 3*	1.00 (reference)	0.77 (0.50 to 1.19)	0.88 (0.56 to 1.38)	1.09 (0.68 to 1.72)	1.05 (0.67 to 1.65)	0.434
P values	–	0.235	0.574	0.727	0.818	–

Data are adjusted OR (95% CI), unless otherwise indicated.
*Model 1 was adjusted for age (continuous data) and gender (male, female); model 2 was adjusted for age (continuous data), Body Mass Index (continuous data), gender (male, female), educational level (high school or above, lower than high school), smoking status (yes, no), activity level (continuous data), alcohol drinking status (yes, no), diabetes (yes, no) and dyslipidemia (yes, no); model 3 was adjusted based on model 2, with additional factor of estimated glomerular filtration rate (continuous data).
HP, hypertension; Mg, magnesium; n, number; OA, osteoarthritis.

Table 5 Multivariable adjusted relations of serum Mg and HU in patients with OA (n=962)

	Quintiles of serum Mg					P for trend
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	
Median Mg concentration (mmol/L)	0.82	0.87	0.91	0.94	0.99	–
Participants (n)	200	215	190	168	189	–
HU (%)	25.5	19.1	13.2	18.5	14.8	–
Model 1*	1.00 (reference)	0.71 (0.44 to 1.14)	0.44 (0.26 to 0.75)	0.68 (0.41 to 1.14)	0.51 (0.30 to 0.85)	0.008
P values	–	0.157	0.002	0.144	0.010	–
Model 2*	1.00 (reference)	0.73 (0.45 to 1.20)	0.38 (0.22 to 0.67)	0.59 (0.35 to 1.02)	0.50 (0.29 to 0.87)	0.006
P values	–	0.210	0.001	0.058	0.013	–
Model 3*	1.00 (reference)	0.68 (0.41 to 1.14)	0.33 (0.19 to 0.59)	0.52 (0.30 to 0.91)	0.39 (0.22 to 0.70)	<0.001
P values	–	0.142	<0.001	0.022	0.001	–

Data are adjusted OR (95% CI), unless otherwise indicated.
*Model 1 was adjusted for age (continuous data) and gender (male, female); model 2 was adjusted for age (continuous data), Body Mass Index (continuous data), gender (male, female), educational level (high school or above, lower than high school), smoking status (yes, no), activity level (continuous data), alcohol drinking status (yes, no), hypertension (yes, no), diabetes (yes, no) and dyslipidemia (yes, no); model 3 was adjusted based on model 2, with additional factor of estimated glomerular filtration rate (continuous data).
HU, hyperuricaemia; Mg, magnesium; n, number; OA, osteoarthritis.

progression may be delayed by elevating the serum Mg level through reducing the prevalence of MetS and DM and decreasing the level of CRP. Above all, the present study indicated that the elevation of serum Mg level has the potential to reduce the prevalence of MetS, DM and HU in patients with knee OA and may delay the progression of knee OA. However, the specific mechanism needs to be further explored.

The present study has several strengths. First, this is the first study examining the associations between serum Mg and the prevalence of MetS, DM, HP and HU in patients with radiographic knee OA. The results of this study will provide a new insight into the treatment of knee OA. Second, the multivariable logistical regression models were adjusted for a considerable number of potential confounding factors, which greatly improved the reliability of the results. Third, the kidney is the key organ in maintaining Mg homoeostasis. This study conducted a sensitivity analysis by adding eGFR into multivariable logistic regression models, which showed that the reverse associations remained significant.

Limitations of the present study should also be admitted. The cross-sectional design precludes causal correlations, so further prospective studies and intervention trials should be undertaken to establish a causal association between serum Mg with the prevalence of MetS, DM, HP and HU in patients with radiographic knee OA. Since no previous research investigated such associations in patients with knee OA, the value of this study should not be blotted out by the cross-sectional nature. Another limitation of this study lies in the relatively small sample size, and thus, extensive high-quality researches based on a larger sample are needed. Moreover, the dietary intake of Mg in relation to the prevalence of MetS, DM, HP and HU was not assessed in the present study. Last but not the least, it is important to highlight that Mg is an intracellular ion; therefore, the serum Mg concentration must be considered as a poor indicator of body Mg content[72] even though it has been used in many studies. However, blood Mg level is the second best indicator of body status.[73]

CONCLUSIONS

The present study concluded that the serum Mg concentration was inversely associated with the prevalence of MetS, DM and HU in patients with radiographic knee OA.

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Contributors All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. GL, YW and JW conceived the study. GL, YW and JW were responsible for conception and design of the study and drafted the manuscript. CZ, TY, HL, YC and DX contributed to data collection. JW contributed to preparation and data analysis. BX, ZL, JL and SJ contributed to study retrieval. GL and YW contributed to revision of the manuscript. All the authors contributed to the interpretation of the data and critically reviewed the manuscript for publication.

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Patient consent Obtained.

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