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The association between serum and dietary magnesium with cardiovascular disease risk factors in Iranian adults with metabolic syndrome

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ABSTRACT

Background: Chronic magnesium deficiency is associated with obesity, hyperglycemia, hypertension and dyslipidemia. The aim of this study was to investigate the relationship between serum and dietary magnesium levels among Iranian adults with metabolic syndrome (MetS).
Methods: A total of 853 participants (including 269 and 584 subjects with, or without MetS, respectively) were recruited as part of the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study. Demographic data, anthropometric measurements, blood pressure, biochemical parameters and serum magnesium were determined in all participants. The first quartile of serum magnesium (<0.94 mg/dl) was considered as a low value for serum magnesium.
Results: In this study a low serum magnesium was found in 22.7% (n = 61) of subjects with MetS and in 22.1% (n = 129) in individuals without MetS (P-value > 0.05). Dietary magnesium insufficiency [<67% of the recommended daily allowances (RDA)] was observed in 30.3% (n = 44) of individuals with MetS and 69.7% (n = 101) of individuals without MetS (P > 0.05). There were no significant differences between serum and dietary magnesium levels among subjects with MetS and individuals without MetS (P-value > 0.05). Moreover, there was no significant difference in serum and dietary magnesium levels between individuals with or without MetS (P > 0.05).
A low serum magnesium was associated with a higher fasting plasma glucose in individuals with MetS (P < 0.05).
Conclusions: The results showed that serum and dietary magnesium status is related to several cardiovascular risk factors including body mass index, waist circumference, total cholesterol, systolic and

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diastolic blood pressure. Furthermore, an inverse association was found between serum magnesium levels with diabetes mellitus.

Abbreviations

MetS	metabolic syndrome
MASHAD study	Mashhad stroke and heart atherosclerotic disorder study
CVD	cardiovascular disease
WHO	World Health Organization
IDF	International Diabetes Federation
WC	waist circumference
RDA	recommended daily allowances
BMI	body mass index
JNC	Joint National Committee
HDL-C	high density lipoprotein-cholesterol
LDL-C	low density lipoprotein-cholesterol
TG	triglyceride
TC	total cholesterol
CV	coefficient of variation
FFQ	food frequency questionnaire
EAR	estimated average requirement
SPSS	statistical package for the social sciences
HC	hip circumference
WHR	waist to hip ratio
SBP	systolic blood pressure
DBP	diastolic blood pressure
FPG	fasting plasma glucose
PAL	physical activity level

1. Introduction

Cardiovascular disease (CVD) is a preventable but growing, public health problem, and a leading global cause of morbidity and mortality, and therefore a substantial economic burden.[1] The prevalence of this non-communicable disease has risen steeply during the last decade.[2] It has been estimated that millions of people die from CVD each year.[3] The World Health Organization (WHO) has reported that CVD is responsible for nearly 17 million death worldwide annually,[4] and this is expected to increase to about 23 million deaths by 2030.[5] Risk factors for CVD include: increasing age, tobacco use, high salt consumption, low physical activity, obesity, high fasting glucose, dyslipidemia, hypertension, elevated red blood cell distribution width and increased C-reactive protein,[6] and the risk of CVD increases with the coexistence of multiple CVD risk factors.[7,8] Metabolic syndrome (MetS) is defined by a clustering of several CVD risk factors including obesity, impaired glucose tolerance, hypertension and hyperlipidemia.[9] The reported global prevalence of MetS varies between 10% and 84% in different populations and using different definitions[10]; it is associated with a substantial increased mortality and morbidity due to a high risk of CVD and diabetes mellitus.[11]

Magnesium is an important intracellular cation that plays a role in the function of more than 600 enzymes and the regulation of many biological processes.[12] It acts as a vasodilator and is important in normal cardiac and vascular function.[13] Magnesium is present in several foods, that include: nuts, whole grains, seeds, green leafy vegetables, legumes and coffee.[14] Chronic magnesium deficiency has been reported to be associated with hyperglycemia and impaired glucose metabolism, elevation in blood pressure and alterations in lipid metabolism. There is growing evidence of a relationship between serum magnesium concentration and chronic disease including CVD.[15,16] However, the exact role of magnesium in the pathogenesis of CVD is not fully understood.[15,16] The reference range for normal serum magnesium level is 1.70–2.60 mg/dl.[9] Hypomagnesemia is defined as the serum magnesium concentration <1.7 mg/dl. Primary magnesium deficiency is the result of reduced dietary magnesium intake, whilst secondary magnesium deficiency is due to increased renal and/or gastrointestinal loss.[11] Animal and human studies show that magnesium deficiency is inversely associated with several chronic disorders, in part due its effects on oxidative stress and inflammation.[6] The aim of this study was to investigate the association between serum and dietary magnesium and cardiovascular disease risk factors in subjects with MetS.

2. Method and materials

2.1. Study design and participant selection

This observational study was conducted in subjects who were recruited as part of the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study. A Stratified-cluster sampling method was used for participant selection of those individuals aged 35–65 years. Exclusion criteria involved in patients with malignancies, pregnant women, alcohol consumption and taking any drugs. Besides, all participants were negative for hepatitis and HIV. A total of 853 participants (412 male and 441 female) were recruited and demographic data, anthropometric measurements, blood pressure, biochemical parameters and serum magnesium were determined in all participants. The inclusion and exclusion criteria of the study have been described previously.[17] Each participant gave informed written consent to participate in the study, which was approved by Mashhad University's Advisory Committee on Ethics.

The International Diabetes Federation (IDF) criteria were used to define MetS which comprise: a waist circumference (WC) >94 and >80 (cm) in men and women respectively, plus any 2 of the follow criteria: 1) serum fasted triglyceride ≥150 mg/dl or taking drugs for this type of dyslipidemia. 2) HDL-C <40 and <50 mg/dl in men and women, respectively. 3) Systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension. 4) Fasting plasma glucose ≥100 mg/dl or previously diagnosed type 2 diabetes.

2.2. Anthropometric measurements

In all participants as described previously in the standard methods anthropometric parameters consisting weight, height, hip

circumference and waist circumference were measured. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Based on BMI value, participants were categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (>30 kg/m^2).[17]

2.3. Blood pressure measurements

Blood pressure was determined for each participant using a standard mercury manometer and standard protocol: 15 minutes resting prior to measurement, with subjects in a seated position and with the arm of participant at the heart level. The blood pressure measurement was repeated after 15 minutes and the mean value of two measurements was considered as the participant's blood pressure value. According to Joint National Committee on prevention, detection, evaluation and treatment of high Blood Pressure (JNC7), if the systolic and/or diastolic blood pressure values were ≥140 and ≥90 mmHg, respectively participants were classified as hypertensive.[18] Participants who were already prescribed antihypertensive drugs were also considered as hypertensive.

2.4. Blood sampling and biochemistry analysis

For each participant 10 mL of blood was taken from a peripheral vein after a twelve hour fast and collected into plain and EDTA tubes. The blood samples were centrifuged at room temperature for 30–45 minutes to separate serum and plasma and then into six aliquots (0.5 mL), which were then transported to the Bu Ali Research Institute, Mashhad. Aliquots of serum were also kept frozen at −80 °C for future analysis.[19] Fasting plasma glucose (FPG), lipid profile components including serum high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglyceride (TG) and total cholesterol (TC) concentration were measured with using routine analytical methods and commercial kits of Pars Azmoon (Tehran, Iran) and the BT3000 model of autoanalyzer machine (Biotechnica, Rome, Italy).

All biochemical factors were measured in the biochemistry lab in the Faculty of Medicine and the quality is checked routinely. Moreover, the system is calibrated every 6 months. Internal QC material (TruCal U, Pars Azmoon, Iran) is run with every run and that external QC material is obtained from Imam Reza hospital and is used every 6 months for external quality control scheme.

2.5. Serum magnesium level measurement

Serum magnesium concentrations were determined using the Xylidyl Blue photometric method using Pars Azmoon kits (Tehran, Iran) and the BT3000 autoanalyzer (Biotechnica, Rome, Italy) was used. The reagents include Ethanolamine (PH:11) 1 mol/l, Glycoletherdiamine tetraacetic acid 60 μmol/L, Xylidyl Blue 110 μmol/L and detergents.

Due to lack of previous data available for our local population, the lowest quartile of serum magnesium in the non MetS subjects (<0.94 mg/dl) was considered to be a low value of serum magnesium.

The intra-assay and inter-assay coefficient of variation (CV) for the serum magnesium assay were 0.92 ± 0.02% and 1.09 ± 0.02%. The limit of detection was less than 0.05 mg/L.

2.6. Dietary magnesium intake assessment

Dietary magnesium intake of all participants was evaluated using a validated 65-item food frequency questionnaire (FFQ).[20] Five categories including frequency of use per day, week, month, rarely and never and portion size were defined for each item of the FFQ. The average daily intake was calculated by multiplying the frequency consumption of each food item in its portion size. The daily magnesium intake was compared according to recommended daily allowances (RDA) that is defined for different age groups and gender. The daily RDA of magnesium for healthy men and women older than 31 years is 420 mg/dl and 320 mg/dl respectively.[4] RDA is the daily nutrient intake sufficient to meet the requirements of 97.5% of individuals [Estimated Average Requirement (EAR) ± 2SD intake], if the nutrient needs are distributed normally in the population. Therefore, the proportion of individuals whose requirements are below the RDA is nearly 2.5%. The risk of an insufficient intake is present when nutrient consumption is less than two-thirds of the RDA (67%). Therefore, nutrient intakes <67% of the RDA were used to define as dietary insufficiency.[21]

2.7. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago, IL). The Kolmogorov–Smirnov test was used to checked the normality of numerical variables; t-tests for normal variables, and Mann–Whitney U tests for non-normal variables were used for comparing variables between MetS+ and MetS− groups. After assessing normality a two tailed P-value less than 0.05 was considered as significant. The relationship between continuous variables was examined by the Spearman linear correlation test. Dietary magnesium intake of all participants was adjusted for total energy intake using linear regression. Logistic regression analysis was used to assess the relationship between metabolic syndrome (or its components) and the low value of serum magnesium and insufficient dietary magnesium intake while controlling for age, gender and BMI.

3. Results

3.1. Demographic, anthropometric and biochemical characteristics of study subjects

The basic characteristics of the study participants by MetS status are shown in Table 1. The prevalence of the MetS was higher among women (57.6%) than for men (42.4%). The participants with MetS had higher anthropometric indices (except weight), blood pressure, serum biochemical factors (except LDL-C) and lower high density lipoprotein cholesterol (HDL-C) concentration than the control subjects (P-value < 0.001 for all variables). Moreover, the subjects with MetS had lower level of educational attainment and physical activity level (PAL) compared to the non-MetS subjects (P-value < 0.001).

3.2. Comparing the dietary and serum magnesium according to the presence/absence of metabolic syndrome

After adjusting for confounding factors (age, sex, BMI), serum magnesium and dietary magnesium intake were compared between participants according to presence/absence of MetS and its individuals components, and are shown in Table 2. There was no significant difference of serum and dietary magnesium among individuals in the groups (P-value > 0.05 for all variables).

Table 1
Demographic, anthropometric and clinical parameters of the study subjects according to the presence or absence of MetS.

Variable		MetS$^+$ (n = 269)	MetS− (n = 584)	P-value
Age (years)		49.41 ± 8.03	46.21 ± 7.78	<0.001
Male % (n)		114 (42.4)	298 (51)	
Female % (n)		57.6 (155)	49 (286)	0.019
Education (years)		8.31 ± 4.91	9.22 ± 4.81	0.012
Marital status % (n)	Married	94.1 (253)	95.5 (558)	0.348
	Single/divorced/widow	5.9 (16)	4.5 (26)	
Smoking status % (n)	Ex-smoker	9.7 (26)	10.4 (61)	0.779
	Current smoker	20.4 (55)	22.1 (129)	
PAL		1.51 ± 0.26	1.58 ± 0.30	0.002
Height (cm)		162.31 ± 0.10	162.49 ± 0.09	0.789
Weight (kg)		77.69 ± 12.67	70.86 ± 12.39	<0.001
BMI (kg/m^2)		29.48 ± 4.09	26.89 ± 4.51	<0.001
Waist circumference (cm)		99.97 ± 10.17	91.95 ± 12.02	<0.001
Hip circumference (cm)		106.73 ± 8.97	102.17 ± 8.51	<0.001
WHR		0.94 ± 0.07	0.90 ± 0.08	<0.001
SBP (mmHg)		130.09 ± 19.53	116.26 ± 15.64	<0.001
DBP (mmHg)		84.34 ± 11.59	76.26 ± 9.74	<0.001
Serum triglyceride (mg/dl)		204.38 ± 111.74	110.40 ± 58.30	<0.001
Serum HDL-C (mg/dl)		37.67 ± 7.39	43.73 ± 10.41	<0.001
Serum LDL-C (mg/dl)		119.83 ± 41.78	114.63 ± 33.65	0.053
FPG (mg/dl)		104.86 ± 45.25	82.02 ± 22.28	<0.001
Serum total cholesterol (mg/dl)		204.59 ± 45.25	184.78 ± 39.11	<0.001
Subjects with hypomagnesemia, % (n)		22.7 (61)	22.1 (129)	0.848
Subjects with dietary magnesium insufficiency, % (n)		30.3 (44)	69.7 (101)	0.409

Data presented as mean ± standard deviation or median and inter-quartile range for normal and non-normal distributed data respectively. One-way analysis of variance (ANOVA) and Mann–Whitney U tests were used to compare normal and non-normal variables respectively. BMI: body mass index; WHR: waist/hip ratio; PAL: physical activity level; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; LDL-C: Low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol.

Table 2
Comparison of mean serum Mg level and dietary Mg intake according to the presence/absence of metabolic syndrome or abnormalities in its components among study subjects.

		N	Serum magnesium[a] (mg/dl)	P-value	Dietary magnesium intake[a] (mg/day)	P-value
Metabolic syndrome	Yes	269	1.02 ± 0.01	0.347	331.38 ± 7.80	0.712
	No	584	1.03 ± 0.01		327.79 ± 5.38	
Abdominal obesity	Yes	591	1.02 ± 0.01	0.065	333.19 ± 5.74	0.267
	No	262	1.05 ± 0.01		319.80 ± 9.31	
High FPG	Yes	138	1.03 ± 0.01	0.742	331.29 ± 10.42	0.807
	No	715	1.03 ± 0.01		328.49 ± 4.75	
High serum TG	Yes	277	1.04 ± 0.01	0.214	330.45 ± 7.58	0.813
	No	576	1.03 ± 0.01		328.24 ± 5.31	
Low serum HDL-C	Yes	572	1.03 ± 0.01	0.429	326.88 ± 5.30	0.498
	No	281	1.04 ± 0.01		333.25 ± 7.63	
High BP	Yes	164	1.03 ± 0.01	0.987	333.58 ± 9.77	0.620
	No	689	1.03 ± 0.01		328.06 ± 4.92	

FBG: fasting blood glucose; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; BP: blood pressure.
Abdominal obesity, waist circumference ≥80 cm in women and ≥94 cm in men; high BP, systolic/diastolic BP ≥140/90 mmHg; high TG ≥150 mg/dl; low HDL-C <50 mg/dl in women and <40 mg/dl in men; high fasting blood glucose ≥100 mg/dl.[22]
[a] Adjusted for age, sex and BMI.

Table 3
Correlation of biochemical and anthropometric parameters with serum magnesium levels and dietary magnesium intake.

Parameters	Serum magnesium levels (mg/dl)			Dietary magnesium intake (mg/day)		
	N	Rho	P-value	n	Rho	P-value
FBG	853	−0.026	0.455	853	−0.085	0.037
Serum HDL-C	853	0.037	0.276	853	0.038	0.355
LDL-C	853	0.060	0.079	853	−0.056	0.167
Total cholesterol	853	0.145	<0.001	853	−0.025	0.537
Triglyceride	853	0.040	0.238	853	0.006	0.874
SBP	853	0.082	0.017	853	−0.120	0.003
DBP	853	0.094	0.006	853	−0.040	0.321
Weight	853	0.053	0.119	853	−0.014	0.731
BMI	853	0.012	0.722	853	−0.141	<0.001
WC	853	−0.007	0.848	853	−0.098	0.016
HC	853	−0.005	0.873	853	−0.074	0.066
WHR	853	−0.008	0.815	853	−0.069	0.089

3.3. Correlation of biochemical and anthropometric parameters with serum magnesium levels and dietary magnesium intake

Serum magnesium was correlated with TC and BP, and dietary magnesium intake was correlated with FBG, BP, BMI and WC (Table 3).

3.4. Correlation of the low value of serum magnesium with the metabolic syndrome and its components

The association of hypomagnesemia and the risk of MetS and its components are shown in Table 4. Hypomagnesemia was associated with a significantly higher fasting plasma glucose [CI: 1.60 (1.05–2.44); (P-value = 0.028)] while no significant association was found with MetS or other components of the MetS.

Table 4
Odds ratios and 95% confidence intervals of the low value of serum magnesium with the risk of metabolic syndrome and its components in study subjects.

	OR (95% CI)	P-value
Metabolic syndrome	0.98 (0.68–1.42)	0.935
Abdominal obesity	1.19 (0.73–1.93)	0.489
High FPG	1.60 (1.05–2.44)	0.028
High serum TG	0.84 (0.59–1.21)	0.350
Low serum HDL-C	0.97 (0.68–1.39)	0.890
High BP	0.94 (0.60–1.46)	0.772

The OR was adjusted for age, sex, and body mass index.

3.5. Correlation of insufficient dietary magnesium intake with the metabolic syndrome and its components

The association of insufficient dietary magnesium intake with the risk of metabolic syndrome and its components are shown in Table 5. According to the recommendations for daily intake (RDA), an insufficient dietary magnesium intake is defined as <420 mg/d in males and <320 mg/d in females. There was no significant association between insufficient dietary magnesium intake and metabolic syndrome or its components risk (P-value> 0.05 for all variables).

4. Discussion

This observational study showed the prevalence of a low serum magnesium levels in subjects with and without MetS was 22.7% and 22.1%, respectively among adults in a representative population sample from Mashhad. There was no significant difference in serum and dietary magnesium levels among individuals between the groups. A low serum magnesium was significantly associated with higher fasting plasma glucose in the study participants while no significant association was found with metabolic syndrome and other components.

4.1. Diabetes mellitus and magnesium

Magnesium plays an important role in insulin secretion, glucose metabolism and homeostasis.[23] Therefore, magnesium deficiency might be involved in the pathogenesis of diabetes mellitus. It has been shown that hypomagnesemia affects insulin receptor and post-receptor processes by decreasing tyrosine kinase activity. Interventional studies have revealed that administration of magnesium supplement could improve insulin resistance and glucose tolerance.[24] Serum magnesium level was found to be significantly lower in diabetic patients.[25] A study evaluated plasma magnesium concentration in Chinese adults with normal glucose tolerance, prediabetes and type II diabetes reported that there was independent inverse relationship between plasma magnesium and the risk of prediabetes and diabetes.[26] This result was obtained after adjustment for confounding factors. Consistent with this finding, results from four other studies confirmed the existence of lower magnesium concentration in prediabetic and diabetic patients.[27–30] Our results showed that hypomagnesemia is significantly related to higher fasting plasma glucose in the study population and this is consistent with previous studies.[27–30]

A meta-analysis reported that every 0.48 mg/dl elevation in serum magnesium concentration was correlated with a 30% decrement in risk of CVD incidence and about 17% decrease in risk of ischemic heart disease.[31] Another meta-analysis found that serum magnesium was inversely correlated with the risk of MetS. This meta-analysis confirmed an inverse association between dietary magnesium intake and risk of MetS.[32] In contrast, another meta-analysis revealed that high dietary magnesium intake was not correlated with total CVD, whilst significantly correlated with a decreased risk of type II diabetes, stroke and heart failure.[33] A recent meta-analysis that included a total of 38,808 subjects, demonstrated an inverse association between serum magnesium concentration and incidence of type II diabetes, hypertension and coronary heart disease.[34]

Table 5
Odds ratios and 95% confidence intervals of insufficient dietary magnesium intake with the risk of metabolic syndrome and its components in study subjects.

	OR (95% CI)	P-value
Metabolic syndrome	0.95 (0.61–1.46)	0.811
Abdominal obesity	0.96 (0.55–1.68)	0.882
High FPG	1.10 (0.66–1.81)	0.719
High serum TG	1.12 (0.75–1.69)	0.568
Low serum HDL-C	0.91 (0.61–1.36)	0.635
High BP	0.79 (0.48–1.30)	0.353

The OR was adjusted for age, sex, and body mass index.

4.2. Dietary magnesium intake

Dietary magnesium intake has been observed to be associated with MetS. A meta-analysis study comprised of 9 articles reported an inverse association between dietary magnesium intake and risk of MetS.[32] In addition, the association of dietary magnesium intake with individual components of MetS was investigated by several studies.[22,35–44] Recent cross-sectional studies have examined the association of dietary magnesium intake with diabetes indicated that the dietary magnesium intake was significantly lower in diabetic patients.[35,36] Dietary magnesium intake could affect insulin secretion through its effects on cellular calcium homeostasis.[37]

In a cohort of middle-aged individuals with no diabetes of Atherosclerosis Risk in Communities Study, no association was found between magnesium intake and the incidence of diabetes after 6 years of follow-up[38] which is similar to our finding. Several studies have confirmed an inverse association between hypertension and dyslipidemia incidence with dietary magnesium intake but few studies failed to show this association.[39–41] Dietary magnesium intake has been reported to reduce the risk of MetS, diabetes and hypertension events by improving inflammation.[42,22] He et al, found an inverse association between magnesium intake and waist circumference.[39] Although, the mechanism of the inverse association between dietary magnesium intake and abdominal obesity is unclear, the anti-obesity effect of higher magnesium intake may be explained by its role in the formation of soaps with fatty acids, and therefore potentially reducing the digestible energy content of diet.[43,44]

In the present study dietary magnesium intake was not associated with the risk of MetS or its individual components, however in agreement with previous studies an inverse association was found between dietary magnesium intake and several cardiovascular disease risk factors including fasting blood glucose, systolic blood pressure, body mass index and weight. This might be due in part to demographic characteristics of participants with lower dietary magnesium intake, since they were younger and had a higher level of educational attainment compared to those with higher dietary magnesium intake. Moreover, a healthier lifestyle (higher physical activity level) was observed among participants with lower magnesium intake.

5. Conclusions

We found that serum magnesium is positively associated with total cholesterol, systolic and diastolic blood pressure while dietary

magnesium intake was inversely correlated with fasting blood glucose, systolic blood pressure, body mass index and waist circumference in total population. Furthermore an inverse association was found between magnesium concentration and diabetes.

Authors statement

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Conflict of interest

The authors confirm no conflict of interests.

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