Atherosclerosis 282 (2019) 196–201

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Serum magnesium and the prevalence of peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) study

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HIGHLIGHTS

- Serum magnesium (Mg) was inversely and independently associated with the risk of peripheral arterial disease (PAD).
- The relation between serum magnesium and peripheral arterial disease was non-linear.
- Serum Mg may become a new biomarker for PAD risk prediction.

ARTICLE INFO

Keywords:
Serum magnesium
Peripheral arterial disease
Atherosclerosis

ABSTRACT

Background and aims: Peripheral arterial disease (PAD) is a clinical manifestation of extracoronary atherosclerosis. Many risk factors are involved in the process of PAD, but the association between serum magnesium (Mg) and PAD is not clear. Our study aimed to investigate whether serum Mg is associated with PAD incidence.
Methods: A total of 13,826 participants (aged 40–64 years) in the Atherosclerosis Risk in Communities (ARIC) study (1987–1989) without prior PAD were included in the final analysis. Serum Mg levels were measured at visits 1 and 2. PAD was defined as an ankle brachial index less than 0.9, or hospitalization with a PAD diagnosis. Cox regression was used to calculate hazard ratios (HRs) for incidence of PAD and serum Mg.
Results: During a median follow-up of 24.4 years, 1364 (48.4% female) PAD events were observed. After multiple adjustment, participants in the lowest (≤1.4 mEq/L) category of serum Mg compared with the highest (≥1.8 mEq/L) ones were at higher PAD risk (HR: 1.3; 95% confidence interval (CI): 1.06–1.58) (p value = 0.004). The HRs for PAD in 1.5, 1.6 and 1.7 mEq/L of serum Mg were 1.29 (95% CI: 1.08–1.54), 1.05 (95% CI: 0.89–1.24), and 1.0 (95% CI: 0.85–1.18), respectively.
Conclusions: Low serum Mg was independently associated with an increased prevalence of PAD in the large population-based study; further studies are needed to confirm our findings.

1. Introduction

Peripheral artery disease (PAD) has become a severe public health problem, affecting almost 202 million people worldwide by 2010 [1]. PAD is one of the leading causes of morbidity and mortality for atherosclerotic cardiovascular disease (ASCVD) [2–4]. PAD is a strong and independent predictor of CVD and cerebrovascular disease as well [5]. Many previous studies have shown that diabetes, hypertension, dyslipidemia, smoking, as well as inflammation, urinary albumin, C-reactive protein (CRP), could accelerate the process of PAD [6–10]. Identifying new potential biomarkers may help clinicians to diagnose PAD and give intervention at an early stage.

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https://doi.org/10.1016/j.atherosclerosis.2018.12.004
Received 21 September 2018; Received in revised form 1 December 2018; Accepted 13 December 2018
Available online 20 December 2018

Magnesium (Mg) is one of the most important minerals in the human body, involved in many key metabolic reactions such as energy production, glycolysis and electrolyte balance [11]. Serum Mg plays an important role in protection against stress, vasodilation of the coronary and peripheral arteries, and reduction of platelet aggregation [12]. Earlier studies demonstrated low serum Mg levels is associated with a greater risk of coronary heart disease (CHD), hypertension, sudden cardiac death (SCD) and heart failure (HF) [13–15]. Dietary Mg intake is not related to hypertension and CHD, but there is an inverse association with diabetes and ischemic stroke [15–17]. However, studies on the association of serum or dietary Mg with PAD are still limited.

We hypothesized that low serum Mg is involved in the process of arteriosclerosis (AS). In this study, we aimed to investigate the relation of baseline serum Mg levels with the incidence of PAD using data from the community-based Atherosclerosis Risk in Communities (ARIC) study.

2. Materials and methods

2.1. Study population

The ARIC study is a prospective epidemiologic study conducted in four U.S. communities (Forsyth County, NC; Jackson, MS (African Americans only); the northwest suburbs of Minneapolis, MN; and Washington County, MD). The study began in 1987, a total of 15,792 individuals (aged 45–64 years old) received an extensive examination, including medical, social and demographic data. Participants were re-examined every three years after the first screening (baseline, visit 1) occurring in 1987–1989, the second (visit 2) in 1990–1992, the third (visit 3) in 1993–1995, and the fourth (visit 4) in 1996–98, and the last exam (visit 5) was in 2011–2013.

We excluded participants with prior PAD (n = 1023) or missing covariates (n = 794), as well as those without serum Mg measurement at visit 1 (n = 149), leaving 13,826 participants in the final analysis.

2.2. Serum Mg measurement

Participants were asked to fast for 12 h before blood sample collection. Blood was drawn from an antecubital vein of participants into vacuum tubes containing ethylenediaminetetraacetic acid (for measurement of lipids) or a serum separator gel (Mg, potassium, creatinine and glucose). Aliquots were stored at −70 °C for further analyses. Serum Mg levels were measured using the metallochromic dye calmagite at visits 1 and 2, following the Gindler and Heth's procedure [18].

2.3. Peripheral artery disease definition

Follow-up for events started from the first visit and continued when PAD occurred or until 31 December, 2012, whichever happened first. PAD was defined as an ankle brachial index (ABI) less than 0.9 at ARIC visits 3, 4 or 5, or a hospital discharge diagnosis of PAD, peripheral artery revascularization procedure, or peripheral artery intervention therapy during follow-up [4]. ABI was defined as the ratio of the ankle systolic blood pressure (SBP) to the brachial SBP.

ABI was measured in almost all subjects at visit 1(96.4%), only a random sample at visits 3 (n = 4325), 4 (n = 6107) and 5 (n = 5194) [19]. ABI was not measured at visit 2. Dinamap 1846 automated oscillometric device (Criticon, Tampa, FL) was used by well-trained staff to measure ankle SBP at the posterior tibial artery with the participant prone, and brachial SBP in the right arm with the participant supine [20]. Ankle and brachial SBPs in a randomly selected leg and the right arm were measured twice at visits 1 and 5. At visits 3 and 4, one ankle SBP and one brachial SBP of participants were measured. We also used the following ICD codes to define PAD: 39.25 (aorto-iliac-femoral bypass), 39.29 (leg bypass surgery), 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below-knee amputation), 84.17 (above-knee amputation), 38.18 (leg endarterectomy), 443.9 (claudication, peripheral arterial disease not otherwise specified, peripheral angiopathy not otherwise specified, spasm of artery).

2.4. Other variables of interests

Information about age, race, sex, smoking and drinking status, history of stroke and medication use was self-reported. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Hypertension (HT) was defined as a SBP ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg or use of antihypertensive medication, or a self-reported physician diagnosis. Prevalent diabetes mellitus (DM) was defined as fasting plasma glucose (FPG) level ≥ 126 mg/dL (≥7 mmoL/L), nonfasting glucose level ≥ 200 mg/dL (≥11.1 mmoL/L), or medication use, or self-reported physician diagnosis. Prevalent CHD was acquired by self-reported history of myocardial infarction, heart surgery, coronary bypass or balloon angioplasty, or current medication use. And Gothenburg Score or current medication use for HF were used to identify prevalent HF.

Serum potassium (K), and sodium (Na) were assessed with a Coulter DACOS analyzer (Coulter Instruments, Hialeah, FL) using a direct ion-selective electrode. Serum calcium (Ca) was measured using θ-cresolphthalein complexone. Serum creatinine was measured using a modified kinetic Jaffe method and uric acid (UA) using urease method. An estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease equation [21]. Enzymatic method was used to measure high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG) and Friedewald equation was used to calculate low-density lipoprotein cholesterol (LDL-C) [18].

2.5. Statistical analysis

Baseline characteristics of participants were described by means and proportions. ANOVA was used to compare baseline categories of serum Mg for continuous variables and chi-square tests for categorical variables. The statistical significance level was set at $\alpha = 0.05$ (two-sided). A p-value of < 0.05 was considered statistically significance.

We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (CI) between serum Mg categories and time to incident PAD, according to baseline serum Mg levels. Three multivariate models with progressive degrees of adjustment were used to adjust for potential confounders. The first model included adjustment for baseline age, sex, race, smoking and drinking status. Model 2 was Model 1 plus continuous measures of BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, FPG, eGFR, serum K, Na and Ca, UA. And adjustment for dietary Mg intake, prevalent CHD, HF, DM, history of stroke and use anti-HT medication were added to Model 3. In the spline models, as serum Mg values were reported to one decimal point; therefore, we categorized serum magnesium in a manner into five groups that approximated quintiles.

We performed subgroup analyses stratifying by key demographic and clinical subgroups of age (45–50, 51–57 *vs.* 58–65 years), gender (female vs. male), race (white *vs.* black), smoking status (current *vs.* former), kidney function (eGFR < 60 *vs.* ≥ 60 mL/min/1.73 m^2), serum K (< 4.5 *vs.* ≥ 4.5 mmoL/l) and abnormal ABI vs. actual PAD clinical events. We used missing data from cardiovascular disease (prevalent of coronary heart disease, heart failure or history of stroke) to conduct the sensitivity analysis. The likelihood ratio test was used to test potential effect modification comparing models with and without interaction terms of interest. The proportional hazards assumption for all variables was confirmed. All analyses were done using SPSS 22.0 and R 3.3.0 (http://www.R-project.org).

Table 1
Baseline characteristics of participants according to serum Mg levels.

	Category					
Characteristics	Group 1	Group 2	Group 3	Group 4	Group 5	*p* value
Mg level, (mEq/L)	< 1.5	1.5	1.6	1.7	≥1.8	
N	1567	2234	3551	3478	2996	
Age, years	54.31 ± 5.87	53.94 ± 5.82	54.06 ± 5.76	54.17 ± 5.71	54.33 ± 5.62	0.084
Sex						< 0.0001
Female	905 (57.8%)	1284 (57.5%)	1901 (53.5%)	1828(52.6%)	1560 (52.1%)	
Male	622 (42.2%)	950 (42.5%)	1650 (46.5%)	1650 (47.4%)	1436 (47.9%)	
Race						< 0.0001
White	833 (53.2%)	1542 (68.2%)	2678 (75.4%)	2836 (81.5%)	2501 (83.5%)	
Black	734 (43.8%)	710 (31.8%)	873 (24.6%)	642 (18.5%)	495 (16.5%)	
Smoking status						
Current	440 (28.1%)	549 (22.8%)	925 (26.1%)	893 (25.7%)	718 (24.0%)	0.025
Former	488 (31.2%)	713 (32.2%)	1143 (32 2%)	1155 (33.2%)	1027 (34.3%)	0.132
Ever	928 (59.3%)	1262(56.9%)	2069 (58.3%)	2048 (58.9%)	1746 (58.3%)	0.638
Drinking status						< 0.0001
Current	737 (47.3%)	1148 (51.8%)	1995 (56.4%)	2105 (60.5%)	1833 (61.4%)	
Former	360 (23.1%)	440 (19.8%)	683 (19.3%)	596 (17.1%)	509 (17.1%)	
Ever	1095 (70.3%)	1588 (71.6%)	2678 (75.6%)	2701 (77.7%)	2345 (78.6%)	
BMI, kg/m^2	29.22 ± 6.14	28.34 ± 5.55	27.58 ± 5.18	27.17 ± 4.92	26.92 ± 4.74	< 0.0001
SBP, mmHg	125.98 ± 20.55	123.32 ± 18.93	120.72 ± 18.67	121.03 ± 18.85	121.49 ± 18.92	< 0.0001
DBP, mmHg	75.85 ± 11.91	74.70 ± 11.59	73.43 ± 11.35	73.58 ± 11.23	73.69 ± 11.55	0.23
FPG, mg/dl	133.36 ± 70.97	112.66 ± 46.78	106.46 ± 35.33	103.15 ± 24.56	101.44 ± 19.45	< 0.0001
Potassium, mmol/l	4.18 ± 0.51	4.32 ± 0.47	4.42 ± 0.45	4.48 ± 0.46	4.56 ± 0.48	< 0.0001
Sodium, mmol/l	140.23 ± 2.67	140.71 ± 2.42	140.87 ± 2.40	141.17 ± 2.29	141.38 ± 2.33	< 0.0001
Calcium, mg/dl	9.78 ± 0.46	9.76 ± 0.45	9.76 ± 0.42	9.79 ± 0.41	9.81 ± 0.42	< 0.0001
Creatinine, mg/dl	1.09 ± 0.39	1.09 ± 0.22	1.09 ± 0.48	1.11 ± 0.23	1.14 ± 0.58	< 0.0001
eGFR, $mL/min/1.73\,m^2$	85.61 ± 24.67	82.33 ± 21.33	79.99 ± 20.33	78.44 ± 18.84	76.71 ± 18.89	< 0.0001
Albumin, mg/dl	3.77 ± 0.30	3.83 ± 0.27	3.87 ± 0.25	3.90 ± 0.25	3.93 ± 0.26	< 0.0001
Uric acid, mg/dl	6.46 ± 1.74	6.14 ± 1.61	6.00 ± 1.55	5.93 ± 1.47	5.93 ± 1.45	< 0.0001
TC, mmol/l	5.49 ± 1.13	5.51 ± 1.08	5.52 ± 1.17	5.55 ± 1.04	5.61 ± 1.05	0.002
LDL-C, moll/l	3.39 ± 1.05	3.5 ± 1.01	3.54 ± 1.01	3.59 ± 0.99	3.65 ± 1.00	0.001
HDL-C, mol/l	1.34 ± 0.48	1.33 ± 0.44	1.34 ± 0.45	1.34 ± 0.43	1.34 ± 0.42	0.291
TG, mmol/l	1.80 ± 1.44	1.54 ± 1.05	1.46 ± 0.94	1.41 ± 0.88	1.37 ± 0.77	< 0.0001
Dietary Mg, mg/day	250.96 ± 95.74	252.92 ± 96.54	253.80 ± 96.15	254.94 ± 95.41	255.63 ± 94.31	0.814
Use of anti-HT medicine	381 (24.4%)	584 (26.3%)	919 (26.0%)	879 (25.4%)	765 (25.7%)	0.731
Prevalent CHD	106 (6.8%)	108 (4.8%)	162 (4.6%)	154 (4.4%)	128 (4.3%)	0.02
Prevalent HF	131 (8.4%)	109 (4.9%)	165 (4.9%)	121 (3.5%)	93 (3.1%)	< 0.0001
Prevalent DM	405 (25.9%)	293 (13.1%)	301 (8.5%)	200 (5.8%)	115 (3.8%)	< 0.0001
History of stroke	36 (2.3%)	42 (1.9%)	56 (1.6%)	67 (1.9%)	47 (1.6%)	0.342

Values are mean ± SD or number (%).
Mg: magnesium; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; eGFR: estimated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; CHD: coronary heart disease; HF: heart failure; DM: diabetes mellitus.

3. Results

3.1. Baseline characteristics through distributions of serum Mg level

Among 13,826 participants, 54.1% were female, 42% were black, and the mean ± SD age was 54.2 ± 5.7 years. The baseline characteristics of the ARIC study population by serum Mg level are shown in Table 1. Compared with the higher serum Mg groups, participants in the lower groups were mainly female or black, with higher BMI, SBP, TC, TG, LDL-C, FPG, UA, but lower eGFR, serum K and Na. Furthermore, participants with low serum Mg levels were more likely to suffer from CHD, HF and DM at baseline. However, there were no obvious differences among DBP, HDL-C, history of stroke and medication use. No obvious difference of daily dietary Mg intake was observed between these five groups either.

3.2. Serum Mg and PAD

After the median follow-up of 24.4 years, a total of 1364 (9.9%) participants developed incident PAD, with 48.5% (n = 661) females, and 23.7% (n = 323) African-American. Serum Mg levels measured at visit 1 ranged from 0.5 to 3.1 mEq/L, The distribution of baseline serum Mg is shown in Fig. 1.

As shown in Table 2, after adjustment for age, sex, race, the incidence of PAD was inversely associated with circulating Mg (p value < 0.0001). Compared to the highest group (group 5) of Mg, the risk of PAD was increased (HR = 1.81, 95% CI: 1.49–2.19) in the lowest group (group 1). The strong relation still persisted after adjustment for potentially risk factors, including smoking status, lipids, BMI, SBP, DBP, FPG, serum K, serum Na and so on (Model 2) (HR = 1.34 for group 1 *vs.* group 5, 95% CI: 1.10–1.63; and HR = 1.29 for group 2 *vs.* group 5, 95% CI: (1.09–1.54)) (p value = 0.004).

After further adjustment for dietary Mg, prevalent CHD, DM and HF, history of stroke and use of medication (Model 3), participants in the lowest category of serum Mg compared with the highest ones were at higher PAD risk (HR = 1.38, 95% CI: 1.12–1.71) (p value = 0.002). The HRs for PAD in groups 2, 3 and 4 were 1.29 (95% CI: 1.08–1.54), 1.05 (95% CI: 0.89–1.24), and 1.0 (95% CI: 0.85–1.18), respectively (Table 2 and Fig. 2). Spline regression analysis confirmed that serum Mg level was inversely associated with risk of PAD, with a non-linear relationship (Fig. 1). The incidence of PAD was higher in participants with serum Mg less than or equal to 1.5 mEq/L, no significant differences in participants with serum Mg higher than 1.5 mEq/L were found.

Results of subgroup analyses and sensitivity analyses are summarized in Supplementary Fig. 1. The subgroup analyses showed that in participants with abnormal ABI or incident PAD, higher serum Mg was

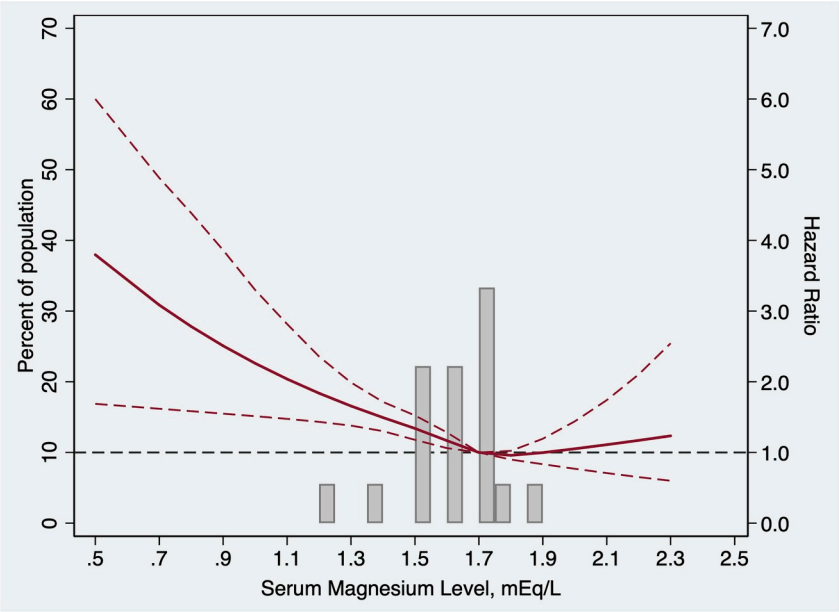


Fig. 1. Hazard ratios for peripheral arterial disease by levels of serum magnesium.
The curves represent adjusted hazard ratios (solid line) and their 95% confidence intervals (dashed lines) by categories of serum magnesium.

Table 2
Hazard ratio (95% Cis) for peripheral arterial disease by serum Mg.

Categories	Events/Total (N)	Model 1		Model 2		Model 3	
	1364/13,826	HR(95% CI)	*p* value	HR(95% CI)	p value	HR(95% CI)	*p* value
Group 1	187/1567	1.81 (1.49–2.19)	< 0.0001	1.34 (1.10–1.63)	0.004	1.30 (1.06–1.58)	0.004
Group 2	252/2234	1.51 (1.27–1.80)	< 0.0001	1.29 (1.09–1.54)	0.004	1.29 (1.08–1.54)	0.01
Group 3	342/3551	1.20 (1.02–1.40)	0.029	1.08 (0.92–1.27)	0.342	1.05 (0.89–1.24)	0.533
Group 4	317/3478	1.06 (0.90–1.25)	0.453	1.01 (0.85–1.18)	0.978	1.00 (0.85–1.18)	0.990
Group 5 (reference)	266/2996	1		1		1	

HR: hazard ratio; CI: confidence interval; BMI: body mass index; SBP: systolic blood pressure; DBP: blood pressure; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; CHD: coronary heart disease; HF: heart failure.
Model 1 was adjusted for age, sex, race.
Model 2, further adjusted for smoking and drinking status, BMI, glucose, SBP, DBP, TC, TG, HDL, LDL, eGFR, potassium, sodium, calcium, albumin, uric acid.
Model 3, further adjusted for dietary Mg, prevalent CHD, DM and HF, history of stroke and use of medication.

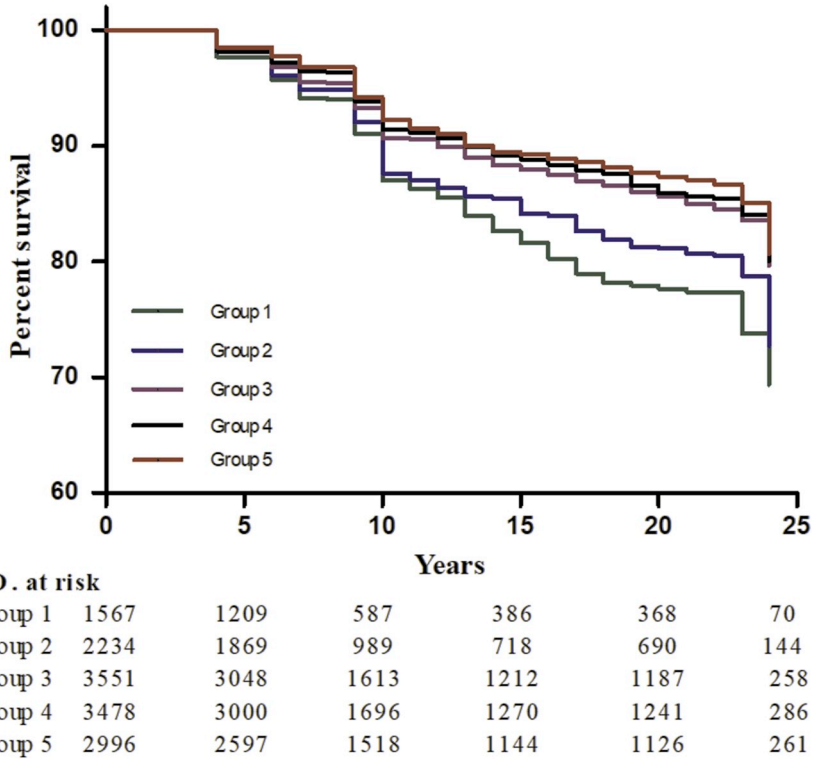
associated with decreased PAD (p for interaction > 0.05). The results did not differ significantly in subgroup analyses stratified by age, race, gender, eGFR (p for interaction > 0.05). In sensitivity analyses, results for the lower serum Mg groups were still consistent.

4. Discussion

The main finding of our study is that serum Mg is inversely and non-linear associated with risk of PAD in the community-based prospective cohort prospective cohort (ARIC) study. Participants in the low quintile ($\leq$1.4 mEq/L) of serum Mg had nearly a 38% higher risk of PAD compared to those in the high quintile ($\geq$1.8 mEq/L). The association between serum Mg and PAD was still present after adjusting for traditional PAD risk factors, indicating that serum Mg is independently related with PAD. Additionally, this novel association was similar among males and females. Our findings imply that low circulating Mg may be a risk marker of PAD.

The observed relations in our study are consistent with previous studies suggesting low serum Mg played an important role in the process of AS. Low serum Mg is linked to a number of chronic diseases, such as CHD, HF, hypertension, diabetes, and could increase total mortality [22–24]. Gobbo et al. analyzed 313,041 participants in 16 studies, and found that circulating Mg (per 0.2-mmol/L increment) is associated with a nearly 30% lower risk of CVD [23]. Moreover, several earlier studies have shown that low serum Mg was related to the increased prevalence of SCD, HF and atrial fibrillation using data from ARIC [13,24,25]. Furthermore, lower intake of Mg is associated with higher levels of total and subclinical CVD events, coronary artery calcification, overall burden of AS [26,27]. Nevertheless, the relation of serum Mg and PAD has not been confirmed. Rusu et al. showed that low serum concentrations ae associated with approximately 20% higher incidence of PAD in 114 type 2 DM patients [28], but the correlations of circulating Mg and PAD have not been well established in this small sample, cross-sectional study. Our study further illustrated the relation of serum Mg to incidence of PAD in the general population. Clinical attention should be paid to early-stage periphery atherosclerosis in patients with low serum Mg.

Previous randomized trials have shown that Mg supplementation could improve endothelial function, lower BP and reduce AS [29]. A meta-analysis, which included more than 1 million participants from forty prospective cohort studies, showed that a 100 mg/day increment in magnesium intake was associated with a 22% reduction in the risk of HF, a 7% reduction of stroke and a 10% reduction of all-cause mortality [30]. As both serum and dietary Mg levels are inversely related to AS, more attention should be paid to the use of pharmacologic drugs and food intake that may decrease magnesium levels. Few prospective



NO. at risk

Group 1	1567	1209	587	386	368	70
Group 2	2234	1869	989	718	690	144
Group 3	3551	3048	1613	1212	1187	258
Group 4	3478	3000	1696	1270	1241	286
Group 5	2996	2597	1518	1144	1126	261

Fig. 2. Kaplan-Meier curve of peripheral arterial disease by levels of serum magnesium.
Cox proportional hazards model adjusted for age, sex, race, smoking and drinking status, body mass index, glucose, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, serum potassium, serum sodium, uric acid, estimated glomerular filtration rate, systolic and diastolic blood pressure, diabetes, use of medication, dietary Mg intake and prevalent coronary heart disease, heart failure, diabetes and history of stroke. The reference group is the fifth serum magnesium group.

clinical trials on the efficacy of Mg supplementation to prevent PAD have been conducted yet, and the precise mechanism between serum Mg and PAD has not been clearly illustrated. Several factors may contribute to the relation of serum Mg to PAD. Firstly, serum Mg plays an important role in the process of anti-atherosclerosis [31]. Low circulating Mg can cause endothelial cell dysfunction, which may partly explain the independent relations between serum Mg and PAD [32]. In addition, Mg is an important cofactor for multiple enzymes involved in glucose metabolism. Deficiency of serum Mg is linked to metabolic syndrome, which could increase the prevalence of PAD [33]. Lastly, Mg has been shown to inhibit osteogenic differentiation of vascular smooth muscle cells. Low serum Mg may increase vascular calcification [26,34,35].

Our study has several important strengths. First of all, as far as we know, this is the first study to investigate the prospective relationship of serum Mg levels to PAD in the general population. Our results indicated that serum Mg is inversely associated with PAD independently of traditional risk factors, and provided new evidence regarding the link between serum Mg and PAD. Secondly, the results of our study came from a large sample size of a prospective cohort study which was well-characterized, bi-racial, and included a long follow-up period for PAD events. Thus, these results are representative of the US general population. Although the 2017 ESC Guidelines on the Diagnosis and Treatment of PAD recognized several new non-traditional predictors of PAD, our results suggest the need to pay attention to serum Mg levels in the future [36].

A few limitations should be considered as well. First, serum Mg levels were measured only at visits 1 and 2. Thus, variability or change of serum Mg over time may affect the results of our study. Secondly, ABI was not measured at visit 2, PAD was identified according to hospitalizations at visit 2. In addition, ABI was assessed in only a randomly sample of participants at visits 3, 4 and 5. ABI was measured in only one leg at visits 3 and 4. Measurement of ABI in only one leg may not be able to fully diagnose PAD. Fourth, the ARIC study enrolled participants aged 45–64 years, therefore, the generalizability of our findings to younger populations remains to be investigated. Lastly, this is an observational study, although several other major risk factors were adjusted, we cannot eliminate the possibility of residual confounding.

4.1. Conclusions

In conclusion, lower levels of serum Mg are strongly associated with an increased incidence of PAD, beyond traditional risk factors in the community-based prospective study. Our findings suggest that low serum Mg may be a new risk factor of PAD. Further prospectively planned clinical trials to confirm our findings and to elucidate possible mechanisms are needed.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

This study was supported by the National Natural Science Foundation of China (Grant NO: 81870195) to Xinxue Liao, and the National Natural Science Foundation of China (Grant NO: 81600206) to Xiaodong Zhuang.

Author contributions

Research idea and study design: XD Z, XT S, XX L and MF Z; data acquisition: X H, YG; data analysis/interpretation: MJ H, PN F; statistical analysis: XD Z, XT S, SZ Z. Manuscript drafting: SZ Z, HM Z, XB Z; Each author contributed important intellectual content during manuscript writing or revision, and all authors read and approved the final manuscript.

Acknowledgements

The authors thank the staff and participants of the ARIC study for their important contributions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2018.12.004.

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