Circulating Serum Magnesium and the Risk of Venous Thromboembolism in Men: A Long-Term Prospective Cohort Study

Setor K. Kunutsor^{a, b} Jari A. Laukkanen^{c, d, e}

^aNational Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, UK; ^bTranslational Health Sciences, Bristol Medical School, University of Bristol, Learning and Research Building (Level 1), Southmead Hospital, Bristol, UK; ^cInstitute of Clinical Medicine, Department of Medicine, University of Eastern Finland, Kuopio, Finland; ^dDepartment of Medicine, Central Finland Health Care District, Jyväskylä, Finland; ^eInstitute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

Keywords

Serum magnesium · Venous thromboembolism · Cohort study

Abstract

Background and Objective: Serum magnesium, an essential trace element involved in processes that regulate cardiovascular function, has been linked to the risk of atherosclerotic cardiovascular disease. However, the potential association between serum magnesium and venous thromboembolism (VTE) has not been previously investigated. We aimed to assess the prospective association of serum magnesium with the risk of VTE. **Methods:** Serum magnesium was measured using atomic absorption spectrometry in 2,361 men aged 42–61 years with no history of VTE at baseline in the Kuopio Ischemic Heart Disease prospective cohort. Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for VTE. **Results:** A total of 159 incident VTE events were recorded during a median follow-up of 27.1 years. The risk of VTE per 1 SD increase in serum magnesium in the age-adjusted analysis was (HR 1.30; 95% CI 0.46–3.69). The association remained consistent in analyses adjusted for systolic blood

pressure, body mass index, total cholesterol, triglycerides, smoking status, a history of type 2 diabetes, a history of coronary heart disease, medication for dyslipidemia, alcohol consumption, physical activity, socioeconomic status, serum active calcium, high-sensitivity C-reactive protein, and a history of cancer (HR 1.38; 95% CI 0.48–3.96). Comparing the extreme tertiles of serum magnesium, the corresponding adjusted HRs were 1.17 (95% CI 0.81–1.70) and 1.17 (95% CI 0.81–1.70), respectively. **Conclusion:** In a middle-aged Caucasian male population, serum-circulating magnesium was not associated with a future risk of VTE. Further studies in women, other age groups, and other populations are required to generalize these findings.

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Introduction

Atherosclerotic cardiovascular disease (CVD), a major manifestation of CVD, is a leading cause of mortality globally [1]. Venous thromboembolism (VTE) is closely linked to atherosclerotic CVD and there is evidence of shared risk factors for developing these two conditions, such as age, obesity, and cigarette-smoking [2, 3]. Al-

though historically viewed as 2 distinct diseases [4], the evidence suggests that they share pathophysiological mechanisms such as coagulation, platelet activation, and dyslipidemia [5]. Like atherosclerotic CVD, VTE (which comprises deep-vein thrombosis [DVT] and pulmonary embolism [PE]), constitutes a substantial public health burden and is associated with substantial morbidity, high economic costs, and premature mortality [6, 7]. Magnesium is an essential trace element involved in processes that regulate cardiovascular function, including muscular function, endothelial cell function, myocardial excitability, and the activation of sodium potassium ATPase [8–11]. Most of the magnesium content in the human body is found in the cells or bones, with only 1% present in extracellular fluids and 0.3% in the serum [12]. Therefore, serum magnesium concentration does not reflect the total body magnesium content. In normal adults, total serum magnesium ranges between 0.70 and 1.10 mmol/L. Approximately 20% of this is protein-bound, 65% is ionized, and the rest is complexed with various anions such as phosphate and citrate [8]. Serum magnesium concentration is kept within narrow limits and regulated by a delicate balance between intestinal absorption, skeletal resorption, and excretion by the kidneys, and depends on magnesium intake from food and water; a deficiency results from low intake from these sources [9]. Magnesium deficiency can also be potentiated by old age, inflammatory bowel disorders, malabsorption syndromes, diabetes, certain medications (e.g., diuretics, some antibiotics, and proton-pump inhibitors), as well as renal impairment [13, 14]. Magnesium concentrations are also affected by calcium and phosphate. Magnesium competes with calcium for membrane binding sites and is known as a natural calcium antagonist [12]. Phosphate depletion causes a substantial increase in the urinary excretion of magnesium which may cause hypomagnesemia [9].

Serum magnesium has been inversely linked with the risk of atherosclerotic CVD outcomes including coronary heart disease (CHD) [15, 16] and stroke [17]. Magnesium has been shown to have direct myocardial effects [18], suggesting that it may have cardioprotective effects. Given the close interrelationship between magnesium, atherosclerotic CVD, and VTE, we hypothesized that serum magnesium levels may be linked to the risk of VTE. In this context, we aimed to assess the prospective association of serum-circulating magnesium with the risk of VTE, using a population-based prospective cohort of 2,361 middle-aged Caucasian men.

Methods

We used data based on the Kuopio Ischemic Heart Disease (KIHD) Risk Factor study, a general population-based prospective cohort study comprising middle-aged men (42–61 years) who were recruited from Kuopio in eastern Finland. The study design, recruitment methods, assessment of lifestyle factors, medical history, and blood-based markers have been described in previous related reports [19–25].

Briefly, 3,433 randomly selected men participated in the baseline study conducted between March 1984 and December 1989. Of these, 3,235 were found to be eligible; 2,682 volunteered to participate, 186 did not respond to the invitation, and 367 declined to give informed consent. Our analysis is based on 2,361 men and women with complete information on serum magnesium, relevant covariates, and VTE events. Serum magnesium was measured using atomic absorption spectrometry (Perkin Elmer Zeeman 5000, Perkin Elmer, Norwalk, CT, USA) which involved the use of the acetylene-air (1: 4) flame technique. Serum magnesium was diluted at a ratio of 1: 50 with distilled water. The wavelength was 185.2 nm for magnesium. The between-run coefficient of variation for the method was 2.4% (37 assays) [26]. All VTE cases that occurred from enrollment to 2018 were included. No losses to follow-up were recorded as all participants in the KIHD study (using unique Finnish personal identification codes) are under continuous surveillance for the development of new outcomes including VTE cases. The diagnosis of VTE (DVT or PE) required positive imaging tests and these were identified by computer linkage to the National Hospital Discharge Registry data maintained by the Finnish Institute for Health and Welfare. The medical documents for each potential VTE case were cross-checked in detail and VTE events were validated by 2 physicians blinded to the exposures. ICD-10 codes (I26, I80, and I82) were used to code and classify each potential VTE case. Hazard ratios (HRs) with 95% confidence intervals (CIs) for VTE were calculated using the Cox proportional-hazard models. All statistical analyses were conducted using Stata v16 (Stata Corp., College Station, TX, USA).

Results

The baseline characteristics of the study participants and cross-sectional correlates of serum magnesium are presented in Table 1. Mean age and serum magnesium concentration of the 2,361 men at baseline was 53 (SD 5) years and 1.98 (SD 0.15) mg/dL, respectively. Significant inverse correlations were observed between serum magnesium and alcohol consumption, socioeconomic status (SES), and high-sensitivity C-reactive protein (hsCRP). Significant positive correlations were observed between serum magnesium and total cholesterol and serum active calcium.

During a median follow-up time of 27.1 (IQR 16.9–31.0) years, a total of 159 VTE cases (annual rate 2.87/1,000 person-years at risk; 95% CI 2.46–3.35) occurred. The HR (95% CI) for VTE per 1 SD increase in serum magnesium

Table 1. Baseline participant characteristics and correlates of serum magnesium

	Participants (<i>n</i> = 2,361)	Pearson correlation ^a , <i>r</i> (95% CI)
Serum magnesium concentration, mg/dL	1.98 (0.15)	–
Questionnaire/prevalent conditions		
Age at survey, years	52.9 (5.2)	0.03 (–0.01 to 0.07)
Alcohol consumption, g/week	32.0 (6.3–93.2)	–0.07 (–0.11 to –0.02)**
Socioeconomic status	8.45 (4.23)	–0.06 (–0.10 to –0.02)**
A history of type 2 diabetes		
No	2,266 (96.0)	–
Yes	95 (4.0)	–
Smoking status		
Other	1,607 (68.1)	–
Current	754 (31.9)	–
A history of CHD		
No	1,767 (74.8)	–
Yes	594 (25.2)	–
On medication for dyslipidemia		
No	2,346 (99.4)	–
Yes	15 (0.6)	–
A history of cancer		
No	2,319 (98.2)	–
Yes	42 (1.8)	–
Physical measurements		
BMI	26.9 (3.6)	–0.02 (–0.06 to 0.02)
SBP, mm Hg	134 (17)	–0.03 (–0.07 to 0.01)
DBP, mm Hg	89 (10)	–0.02 (–0.02 to 0.02)
Physical activity, kJ/day	1,186 (623–1,995)	0.01 (–0.03 to 0.05)
Blood-based markers		
Total cholesterol, mmol/L	5.90 (1.08)	0.07 (0.03 to 0.11)**
HDL-C, mmol/L	1.29 (0.30)	–0.02 (–0.06 to 0.02)
Serum active calcium, mmol/L	1.18 (0.05)	0.05 (0.01 to 0.09)*
Triglycerides, mmol/L	1.11 (0.81–1.59)	0.01 (–0.04 to 0.05)
hsCRP, mg/L	1.29 (0.71–2.46)	–0.05 (–0.09 to –0.01)*

Values express *n* (%), mean (SD), or median (IQR). * *p* < 0.05, ** *p* < 0.01, and *** *p* < 0.001. BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure.

^a Between serum magnesium and the row variables.

in the age-adjusted analysis was 1.30 (0.46–3.69), which was minimally attenuated in analyses further adjusted for systolic blood pressure, body mass index, total cholesterol, triglycerides, smoking status, a history of type 2 diabetes, a history of CHD, medication for dyslipidemia, alcohol consumption, physical activity, SES, and serum active calcium. The HR (95% CI) remained similar on additional adjustment for hsCRP and a history of cancer 1.38 (0.48–3.96; Table 2). The corresponding adjusted HRs (95% CIs) were 1.17 (0.81–1.70), 1.17 (0.80–1.70) and 1.17 (0.81–1.70) respectively, when comparing the top and bottom tertiles of serum magnesium levels.

Discussion

Previous findings from epidemiological observational cohorts support an inverse association between serum-circulating magnesium and adverse arterial thrombotic outcomes such as CHD [15, 16] and stroke [17]. In this study, we investigated the prospective association between serum magnesium and VTE risk in a general population-based cohort of middle-aged Caucasian men. We observed that increased serum levels of magnesium were not associated with a future risk of VTE. As this is the first population-based study to evaluate this association, these

Table 2. Association between serum magnesium and risk of venous thromboembolism

Magnesium, mg/dL	Events/total	Model 1		Model 2		Model 3	
		HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Per 1 SD increase	159/2,361	1.30 (0.46–3.69)	0.63	1.36 (0.47–3.90)	0.57	1.38 (0.48–3.96)	0.55
T1 (0.92–1.91)	50/789	ref.		ref.		ref.	
T2 (1.92–2.04)	45/787	0.83 (0.55–1.24)	0.35	0.83 (0.56–1.25)	0.37	0.84 (0.56–1.26)	0.39
T3 (2.05–2.55)	64/785	1.17 (0.81–1.70)	0.40	1.17 (0.80–1.70)	0.42	1.17 (0.81–1.70)	0.41

Model 1: adjusted for age. Model 2: model 1 plus systolic blood pressure, body mass index, total cholesterol, triglycerides, smoking status, a history of type 2 diabetes, a history of coronary heart disease, medication for dyslipidemia, alcohol consumption, physical activity, socioeconomic status, and serum active calcium. Model 3: model 2 plus high-sensitivity C-reactive protein and a history of cancer. CI, confidence interval; HR, hazard ratio; ref., reference; SD, standard deviation; T, tertile.

results are unchallenged and cannot be compared with other studies.

Magnesium, one of the most abundant intracellular cations, plays a role in several cellular processes including enzymatic reactions, nucleic acid synthesis, and cell replication; it is also involved in processes that regulate cardiovascular function [8–11]. The mechanistic pathways proposed to link low serum levels of magnesium to an increased risk of atherosclerotic CVD include impaired glucose homeostasis and insulin resistance, increased platelet aggregation, abnormal lipid metabolism, diabetes, high blood pressure, chronic inflammatory processes, impaired vascular tone and peripheral blood flow, and endothelial dysfunction [9, 27, 28]. Magnesium plays a major role in the enzyme systems that regulate glucose homeostasis, and affects glucose homeostasis by influencing insulin secretion, in addition to glucose uptake by cells; a deficiency is known to inhibit the acute phase of insulin release in response to glucose challenge [9]. Animal and in vitro studies suggest that magnesium deficiency induces inflammatory stress, leading to leukocyte and macrophage activation, and the release of inflammatory cytokines and acute-phase proteins [29] which lie in the pathway for many chronic diseases. Magnesium regulates vascular tone and reactivity via its influence on nitric oxide secretion [30]. Its deficiency increases angiotensin II-induced plasma aldosterone concentration and the production of thromboxane and vasoconstrictor prostaglandins [31]. Low magnesium levels slow the proliferation of endothelial cells, stimulate the adhesion of monocytes, and affect the synthesis of vasoactive molecules, subsequently impairing endothelial function [12]. Magnesium also affects myocardial contractility by influencing the intracellular calcium concentration, the electrical activity of myocardial cells,

and the specialized conducting system of the heart [9]. A magnesium deficiency causes electrocardiogram abnormalities (e.g., prolonged QTc interval) which increase the risk of cardiac arrhythmias [27] and, subsequently, embolisms. Given the link between atherosclerotic CVD and VTE via their shared risk factors and pathophysiological mechanisms [5] as well as the wealth of evidence on the relationship between serum magnesium and the risk of atherosclerotic CVD [15, 16], these findings may seem unexpected. However, the null association observed between serum magnesium and VTE is suggestive of pathophysiologic differences between arterial thrombotic disease and VTE. Though there is evidence to suggest that these 2 conditions are closely related, they have historically been viewed as 2 distinct diseases [4]. The evidence of a relationship between atherosclerotic CVD and VTE has not been very consistent. It has been reported that atherosclerotic CVD is an underlying condition and precedes the development of VTE [32], but evidence to the contrary suggests otherwise [33, 34]. Furthermore, findings on traditional risk factors for VTE and atherosclerotic CVD are not consistent. Whereas some studies have demonstrated significant associations between traditional CVD risk factors and VTE risk, [3, 35], others have not [36, 37]. The absence of evidence of an association between serum magnesium and VTE risk could also be related to population characteristics and study design factors such as age and sex, low statistical power due to low VTE event rates, and regression dilution bias due to the long follow-up duration. Regression dilution bias is known to underestimate the true association between an exposure and outcome, particularly for cohorts with long-term follow-up [38]. Given the absence of previous studies on the topic, large-scale studies are warranted to confirm or refute these findings, with

more focus on other age groups, women, and other populations.

The strengths of this study include the novelty, the utilization of a large-scale population-based prospective cohort design with a selection of men who were nationally representative, zero loss to follow-up, and a comprehensive analysis with adjustment for a broad panel of established and emerging risk factors. The limitations are inability to generalize the results to women, other age groups, and other populations, the relatively low VTE event rate, and the lack of data on VTE subtypes.

Conclusion

In a middle-aged Caucasian male population, it was found that serum-circulating magnesium is not associated with a future risk of VTE. Further studies in women, other age groups, and other populations are required to confirm and generalize these findings.

Acknowledgement

We thank the staff of the Kuopio Research Institute of Exercise Medicine and the Research Institute of Public Health and University of Eastern Finland, Kuopio, Finland, for the data collection in the study.

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Statement of Ethics

Written informed consent was obtained for each participant prior to baseline and follow-up data collections. This study was approved by the Institutional Review Board of the University of Eastern Finland (ref. 143/97) and complies with the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

J.A.L. acknowledges support from The Finnish Foundation for Cardiovascular Research, Helsinki, Finland. S.K.K. is supported by the NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health and Social Care. These sources had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Author Contributions

Both authors contributed to study conceptualization, methodology, and critical revision. S.K.K. performed the statistical analysis and wrote the article.

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