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

Running Head: Serum Magnesium and Venous Thromboembolism

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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 without a history of VTE at baseline in the Kuopio Ischemic Heart Disease prospective cohort. Cox-regression models were used to calculate hazard ratios (HR) with 95% confidence interval (CI) 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 standard deviation increase in serum magnesium in 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, histories of type 2 diabetes and coronary heart disease, medication for dyslipidemia, alcohol consumption, physical activity, socioeconomic status, serum active calcium, high sensitivity C-reactive protein and 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). ***Conclusion:*** In a middle-aged Caucasian male population, serum circulating magnesium was not associated with future risk of VTE. Further studies in women, other age-groups and other populations are required to generalize these findings.

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 evidence suggests both conditions share some common risk factors such as age, obesity and cigarette smoking [2, 3]. Though both disease states have historically been viewed as two distinct diseases [4], evidence suggests they share pathophysiological mechanisms such as coagulation, platelet activation and dyslipidemia [5]. Venous thromboembolism (VTE) (which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE)), constitutes a substantial public health burden just like atherosclerotic CVD; it is associated with substantial morbidity, high economic costs and premature mortality [6, 7]. Magnesium is an essential trace element that is involved in processes that regulate cardiovascular function, including regulation of muscular function, endothelial cell function, myocardial excitability, and activation of sodium potassium ATPase [8-11]. Most of the magnesium content in the human body is found in the cells or in the 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 which is regulated by a delicate balance between intestinal absorption, skeletal resorption and excretion by the kidneys. Serum magnesium concentration depends on magnesium intake from food and water; hence, its 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, proton-pump inhibitors), as well as renal impairment [13, 14]. Magnesium concentrations are also affected by calcium and phosphates – magnesium competes with calcium for membrane binding sites and is known as a natural calcium antagonist[12]; phosphate depletion causes a substantial increase in urinary magnesium excretion which may cause hypomagnesaemia [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 cardio-protective effects. Given the close inter-relationship 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 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 of middle-aged men aged 42-61 years who were recruited from Kuopio in eastern Finland. Study design, recruitment methods and assessment of lifestyle factors, medical history and blood-based markers have been described in previous related reports [19-25]. Written informed consent was obtained from all participants and the research protocol was approved by the institutional review board of the University of Eastern Finland (reference #:143/97) and all study procedures were conducted according to the Declaration of Helsinki. Briefly, 3,433 randomly selected men participated in the baseline study conducted between March 1984 and December 1989. Of the 3,433 men, 3,235 were found to be eligible; and of this number, 2,682 volunteered to participate, 186 did not respond to the invitation and 367 declined to give informed consent. The current 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 acetylene-air (1:4) flame technique. Serum magnesium was diluted in 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 they 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 two physicians who were blinded to the exposures. The 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 Cox proportional hazard models. All statistical analyses were conducted using Stata version MP 16 (Stata Corp, College Station, Texas).

Results

The baseline characteristics of study participants and cross-sectional correlates of serum magnesium are presented in **Table 1**. The mean [standard deviation (SD)] age and serum magnesium of the 2,361 men at baseline were 53 (5) years and 1.98 (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); whereas, significant positive correlations were observed with total cholesterol and serum active calcium.

During a median (interquartile range) follow-up of 27.1 (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 to 3.35) occurred. The HR (95% CI) for VTE per 1 SD increase in serum magnesium in age-adjusted analysis was 1.30 (0.46-3.69), which was minimally attenuated in analyses further adjusted for systolic blood pressure, BMI, total cholesterol, triglycerides, smoking status, histories of type 2 diabetes and 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 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 versus 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 that 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 the future risk of VTE. Given that this is the first population-based study to evaluate the association of serum magnesium with future risk of VTE in a general population, these results are unchallenged or cannot be compared.

Magnesium, one of the most abundant intracellular cations, plays a role in several cellular processes including enzymatic reactions, nucleic acid synthesis, and cell replication and also involved in processes that regulate cardiovascular function [8-11]. Mechanistic pathways proposed to link low serum levels of magnesium to 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 [27, 9, 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 [9]. Its deficiency is known to inhibit the acute phase of insulin release in response to a glucose challenge. cells [9]. Animal and in vitro studies suggest that magnesium deficiency induces an inflammatory stress leading to leukocyte and macrophage activation, and 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] and its deficiency increases angiotensin II induced plasma aldosterone concentration and production of thromboxane and vasoconstrictor prostaglandins [31]. Low magnesium levels slow 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 and the electrical activity of myocardial cells and the specialized conducting system of the heart

[9]; its deficiency causes electrocardiogram abnormalities (eg, prolonged QTc interval) which increase the risk of cardiac arrhythmias [27], and subsequently embolisms. Given the link between atherosclerotic CVD and VTE via shared risk factors and pathophysiological mechanisms [5] and the wealth of evidence on the relationship between serum magnesium and risk of atherosclerotic CVD [15, 16], these findings may seem unexpected. However, the null association observed between serum magnesium and VTE may suggest pathophysiologic differences between arterial thrombotic disease and VTE. Though there is evidence to suggest that these two conditions are closely related, they have historically been viewed as two distinct diseases [4]. The evidence on the 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]; whereas evidence on 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]. On the other hand, the absence of evidence of an association between serum magnesium and VTE risk could 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 the current study include the novelty, utilization of a large-scale population-based prospective cohort design with selection of men who were nationally representative, zero loss to follow-up and the 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 lack of data on VTE subtypes.

Conclusions

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

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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 (reference #:143/97) and complies with the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualisation: all authors; methodology: all authors; statistical analysis: S.K. Kunutsor; writing of article: S.K. Kunutsor; critical revision: all authors

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