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Editorial

Association between serum magnesium levels and peripheral artery disease: A leg too short?

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The only way to keep your health is to eat what you don't want, drink what you don't like, and do what you'd rather not

Mark Twain

Magnesium ($Mg2+$) is the fourth most plentiful cation in the human body, being continuously re-stocked by means of food and water intake, and playing an active role in a plethora of essential physiological, biochemical, and cellular processes regulating cardiovascular function [1,2]. It plays a critical role in modulating smooth vascular muscle tone, endothelial cell function and myocardial excitability and thus it is essential in the pathogenesis of several cardiovascular disorders such as hypertension, atherosclerosis, coronary artery disease, congestive heart failure and cardiac arrhythmias [2]. Notably, clinical and experimental evidence highlights how magnesium favors vasodilation, reduces vascular resistance and improves blood flow in systemic, coronary, cerebral and renal circulations [3]. Despite extensive data on the cardiac role of magnesium, its impact on peripheral vascular disease is less established. Notably, peripheral artery disease (PAD) is a strong, independent predictor of CVD risk and has become in itself an extremely serious public health problem, impacting hundreds of million people, with major morbidity and mortality implications [4].

This important clinical and research question is finally addressed explicitly in the paper published by Sun and colleagues in this issue of *Atherosclerosis* [5]. Specifically, Sun et al. exploited the established Atherosclerosis Risk in Communities (ARIC) cohort study, using baseline serum magnesium measurements and repeat clinical and ankle-brachial index (ABI) testing, eventually demonstrating the existence of an inverse correlation between serum magnesium and development of PAD. The same cohort study had previously demonstrated a protective role of magnesium on the occurrence of carotid atherosclerosis, while the Paris Prospective Study 2 reported a correlation between low serum magnesium and cardiovascular mortality in middle-aged men [6,7]. In addition, in patients undergoing dialysis, a condition that accelerates atherosclerosis, magnesium plays a preventative role in the evolution of the disease and, in renal transplant recipients, hypomagnesaemia is an independent arterial stiffness predictor [8].

Focusing more in detail on Sun et al., in their study PAD was defined as ABI less than 0.9 at examinations 3,4 or 5 or following a hospital discharge diagnosis of PAD, a peripheral artery revascularisation procedure or intervention therapy during follow-up [5]. The serum levels of 13,826 patients taking part in the cohort were analysed, of which 54.1% were female and 42% of Afro-Americans, with an average age between 54 and 57, dividing them into 5 groups in relation to the serum magnesium levels. Those with lower magnesium levels were frequently female, Afro-American, with a high body mass index, hypertension, hypertriglyceridemia, hypercholesterolemia, poor renal function, lower levels of potassium and sodium, and, moreover, they often suffered from cardiovascular disease and heart failure. The follow-up for events started from the first examination and continued at the onset of PAD or until 31st December 2012, whichever happened first.

After an average follow-up of 24.4 years, a total of 1364 (9.9%) participants had developed PAD, 48.5% (n = 661) were female and 23.7% (n = 323) were Afro-American. After adjustment for age, sex, and race, the incidence of PAD was inversely correlated to circulating magnesium ($p < 0.001$). By comparing the group with a higher concentration of serum magnesium with one with a lower concentration, the risk of PAD was significantly higher. The strong correlation persists by correcting the data as per risk factors, including smoking, dyslipidemia, body mass index, systolic bloood pressure, diastolic blood pressure, and serum levels of fasting plasma glucose, potassium, and sodium. Moreover, by carrying out further adjustments, including also diabetes mellitus, heart failure and the prevalence of cardiovascular disease, the category with the lowest concentration of serum magnesium showed a greater risk of incident PAD compared to those with higher concentrations. Indeed, the incidence of PAD was higher in participants with a serum magnesium level either less than or equal to 1.5 mEq/L, with no significant differences in participants with a serum magnesium level higher than 1.5 mEq/L with a non-linear correlation. Participants in the low quintile ($\leq$1.4 mEq/L) of serum magnesium had nearly a 38% higher risk of developing PAD with regard to those present in the high quintile ($\geq$1.8 mEq/L). The association between serum

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magnesium and PAD levels was still present after adjusting for traditional PAD risk factors, indicating that the level of serum magnesium was independently linked with PAD and this association appeared similar among females and males.

In the light of these considerations, as well as of numerous studies that have disclosed that magnesium is closely linked to the endothelial dysfunction [9], and with an increase in endothelial permeability of low density lipoprotein and thus besides the atherosclerotic process [8], magnesium should be fully involved in the assessment of the hematochemical profile of patients of cardiovascular relevance. In fact, dietary studies conducted both in Europe and in the United States have shown that often magnsium intake is quite lower than recommended minimum [10], that is for adults of 320–400 mg/day (or 6 mg/kg/bodyweight for both sexes) [11]. Indeed, several epidemiological studies have shown that people who habitually follow western-style diets have a low magnesium intake, typically < 30–50% of the recommended daily amount, and that this low intake typically reflects a progressive decrease over the decades from about 500 mg/day to 175–225 mg/day, most likely due to the increasing use of fertilizers and processed food of chosen foods [12]. These findings sustain the significance of a dietary regime including plenty of magnesium, such as in combination diets. Not unexpectely, the well-known Dietary Approaches to Stop HTN (DASH) diet contains large amounts of magnesium, together with potassium, calcium, dietary fiber, protein and smaller amounts of total and saturated fat, as well as cholesterol, when compared to both the typical western and mediterranean diets, also however containing a wealth of nutrients full of antioxidant agents and polyphenolic compounds [13–15]. Furthermore, the use of magnesium supplements should be taken into account in case of significant magnesium deficiencies alongside patients with other cardiovascular risk factors.

Scientific evidence highlights, on the one hand, the need for a correct dietary intake, while on the other hand, the requirement to exploit biological properties for pharmacological purposes, not only with dietary supplements but also by means of the development of medical devices that release magnesium suitable above all for the treatment of PAD. Indeed, a new-generation magnesium-based coronary stent (Magmaris, Biotronik, Berlin, Germany) appears as a promising forerunner in the forthcoming generations of fully-degradable stents [16]. In such realm, it is not entirely clear whether magnesium plays a significant role in both the low thrombogenicity and the re-endothelisation mechanisms of these stents. There are also still limited data on the long-term follow-up after the implantation of the Magmaris device and on possible restenosis mechanisms, and in keeping with the recent ups and downs of bioresorbable vascular scaffolds, cautious is recommended before widespread use [17–19].

In conclusion, magnesium may play a pivotal role in the treatment and prevention of atherosclerosis and cardiovascular disease, just as it might prove to be an effective, low-cost aid in PAD prevention and treatment, routinely dosed to patients with a medium to high risk. Further pre-clinical and clinical studies need to be conducted to shed light on this topic of paramount importance.

Conflicts of interest

Prof. Biondi-Zoccai has consulted for Abbott Vascular and Bayer. The other authors have nothing to disclose.

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