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Low serum magnesium is associated with coronary artery calcification in a Korean population at low risk for cardiovascular disease

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Abstract *Background and aims:* Previous studies suggested an association between low serum magnesium levels and metabolic or cardiovascular disease. Additionally, several studies have shown that low serum magnesium is associated with vascular calcification, but there are no studies exploring its relation to coronary artery calcification (CAC). We investigated the relationship between low serum magnesium and CAC by using health examination data.
Methods and results: We cross-sectionally analyzed 34,553 participants who underwent coronary multi-detector computed tomography and serum magnesium level measurement in 2010–2012 as part of a health examination program at a tertiary hospital in Korea. CAC was defined as a coronary artery calcium score > 100. Participants were divided into three groups according to their serum magnesium level as follows: low < 1.9 mg/dL (n $= 931$), normal $= 1.9$–2.3 mg/dL (n $= 32{,}341$), and high > 2.3 mg/dL (n $= 1281$). The percentages of participants with CAC were 3.7, 1.5, and 2.3 in each group, respectively. According to multivariate analysis, low serum magnesium was associated with CAC after adjustment for age, sex, BMI, diabetes, hypertension, cardiovascular disease, systolic BP, LDL cholesterol, HDL cholesterol, eGFR, serum calcium and phosphorus, hsCRP, current smoking status, alcohol intake and vigorous exercise frequency. The odds ratio for CAC in the low serum magnesium group compared to the normal group was 2.10 (1.40–3.15, $P < 0.001$).
Conclusion: Low serum magnesium level is associated with CAC in a Korean population at low risk for cardiovascular disease. Further studies are needed to generalize this finding and to verify the causal relationship between low serum magnesium and CAC.

Introduction

Magnesium is the fourth most abundant electrolyte in the human body [1]. Adult human bodies contain approximately 25 g of magnesium, with 60–65% of magnesium residing in the skeleton and most of the rest in the intracellular compartments of muscle and soft tissues [2]. The balance of magnesium is primarily regulated by intestinal absorption from dietary intake and by renal excretion. Magnesium is a cofactor for more than 300 metabolic reactions in the body, and it plays essential roles in cardiac excitability, neuromuscular conduction, muscular contraction, vasomotor tone, blood pressure (BP), bone integrity, and glucose and insulin metabolism [3].

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Magnesium may have a role in cardiovascular diseases, according to previous studies. Low magnesium intake was found to be associated with future risk of hypertension [4], diabetes [5], and stroke [6]. Low serum magnesium levels also showed a strong relationship with metabolic syndrome [7], and were reported as a risk factor for type 2 diabetes mellitus [8] and coronary heart disease [9,10]. Furthermore, low serum magnesium is associated with increased cardiovascular mortality in different groups [9,11,12]. However, how dysregulation of magnesium could lead to poor cardiovascular outcome is not well understood.

Verifying a relationship between serum magnesium and subclinical cardiovascular disease could help improve understanding of the mechanism underlying the association between magnesium and cardiovascular outcomes. Therefore, we investigated the relationship between serum magnesium level and coronary artery calcification (CAC) using a large data set from a health examination program at a tertiary hospital in Korea.

Methods

Study population

The study population of this cross-sectional study consisted of individuals who underwent comprehensive health examinations in 2010–2012 at Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. Many of them are workers and their family members. Annual or biannual health screening exams are mandatory for workers in Korea by the Industrial Safety and Health Law. Cardiac CT scanning has become a common component of these screening exams to evaluate the increasing risk of coronary artery disease. A total of 41,995 participants who measured serum magnesium levels and received cardiac computed tomography (CT) to measure coronary artery calcium scores (CACS) were considered for inclusion in this study. After exclusion of 7029 individuals due to records with missing data for the variables of interest, we further excluded 413 patients with previous cardiovascular disease. Cardiovascular disease was defined by a history of heart disease, coronary disease, or stroke. Finally, data from 34,553 participants were analyzed (Fig. 1). This study was approved by the institutional review board at Kangbuk Samsung Hospital.

Measurements

Data regarding medical history, medication usage, and health-related behaviors were collected through a self-administered questionnaire. Trained staff collected anthropometry, blood pressure, and serum biochemical measures. A more detailed protocol of this examination program has been previously described [13]. In addition, trained nurses measured height and weight with an automated scale while the participants were wearing a light hospital gown and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

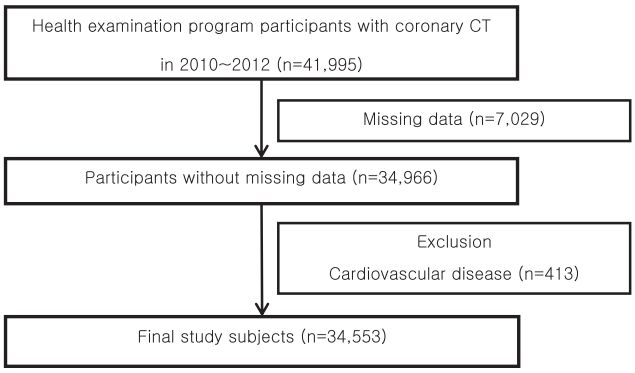

Figure 1 Algorithm for selecting study subjects from health check-up participants. CT, computed tomography.

Blood samples were taken from an antecubital vein after fasting at least 10 h. Serum total cholesterol, triglycerides, and uric acid levels were determined using an enzymatic colorimetric assay. Low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were directly measured using a homogenous enzymatic colorimetric assay. Serum high-sensitivity C-reactive protein (hsCRP) was determined using a particle-enhanced immunoturbidimetric assay on a Modular Analytics P800 apparatus (Roche Diagnostics). Serum insulin was measured using an electrochemiluminescence immunoassay on a Modular Analytics E170 apparatus (Roche Diagnostics). Serum glucose was measured using the hexokinase method on a Cobas Integra 800 apparatus (Roche Diagnostics; Rotkreuz, Switzerland). Insulin resistance was assessed with a homeostatic model assessment of insulin resistance (HOMA-IR) according to the following equation: fasting blood insulin (uU/mL) × fasting serum glucose (mg/dL)/405. Concentrations of serum magnesium were measured by the colorimetric endpoint method using an automated clinical chemistry analyzer (Modular P analyzers; Roche Diagnostics, Tokyo, Japan). Serum creatinine levels were measured by isotope dilution mass spectroscopy (IDMS)-traceable method using Modular D2400 (Roche, Tokyo, Japan). We calculated the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14].

The Laboratory Medicine Department at Kangbuk Samsung Hospital in Seoul, Korea has been accredited by the Korean Society of Laboratory Medicine (KSLM) and the Korean Association of Quality Assurance for Clinical Laboratories (KAQACL). The laboratory participates in the College of American Pathologists (CAP) survey proficiency testing.

CT scans were performed with a Lightspeed VCT XTe-64 slice MDCT scanner (GE Healthcare, Tokyo, Japan) using a standard scanning protocol described as follows: 2.5 mm thickness, 400 ms rotation time, 120 kV tube voltage, and 124 mA s (310 mA*0.4 s) tube current under ECG-gated dose modulation. The quantitative CACS was calculated according to the method described by Agatston et al. [15]. Although a CACS $>$ 0 indicates the presence of coronary artery atherosclerosis in general, the presence of CAC was