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The association between serum uric acid and asymptomatic intracranial arterial stenosis in middle-aged Koreans

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Abstract *Background and aims:* Intracranial arterial stenosis (ICAS) is one of the most common causes of stroke, especially in Asians. Hyperuricemia has been associated with an increased risk of comorbidities such as metabolic syndrome or cardiovascular diseases. However, there are few studies focusing on the association between serum uric acid (SUA) levels and asymptomatic ICAS. The aim of this study was to explore the association between SUA and the prevalence of ICAS in middle-aged Korean health screening examinees.

Methods and results: A cross-sectional study was performed on 9417 males and 7755 females who underwent a comprehensive health examination including transcranial Doppler (TCD) ultrasonography. The association of SUA and ICAS was analyzed using multivariate logistic regression. The prevalence of ICAS among the total examinee population was 3.55%. In females, the multivariate-adjusted odds ratio for ICAS was 1.52 (confidence interval 1.13–2.04) in the 3rd quartile of SUA and 1.45 (1.05–2.00) in the highest quartile, compared to the reference (*P* for trend 0.008). This trend was evident in all clinically relevant subgroups evaluated, including women with low inflammation status. SUA was not significantly associated with the prevalence of ICAS among males. In a sensitivity analysis, the multivariate-adjusted odds ratio of middle cerebral artery stenosis in females was 1.60 (1.09–2.37) in the highest quartile compared to the reference (*P* for trend 0.023).

Conclusions: Higher SUA level was associated with increased risk of ICAS among middle-aged females but not males. A further cohort study is warranted to elucidate the effect of SUA on asymptomatic ICAS.

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Introduction

Intracranial arterial stenosis (ICAS) is the presence of atherosclerotic lesions in arteries inside the brain, resulting in an ischemic stroke [1]. ICAS is one of the most common causes of stroke and is associated with a high risk of recurrent stroke compared with other stroke subtypes [1]. Asian and African-American patients have significantly higher rates of ICAS than white patients [1]. It is necessary to identify the risk factors contributing to ICAS to improve preventive strategies and to find new therapeutic targets. To date, traditional risk factors associated with ICAS include hypertension, smoking, diabetes mellitus, metabolic syndrome, and hyperlipidemia [1,2].

Uric acid is the end product of purine metabolism in the body. Serum uric acid (SUA) is known to be a marker of impaired oxidative metabolism [3] and has also been shown to be a powerful endogenous antioxidant and scavenger of nitric oxide radicals in the body [4]. The double-edged characteristics of SUA have complicated interpretations of whether SUA increases the risk of cerebrovascular disease [5–7]. Evidence from two meta-analyses suggested that hyperuricemia may parallel an increased risk for stroke and mortality [6,7]. A higher SUA concentration was measured in atherosclerotic plaque specimens than non-atherosclerotic control specimens, suggesting that SUA might play a role in the development of atherosclerosis [8]. However, to date there is no direct evidence that higher SUA increases the risk of ICAS.

Transcranial Doppler (TCD) ultrasonography is a widely used, noninvasive and inexpensive method of measuring the velocity of blood flow through vessels in the brain. It is advantageous for detecting ICAS because it provides real-time flow information in contrast to static imaging methods such as computed tomographic angiography or magnetic resonance angiography [9,10].

Because the role of SUA in ICAS has not been clarified yet, we hypothesized that an increased SUA level would be associated with ICAS prevalence, leading to increased risk of stroke. Therefore, we aimed to evaluate the association between SUA level and ICAS detected by TCD ultrasonography in middle-aged Korean healthy screening examinees.

Methods

Study population

The Kangbuk Samsung Health Study (KSHS) was a cohort study of South Korean men and women in which participants underwent a comprehensive annual or biennial health examination at one of the Kangbuk Samsung Hospital Health Screening Centers located in Seoul and Suwon, South Korea. More than 80% of the participants and their spouses were employees of various companies and local governmental organizations because the South Korean Industrial Safety and Health Law requires annual or biennial health screening of employees. The remaining participants voluntarily purchased self-paid screening examinations at the health screening center.

This cross-sectional study was part of KSHS. We selected 11,957 males and 9874 females from a health screening program. The population of the present study consisted of examinees that underwent a comprehensive health examination and TCD ultrasound between March 2011 and December 2014. As shown in Fig. 1, the final number of male and female subjects eligible for the study was 9417 and 7,755, respectively.

The Institutional Review Board of Kangbuk Samsung Hospital approved this study (#KBSMC 2017-01-022). The requirement for informed consent was waived because the patients were not identifiable from the data used.

Data collection

At each visit, the following parameters were recorded using a standardized, self-administered questionnaire [11]: demographic characteristics, smoking status, alcohol consumption, physical activity, medical history, and medication use. Smoking status was categorized into “never”, “former”, and “current” smokers. Alcohol consumption was categorized into “none”, “moderate” (<20 g/day), and “high” (>20 g/day). Physical activity levels and sitting time were assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form [12,13]. Physical activity levels were classified into three categories: inactive, minimally active (600 MET-minutes per week), and health-enhancing physically active (HEPA; 3000 MET-minutes per week) as previously described [14]. Usual dietary intake was assessed using a 103-item, self-administered food frequency questionnaire designed and validated for use in Korea [15]. Total energy and nutrient intake was calculated using a food composition table developed by the Korean Nutrition Society [15]. Anthropometry and blood pressure were measured by trained nurses during the health examinations. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI $\geq$25 kg/m^2 (the proposed cutoff for Asian populations) [16]. Blood pressure (BP) was measured using an automated oscillometric device (53000, Welch Allyn, New York, USA) while subjects were seated with the arm supported at heart level. Hypertension was defined as systolic BP $\geq$140 mm Hg, diastolic BP $\geq$90 mm Hg, or current use of antihypertensive medication. Because of the gender difference in SUA concentrations, hyperuricemia was defined as SUA >7 mg/dl in males and >6 mg/dl in females.

TCD ultrasonography evaluation and diagnosis of intracranial artery stenosis

TCD ultrasonography was performed by a trained ultrasonographer using a single-channel TCD ultrasonograph (Nicolet SONARA TCD system, Natus Medical Incorporated, San Carlos, CA, USA) according to a previously reported method [17]. The mean flow velocity (MFV) cut-offs for TCD ultrasonography were used for identification of $\geq$50% stenosis according to the SONIA (Stroke Outcomes and

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