Atherosclerosis 231 (2013) 145–151

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

The impact of serum uric acid level on arterial stiffness and carotid atherosclerosis: The Korean Multi-Rural Communities Cohort study

Ji Suk Bae [a], Dong Hoon Shin [b], Pil Sook Park [c], Bo Youl Choi [d], Mi Kyung Kim [d], Min-Ho Shin [e], Young-Hoon Lee [f], Byung-Yeol Chun [g,*,1], Seong-Kyu Kim [h,**,1]

[a] Department of Preventive Medicine, Catholic University of Daegu School of Medicine, Daegu, Republic of Korea
[b] Department of Preventive Medicine, School of Medicine Keimyung University, Daegu, Republic of Korea
[c] Department of Food and Nutrition, Kyungpook National University, Daegu, Republic of Korea
[d] Department of Preventive Medicine, Hanyang University, College of Medicine, Seoul, Republic of Korea
[e] Department of Preventive Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea
[f] Department of Preventive Medicine & Institute of Wonkwang Medical Science, Wonkwang University College of Medicine, Iksan, Jeonlabuk-do, Republic of Korea
[g] Department of Preventive Medicine, Kyungpook National University School of Medicine, 101, Dongin-dong 2-ga, Jung-gu, Daegu 700-842, Republic of Korea
[h] Division of Rheumatology, Department of Internal Medicine, Arthritis and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, 3056-6 Daemyung 4-Dong, Namgu, Daegu 705-718, Republic of Korea

A R T I C L E I N F O

Article history:
Received 7 June 2013
Received in revised form
20 August 2013
Accepted 21 August 2013
Available online 29 August 2013

Keywords:
Uric acid
Atherosclerosis
Carotid plaque
Arterial stiffness
Intima–media thickness

A B S T R A C T

Objective: Serum uric acid level has been found to be associated with a risk factor for cardiovascular diseases. However, the topic has not been explored in the general population, especially in Korea. This study was designed to determine whether serum uric acid is associated with carotid atherosclerosis and arterial stiffness in the Korean Multi-Rural Communities Cohort study.

Methods: A total of 5568 participants from the Korean Multi-Rural Communities Cohort were evaluated for the risk of hyperuricemia in cardiovascular atherosclerosis. Important surrogates for cardiovascular atherosclerosis such as intima–media thickness (IMT) and brachial-ankle pulse wave velocity (baPWV) were assessed. We evaluated the association between these atherosclerosis indices and serum uric acid level or hyperuricemia through multivariate-adjusted logistic and linear regression analyses.

Results: There was a significant difference of carotid IMT and baPWV between males and females ($p < 0.0001$, respectively). Both male and female subjects with hyperuricemia showed higher baPWV than subjects without hyperuricemia ($p = 0.0004$ for males; $p = 0.001$ for females). Serum uric acid level was positively correlated with baPWV in males ($\beta = 0.0006$, $p < 0.0001$) and in females ($\beta = 0.0001$, $p = 0.04$), whereas no association between serum uric acid and carotid IMT was found in either gender. A linear relationship of baPWV with increasing serum uric acid level was observed in males ($p = 0.0005$) and in females ($p = 0.004$).

Conclusion: Serum uric acid level could be considered an important risk factor for arterial stiffness in Korean population, whereas carotid IMT is not associated with serum uric acid in either gender when using data from the Korean Multi-Rural Communities Cohort study.

1. Introduction

Several epidemiological studies have addressed the concept that serum uric acid level could be considered a risk indicator for cardiovascular diseases (CVD) including metabolic syndrome, coronary artery disease, and carotid atherosclerosis [1–3]. Regarding the association between hyperuricemia and CVD, recent epidemiologic data and meta-analysis of 26 eligible studies showed consistent results, suggesting hyperuricemia increased the risk of CVD [4–6]. Based on the experimental studies, uric acid was implicated in various pathological mechanisms in CVD pathogenesis such as endothelial dysfunction [7], promotion of vascular smooth muscle cell proliferation [8], and induction of vasoconstrictive mediators such as entdothelin-1 and angiotensin II [9,10]. These results suggest that uric acid has a role in the aberrant changes of vascular properties. In

* Corresponding author. Tel.: +82 53 4252447; fax: +82 53 4204868.
** Corresponding author. Tel.: +82 53 6503038; fax: +82 53 6298248.
E-mail addresses: mhyeh@knu.ac.kr (B.-Y. Chun), kimsk714@cu.ac.kr (S.-K. Kim).
1 Corresponding authors contributed equally to this work.

0021-9150/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.atherosclerosis.2013.08.017

contrast, uric acid was thought to be only an embedded component involved in the clustering of traditional CVD risk factors [11]. Recent data from a prospective study and meta-analysis found no predictive importance of coronary heart disease [12]. Based on these contrasting opinions, the association of uric acid and CVD remains controversial.

Brachial-ankle pulse wave velocity (baPWV) for arterial stiffness [13,14] and intima–media thickness (IMT) for carotid atherosclerosis [15] are regarded as non-invasive indicators of cardiovascular events. Several previous studies have suggested that uric acid is associated with baPWV [16,17] and IMT [18]. However, the association of uric acid with a risk of increased arterial stiffness and atherosclerosis in epidemiologic and retrospective studies in the Korean population [16,19] remains controversial. Therefore, additional data to confirm these associations is needed by using variable indices for CVD such as IMT and baPWV. This study was designed to identify the role of hyperuricemia and serum uric acid level in PWV and IMT as surrogate markers indices for arterial stiffness and carotid atherosclerosis in the Korean Multi-Rural Communities Cohort study.

2. Subjects and methods

2.1. Study population

The Korean Multi-Rural Communities Cohort study is a part of the Korean Genome Epidemiology study. This community-based prospective cohort has been constructed since 2004 to identify risk factors for cardiovascular diseases in the Korean population. The target population for this multi-center cohort included residents who were ≥40 years old at enrollment in three rural areas nationwide: Yangpyeong (located in the eastern part of Seoul, the capital of South Korea), Namwon (located in the southwestern part of South Korea), and Goryeong (located in the southeastern part of South Korea). A total of 9697 participants were recruited in the cohort from January 2005 to August 2009. Among these participants, those who had medical histories of hypertension, hyperlipidemia, diabetes, heart disease, cerebrovascular disease, or cancer at the time of the baseline survey were excluded from the eligible population for this study ($n = 3725$). Those with missing data on dependent (serum uric acid level) or independent variables (as an exception, those with missing data on PWV were included in the final dataset, but excluded from the analyses of PWV as an independent variable.) and those with implausible self-reports on dietary intake (total energy intake <500 or >4000 kcal/day; more than 10 missing food items; or missing data on rice as the staple food for most Koreans) were also excluded from the eligible population ($n = 404$). As a result, a total of 5568 participants were used for the final analyses. This study was performed in adherence with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Boards of Hanyang University, Chonnam National University Hospital, and Keimyung University in Korea.

2.2. Data collection

A standardized protocol for questionnaire survey and examination procedures was used to ensure uniform data collection methods at the three study centers. In-person interviews using a structured questionnaire were administered by trained interviewers to obtain baseline data of the study participants. The questionnaire included a set of questions on demographic characteristics (i.e., age, gender, education, and marital status), histories of physician-diagnosed diseases (i.e., hypertension, hyperlipidemia, diabetes, heart disease, cerebrovascular disease, and cancer), lifestyle factors such as cigarette smoking, alcohol consumption, and physical activity. As far as cigarette smoking is concerned, non-smokers were defined as those who had never smoked or smoked <400 cigarettes during their lifetime. Those who had smoked ≥400 cigarettes during their lifetime were categorized into two groups, former smokers and current smokers, according to their current status of smoking. With regards to alcohol consumption, non-drinkers were defined as those who had never had one drink (not a sip of drink) during their lifetime. Those who had had ≥ one drink during their lifetime were divided into two groups, former drinkers and current drinkers, according to their current status of drinking. Regular exercise was defined as a positive response to the following question: “Do you exercise regularly enough to make you break into a sweat?”

In the baseline survey, anthropometric measurements were also obtained using standardized methods. Height was measured using a standard height scale and recorded to the nearest 0.1 cm. Weight was measured using a metric weight scale and recorded to the nearest 0.01 kg. The scale was zero-balanced before each study participant was weighed in light clothing without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured midway between the inferior border of the lowest rib and the superior border of the iliac crest and recorded to the nearest 0.1 cm. Systolic and diastolic blood pressures were measured using a standard mercury sphygmomanometer with a connected inflatable cuff and recorded to the nearest 2 mmHg. After each participant was asked to rest for at least 5 min, two consecutive blood pressure measurements were obtained. We used the average values of the two systolic and diastolic measurements for the analyses. In case the difference between the two measurements was greater than 5 mmHg, the third measurement was obtained, and the average values of the second and third systolic and diastolic measurements were used for the analyses.

Laboratory evaluations were performed using blood samples which were obtained in the overnight fasting state (at least 8 h of fasting). The samples were analyzed for biochemical markers the same day they were obtained. The ADVIA1800 Auto Analyzer (Siemens Medical Solutions USA, Inc., Malvern, PA, USA) was used to determine the levels of serum uric acid, creatinine, triglyceride, HDL cholesterol, and fasting serum glucose. Glomerular filtration rate (GFR) was calculated using the simplified equation of the Modification of Diet in Renal Disease study [20]: GFR (mL/minute per 1.73 m^2) = 186 × (serum creatinine level [mg/dL])$^{-1.154}$ × (age)$^{-0.203}$ × [0.742, if female].

2.3. Dietary assessment

For the assessment of dietary intake, in-person interviews using a semi-quantitative food frequency questionnaire (FFQ) were administered by trained interviewers. The FFQ has been validated and the results of the validation study have been reported in detail elsewhere [21]. The FFQ was used to identify the average frequency (9 categories ranging from ‘never or rare’ to ‘three times per day’) and portion size (3 specified portion sizes) of consumption of 106 food items over the past year. The duration of intake (4 categories: 3, 6, 9, and 12 months) was also identified for the consumption of seasonal food items. The average daily intakes of each food item (i.e., intakes of coffee, tea, and soft drink) were estimated using the weighted frequency per day and the portion size per unit of each food item. The average daily intakes of each food groups (i.e., intakes of meat, seafood, and dairy food) were computed by summing the average daily intakes of related food items: meat intake (beef, pork, and poultry products, sausages and luncheon meats, and edible offal); seafood intake (finfish and shellfish products, and seaweed); and dairy food intake (milk, yogurt, ice cream, and cheese). For the conversion of intakes of food items into nutrients