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Lipoprotein subfractions partly mediate the association between serum uric acid and coronary artery disease

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ABSTRACT

Background: Serum uric acid (SUA) has been established to be highly associated with coronary artery disease (CAD) susceptibility and lipid metabolism, but the underlying mechanisms are unclear. Recently, lipoprotein subfractions have been proposed to be more valuable in CAD risk evaluation. Hence, we sought to investigate whether the relationship between SUA and CAD is partly mediated by lipoprotein subfractions.
Methods: A total of 401 consecutive subjects undergoing coronary angiography were enrolled. The baseline clinical data including the SUA level and lipid profiles were collected. The lipoprotein subfractions were determined using the Lipoprint system.
Results: In the overall population, the upper SUA quintiles had significantly higher atherogenic lipid parameters and unbalanced lipoprotein subfractions especially higher small dense low-density lipoprotein-cholesterol (sdLDL-C) and lower large high-density lipoprotein-cholesterol (HDL-C) ($p < 0.05$). The levels of SUA and lipoprotein subfractions were dramatically different between male and female. After adjusting for traditional risk factors including gender, multivariate linear regression analysis suggested that SUA was positively associated with sdLDL-C ($\beta = 0.113$, $p = 0.013$) but negatively related to large HDL-C level ($\beta = -0.152$, $p = 0.002$). Given the significant association of the SUA level with lipoprotein subfractions and incident CAD (adjusted OR = 1.312, 95% CI 1.069–1.609, $p = 0.009$), we performed the mediation analyses and found that 8.7–10.5% of the effect of SUA on CAD susceptibility was mediated by the increased sdLDL-C or decreased large HDL-C level ($p < 0.05$).
Conclusions: The SUA level was proved to be associated with lipoprotein subfractions including sdLDL-C (positive) and large HDL-C (negative), which partly mediated the association between SUA and CAD susceptibility.

1. Introduction

Serum uric acid (SUA), the final product of purine metabolism, has been observed to be highly associated with the development of cardiovascular disease for more than 50 years. A number of epidemiologic studies have reported a relation between the SUA level and a wide variety of cardiovascular disorders such as hypertension [1], congestive heart failure [2] and coronary artery disease (CAD) [3]. The SUA level is significantly higher in patients with CAD than in healthy controls [4]. Moreover, multiple prospective studies indicated that elevated SUA level was independently associated with the increased cardiovascular morbidity and mortality in the general population [5] as well as among subjects with significant, angiography defined CAD [6,7] independent of traditional risk factors.

Although multiple studies have proposed uric acid as a cardiovascular risk factor, there is much controversy concerning the nature of the relation between SUA and CAD susceptibility [8–10] due to its close relation to other traditional risk factors involved in CAD [11] such as lipid metabolism, inflammation, and chronic kidney disease. Thus, the exact mechanism underlying the relationship between the SUA level and incident CAD remains unclear. The previous evidence indicated that uric acid had a potential link with atherogenic lipid profiles including triglycerides (TG), the atherogenic index of plasma (AIP), and total cholesterol to high-density lipoprotein-cholesterol ratio (TC/HDL-C) [12], which are well-established pivotal risk factors for CAD [13].

Recently, lipoprotein subfractions have been emerging as promising new measurements significantly improving CAD risk prediction algorithms based on plasma levels of lipid profiles [14]. In respect of the definite relation of the SUA level to atherogenic lipid profiles and CAD susceptibility, we postulated that there may be a certain correlation between the SUA level and lipoprotein subfractions and the latter may in part mediate the relationship between SUA and CAD susceptibility. Therefore, the objective of the present study was to investigate the association of the SUA level with lipoprotein subfractions and then explore whether the relationship between SUA and CAD susceptibility is partly mediated by lipoprotein subfractions.

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2. Methods

2.1. Study design and population

The study protocol complied with the Declaration of Helsinki, and was approved by the hospital ethical review board (FuWai Hospital & National Center for Cardiovascular Diseases, Beijing, China). All patients gave their informed, written consent.

This was a hospital-based prospective and observational study. From October 2012 to January 2014, we consecutively recruited 401 patients who underwent selective coronary angiography for suspected coronary atherosclerosis at our center. Recruitment was done on regular working days and there was no deliberate exclusion of subjects for reasons other than the exclusion criteria specified in this study. Complete medical history was taken from all subjects. The diagnosis of CAD was defined as the presence of coronary lesions ≥50% in at least one major epicardial artery segment assessed by at least 2 independent senior interventional cardiologists who had no knowledge of the patients' clinical characteristics and biochemical results.

To avoid the effect of lipid-lowering drugs on lipoprotein subfractions, we enrolled subjects with no treatment history of statins and/or other lipid-lowering drugs at least 3 months before entering the study. Exclusion criteria were the existence of any infectious or systematic inflammatory disease, acute coronary syndrome, heart failure, significant hematologic disorders, thyroid dysfunction, severe liver and/or renal insufficiency and malignant tumors.

2.2. Definition of traditional cardiovascular risk factors

Main cardiovascular risk factors were defined using standard criteria. Hypertension was defined as repeated systolic and/or diastolic blood pressure ≥140 and/or ≥90 mm Hg on two different occasions or if patients were currently taking anti-hypertensive drugs. Diabetes mellitus (DM) was diagnosed as fasting serum glucose levels ≥126 mg/dl in multiple determinations or was receiving hypoglycemic treatments (dietary, oral anti-diabetic agents, or insulin). Dyslipidemia was defined by medical history or fasting TC ≥200 mg/dl or TG ≥150 mg/dl. Metabolic syndrome was diagnosed when a subject fulfilled three or more of the following components: waist circumference ≥90 cm for male or ≥80 for female; TG ≥150 mg/dl; HDL-C <40 mg/dl for male or <50 mg/dl for female; systolic blood pressure/diastolic blood pressure (SBP/DBP) ≥130/85 mm Hg or current use of antihypertensive medications; fasting blood glucose ≥101 mg/dl or previously diagnosed type 2 diabetes or current use of hypoglycemic agents or insulin [15]. Smoking status was ascertained by the medical history.

2.3. Biochemical analyses

Blood samples were taken after at least 12-hour fast in the morning and collected into vacuum tubes containing ethylene diamine tetraacetic acid (EDTA) for the measurement of SUA, lipid profiles, serum creatinine, and fasting blood glucose, and all of which were analyzed by automatic biochemistry analyzer (Hitachi 7150). In detail, the low-density lipoprotein-cholesterol (LDL-C) concentration was analyzed by selective solubilization method (low density lipid cholesterol test kit, Kyowa Medex). HDL-C concentration was determined by a homogeneous method (Determiner L HDL, Kyowa Medex). TC, TG, apolipoprotein AI (apo A1), apolipoprotein B (apo B) and lipoprotein (a) were measured with commercial kits. Non-high-density lipoprotein-cholesterol (non-HDL-C) was calculated as TC minus HDL-C. The AIP was calculated as log (TG / HDL-C), with TG and HDL-C expressed in molar concentrations [16]. Remnant cholesterol was calculated as TC − HDL-C − LDL-C as previously reported [17]. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study equation: eGFR = 186 × ((serum creatinine)^(−1.154)) × ((age)^(−0.203)) × [0.742 if female] [18].

2.4. High-density lipoprotein subfraction analysis

High-density lipoprotein (HDL) subfraction analysis was performed electrophoretically by the use of high-resolution 3% polyacrylamide gel tubes and the Lipoprint HDL System (Lipoprint™ HDL System; Quantimetrix Corp.) according to the manufacturer's instructions as previously described [19,20]. By this analysis, HDL was divided into 10 subfractions. Subfractions 1–3 represented large HDL particles, subfractions 4–7 indicated intermediate HDL particles, and subfractions 8–10 showed small HDL particles. The cholesterol concentration (mg/dl) of each HDL subfraction and the proportion (%) of the cholesterol concentration of each HDL subfraction over the HDL-C concentration were subsequently determined.

2.5. Low-density lipoprotein subfraction analysis

The cholesterol contents of low-density lipoprotein (LDL) subfractions were also determined electrophoretically using high-resolution 3% polyacrylamide gel tubes and the Lipoprint LDL System (Quantimetrix) as previously described [20,21]. Seven LDL subfractions were obtained. Subfraction 1 represented large LDL particles, subfraction 2 indicated intermediate LDL particles, and subfractions 3–7 were defined as small dense LDL particles. The cholesterol mass (mg/dl) of each lipoprotein subfraction, the mean LDL particle size (Å), and the proportion (%) of the cholesterol mass of each lipoprotein subfraction over the TC mass were determined by this assay.

2.6. Statistical analysis

The values were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) for the continuous variables and the numbers (percentages) for the categorical variables. The analysis of variance, Student's *t* test, Mann–Whitney U test or Kruskal–Wallis test was used for the comparisons between continuous variables, and the chi-squared test was applied for the categorical variables. Multivariate linear regression analyses were used to corroborate the association between SUA and lipoprotein subfractions as well as lipid parameters. The binary logistic regression analysis was performed to determine the relationship between SUA and prevalent CAD. Receiver operating characteristic (ROC) curves were constructed to document the predictive value of SUA for prevalent CAD. A causal mediation analysis was used to examine the lipoprotein subfractions as potential mediators of the relationship between SUA and CAD susceptibility [22]. A $p < 0.05$ was considered statistically significant. Statistical studies were carried out with the SPSS program (ver 19.0, SPSS).

3. Results

3.1. Baseline characteristics

The study population of the current observation consisted of subjects referred to coronary angiography with an average age of 56.5 ± 10.1 y, and 258 (64.3%) of this study population were male. The mean SUA level was 5.69 ± 1.45 mg/dl. The baseline demographic, clinical characteristics and laboratory findings according to the quintile value of the SUA level (Q1 0.53–4.58, n = 80; Q2 4.59–5.24, n = 81; Q3 5.25–5.92, n = 80; Q4 5.93–6.74, n = 80; Q5 6.75–11.19, n = 80) for the whole study population were summarized in Table 1. The upper SUA quintile was often accompanied with higher traditional cardiovascular risk factors including smoking, alcohol, hypertension, dyslipidemia, metabolic syndrome, and family history of CAD. As indicated in Table 1, the atherogenic lipid parameters dramatically increased according to SUA quintiles such as TG ($p = 0.001$), non-HDL-C ($p = 0.016$), apoB ($p = 0.010$), TC/HDL-C ratio ($p < 0.001$), apoB/apoA1 ratio ($p < 0.001$), and remnant cholesterol ($p < 0.001$) levels. Among lipoprotein subfractions, the levels of large HDL-C and