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Original Investigation

A Genetic Marker of Uric Acid Level, Carotid Atherosclerosis, and Arterial Stiffness: A Family-Based Study

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Background: Hyperuricemia associates with atherosclerosis complications, but it is uncertain whether this relationship is causal in nature. The urate transporter GLUT9 (encoded by the *SLC2A9* gene) is a major genetic determinant of serum uric acid level in humans. Because polymorphisms are distributed randomly at mating (Mendelian randomization), studies based on GLUT9 polymorphisms may provide unconfounded assessment of the nature of the link between uric acid and atherosclerosis.

Study Design: Cross-sectional study.

Setting & Participants: Family-based study including 449 individuals in 107 families in a genetically homogeneous population in Southern Italy.

Factor: Serum uric acid level, rs734553 allele, and age.

Outcome: Ultrasound biomarkers of atherosclerosis (intima-media thickness [IMT] and internal diameter) and pulse wave velocity (PWV).

Results: Serum uric acid level was dose-dependently associated with the T allele of rs734553, a polymorphism in *SLC2A9* ($P = 8 \times 10^{-6}$). Serum uric acid level was a strong modifier of the relationship between age and IMT in fully adjusted analyses ($\beta = 0.33$; $P = 0.01$), whereas no such relationship was found for internal diameter ($\beta = -0.15$; $P = 0.3$) or PWV ($\beta = 0.10$; $P = 0.6$). The T allele coherently associated with carotid IMT, internal diameter, and PWV and emerged as an even stronger modifier of the age-IMT and age–internal diameter relationships in both crude and fully adjusted ($\beta = 0.40$ [$P < 0.001$] and $\beta = 0.48$ [$P = 0.003$], respectively) analyses.

Limitations: This is a hypothesis-generating study.

Conclusions: Results in this family-based study implicate uric acid as an important modifier of the age-dependent risk for atherosclerosis. Trials testing uric acid–lowering interventions are needed to prove this hypothesis.

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INDEX WORDS: Atherosclerosis; glucose transporter type 9 (GLUT9); hyperuricemia; SLC2A9; rs734553; uric acid; intima-media thickness (IMT); pulse-wave velocity (PWV); cardiovascular disease.

Hyperuricemia has long been suspected as a risk factor for atherosclerosis. The link between uric acid level and vascular health has been investigated intensively over the past 3 decades, but the question remains largely unsettled (reviewed in[1]). Although the biological interference of uric acid with oxidative stress and vascular integrity is complex and in many respects controversial,[2] plausible biological mechanisms whereby hyperuricemia may cause atherosclerosis have been described.[3] Case-control and cohort studies investigating the relationship between uric acid and cardiovascular disease have produced conflicting results, and it is the prevailing view that the hyperuricemia-atherosclerosis association described in these studies most likely depends on the confounding effect of comorbid conditions that go along with hyperuricemia, including hypertension, diabetes, dyslipidemia, and obesity.[4]

Whether high uric acid levels may cause atherosclerosis is a question with major clinical and public health implications. In the most recent National Health and Nutrition Examination Survey, the prevalence of hyperuricemia in the general population was 21%, with trends over time suggesting that levels of this biomarker are continuing to increase.[5] Variability in uric acid levels attributable to environmental factors is a possible explanation for why some observational studies have not succeeded in observing a link between uric acid level and cardiovascular events.[4] Environmental factors such as hydration status, acid-base

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balance, nutrient intake, and use of diuretics and other drugs may substantially affect uric acid levels.

With genes being transmitted randomly (Mendelian randomization),[6] polymorphisms in genes that regulate serum uric acid concentration may represent an unbiased approach to further explore the link between uric acid and atherosclerosis. However, large-scale case-control studies across various populations and ethnicities have failed to show a link between uric acid–regulating genes and cardiovascular events.[7-9] One potential reason for this failure is that, due to population admixture and population stratification, these studies tend to dilute any underlying link between a given gene and clinical outcomes. By contrast, studies based on families in homogeneous populations might yield key information about genetic associations.[10] Although more difficult to perform, family-based studies have the advantage of controlling by design the issue of population stratification and minimizing the risk of false-positive and -negative genetic associations deriving from population admixture.[11] Studies based on families in homogeneous populations also are advantageous because these communities are more homogeneous for exposure to environmental factors.[10]

With this background in mind and pending definitive proof (ie, a proper clinical trial) that the uric acid–atherosclerosis link is causal in nature, we investigated the relationship between a genetic marker of uric acid level and phenotypic markers of atherosclerosis in a family-based study. In particular, we looked at relevant intermediate phenotypes of the atherosclerosis process, such as intima-media thickness (IMT) or internal diameter in carotid arteries, or biomarkers of arterial rigidity, such as pulse wave velocity (PWV), which to our knowledge have not been studied for association with uric acid level. As the genetic marker of uric acid level, we used the single-nucleotide polymorphism (SNP) rs734553, which is located in an intron of *SLC2A9*, the gene encoding the urate transporter GLUT9. This SNP was reported to be the strongest genetic marker of uric acid level in a meta-analysis including 28,000 individuals.[12] We conducted our study in a community with a shared genetic background[13] and shared nutritional habits.[14]

Because previous observations in the ARIC (Atherosclerosis Risk in the Communities) Study showed that age not only is associated positively with carotid atherosclerosis, but also has a larger effect in individuals with stronger and/or longer exposures to risk factors for atherosclerosis,[15] we tested the effect modification by rs734553 allele and uric acid level on the relationship between age and severity of carotid atherosclerosis. Of note, in our study, the age interaction was present for both serum uric acid level and the rs734553 allele.

METHODS

Study Protocol

The protocol conformed with the ethical guidelines of our institution, and informed consent was obtained from each participant.

Study Population

We enrolled 449 individuals who participated in a health screening offered to 107 families. This screening was undertaken as a part of a large project promoted and supported by the Italian Society of Hypertension to investigate genetic factors of human hypertension.[16] These families were part of a Southern Italy population, that is, a population with a shared genetic background[13] and a peculiar Mediterranean nutrient intake characterized by relatively high intakes of vitamin E and monounsaturated fatty acids.[14] The diagnosis of primary hypertension in these families was based on the diagnostic protocol routinely applied at our hypertension center, which includes routine biochemical tests; measurement of 24-hour catecholamines, supine and erect plasma renin activity, and plasma aldosterone; captopril renography and/or digital subtraction angiography; and echo-color Doppler of renal arteries.

Blood Pressure Measurements

Blood pressure (BP) was measured in a quiet well-lit room kept at a constant temperature. When a participant arrived at the research center, the individual rested in a semirecumbent position for 20 to 30 minutes in a comfortable armchair. BP then was measured 3 times by an automatic device with an interval of about 2 minutes between measurements, and the average of these 3 measurements was registered as the study BP.

Carotid Ultrasonography and PWV Studies

In all patients, ultrasonographic studies of the common carotid arteries were performed with a Hewlett Packard Sonos 1500 (7.5-MHz high-resolution probe) by a single observer (R.T.). IMT, internal diameter of the carotid arteries, and plaque were assessed according to the protocol validated and systematically applied at our research unit, as described in detail in a previous study.[17]

Pulse Wave Analysis: Carotid-Radial

The assessment of arterial wave reflection characteristics was performed noninvasively using the SphygmoCor Pulse Wave Analysis Px system and SCOR-2000, version 6.31, software (both AtCor Medical). Carotid-radial PWV was measured in triplicate from the left common carotid pulse to the left radial pulse using applanation tonometry, as described elsewhere.[18] Carotid-radial PWV was estimated by dividing central transit distance by transit time (Δt), using the SphygmoCor Pulse Wave Velocity Vx system and SCOR-2000, version 6.31, software.

Laboratory Measurements

Fasting blood sampling was undertaken and plasma was stored at $-80^{\circ}C$ until analysis. Serum uric acid, creatinine, lipids, and hemoglobin were measured by standard methods in the routine clinical laboratory. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation,[19] and microalbuminuria, by 24-hour urine collection.

Genotyping of GLUT9 Gene Polymorphism

Genomic DNA was extracted from peripheral-blood leukocytes by the standard salting-out technique. rs734553 genotype was determined with a validated TaqMan SNP Genotyping Assay, performed on an ABI PRISM 7900HT according to the

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