The Impact of Uric Acid on Long-term Mortality in Patients with Asymptomatic Carotid Atherosclerotic Disease

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Background: Serum uric acid (SUA) has been discussed to be related to cardiovascular (CV) disease and outcome. We investigated whether levels of SUA predict long-term mortality in neurologically asymptomatic patients with carotid atherosclerotic disease. *Methods:* We prospectively studied 959 consecutive patients with carotid atherosclerosis as evaluated by duplex Doppler sonography for all-cause and CV death, respectively. *Results:* During a median follow-up time of 6.3 years (interquartile range [IQR], 5.4-7.1 years), 246 deaths (25.7%), including 160 CV deaths (16.7%), were recorded. Median baseline SUA levels were 5.9 mg/dL (IQR, 5.0-7.0 mg/dL). SUA was significantly associated with all-cause death and CV death. Adjusted hazard ratios (HRs) for an increase of 1 mg/dL of SUA levels were 1.12 (95% confidence interval [CI], 1.04-1.21; $P = .003$) and 1.20 (95% CI, 1.11-1.30; $P < .001$) for all-cause and CV death, respectively. Quartiles of SUA levels showed a significant association with CV mortality (log-rank $P = .002$). For CV death, adjusted HRs for quartiles of increasing SUA levels were 1.45 (95% CI, .87-2.43), 1.44 (95% CI, .85-2.46), and 2.26 (95% CI, 1.36-3.76; $P < .01$), compared with the lowest quartile, respectively. Patients with baseline carotid stenosis of more than 50% and/or increased levels of SUA (≥median) had an approximately 2-fold increase in risk of (CV) death, compared with patients with carotid narrowing of less than 50% and/or SUA levels less than the median ($P < .001$). *Conclusions:* Levels of SUA represent independent predictors for CV mortality in a cohort of patients with asymptomatic carotid atherosclerosis. **Key Words:** Carotid atherosclerosis—uric acid—biomarker—risk factor.

Introduction

In humans, uric acid represents the end product of purine catabolism, with hypoxanthine and xanthine as important intermediate products. The enzyme xanthine oxidase catalyzes the oxidation of xanthine to uric acid. In most other mammals, uric acid is not the end product, but the enzyme uricase oxidizes uric acid to allantoin. Humans lost this enzyme because of a mutation and the ability to degrade uric acid into the highly soluble allantoin. Consequently, humans often develop hyperuricemia—defined as more than 6 mg/dL (360 μmol/L) in women and more than 7 mg/dL (420 μmol/L) in men,[1] which can lead to precipitation of uric acid crystals in joints and tissues with complications, such as gout or nephrolithiasis.

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The levels of serum uric acid (SUA) vary, and the causes for the variation are multifactorial and influenced by genetic and environmental factors. After introduction of the purine-rich Western diet, SUA levels have continuously been rising, reaching mean levels more than 5.5 mg/dL in women and more than 6.0 mg/dL in men today.[2] Beside these well-known conditions, an association of gout with cardiovascular (CV) diseases has been described already in the late 19th century. As SUA is closely related with important CV risk factors, such as hypertension,[3] diabetes,[4] and obesity,[5-7] it has been difficult to assess whether an independent association exists between SUA and CV disease. Some studies showed a significant and independent association between levels of SUA and risk of adverse CV outcome,[8-12] whereas others have failed to demonstrate this association after controlling for risk factors.[13,14] Kim et al[15] showed in a meta-analysis including more than 400,000 adults that hyperuricemia may slightly increase the risk of CHD events, independently of traditional CHD risk factors. In 2012, Lin et al[16] reported that SUA is associated with arterial stiffness—measured by brachial-ankle pulse wave velocity—in more than 5000 participants of the Fujian Province in South China. One year later, Bae et al[17] confirmed these results in 5568 participants of the Korean Multi-Rural Communities Cohort. Taken together, these studies indicate that SUA might have an effect on aberrant changes of vascular properties.

Recent investigations focused on the role of SUA in carotid atherosclerosis. Some studies indicate that SUA levels might be significantly associated with carotid intima–media thickness,[18] whereas other studies do not support this hypothesis.[19] To the best of our knowledge, no previous study has examined the relationship between SUA and mortality in patients with carotid atherosclerosis.

The purpose of our study was, therefore, to investigate the relationship between SUA and long-term mortality in a prospectively collected cohort of patients with carotid atherosclerosis who were neurologically asymptomatic.

Patients and Methods

Inclusion and Exclusion Criteria

Between March 2002 and March 2003, we prospectively enrolled 1512 Caucasian patients, who underwent duplex ultrasound investigations of the extracranial carotid arteries, into the Inflammation in Carotid Arteries Risk for Atherosclerosis Study. Of these, 149 patients were not included in the study because of symptomatic carotid artery disease (n = 89), recent surgical interventions or current infections (n = 51), refusal to participate in the study (n = 9), and missing ultrasound follow-up data (n = 95), which left 1268 patients for the final analysis. Study design and patients characteristics have been published previously.[20] In brief, the main indications for performing sonographic examinations of the carotid arteries were carotid bruits, known as coronary heart disease or peripheral atherosclerotic disease, and scheduled major heart surgery. These indications provided the basis for a study cohort of subjects likely to exhibit carotid atherosclerosis. Only patients with atherosclerotic carotid narrowing, who were neurologically asymptomatic (defined as absence of transient ischemic attacks, amaurosis fugax, or stroke within 12 months before inclusion), were included. Patients with active malignancies, current infectious and/or inflammatory diseases, symptomatic carotid atherosclerosis that necessitated revascularization therapy, patients after bilateral carotid occlusions, bilateral stent implantation or bilateral carotid endarterectomy, and patients with a recent CV event (myocardial infarction, stroke, coronary revascularization and/or peripheral vascular surgery) within the preceding 6 months were not included in Inflammation in Carotid Arteries Risk for Atherosclerosis Study. The latter patients were excluded to avoid any impact of acute CV events on inflammatory parameters, which could reflect an acute event rather than chronic condition of carotid atherosclerosis. The study complied with the Declaration of Helsinki and was approved by the institutional review board of the Medical University of Vienna. All patients gave their written informed consent.

Clinical and Laboratory Data

After enrollment, the medical history and data from physical examination were recorded. All parameters were ascertained for completeness and exactness by 2 independent observers. Clinical history and physical examination were assessed with special attention to the CV risk factors and comorbidities of age, sex, smoking habits, hyperlipidemia, body mass index, arterial hypertension, diabetes mellitus, coronary artery disease, history of myocardial infarction, history of cerebrovascular events, and current medication. Blood was drawn and analyzed directly without freezing according to local standard laboratory procedures. Uric acid was measured by the enzymatic uricase method. Treating physicians and sonographers were blinded for laboratory data and demographic parameters.

Ultrasound

Duplex Doppler ultrasound examinations were performed on an Acuson 128 XP10 with a 7.5-MHz linear array probe (Acuson, Malvern, PA). Patients were scheduled for a follow-up ultrasound investigation of the carotid arteries 6-9 months after the initial presentation. Grading of carotid stenosis was quantified as described previously.[20] In brief, duplex grading of the carotid stenosis was determined by measuring the peak systolic and end-diastolic velocities in the internal carotid arteries (ICAs) and common carotid arteries.