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Uric acid and endothelial function in elderly community-dwelling subjects

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ABSTRACT

The role of serum uric acid (SUA), an inflammatory agent and potential mediator of cardiovascular diseases, in endothelial function (EF) has been tested only in middle-aged subjects affected by specific diseases. Our aim was to assess the relationship between SUA and measures of EF in a cohort of elderly community-dwellers. This study involved 424 males and 426 females aged 70 years from the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS), having complete data on SUA and EF assessed by flow-mediated vasodilation (FMD) and by intra-arterial infusion of acetylcholine (endothelium-dependent vasodilation, EDV) and sodium nitroprusside (endothelium-independent vasodilation, EIDV). Univariate and multivariate regression models obtained by backward selection from initial fully-adjusted models were built to assess the relationship between SUA and measures of EF in both genders. Cardiovascular risk factors, serum hormonal and metabolic mediators, and body composition were considered as potential confounders. In the univariate model, SUA was inversely associated in both genders with log(EDV) ($\beta \pm$ SE males -0.39 ± 0.17, $p = 0.03$; females -0.57 ± 0.19, $p = 0.003$) and log(EIDV) (males -0.23 ± 0.12, $p = 0.05$; females -0.49 ± 0.15, $p = 0.002$), but not with log(FMD). After adjustment for BMI, only the association between SUA and log(EIDV) in females persisted, though attenuated (-0.32 ± 0.16, $p = 0.049$), and was no longer significant in the fully-adjusted multivariate model including waist/hip ratio. In conclusion, in older subjects, especially women, SUA is associated with EF not independently of a list of confounders including BMI and trunk fat mass, suggesting a role as surrogate metabolic marker rather than an active player in EF.

1. Introduction

In adult subjects, serum uric acid (SUA) levels have been positively associated with cardiovascular diseases including hypertension, coronary artery disease (CAD), heart failure and stroke (Kanbay et al., 2013). However, the physio-pathological correlates of this epidemiological association are still controversial.

Despite having some *anti*-oxidant properties, demonstrated in experimental intervention studies under controlled conditions (Waring et al., 2004; Waring et al., 2006), uric acid is widely recognized as a pro-oxidative and inflammatory agent (Ruggiero et al., 2006; Kang et al., 2005). In fact, it induces the activation of renin-angiotensin system and impairs nitric oxide (NO) release by endothelial cells (Kang et al., 2005; Yu et al., 2010). These mechanisms may result in endothelial dysfunction, a marker of high cardiovascular risk and adverse events in both adult and elderly subjects (Maruhashi et al., 2013b; Lind et al., 2011).

In selected adult cohorts with hyperuricemia or high cardiovascular risk profile, elevated SUA levels have been negatively associated with brachial artery flow-mediated vasodilation (FMD), an indirect measurement of endothelial function (Ho et al., 2010; Kato et al., 2005; Kanbay et al., 2011; Mercuro et al., 2004; Tomiyama et al., 2011). However, the gold standard technique for endothelial function assessment, the endothelium-dependent vasodilation (EDV) measurement after intra-arterial acetylcholine infusion, is not optimally correlated with FMD (Lind, 2013). Only few studies have assessed the effects of SUA on EDV, particularly on older individuals.

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Moreover, the relationship between SUA and endothelium-independent vasodilation (EIDV), evaluated by invasive forearm technique with intra-arterial infusion of sodium nitroprussiate, has been poorly investigated as well. This is somewhat surprising because EIDV is related to Framingham risk score (Lind et al., 2005) and is considered an indicator of age-related vascular stiffness (Maggio et al., 2014). In a study carried out on healthy adult volunteers, SUA exhibited an inverse correlation with endothelium-independent vasodilation (EIDV) but not with EDV (Jalal et al., 2012). Data about older individuals are however lacking. As such, the evaluation of the possible association between SUA and EIDV in this age-group may be of paramount importance to assess the physio-pathological role of SUA in the processes of vascular aging and disease-related vascular dysfunction.

Thus, using data from a population-based cross-sectional study of 70-year-old community-dwellers, we assessed the relationship between SUA and measures of endothelium-dependent and independent vascular function. We hypothesized that SUA is inversely associated with both EDV and EIDV, modulating endothelial function through oxidative stress and inflammation and representing a marker of altered metabolic status. However, given the known strong negative association between fat mass and measures of endothelium-dependent and -independent vasodilation (Corretti et al., 2002; Maggio et al., 2013), we also hypothesized the role of proxies of body fat mass, such as waist/hip ratio, as potential mediators of this association.

2. Materials and methods

2.1. Study population

We studied subjects enrolled in the large population-based Prospective Study of the Vasculature in Uppsala Seniors (PIVUS). All community-dwelling subjects aged 70 years in Uppsala, Sweden, were eligible for study enrolment. The study population was chosen from a registry of community-living individuals and invited in randomized order by letter within 2 months from their 70th birthday. The final number of participants was 1016 (507 M, 509 F), out of 2025 invited subjects (participation rate 50.1%). The baseline investigation began in April 2001 and was completed in June 2004. For the purposes of the present analysis, we excluded those individuals, with lacking information on SUA and complete measures of EF. Subjects with severe comorbidities (including malnutrition, NYHA class III-IV congestive heart failure, active cancer, cirrhosis), subjects under active urate-lowering treatment and with severe hypertriglyceridemia (≥400 mg/dl) were excluded as well. Thus, 166 subjects (83 M, 83 F) were excluded so that the analysis was performed on 850 subjects (424 M, 426 F).

The study protocol was approved by the Ethics Committee of Uppsala University. All participants signed an informed participation consent form after having received a detailed description of the purposes and design of the study. All investigations were carried out in line with the principles expressed in the Declaration of Helsinki.

2.2. Baseline clinical investigations

A complete questionnaire about personal medical history, regular medications, dietary and smoking habits was answered by each participant. Namely, history of any cardiovascular diagnosis or medication, hypertension (ongoing antihypertensive treatment or blood pressure > 140/90 mm Hg), diabetes (specific dietary or pharmacological treatment or fasting blood glucose > 6.1 mmol/L), hyperlipidemia (ongoing lipid-lowering treatment, low-density lipoprotein [LDL]-cholesterol > 3.5 mmol/L, or serum triglycerides > 1.7 mmol/L) were addressed. Blood pressure was measured with a calibrated mercury sphygmomanometer after at least 30 min of rest, considering the average of three different recordings. Standing height was measured to the nearest whole 0.5 cm with a Harpender Stadiometer (Holtain Ltd.), and body weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as body weight / (height)^2 (kg/m^2). Obesity was defined as BMI > 30 kg/m^2. Exercise habits were categorized as follows: very light exercise (no sweat) less than two times per week, light exercise two times per week, moderate exercise (sweat) one or two times per week, heavy exercise (sweat) more than two times per week.

Waist/hip ratio was measured for each participant and considered as a proxy of body composition.

2.3. Laboratory investigations

Blood samples were collected in the morning, after an overnight fast. Medications and smoking were not allowed in the 8-hour period before blood sample collection. SUA was analyzed with an uricase method on an Architect Ci8200 Analyzer (Abbott Laboratories, Abbott Park, Ill., USA) with reagents (7D76-20) from the same manufacturer. Reference values (90% CI) based on the study population were from 3.98 (3.73–4.25) to 9.26 (8.83–9.7) mg/dL in males and from 3.18 (2.99–3.36) to 7.92 (7.58–8.25) mg/dL in females. These reference values are consistent with those found for healthy individuals from Scandinavian countries in the Nordic Reference Interval Project (NORIP) (Carlsson et al., 2010).

Liver function was assessed through plasma alanine aminotransferase (ALT, normal range 0–40 U/L) and plasma albumin (spectrophotometry using bromine cresol purple, normal range 37–48 g/L). Renal function was assessed with creatinine clearance calculated through the Cockcroft-Gault formula (normal range 97–137 mL/min in men, 88–128 mL/min in women). Plasma creatinine was analyzed with spectrophotometry using a modified Jaffe's reaction (normal range, 60–106 μmol/L). Total plasma cholesterol (normal range 2.6–7.1 mmol/L) and plasma high-density lipoprotein (HDL) cholesterol (normal range 0.8–1.9 mmol/L) were assessed through enzymatic assay. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula. High-sensitivity C-reactive protein (hs-CRP) was measured in serum by latex-enhanced turbidimetry (Architect Ci8200 Analyzer, Abbott Laboratories).

Serum sex-hormone binding-globulin (SHBG) and total testosterone (T) were assessed by chemiluminescence immunoassay on the immunochemistry platform Access (Beckman Coulter). The minimal detectable concentrations were 2 nmol/L and 0.35 nmol/L, respectively. Plasma fasting insulin was determined through chemiluminescence assay (Roche). Vitamin D was assessed in serum by chemiluminescence immunoassay technology (LIAISON 25-hydroxyvitamin D Assay, DiaSorin).

2.4. Measures of endothelial and vascular function

Endothelium-dependent vasodilation (EDV) in the peripheral circulation was simultaneously assessed through different methods, whose details have been previously described elsewhere (Lind et al., 2005). Endothelium-independent vasodilation (EIDV) was also assessed contextually.

Briefly, the resting forearm blood flow (FBF) was determined by venous occlusion pletismoghraphy (Elektromedicina). Local intra-arterial drug infusions were then given over 5 min for each dose. To evaluate EDV, 25 and then 50 μg/min of acetylcholine (Clin-Alpha) were administered. EDV was calculated as FBF during infusion of 50 μg/min of acetylcholine minus resting FBF divided by resting FBF. To evaluate EIDV, 5 and then 10 μg/min of sodium nitroprussiate were administered. EIDV was calculated as FBF during infusion of 10 μg/min sodium nitroprusside minus resting FBF divided by resting FBF.

Flow-mediated vasodilation (FMD) was also measured as index of EF. It was induced by inflation of a pneumatic cuff placed around the forearm to a pressure at least 50 mm Hg above the subject's systolic blood pressure for 5 min. Brachial arterial diameter before and during the procedure was measured through external B-mode ultrasound imaging 2–3 cm above the elbow (Acuson XP128 with a 10 MHz linear