Atherosclerosis 272 (2018) 101–107

Contents lists available at ScienceDirect

Atherosclerosis

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

Elevated serum uric acid levels are associated with endothelial dysfunction in HIV patients receiving highly-active antiretroviral therapy

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ARTICLE INFO

Article history:
Received 19 September 2017
Received in revised form
3 March 2018
Accepted 16 March 2018
Available online 17 March 2018

Keywords:
HIV
HAART
Uric acid
Metabolic syndrome
Endothelial function

ABSTRACT

Background and aims: Elevated serum uric acid (SUA) levels may be associated with endothelial dysfunction. Increased rates of metabolic syndrome (MS) and elevated SUA levels were described in human immunodeficiency virus (HIV) infected patients. We investigated whether SUA levels are associated with endothelial dysfunction in HIV positive patients receiving highly-active antiretroviral therapy (HAART) irrespective of MS.

Methods: In this cross-sectional study of 250 HIV positive patients receiving stable HAART, we evaluated the relationship between MS, SUA levels and endothelial function. SUA levels and brachial artery flow-mediated dilation (bFMD) were measured. The relationship between logarithmic (LG)-transformed SUA levels and bFMD was evaluated after correction for MS.

Results: MS was detected in 28.4% of patients and elevated SUA levels (≥6 mg/dL) in 25.2%. MS was associated with higher LG-SUA levels (age-, gender- and glomerular filtration rate-adjusted beta = 0.204, $p = 0.001$). The crude linear association between LG-SUA levels and LG-bFMD (beta = −0.166, $p = 0.008$) was abolished after correction for MS (beta = −0.089, $p = 0.172$). When SUA levels were used as a categorical variable (≥6 mg/dL or <6 mg/dL and SUA quartiles, respectively), the association between LG-SUA levels and LG-bFMD remained significant after adjustment for MS (beta = −0.142, $p = 0.022$ and beta = −0.163, $p = 0.010$, respectively).

Conclusions: MS significantly affects SUA levels in HAART-treated HIV infected patients. The negative association between SUA and bFMD is independent of MS only for elevated SUA levels.

1. Introduction

Uric acid (UA), the end product of purine catabolism, is far from being an inert metabolic product as it exerts either antioxidant or pro-oxidant activities [1]. Evidence reporting the association between serum UA (SUA) levels and the metabolic syndrome (MS) is robust [2–4]. For instance, a recent large longitudinal study in 18,907 subjects aged above 65 years found that increased SUA concentrations predicted an increased risk of developing MS [5].

A positive association between SUA elevation and different markers of preclinical atherosclerosis has been described [6–10]. Specifically, UA may contribute to endothelial dysfunction by inhibiting endothelial cell proliferation and migration and decreasing nitric oxide production and bioavailability [10–12]. In agreement with the reported detrimental impact of SUA on the endothelium, treatment with allopurinol, a non-selective inhibitor of xanthine oxidase, improved endothelial dysfunction [7,13]. By contrast, results supporting the association between SUA levels and endothelial dysfunction have been questioned by other

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https://doi.org/10.1016/j.atherosclerosis.2018.03.031
0021-9150/

observational and interventional studies [14–18]. For example, a neutral effect of urate-lowering agents on endothelial function has been reported [16–18], whereas UA intravenous infusion improved forearm blood flow responses to intrabrachial acetylcholine and sodium nitroprusside [14]. The ambiguous impact of UA on endothelial homeostasis is further supported by the controversial relationship between SUA levels and cardiovascular (CV) disease risk [19–28]. In particular, the Mendelian randomization analysis, that used randomly inherited urate-raising genetic variants (e.g. in *SLC2A9*) as non-confounded proxies for lifelong SUA exposure [29], provided no evidence for a causal role of SUA in CV disease.

Human immunodeficiency virus (HIV) infection is associated with an increased prevalence of the MS, which in turn may contribute to an increased risk of endothelial dysfunction and CV risk [30–33]. In line with the strong association between metabolic risk factors and SUA levels in HIV negative patients [2–4], average SUA levels were found to be elevated in HIV positive patients [34] and a significant association was reported between SUA levels and multiple components of the MS in this population [35].

Because the association between MS and either SUA [35] or endothelial dysfunction [31] has been reported in HIV-infected patients, whether the possible association between SUA levels and endothelial function might be mediated by the presence of the MS needs to be investigated in HIV-infected patients. This is of particular importance in HIV positive patients receiving highly-active antiretroviral therapy (HAART), which is known to have a significant impact on several components of the MS [36–39] and SUA levels as well [34].

Hence, in this cross-sectional study of HIV-infected patients receiving stable HAART, we explored the relationship between SUA and endothelial function and the potential impact of the MS on this association.

2. Materials and methods

2.1. Study subjects

Between January 15, 2016 to January 30, 2017 we recruited for this cross-sectional study 250 HIV-infected patients receiving stable HAART for at least 6 months, who were referred to the Day Hospital of Infectious Diseases Clinic in Perugia. We used a period of at least 6 months to attenuate the possibility that closer HAART initiation might interfere with baseline FMD levels [40,41]. Exclusion criteria included: age under 18 years, current pregnancy, estimated Glomerular Filtration Rate (GFR) < 60 ml/min (calculated using the "Modification of Diet in Renal Disease-4" – MDRD-4 - equation), opportunistic infections within the past three months, having received an organ transplants and recent interferon therapy, current treatment with drugs affecting SUA levels, including allopurinol and febuxostat. Data regarding viro-immunological profile and current medications were collected. The study was approved by the local Ethics Committee of University of Perugia (Perugia, Italy). The methods were carried out in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all participants prior to enrolment.

2.2. Clinical evaluation, laboratory parameters and assessment of endothelial function

All the determinations were made at the medical center at 8.00 a.m., with a room temperature between 21 and 23 °C, after a 13-h overnight fast. Measurement of height, weight, body mass index (BMI), waist circumference and brachial blood pressure was done as previously described [31,42]. CD4 cell count was determined by flow-cytometry analysis (Citomics FC 500, Beckman Coulter, Brea, USA) by whole blood staining with anti-CD45-PC5 and anti-CD4-PE fluorescent antibodies (Beckman Coulter, Marseille, France). HIV-RNA levels were measured using the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0 (Roche Molecular Systems, NJ, USA). Total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and glucose were measured by an enzymatic colorimetric method (Autoanalyzer KONE-PRO; DASIT S.p.A, Cornaredo, Milano, Italy); low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation. SUA levels were measured by ADVIA 1800 Chemistry (Siemens, Healthcare Diagnostic Ltd., Frimley, Camberley, UK). The revised National Cholesterol Educational Program (NCEP) guidelines were used for the diagnosis of the MS [43] (presence of any 3 of 5 following criteria: waist circumference ≥102 cm in men or ≥88 cm in women; triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides; HDL-cholesterol <40 mg/dL in men or <50 mg/dL in women or drug treatment for reduced HDL-cholesterol; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or antihypertensive drug treatment; fasting glucose ≥100 mg/dL or drug treatment for elevated glucose levels).

Brachial artery flow-mediated vasodilation (bFMD) was assessed by ultrasonography using a linear multifrequency 5- to 12-MHz transducer (HDI 3500, Advanced Technology Laboratories, Cherry Hill, NJ). All the patients who were current smokers were asked to refrain from smoking since at least midnight (at least 8 h before bFMD measurement). After 10–20 min rest in the supine position, bFMD measurement was performed for each patient on the non-dominant arm. A linear multifrequency 5- to 12-MHz transducer (HDI 3500, Advanced Technology Laboratories, Cherry Hill, NJ) was used to scan longitudinally the brachial artery, just above the antecubital crease. After image freezing, the diameter of the brachial artery was measured at the R wave of the electrocardiogram, on the interface between the media and adventitia of the anterior and posterior wall. Inflation of a pneumatic cuff (12.5 cm wide) at 230–250 mmHg for 4 min was performed on the most proximal portion of the forearm. Hyperemia was induced by sudden deflation of the cuff and measurement of the arterial diameter was repeated after 45–60 s. Tracings were recorded and read by the same investigator who was blinded to the participant's clinical data. The average of 3 measurements of basal and post-hyperemia diameters was used for statistical analysis. bFMD was calculated as 100 × [(posthyperemia diameter - basal diameter)/basal diameter] [31]. The intraobserver between occasion reproducibility of bFMD in our laboratory was 1.0 ± 1.5%.

2.3. Statistical analysis

SPSS statistical package, release 17.0 (SPSS Inc, Chicago, Ill) was used for statistical analyses. Values are expressed as the mean ± SD. Base 10 logarithmic (LG) transformation was performed for skewed variables. Patients were grouped according to either SUA quartiles (≤4.3, 4.4–5.0, 5.1–5.9 and ≥ 6 mg/dL, respectively), the presence of the MS (yes *vs* no) or the number of components of the MS (0, 1, 2, ≥3). Independent samples *t*-test and ANOVA with Bonferroni *post-hoc* test were used for between-group comparisons. Correlation analyses were performed using the Pearson's coefficient of correlations. Three different models of multivariable analysis were performed with LG-SUA as the dependent variable and the following independent variables: age, gender, GFR and either MS (1st model), the number of MS components (2nd model) or each individual criteria of the MS (3rd model). An additional multiple linear regression analysis was used to estimate prediction of LG-bFMD by including the following independent variables in the model: age, gender, MS. Nested model comparisons using the R^2 change F-test was used to compare multivariable models including