Journal of the American Society of Hypertension 10(7) (2016) 559–569

Research Article

Association between uric acid and renal function in hypertensive patients: which role for systemic vascular involvement?

Giulio Geraci, MD*, Giuseppe Mulè, MD, Massimiliano Morreale, MD, Claudia Cusumano, MD, Antonella Castiglia, MD, Francesca Gervasi, MD, Francesco D'Ignoto, MD, Manuela Mogavero, MD, Calogero Geraci, MD, and Santina Cottone, MD

Dipartimento Biomedico di Medicina Interna e Specialistica (DIBIMIS), Unit of Nephrology and Hypertension, European Society of Hypertension Excellence Center, University of Palermo, Italy

Manuscript received January 16, 2016 and accepted May 3, 2016

Abstract

The role of systemic vascular involvement in mediating the association between serum uric acid (SUA) and renal function in hypertension has not been explored. Main purpose of our study was to investigate whether morphofunctional vascular changes, assessed as carotid intima-media thickness (cIMT) and aortic pulse wave velocity (aPWV), might mediate the association between SUA and renal damage. We enrolled 523 hypertensive subjects with or without chronic kidney disease and divided population into tertiles of SUA based on sex-specific cutoff values. cIMT and aPWV were higher in uppermost SUA-tertile patients when compared to those in the lowest ones (all $P < .001$). Uricemia strongly correlated with cIMT and aPWV at univariate analysis ($P < .001$) and with cIMT after adjustment for confounders ($P < .001$). Adjustment for cIMT attenuated the relationship between SUA and estimated glomerular filtration rate ($P = .019$). Systemic vascular changes seem partially to mediate the association between SUA and renal function in hypertensive patients, regardless of kidney function. J Am Soc Hypertens 2016;10(7):559–569.

Keywords: Atherosclerosis; hypertension; renal damage; uricemia.

Introduction

The link between uricemia and hypertension is not completely clarified. A close association between increased serum uric acid (SUA) and high blood pressure (BP) has been demonstrated by several studies conducted in animal models as well as in humans, even if the causal connection remains to be fully elucidated.[1–5] Furthermore, the relationship between kidney damage and SUA is controversial: hyperuricemia is associated with decreased renal function in hypertensive patients, although it is unclear whether the increased SUA is the cause or the expression of renal injury itself.[3–8]

Despite all these uncertainties, several assumptions have been made about the mechanisms underlying these strong associations. Some evidences suggest that uric acid may play a causal role in the pathogenesis of endothelial dysfunction and atherosclerosis.[9,10] As matter of fact, several studies described a strong direct association between SUA and structural and functional changes of arterial vessels.[11–14] These alterations could somehow represent the pathophysiological bridge between SUA and kidney damage, being able to mediate at least in part this relationship.[8,9] On the other hand, it is well known that patients with chronic kidney disease (CKD) have a greater prevalence and extent of systemic vascular damage compared to subjects with normal renal function,[13] and several investigations have also highlighted how vascular changes can play a role in causing kidney damage.[14]

Supplemental Material can be found at www.ashjournal.com.

Conflict of interest: The authors declare no conflict of interest.

*Corresponding author: Giulio Geraci, MD, Via del Vespro, 141, 90127 Palermo, Italy. Tel: (0039)-091-6554578; Fax: (0039)-091-6554331.

E-mail: giulio.geraci@unipa.it

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2016.05.001

Nevertheless, to the best of our knowledge, there are currently no studies that analyze the different role of systemic vascular changes, as assessed by ultrasonographic carotid intima-media thickness (cIMT) and aortic pulse wave velocity (aPWV) evaluation, in mediating the association between uricemia and kidney damage in subsets of hypertensive patients with different renal impairment.

Therefore, the purposes of our study are: (1) to investigate the relationship between SUA with both cIMT and aPWV in hypertensive subjects; (2) to assess the influence of renal function on these relationships; and (3) to study whether systemic vascular changes may mediate the association between SUA and renal function in this population.

Materials and Methods

Subjects

This cross-sectional study includes a total of 523 Italian hypertensive subjects. This population was selected from Caucasian hypertensive patients consecutively attending, as outpatients, our unit of Nephrology and Hypertension.

The exclusion criteria were as follows: age <30 years and >75 years; renovascular, malignant, endocrine hypertension, or hypertension associated with obstructive sleep apnea syndrome; treatment with xanthine oxidase inhibitors; severe obesity, defined as a body mass index (BMI) $\geq$ 40 kg/m^2; rapid deterioration of renal function, defined as a reduction in estimated glomerular filtration rate (eGFR) > 25% within 7 days; end-stage renal disease (eGFR<15 mL/min/1.73 m^2) or renal replacement therapy (transplanted or dialyzed patients); carotid percutaneous angioplasty or endoarterectomy, heart failure (defined according to the Framingham study criteria)[15]; permanent atrial fibrillation; moderate to severe aortic/mitral valve disease; previous coronary or cerebrovascular events; major noncardiovascular diseases.

All the exclusion criteria were identified by both chart review and study visits. Endocrine hypertension and renovascular hypertension were ruled out by clinical examination, by Duplex-Doppler assessment of intrarenal and extraparenchymal renal arteries and by laboratory determination of serum electrolytes, plasma renin activity, and plasma aldosterone concentration; when appropriate, plasma catecholamine level was determined and renoscintigraphy was performed. To screen for obstructive sleep apnea, we used the Berlin questionnaire and the Epworth Sleepiness Scale, followed by polysomnography when appropriate.[16]

Written informed consent was obtained from each subject. The study protocol conformed to the ethical guidelines of the declaration of Helsinki and was approved by the local review board.

Study Design

In all subjects, clinical history and physical examination were performed. Subjects who reported smoking cigarettes regularly during the past year were considered current smokers. Body weight and height were measured by a nurse. Clinic BP was recorded by a doctor, following the recommendations of the 2013 European Society of Hypertension/European Society of Cardiology guidelines.[17] Aortic PWV was assessed, and a 24-hour ambulatory blood pressure monitoring was performed. Moreover, a B-mode and Doppler ultrasonographic examination of carotid vasculature was carried out through a GE Logiq P5-PRO instrument (General Electric Company, Milan, Italy).

Main laboratory tests were performed, including the SUA determination, and a 24-hour urine sample was collected on nonworking days to evaluate albumin excretion rate.

Measurements

Clinic BP was considered as the mean of three consecutive measurements obtained, at 2-minute intervals, by an electronic oscillometric validated device (Microlife Watch BP Office, Widnau, Switzerland),[18] after 5 minutes of rest in sitting position. A portable, noninvasive SpaceLabs 90,207 recorder (Redmond, WA) was used to perform 24-hour ambulatory blood pressure monitoring. BP was recorded automatically at 15-minute intervals during the day and at 20-minute intervals during nighttime resting. Only records with more than 80% of valid data were accepted.

Routine biochemical parameter determination was performed with standard techniques using an autoanalyzer (Boehringer Mannheim for Hitachi system 911, Mannheim, Germany). SUA was measured using an uricase/peroxidase method. Low-density lipoprotein cholesterol was calculated by the Friedwald formula. The 24-hour albumin excretion rate was assayed by a solid-phase enzyme immunoassay (Microalbumin-ELISA, DRG Diagnostics, Marburg, Germany). Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[19]

The definition of CKD was based on the combination of biochemical data obtained before the study visit and clinical information provided by the referring physicians with the laboratory tests performed in our unit. CKD was defined as eGFR < 60 mL/min/1.73 m^2 for 3 months or as albuminuria if eGFR is $\geq$ 60 mL/min/1.73 m^2. Patients without CKD were defined in the text as subjects with normal renal function.

Pulse Wave Velocity

All measurements were performed in a supine position after 15-minute rest in a quiet, temperature-controlled