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Serum uric acid as a marker of microvascular damage in systemic sclerosis patients

Antonietta Gigante [a], Biagio Barbano [a], Giuseppe Barilaro [a], Silvia Quarta [a], Maria Ludovica Gasperini [a], Francesca Di Mario [b], Antonella Romaniello [c], Antonio Amoroso [a], Rosario Cianci [a], Edoardo Rosato [a,*]

[a] Department of Clinical Medicine, Clinical Immunology Unit-Scleroderma Center, Sapienza University of Rome, Italy
[b] Department of Nephrology and Dialysis Unit, Sapienza University of Rome, Italy
[c] Department of Clinical and Molecular Medicine, Cardiology Unit, S'Andrea Hospital, Sapienza University of Rome, Italy

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ABSTRACT

Background: Microvascular damage of skin and internal organs is a hallmark of systemic sclerosis (SSc). Serum uric acid (UA) represents a marker of inflammation and endothelial dysfunction. The aims of this study were to evaluate the correlation between serum UA and intrarenal arterial stiffness evaluated by Doppler ultrasound in SSc patients with normal renal function. We also evaluated the correlation between serum UA and other clinical variables of the disease.

Methods: Forty-five SSc patients underwent clinical assessment, Doppler ultrasound of intrarenal arteries with evaluation of resistive index (RI), pulsatile index (PI), and systolic/diastolic ratio (S/D), echocardiography with systolic pulmonary artery pressure (PAPs), baseline pulmonary function tests, and nailfold videocapillaroscopy (NVC). In all patients serum UA was measured.

Results: The serum UA showed a significant positive correlation with sCr ($r = 0.33$, $p < 0.0001$) and PAPs ($r = 0.38$, $p < 0.01$) >and negative correlation with CKD-EPI ($r = -0.35$, $p < 0.01$). The mean value of serum UA increased with severity of NVC damage. Using this cut-off value of 4.7 mg/dl, the mean value of Doppler indices of intrarenal stiffness is significantly different ($p < 0.05$) in SSc patients with low normal or high normal serum UA.

Conclusions: Serum UA concentration is higher in patients with high microvascular damage than in patients with low microvascular damage. These preliminary data must be confirmed in large prospective studies.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by endothelial dysfunction and fibrosis of both skin and internal organs. Endothelial dysfunction, microvascular and macrovascular damage are the hallmarks of SSc (Matucci-Cerinic et al., 2013).

The most important renal complication in SSc is scleroderma renal crisis, but latent renal involvement is present such as isolated reduced glomerular filtration rate (GFR), reduced renal functional reserve, microalbuminuria and increased intrarenal arterial stiffness. A reduction of glomerular filtration rate (GFR) can be present in SSc patients with normal serum creatinine (sCr) (Shanmugam and Steen, 2012). In SSc patients, GFR can be evaluated by estimated GFR (eGFR). Gigante et al. found that Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation provides more accurate eGFR in comparison to 7-variable MDRD (Gigante et al., 2012). Increased arterial stiffness is known to be associated with sclerodermic kidney dysfunction. It is known that Doppler renal ultrasound is a useful and non-invasive diagnostic tool to evaluate intrarenal arterial stiffness. The Doppler indices of intrarenal arterial stiffness showed a negative correlation with GFR and they increase with the severity of microvascular damage of hands.

Elevated serum uric acid (UA) has been shown to be associated with impaired endothelium-mediated relaxation, vascular stiffness (Sowers, 2013) and a restrictive left ventricular filling pattern or diastolic dysfunction (Hayden and Tyagi, 2004). Recently, the DETECT study has been performed with the aim of identifying predictors of pulmonary arterial hypertension (PAH) in patients with SSc. Serum urate has not been described previously as being predictive of PAH, but was identified as such in this study where low values were associated with a low PAH risk (Coghlan et al., 2013).

The aims of this study were to evaluate the correlation between serum UA and intrarenal arterial stiffness evaluated by Doppler ultrasound in SSc patients with normal renal function. We also evaluated the correlation between serum UA and other clinical variables of the disease.

* Corresponding author at: Sapienza University of Rome, Department of Clinical Medicine, Clinical Immunology Unit-Scleroderma Center, Italy.
E-mail address: edoardo.rosato@uniroma1.it (E. Rosato).

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Materials and methods

Forty-five patients (36 female and 9 male; mean age 45 ± 13.8 years) fulfilling the American College of Rheumatology/European League criteria for classification and diagnosis of SSc were enrolled in this study (van den Hoogen et al., 2013). Seventeen patients had limited cutaneous SSc (lcSSc) and 28 presented diffuse cutaneous SSc (dcSSc) as defined by LeRoy et al. (1998). Table 1 shows the SSc patients' epidemiological and clinical features.

All SSc patients underwent treatment with calcium channel blockers (nifedipine 30 mg/day). None of the patients were treated with immunosuppressive agents (e.g. cyclophosphamide or mycophenolate mofetil), steroid, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers, diuretics or xanthine oxidase inhibitors. Patients with elevated serum creatinine (sCr), elevated blood urea, urinary tract infections, abnormal urinary sediment, glomerulonephritis, kidney stones, anti-phospholipid-associated nephropathy, diabetes, cardiovascular diseases such as hypertension, myocardial infarction, arrhythmias, heart failure, hyperlipidemia, coagulopathy, obesity, scleroderma renal crisis or smokers were excluded.

The subjects' written consent was obtained according to the Declaration of Helsinki and the study was approved by the ethics committee of Sapienza University (IRB approval 3377/2014).

Laboratory parameters

Laboratory investigations included sCr (normal range: 0.5–0.9 mg/dl), blood urea nitrogen (normal range: 10.20–49.80 mg/dl), serum UA (normal range: 3.40–7.20 mg/dl), sodium, potassium, glucose, albumin, urinalysis and 24 h proteinuria. sCr was measured using a Jaffe alkaline picrate assay (Abbott Aeroset analyzer) (Wetzels et al., 2007). Serum UA was measured with an automatic analyzer (7700 series; Hitachi, Tokyo, Japan).

Calculation of GFR

GFR was calculated using the CKD-EPI equation, already validated in SSc patients (Gigante et al., 2012), expressed as a single equation: GFR = 141 × min (sCr/k, 1) α × max (sCr/k, 1)-1.209 × 0.993Age × 1.018 (if female) × 1.159 (if black), where k is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of sCr/k or 1 and max indicates the maximum of sCr/k or 1 (Levey et al., 2009).

Nailfold videocapillaroscopy (NVC)

NVC was performed with a videocapillaroscope (Pinnacle Studio Version 8) equipped with a 500× optical probe. The nailfold of the second, third, fourth and fifth fingers was examined in each patient. According to Cutolo et al. patterns identified within the "SSc pattern" include: early, active and late. The NVC is the best technique to evaluate microvascular damage in SSc patients (Cutolo et al., 2006).

Table 1
SSc patients' epidemiological and clinical features.

Sex (female/male)	36/9
Age, years	45 ± 13.8
Disease duration, years	9 ± 6
DAI	3 ± 2
DSS	6 ± 3
dcSSc/lcSSc	28/17
SSc-specific autoantibodies n (%)	
Anti-topoisomerase I	24 (53)
Anticentromere	13 (29)
None	8 (18)
Capillaroscopic pattern n (%)	
Early	13 (28.9)
Active	12 (26.7)
Late	20 (44.4)

Disease Activity index (DAI); Disease Severity Scale (DSS); limited cutaneous SSc (lcSSc); diffuse cutaneous SSc (dcSSc).

Clinical assessment

Modified Rodnan total skin score (mRSS) was chosen as the most used method to assess skin induration in SSc. It is determined at a standardized location of 17 different sites of the body with a standardized pinching method and it is scored from 0 to 3 (Clements et al., 1995). Disease activity in SSc was measured using Disease Activity Index (DAI), which consists of 10 weighted variables: total skin score >14, scleroderma, digital necrosis, arthritis, total lung capacity <80%, erythrocyte sedimentation rate (ESR) >30, hypocomplementemia and change in cardiopulmonary, skin and vascular symptoms in the past month (Valentini et al., 2001). Disease severity was measured by Medsger Disease Severity Scale (DSS). The original scale assessed disease severity in 9 organs or systems, namely general health, peripheral vascular, skin, joint/tendon, muscle and gastrointestinal tract, lungs, heart and kidneys. Each organ/system is scored separately from 0 to 4 depending on whether there is no, mild, moderate, severe or end-stage involvement (Medsger et al., 1999).

Doppler ultrasound

SSc patients were placed for at least 15 min before the Doppler ultrasound examination in a temperature-controlled room at 22 + 0.4 °C. The size of the left and right kidneys and the flow in the aorta and renal arteries were evaluated to detect a morphologic abnormality or renal artery stenosis. During the measurements, the patients were supine and held their breath. Doppler ultrasound examinations were performed by the same senior nephrologist blinded to the clinical features of the patient. Renal Doppler ultrasound was performed using a Toshiba Aplio Ultrasound System SSA-790 equipped with a convex 3.5-MHz probe. Renal Doppler flow was obtained in 3 different interlobar arteries of both kidneys (mesorenal, superior, and inferior pole), guided by color-flow mapping. The Doppler gate width was kept small, and the angle of insonation was maintained at <60°. We used an anterior approach for detecting the renal artery origin and an oblique, lateral approach for the intermediate tract and intrarenal vessels. No aliasing was allowed in the interlobar arteries while the following parameters were measured: peak systolic velocity (PSV), end diastolic velocity (EDV), resistive index (RI), pulsatile index (PI), and systolic/diastolic ratio (S/D). RI was calculated as (peak systolic frequency shift- minimum diastolic frequency shift)/peak systolic frequency shift and the PI was calculated as (peak systolic frequency shift)/minimum diastolic frequency shift)/mean frequency shift. The PSV and EDV are expressed as cm/s. The mean value of 3 measurements of interlobar arteries from each kidney was calculated. For each patient, Doppler ultrasound parameters were calculated as the mean of measurements of both kidneys. While performing the renal Doppler examination, the operator evaluated the heart function. The Doppler examination was not performed in SSc patients with arrhythmia or tachycardia or bradycardia. Weighted kappa was used to evaluate the interrater reliability by the same observer. The kappa values for RI and S/D were 0.971 and 0.975, respectively. The intrapatient coefficient of variation for RI and S/D measurement was 1.3% and 1.4%, respectively. Calcium-channel blocker therapy was discontinued 72 h before the Doppler ultrasound (Rosato et al., 2012). The mean references value for normal RI in adults is determinate to be 0.60 ± 0.10, with 0.70 as the upper limit of normal (Parolini et al., 2009). Patients receiving iloprost therapy underwent Doppler examination the day before the next infusion.