

Intrarenal Hemodynamic Parameters Correlate with Glomerular Filtration Rate and Digital Microvascular Damage in Patients with Systemic Sclerosis

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Objectives: To evaluate intrarenal arterial stiffness by Doppler ultrasound and examine the correlation between renal Doppler indices, glomerular filtration rate, and digital microvascular damage in systemic sclerosis patients.

Methods: Thirty systemic sclerosis patients and 30 healthy controls were enrolled in this study. Doppler indices of intrarenal arterial stiffness, peak systolic flow velocity, end diastolic flow velocity, resistive index, pulsative index, and systolic/diastolic (S/D) ratio were measured on the interlobar artery of both kidneys. Glomerular filtration rate was measured using Tc^{99m} diethylenetriamine pentaacetic acid (DTPA). Equation 7 from the Modification of Diet in Renal Disease was used to estimate glomerular filtration rate. Nailfold videocapillaroscopy findings were classified as early, active, and late patterns.

Results: The intrarenal arterial stiffness, evaluated by Doppler indices, was higher in systemic sclerosis patients than healthy controls. In systemic sclerosis patients pulsative index ($r = -0.69$), resistive index ($r = -0.75$), and S/D ratio ($r = -0.74$) showed a negative correlation with measured glomerular filtration rate ($P < 0001$). High correlation ($P = 0008$) was observed between measured and estimated glomerular filtration rate ($r = 0.55$). Pulsative index, resistive index, and S/D ratio significantly increased with progression of capillaroscopic damage. Conversely, measured glomerular filtration rate significantly decreased with capillaroscopic damage progression.

Conclusions: Doppler indices of intrarenal arterial stiffness are noninvasive diagnostic tests to evaluate renal damage in SSc patients. Intrarenal arterial stiffness and glomerular filtration rate correlate with capillaroscopic microvascular damage.

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Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by endothelial dysfunction and fibrosis of the skin and internal organs. Vascular dysfunction is 1 of the hallmarks of SSc and involves both the macro- and the microvasculature (1).

Autopsy studies reveal occult renal pathology in 60% to 80% of SSc patients (2). Several forms of renal involvement are recognized in SSc (glomerulonephritis, chronic renal vasculopathy). The scleroderma renal crisis (SRC) has been reported in approximately 10% of SSc patients (3,4).

Serum creatinine is a poor marker of renal function in

SSc patients, while glomerular filtration rate (GFR), either measured by renal scintigraphy (mGFR) or estimated using equation 7 developed in the Modification of Diet in Renal Disease (MDRD) study (eGFR), is an important index of renal damage in asymptomatic SSc patients (5).

With the advent of new imaging techniques, the use of noninvasive techniques to evaluate renal damage in SSc patients has been investigated by several groups, and Doppler ultrasound is emerging as a screening modality for evaluating renal arterial stiffness. Doppler indices of interlobar arteries have been shown to be reliable markers of renal resistance and have been related to severity of target organ damage. The following Doppler indices have been used for evaluating renal damage: peak systolic flow velocity (PSFV), end diastolic flow velocity (EDFV), resistive (RI) and pulsatile (PI) indices, and S/D ratio. Intrarenal resistance increases (high values of RI, PSFV, PI, and EDFV) when stiffness or vasoconstriction prevails in interlobar arteries. Doppler indices have also been reported to be a predictor of declining renal function in patients with renal artery stenosis and renal disease (essential hypertension, diabetes, and nephroangiosclerosis). Increased arterial stiffness is known to be associated with scleroderma kidney disease. Rivolta and coworkers demonstrated that RI of main and interlobar vessels correlates with disease duration but not creatinine clearance (6). Aikimbaev and coworkers demonstrated that Doppler ultrasound is a useful and informative technique in the monitoring of SSc patients with renal involvement. Doppler indices of renal vascular resistance have been shown to be closely related to the duration of the disease, age, and plasma renin activity (7). Finally, Doppler ultrasound has been used successfully to evaluate the renal response to vasoactive drugs (8,9).

The aim of this study was to assess intrarenal arterial stiffness by Doppler ultrasound and to evaluate the correlation between renal Doppler indices, GFR, and digital microvascular damage in SSc patients.

METHODS

Subjects

Thirty patients (26 female and 4 male; median age, 44 years [range, 23-69], median duration of Raynaud's phenomenon, 8 years [range, 3-30], and median duration of SSc 5 years [range, 1-28]) fulfilling the American College of Rheumatology criteria for the classification of SSc (10) were enrolled in this study. Nine patients had limited cutaneous SSc and 21 had diffuse cutaneous SSc according to LeRoy and coworkers (11). The demographic characteristics and clinical features of the SSc patients are shown in Table 1.

None of the patients had received treatment with drugs interfering with tubular secretion or measurement of creatinine (eg, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, H2 blockers, and trimethoprim), parenteral prostanoids, phosphodiester-

Table 1 SSc Patients' Epidemiological and Clinical Features

Sex (female/male)	26/4
Age, yr (median and range)	44 (23-69)
SSc duration (median and range)	5 (1-28)
Raynaud's phenomenon duration (median and range)	8 (3-30)
dcSSc/lcSSc	21/9
Capillaroscopic pattern, <i>n</i> (%)	
Early	10 (33.3)
Active	7 (23.3)
Late	13 (43.4)

ase 5 inhibitors, or bosentan for at least 3 months before this study point.

Patients with obstructive kidney disease or renal artery stenosis and those with microscopic or macroscopic hematuria, abnormal urinary sediment, scleroderma renal crisis, history of glomerulonephritis or nephroureterolithiasis, antiphospholipid-associated nephropathy, coexistent Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-associated glomerulonephritis, dilated renal pelvis or atrophied kidney on ultrasonography, overt proteinuria, or elevated serum creatinine concentration ($>106 \mu\text{mol/L}$) were excluded.

Patients with a history of uncontrolled systemic hypertension, hyperlipidemia, heart failure, liver failure, diabetes mellitus, cerebrovascular diseases, peripheral vascular diseases, coagulopathy, and smokers and pregnant or breastfeeding women were excluded.

All SSc patients underwent treatment with calcium channel blockers (nifedipine 30 mg/d). Median duration of therapy was 7 years (range, 3-28). Therapy was discontinued 72 hours before the Doppler ultrasound and renal scintigraphy examination.

Thirty healthy controls (25 female and 5 male, median age 39 years [range, 26-63]) were also recruited.

The subjects' written consent was obtained according to the Declaration of Helsinki and the study was approved by the ethics committee of Sapienza University of Rome.

Doppler Ultrasound

SSc patients and healthy controls were asked to lie down for at least 15 minutes before the Doppler ultrasound examination. Renal Doppler ultrasound was performed using a Toshiba Aplio Ultrasound System SSA-790 (Tokio, Japan) equipped with convex 3.5-MHz probe. Renal Doppler flow was obtained from the interlobar arteries by placing the probe at 3 different positions (mesorenal, superior, and inferior pole) over both kidneys, guided by color flow mapping. Doppler ultrasound was performed after resting the subject in a temperature-controlled room at $22 \pm 0.4^\circ\text{C}$ for 15 minutes. Doppler ultrasound examinations were performed by a single investigator, blinded to clinical features of patient. The

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