Renal Parenchymal Thickness in Patients with Systemic Sclerosis Is Related to Intrarenal Hemodynamic Variables and Raynaud Renal Phenomenon

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ABSTRACT ***Objective.*** Renal involvement in systemic sclerosis (SSc) ranges from urinary abnormalities, reduction of glomerular filtration rate, and high renal resistive index, to scleroderma renal crisis. Intrarenal resistance indices are considered markers of renal SSc-associated vasculopathy. The aim of this study is to evaluate renal morphological variables, such as renal length, parenchymal thickness, atrophy index, and renal sinus in patients with SSc and to correlate it with renal function and hemodynamic variables.

Methods. There were 92 patients with SSc and 40 healthy controls (HC) enrolled in this study. Doppler and renal ultrasound (US) including renal length, parenchymal thickness, atrophy index, renal sinus, and intrarenal resistive index were measured in patients with SSc and HC.

Results. Renal US showed significant differences between HC and patients with SSc. The renal length (mm; 106.7 ± 5.1 vs 102.3 ± 8.4) and renal sinus (70.7 ± 7.9 vs 65.3 ± 7.7 mm) were significantly ($p = 0.001$) higher in HC than patients with SSc. The parenchymal thickness was significantly ($p = 0.004$) higher in HC than patients with SSc (18 ± 3.1 vs 16.3 ± 2.5 mm). Pulsatility index, resistive index, and systolic/diastolic ratio were significantly ($p < 0.0001$) lower in HC than patients with SSc. The renal length was significantly ($p = 0.004$) higher in diffuse cutaneous SSc (105 ± 8.4) than in limited cutaneous SSc (99.5 ± 7.5).

Conclusion. In SSc, kidney involvement is subclinical and is related to vascular injury, Raynaud phenomenon, and chronic hypoxia that can modify renal morphology. Serum creatinine is a poor marker of renal damage, and renal US could be a useful tool — together with Doppler — to evaluate renal involvement in a systemic and chronic disease such as SSc. (J Rheumatol First Release September 15 2019; doi:10.3899/jrheum.190165)

Key Indexing Terms:
RENAL ULTRASONOGRAPHY RENAL RESISTIVE INDEX RENAL LENGTH
ATROPHIC INDEX CORTICAL THICKNESS SYSTEMIC SCLEROSIS

Renal ultrasound (US) helps to estimate renal function in the general population by measuring variables such as longitudinal length and cortical thickness. Chronic kidney disease (CKD) is characterized by the reduction of glomerular filtration rate (GFR), urinary abnormalities, and renal US alterations[1]. Modifications related to CKD in US include renal length, parenchymal thickness, cortical echogenicity, atrophy index, and renal sinus. Renal length is normally used as a predictor of CKD and cortical thickness provides an estimate of renal function[2]. Renal Doppler ultrasound is a functional assessment of renal blood flow and it is used to evaluate macroscopic abnormalities such as presence of renal artery stenosis or changes of small vessels related to microscopic alterations[3].

Among the most studied variables, renal resistive index (RRI) represents renal vascular damage and correlates with early renal injury and with progression of chronic renal disease[4].

Systemic sclerosis (SSc) is an autoimmune disease characterized by endothelial dysfunction, collagen deposition, and fibrosis in the skin and internal organs. Raynaud phenomenon (RP) is the hallmark of the disease, generating vasospastic attacks in the digital arteries. Renal involvement in SSc ranges from mild proteinuria, reduction of GFR, and high resistive indices, to scleroderma renal crisis (SRC)[5]. In SSc, RRI correlates with GFR, digital ulcers (DU)[6], anti-RNA

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Accepted for publication May 30, 2019.

polymerase III antibodies[7], and SRC[8]. To date, no studies in SSc regarding morphologic renal US have been conducted, to our knowledge. The aim of our study is to evaluate renal US morphological variables such as renal length, parenchymal thickness, atrophy index, and renal sinus in patients with SSc and to correlate it with renal function and hemodynamic variables.

MATERIALS AND METHODS

There were 92 consecutive patients with SSc and 40 healthy controls (HC) enrolled in our study. All patients met the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative criteria for the classification of SSc[9]. Table 1 shows clinical characteristics of patients with SSc. Patients were excluded if they had a history of CKD, SRC, glomerulonephritis, urinary infections, renal artery stenosis, pulmonary disease, diabetes, cardiovascular diseases, kidney stones, hypertension (HTN), and smokers. All patients with SSc were treated with calcium channel blockers (nifedipine 30 mg/day). None of the patients were treated with immunosuppressive agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, or corticosteroid therapy at an equivalent dose of prednisone ≥ 10 mg/day.

The subjects' written consent was obtained according to the Declaration of Helsinki and the study was approved by the ethics committee of Sapienza University (n. 1163).

Laboratory variables. Laboratory investigation in patients with SSc and HC included serum creatinine, blood urea nitrogen, and urinalysis. Estimated GFR (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[10] previously validated in SSc, demonstrating a greater correlation than other formulae[11].

Clinical assessments. We evaluated the following data: disease duration, limited cutaneous (lc) and diffuse cutaneous (dc) subset[12], history of digital ulcers, Disease Activity Index[13], disease severity scale[14], and modified Rodnan skin score for the skin thickening[15]. Nailfold videocapillaroscopy equipped with a 500× optical probe was performed to evaluate scleroderma pattern (early, active, late)[16].

Renal and Doppler US. Renal US was performed using standard greyscale B-mode imaging in patients with SSc and HC using a Toshiba Aplio Ultrasound System SSA-790 equipped with a convex 3.5-MHz probe. Bilateral renal length was measured as the greatest pole-to-pole distance (mm) in the sagittal plane. Parenchymal thickness was obtained from at least 3 different points as the shortest distance from the renal sinus to the renal capsule. The atrophy index (AI) was obtained from the ratio between the longitudinal kidney diameter and the maximal diameter of renal sinus.

Doppler US analyzes blood velocity from the interlobar arteries by placing the probe at 3 different positions (mesorenal, superior, and inferior), evaluating peak systolic velocity (PSV) and diastolic velocity (DV). RRI is measured as RRI = (PSV–DV)/PSV. Pulsatility index (PI) was calculated as (peak systolic frequency shift–minimum diastolic frequency shift)/mean frequency shift), and systolic/diastolic (S/D) ratio was also measured.

Renal and Doppler US were performed by a single investigator, blinded to clinical features of patients.

Statistical analysis. All results are expressed as mean ± SD or median and range, as appropriate. Commercially available software (SPSS version 25.0) was used for the statistical analysis. The coefficient of skewness and the coefficient of kurtosis were used to evaluate normal distribution of data. Group comparisons were made by Student unpaired 2-tailed t test or Mann-Whitney U test, as appropriate. Multivariate logistic regression analyses were performed to investigate the association of eGFR with renal US variables. Pearson product-moment correlation coefficient or Spearman's rank correlation coefficient, as appropriate, were used to test for an association between numerical variables. The chi-square test or Fisher's exact test, as appropriate, were used to compare categorical variables. P values < 0.05 were considered significant.

Table 1. Characteristics of patients with systemic sclerosis (SSc).

Characteristics	Values
Age, yrs	54.1 ± 13.7
BMI, kg/m^2	22.7 ± 3.08
Blood glucose, mg/dl	82.3 ± 11
Systolic blood pressure, mmHg	123.7 ± 4.7
Diastolic blood pressure, mmHg	82.6 ± 4.8
Disease duration, yrs	8.7 ± 7.2
mRSS	11.3 ± 6.2
DAI	2.8 ± 2.4
DSS	5 ± 3.2
sPAP, mmHg	30.5 ± 8.3
DLCO, % of predicted	70.4 ± 16.5
dcSSc/lcSSc	47/45
DU, n (%)	51 (55.4)
Antitopoisomerase I, n (%)	50 (54.3)
Anticentromere, n (%)	38 (4.3)
Not specific antibodies, n (%)	4 (4.3)
Capillaroscopic pattern, early, n (%)	23 (25)
Capillaroscopic pattern, active, n (%)	35 (38)
Capillaroscopic pattern, late, n (%)	34 (37)

Data are expressed as mean ± SD, unless otherwise indicated. BMI: body mass index; mRSS: modified Rodnan skin score; DAI: Disease Activity Index; DSS: Disease Severity Scale; sPAP: systolic pulmonary arterial pressure; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; DU: digital ulcers.

RESULTS

No significant differences of serum level of creatinine were observed between HC and patients with SSc; conversely, eGFR was significantly higher (p = 0.038) in HC (101.6 ± 22.5 ml/min) than patients with SSc (93.1 ± 21 ml/min; Table 2).

Renal US showed significant differences about renal length, renal sinus, and parenchymal thickness between HC and patients with SSc (Figure 1). The renal length (106.7 ± 5.1 vs 102.3 ± 8.4 mm) and renal sinus (70.7 ± 7.9 vs

Table 2. Characteristics of patients with systemic sclerosis (SSc) and healthy controls (HC).

Characteristics	HC	SSc	p
Age, yrs	51.9 ± 19.7	54.1 ± 13.7	ns
Female, n (%)	35 (87.5)	79 (85.9)	ns
Serum creatinine, mg/dl	0.8 ± 0.19	0.77 ± 0.28	ns
eGFR, ml/min	101.6 ± 22.5	93.1 ± 21	0.038
Renal length, mm	106.7 ± 5.1	102.3 ± 8.4	0.001
Renal sinus, mm	70.7 ± 7.9	65.3 ± 7.7	0.001
Atrophic index	0.65 ± 0.07	0.64 ± 0.05	ns
Parenchymal thickness, mm	18 ± 3.1	16.3 ± 2.5	0.004
PI	1.13 ± 0.24	1.43 ± 0.29	< 0.0001
RRI	0.61 ± 0.05	0.70 ± 0.06	< 0.0001
S/D	2.56 ± 0.48	3.51 ± 0.79	< 0.0001

Except for p values and where otherwise indicated, data are expressed as mean ± SD. eGFR: estimated glomerular filtration rate; PI: pulsatile index; RRI: renal resistive index; S/D: systolic/diastolic ratio; ns: not significant.

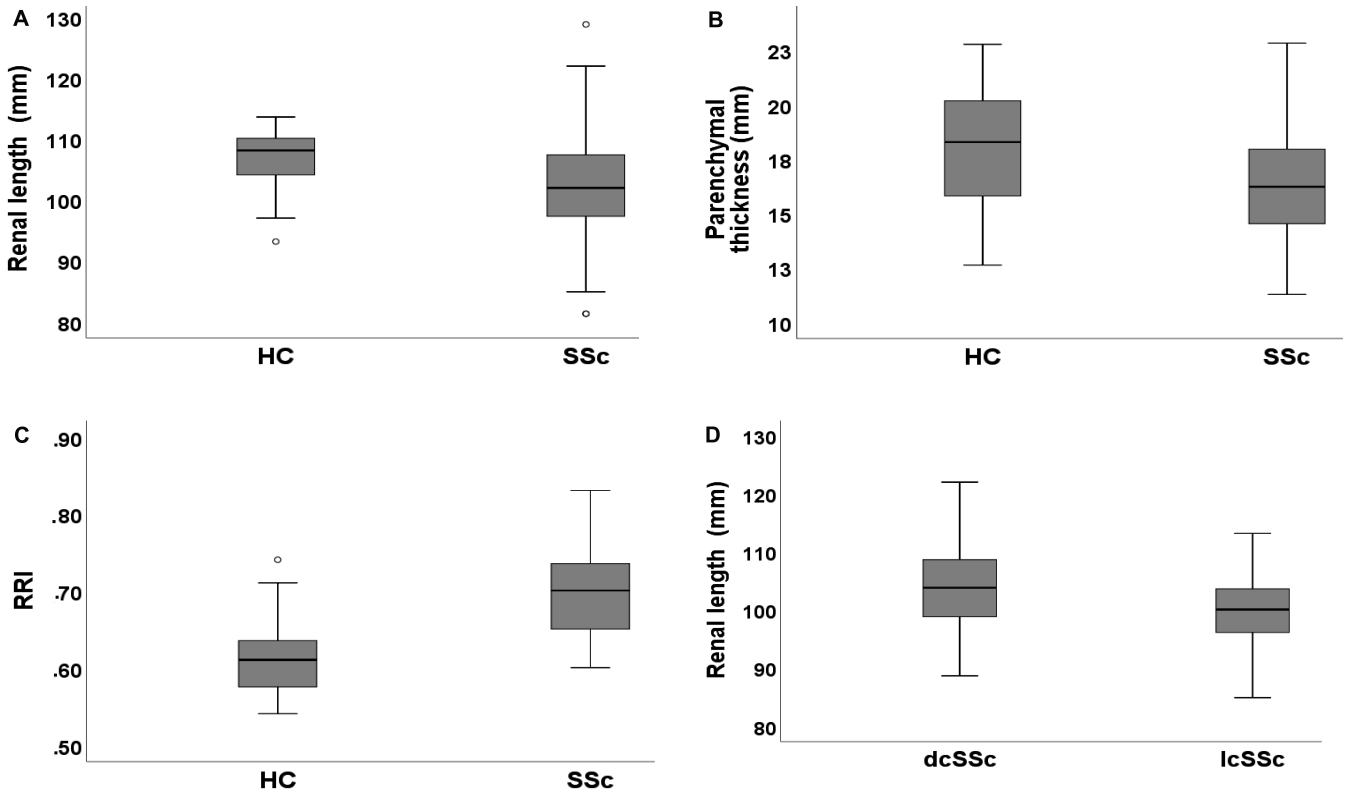

Figure 1. Ultrasound findings and Doppler indices in healthy controls (HC) and patients with systemic sclerosis (SSc). A. Renal length (mm). B. Parenchymal thickness (mm). C. Renal resistive index (RRI). D. Renal length (mm) differences between diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc).

65.3 ± 7.7) were significantly higher (p = 0.001) in HC than patients with SSc. The parenchymal thickness was significantly higher (p = 0.004) in HC than patients with SSc (18 ± 3.1 vs 16.3 ± 2.5 mm). No significant differences were observed about atrophy index between HC and patients with SSc (Table 2). When US variables are adjusted for eGFR, the differences between SSc and HC remain significant except for the AI: renal length (p = 0.001, β coefficient = 0.290) and renal sinus (p = 0.001, β coefficient = 0.281), and parenchymal thickness (p = 0.001, β coefficient = 0.274).

The Doppler examination showed significant differences of intrarenal indices (PI, RRI, and S/D) between HC and patients with SSc. These characteristics were significantly lower in HC than patients with SSc (Table 2): PI (1.13 ± 0.24 vs 1.43 ± 0.29), RRI (0.61 ± 0.05 vs 0.70 ± 0.06), and S/D ratio (2.56 ± 0.48 vs 3.51 ± 0.79; p < 0.0001).

The renal length was significantly higher (p = 0.004) in dcSSc (105 ± 8.4) than in lcSSc (99.5 ± 7.5). No significant differences in other renal US and Doppler variables were observed between dcSSc and lcSSc. No significant differences of renal US and Doppler variables were observed in patients with SSc with or without DU, in 3 capillaroscopic patterns.

In patients with SSc, CKD-EPI showed negative correlation with AI (r = –0.2, p = 0.041), PI (r = –0.36, p = 0.031), RRI (r = –0.29, p = 0.005), and S/D (r = –0.28, p = 0.007). CKD-EPI showed a significant positive correlation with parenchymal thickness (r = 0.33, p = 0.001) and renal length (r = 0.37, p < 0.0001).

DISCUSSION

In our present study, morphological US alterations were found between patients with SSc versus HC. In fact, patients with SSc showed a reduced renal length and parenchymal thickness versus HC. In CKD, several factors contribute to reduce renal size and parenchymal thickness, promoting chronic and irreversible renal damage. Among these factors, HTN is the most prevalent disease in causing renal vasoconstriction leading to CKD[17]. Endothelial dysfunction has a key role in the development of cardiovascular diseases and has the capacity to trigger a proinflammatory status with imbalance of endothelium-derived vasoactive and endothelium-derived vasoconstrictor factors. These alterations contribute to prothrombotic state, inflammation, vascular remodeling, and atherosclerosis[18].

Kidney function is characterized by glomerular filtration, renal tubular reabsorption, and secretion. When endothelial loss and/or dysfunction is present, processes of ultrafiltration and reabsorption are damaged, leading to a progressive glomerulosclerosis and renal hypoxia. CKD is therefore

caused by the continuous GFR reduction established through this process. Glomeruli and tubules are distributed in the parenchymal thickness and that is why, in the course of CKD, parenchymal thickness is reduced and can be observed through renal US[19]. In patients with SSc, the probable mechanism responsible for reducing parenchymal thickness and renal length versus HC is hypoxia secondary to recurrent episodes of RP vasospasm. It is well known that hypoxia enhances renal and systemic vasoconstriction[17].

Intrarenal hemodynamic variables such as RRI, PI, and S/D are influenced by arteriolosclerosis caused by vascular damage[20]. Geraci, *et al* have previously demonstrated that RRI reflects systemic vascular damage and may be considered as a marker of systemic vascular changes and a predictor of cardiovascular risk[21,22,23]. Also, RRI is associated with cardiovascular events and mortality in patients with CKD[24]. Because many SSc complications are vascular, we can assume that RRI reflects systemic vascular damage[25].

In SSc, renal resistance is elevated in the absence of HTN and RRI correlates with measured GFR and digital microvascular damage[6].

Further, regarding vasoconstrictor factors, in renal scleroderma–associated vasculopathy, endostatin — an angiogenic inhibitor — positively correlates with renal Doppler US variables, capillaroscopic damage, and DU. It correlates negatively with eGFR[26].

An imbalance between angiogenic and angiostatic factors is present in hypertensive patients. In 82 hypertensive patients, when compared to HC, Marek-Trzonkowska, *et al* found higher serum levels of endostatin that may cause microvascular damage with loss of arterioles and capillaries, thus favoring an increase of peripheral resistance[27].

We can speculate that in patients with SSc a similar mechanism to the one used in HTN can occur. Histological changes in scleroderma kidneys are very close to those observed in the course of malignant hypertension[28]. The pathophysiological vasospasm due to RP can produce an ischemic injury that primarily affects the small vessels, thus promoting interstitial fibrosis and cortical microcirculation dysfunction with subsequent glomerulosclerosis in the progression of renal damage[3].

In our study, eGFR showed a negative correlation with AI, PI, RRI, and S/D in patients with SSc. Our study showed that the atrophic index — an indirect anatomical US index used to evaluate the degree of atrophy in renal parenchyma — was no different when compared to HC. It has already been proved that intrarenal Doppler variables seem to be reliable markers of renal vascular damage also in SSc[6], while AI in combination with RRI could predict tubular interstitial involvement in glomerulonephritis[29]. In our patients with SSc, AI negatively correlates with eGFR and is related to renal length reduction. Moreover, in patients with SSc, tubules are secondarily affected by the vasa damaged from arterial occlusion[28].

In the renal longitudinal length is also included sinus fat, which does not represent functioning kidney tissue. In our study renal sinus showed a higher reduction in patients with SSc versus HC. Because AI represents a ratio between maximum renal sinus diameter and longitudinal diameter, our suggestion would be to also measure AI to better evaluate the renal functional tissue.

CKD-EPI showed a significant positive correlation with parenchymal thickness and renal length, providing new insights into the utility of renal US in SSc. Diagnosis of renal involvement is often based on serum creatinine, but creatinine cannot be a reliable marker of renal function. Although in SSc the CKD seems to have a benign prognosis, subclinical renal involvement has been demonstrated with autopsy in up to 80% of these patients[30]. There can be several causes for renal injury in SSc and they can range from renal causes such as SRC, antineutrophil cytoplasmic antibody–associated vasculitides, glomerulonephritides associates, and tubule interstitial damage to prerenal causes. Prerenal causes are linked to cardiac and pulmonary arterial involvement. In SSc, pulmonary arterial HTN (PAH) is associated with worse outcome and in most cases is associated with lcSSc[31]. Reem, *et al* found a lower measured GFR in patients with SSc with pulmonary vascular affection. They suggested that a pivotal role is to be attributed to endothelial dysfunction present in SSc with angiogenesis imbalance, capable of promoting vascular lesions with systemic microangiopathy and fibrosis[32]. In our study the renal length was significantly higher in dcSSc than in lcSSc. We can speculate that in our patients the slow renal damage present in lcSSc could present more vascular involvement, such as PAH.

In SSc, kidney involvement is subclinical and is related to vascular injury, RP, and chronic hypoxia that can modify renal morphology. Serum creatinine is a poor marker of renal damage and renal US could be a useful tool — together with Doppler — to evaluate renal involvement in a systemic and chronic disease such as SSc.

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