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Evaluation of estimated glomerular filtration rate and clinical variables in systemic sclerosis patients

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Key words
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Abstract. Objectives: The most important renal complication of systemic sclerosis (SSc) is scleroderma renal crisis (SRC). Many patients demonstrate less severe renal complications, most likely associated with reduced renal blood flow and a consequent reduction in glomerular filtration rate (GFR). The mechanism of this slowly progressive form of chronic renal disease is unclear. The aim of this study was to evaluate GFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the 7-variable Modification of Diet and Renal Disease (MDRD) equations in SSc patients and to correlate estimated GFR (eGFR) with clinical variables of the disease. Methods: 105 unselected and consecutive patients with SSc were enrolled. Serum creatinine was measured in all patients and GFR was estimated by 7-variable MDRD and CKD-EPI equations. Nailfold videocapillaroscopy was performed in all patients. Results: The mean value of eGFR evaluated by both 7-variable MDRD and CKD-EPI was significantly different ($p < 0.0001$) in the three capillaroscopic groups and correlated negatively with the severity of capillaroscopic damage (early: 95 ± 16 mL/min and 101 ± 12 mL/min, active: 86 ± 25 mL/min and 95 ± 17 mL/min, late: 76 ± 21 mL/min and 82 ± 21 mL/min). The mean value of eGFR evaluated by 7-variable MDRD (97 ± 23 mL/min vs. 74 ± 15 mL/min, $p < 0.0001$) and CKD-EPI (0.83 ± 0.20 mL/min vs. 0.68 ± 0.10 mL/min, $p < 0.0001$) was significantly higher in SSc patients without history of digital ulcers than in those with. Conclusion: We can conclude that in SSc patients without renal involvement, eGFR decreases with the progression of digital vascular damage.

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Introduction

Several patterns of renal pathology are recognized in patients with systemic sclerosis (SSc); almost all involve vascular abnormalities. The most important renal complication of SSc is scleroderma renal crisis (SRC). Many patients demonstrate less severe renal complications (e.g., abnormal renal vascular resistance indices), most likely associated with reduced renal blood flow and a consequent reduction in glomerular filtration rate (GFR). The mechanism of this slowly progressive form of chronic renal disease is unclear [1]. Therefore, chronic kidney disease (CKD) could be evaluated by estimated GFR (eGFR).

In patients with SSc, Kingdon et al. [2] showed that eGFR calculated using the 7-variable Modification of Diet in Renal Disease (MDRD) equation and Cockcroft-Gault formula correlated with GFR measured using a radioisotope clearance method. In SSc patients with normal serum creatinine (sCr), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) is a useful formula to assess GFR [3].

The aim of this study was to evaluate the presence of renal involvement in SSc patients by GFR estimated by 7-variable MDRD and CKD-EPI equations and to correlate eGFR with clinical variables of the disease.

Materials and methods

150 consecutive patients who met the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative criteria for SSc were enrolled in this study [4]. Of these, 105 patients were eligible (92 female and 13 male; mean age 54.9 ± 14.4 years). Patients with

elevated sCr, elevated blood urea, urinary tract infection, abnormal urinary sediment, glomerulonephritis, kidney stones, antiphospholipid-associated nephropathy, diabetes, cardiovascular disease (hypertension, myocardial infarction, arrhythmias, heart failure), hyperlipidemia, coagulopathy, SRC, or smokers were excluded.

Mean duration of Raynaud's phenomenon and disease were 10.4 ± 5.8 years and 9.1 ± 5.1 years, respectively. 60 patients had limited cutaneous SSc and 45 had diffuse cutaneous SSc as defined by Le Roy et al. [5].

All SSc patients underwent treatment with calcium channel blockers (nifedipine 30 mg/day). No patients were treated with immunosuppressive agents (e.g., cyclophosphamide or mycophenolate mofetil).

No patients were undergoing treatment with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers. Three patients had elevated sCr values.

Written consent was obtained according to the Declaration of Helsinki and the study was approved by the Ethics Committee of Sapienza University.

Laboratory parameters

Laboratory investigations included sCr, blood urea nitrogen, sodium, potassium, uric acid, and albumin. SCr was measured using a Jaffe alkaline picrate assay (Abbott Aeroset analyzer) [6].

Calculation of GFR

GFR was calculated using the 7 variables developed in the MDRD study. This formula uses demographic and serum variables but does not require urine collection: GFR = 170 × [sCr concentration (mg/dL)]$^{-0.999}$ × (age)$^{-0.176}$ × [serum urea nitrogen concentration (mg/dL)]$^{-0.17}$ × [albumin concentration (g/dL)]$^{0.318}$ × (0.762 if the patient is female) × (1.18 if the patient is black) [7].

CKD-EPI, expressed as a single equation, is GFR = 141 × min (sCr/k, 1)$^{\alpha}$ × max (sCr/k, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if black), where k is 0.7 for females and 0.9 for males, and 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) [8]. Finally, sclerodermic patients were classified in subgroups based on stages of renal failure according to the Kidney Disease Outcomes Quality Initiative guidelines [9].

Nailfold videocapillaroscopy

Nailfold videocapillaroscopy (NVC) was performed with a videocapillaroscope (Pinnacle Studio Version 8) equipped with a 500× optical probe. The nailfold of the 2nd, 3rd, 4th, and 5th finger was examined in each patient. According to Cutolo et al. [10], patterns identified within the "SSc pattern" include early, active, and late. NVC is the best technique to evaluate microvascular damage in SSc patients.

Clinical assessment

Skin involvement was assessed using the modified Rodnan skin thickness score (mRSS), a validated measure of skin thickening in SSc. In the mRSS, skin thickening is assessed at 17 body sites by palpation and rated on a scale with values of 0 (normal), 1 (mild), 2 (moderate) or 3 (severe skin thickening). The total skin score is the sum of the individual skin assessments in the 17 body areas, with a possible range of 0 to 51; the higher the score, the greater the extent and severity of skin thickening [11]. Disease activity in SSc was measured using the 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 > 30, hypocomplementemia and changes in cardiopulmonary, skin, and vascular symptoms in the past month [12]. Disease severity was measured by the Disease Severity Scale (DSS). This scale assesses 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 [13].

Table 1. Association between estimated glomerular filtration rate (CKD-EPI and 7-variable MDRD) and epidemiological and clinical features of SSc patients.

	CKD-EPI			7-variable MDRD		
	β	r	p-value	β	r	p-value
Age	–0.645	–0.73	< 0.0001	–0.635	–0.624	< 0.0001
Disease duration	–0.365	–0.240	< 0.05	–0.345	–0.291	< 0.05
RP duration	–0.152	0.298	0.08	0.102	–0.234	0.61
mRSS	0.416	0.149	0.27	–0.077	0.232	0.62
DAI	0.143	–0.330	0.07	–0.082	0.060	0.70
DSS	0.156	0.240	0.18	0.073	0.042	0.72

β = standard regression coefficient. In the analysis, the estimated glomerular filtration rate (CKD-EPI and 7-variable MDRD) was entered as a dependent variable. The following factors were entered as independent variables: age, disease duration, Raynaud's phenomenon duration, mRSS, DAI, and DSS. RP = Raynaud's phenomenon; mRSS = modified Rodnan skin thickness score; DAI = Disease Activity Index; DSS = Disease Severity Scale.

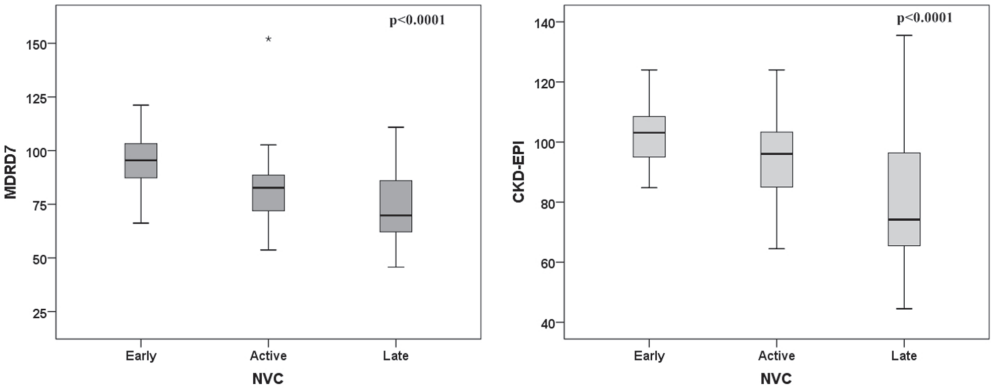

Figure 1. GFR evaluated by 7-variable MDRD and CKD-EPI equations in three capillaroscopic patterns.

Statistical analysis

All results are expressed as mean and standard deviation (SD). Commercial software was used for statistical analysis (SPSS version 20.0). The coefficients of skewness and kurtosis were used to evaluate normal distribution of data. Multiple regression analysis was done to assess the relationship between eGFR and demographic and clinical features (age, duration of disease, mRSS, DAI, DSS). Pearson product-moment correlation coefficient (r) was used to test for an association between numerical variables. Group comparisons were made by Student's unpaired 2-tailed t-test. χ^2- or Fisher's exact tests were used to compare categorical variables as appropriate. A p-value < 0.05 was considered significant.

Results

In all patients, sCr concentrations were normal (0.75 ± 0.17 mg/dL). Median 24-h proteinuria was 125 ± 34 mg/24 h. eGFR was 85 ± 22 mL/min and 91 ± 19 mL/min using 7-variable MDRD and CKD-EPI equations, respectively. Urinalysis showed normal urinary sediment in all SSc patients.

Age correlated negatively with eGFR when evaluated by 7-variable MDRD ($r = –0.59$, $p < 0.0001$) or CKD-EPI ($r = –0.63$, $p < 0.0001$). Duration of disease correlated negatively with eGFR when evaluated by 7-variable MDRD ($r = –0.29$, $p < 0.01$) or CKD-EPI ($r = –0.20$, $p < 0.05$). There were no correlations between eGFR and mRSS, DAI or DSS. These data are summarized in Table 1.

eGFR evaluated by 7-variable MDRD was not significantly different ($p > 0.05$) in patients with limited cutaneous SSc (81 ± 21 mL/min) or diffuse cutaneous SSc (90 ± 23 mL/min). Additionally, eGFR evaluated by CKD-EPI was not significantly different in patients with limited cutaneous SSc (85 ± 17 mL/min) or diffuse cutaneous SSc (99 ± 19 mL/min).

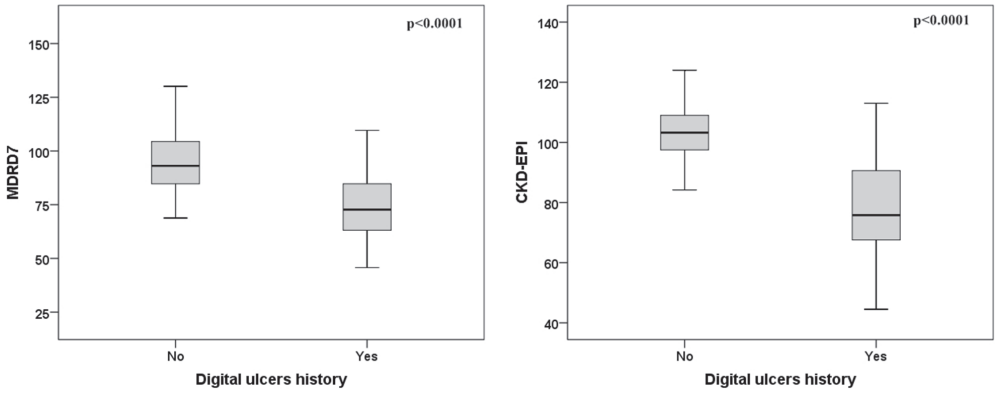

Figure 2. GFR evaluated by 7-variable MDRD and CKD-EPI equations in SSc patients with or without digital ulcer history.

The mean value of sCr concentrations was significantly different in the three capillaroscopic groups ($p < 0.0001$). The mean value of sCr concentrations increased with severity of capillaroscopic damage: early 0.64 ± 0.15, active 0.78 ± 0.17, and late 0.83 ± 0.14 mg/dL.

The mean value of eGFR evaluated by 7-variable MDRD or CKD-EPI was significantly different in the three capillaroscopic groups ($p < 0.0001$). The mean value of eGFR evaluated by 7-variable MDRD decreased with capillaroscopic damage severity: early 95 ± 16 mL/min, active 86 ± 25 mL/min, and late 76 ± 21 mL/min. Similarly, eGFR evaluated by CKD-EPI decreased with capillaroscopic damage severity: early 101 ± 12 mL/min, active 95 ± 17 mL/min, and late 82 ± 21 mL/min (Figure 1).

The mean value of eGFR evaluated by 7-variable MDRD or CKD-EPI was significantly different in SSc patients with or without digital ulcer (DU) history (Figure 2). The mean value of eGFR evaluated by 7-variable MDRD was significantly lower in SSc patients with DU history than in patients without DU history (74 ± 15 mL/min vs. 97 ± 23 mL/min, $p < 0.0001$). eGFR evaluated by CKD-EPI was significantly lower in SSc patients with DU history than in patients without (80 ± 17 mL/min vs. 105 ± 12 mL/min, $p < 0.0001$) (Figure 2). Conversely, sCr concentrations were significantly higher in SSc patients with DU history than in patients without (0.83 ± 0.20 mL/min vs. 0.68 ± 0.10 mL/min, $p < 0.0001$).

Discussion

This study evaluated GFR by the MDRD and CKD-EPI equations in SSc patients without clinical renal involvement. The MDRD formula underestimated GFR compared to CKD-EPI. MDRD has been validated in patients with kidney impairment while CKD-EPI has been used in different populations, including healthy subjects. The CKD-EPI equation has shown better performance in the higher ranges of GFR [7, 8]. Recently, Tent et al. [14] retrospectively evaluated the use of MDRD and CKD-EPI to monitor the long-term course of kidney function and to identify individuals with progressive kidney function loss. In their study, sCr at baseline was 1.30 ± 0.52, MDRD was 63 ± 24, and CKD-EPI was 70 ± 26. This shows acceptable performance of the CKD-EPI equation and a slight underestimation of mean function loss by the MDRD formula in the long-term follow-up of CKD patients.

GFR in patients with SSc appears to be normal or slightly reduced. The two formulas (7-variable MDRD and CKD-EPI) were found to be excellent indicators of renal function in patients with SSc.

Although age represents an independent risk factor for the reduction of eGFR, our study showed a negative correlation with disease duration. We can assume that eGFR, regardless of age, decreases with disease duration which in turn increases renal vascular damage.

We demonstrated that eGFR correlated negatively with severity of microvascular digital damage evaluated by NVC. eGFR was also lower in patients with a history of DUs than in those without.

Many complications of SSc are vascular, including pulmonary arterial hypertension and SRC. Structural vascular damage occurs in many vascular beds concurring to pulmonary, renal, cardiac, and gastrointestinal complications [15]. In contrast to other SSc complications, renal involvement is asymptomatic with the exception of SRC [16]. A significant reduction in renal blood flow and elevated plasma renin activity was found in SSc patients with normal filtration [17]. Autopsy studies have demonstrated renal histopathologic changes in the majority of patients with SSc in which SRC and hypertension have not developed. Subintimal proliferation and luminal narrowing of small- and medium-sized arteries in the kidney are the most prominent findings. Arterial changes coexist with varying degrees of tubule atrophy, interstitial fibrosis, and glomerular obsolescence.

Intrarenal vascular damage is present early on in SSc without clinical renal involvement. In a previous study, Rosato et al. [18] demonstrated that intrarenal arterial stiffness was higher in SSc patients than in healthy controls and correlated with severity of capillaroscopic damage. Intrarenal stiffness showed a negative correlation with eGFR. The authors demonstrated that Doppler indices of intrarenal stiffness were reliable markers to predict the occurrence of new DUs. The pathophysiological mechanism of this slowly progressive form of chronic renal disease in SSc is unclear. Reduced renal blood flow plays a key role in the reduction of GFR. In all renal manifestations of SSc, chronic renal vasculopathy seems to be the main pathogenic mechanism. We can suppose that, in the initial phases of renal damage progression, resistance indices increase and GFR is normal or slightly reduced. This initial reduction of GFR is linked more to reduced blood inflow to intrarenal vessels than to reduced glomerular filtration capacity [19, 20]. GFR is further reduced with the progression of intrarenal vascular damage. The deterioration of GFR is due both to the reduction in intrarenal arteries blood inflow and glomerular injury. Secondary ischemic changes in the glomeruli may occur with the progression of renal ischemic injury. Glomerular injury is the determining factor in the onset of pathological urinary sediment (hematuria and proteinuria) and increased sCr. The relevant factors mediating vascular changes in SSc include the renin-angiotensin system, profibrotic growth factors, transforming growth factor-β, connective tissue growth factor, and reactive oxygen species [21]. In a recent study, we demonstrated that intrarenal arterial elasticity showed a linear correlation with sympathetic activity in a group of SSc patients with normal sCr and high renal resistive index [22].

We can conclude that in SSc patients without renal involvement, eGFR decreases with severity of digital vascular damage. We can hypothesize that renal vascular damage, similar to Raynaud's phenomenon, represents the pathogenetic mechanism of the reduction of eGFR in early stages of the disease.

Conflict of interest

The authors declare no conflict of interest.

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