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ORIGINAL ARTICLE

Renal disease in systemic sclerosis with normal serum creatinine

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Abstract Prognosis of systemic sclerosis largely depends on involvement of internal organs. The aim was to evaluate renal impairment in patients with systemic sclerosis by measuring the Glomerular filteration rate (GFR) and then calculating the GFR using the Cockgroft and Gault formula and the Modification of Diet in Renal Disease Equation (MDRD) formula. Thirty one scleroderma patients were recruited from the Rheumatology and Rehabilitation Department, Cairo University Hospitals, mean age 43.25± 11.28 years, 31 healthy controls were included. Disease severity was done using Medsger score. GFR was measured using classical Gates method TC99mDTPA. The modified Cockcroft and Gault formula and equation 7 from the MDRD were used for calculation of GFR. All patients had within normal serum creatinine levels. A normal GFR (>89ml/min) was found in 45.1%. Gates method showed reduced GFR was reported in 54.9%. Stage II chronic kidney disease (60-89 ml/min) found 32.3%, and stage III (30-59 ml/min) in 22.6%. The formulae used showed reduction of GFR in 35.29% of those affected by the Cockcroft-Gault and in 41.17% of those affected using the MDRD. No correlation to patients' age, disease duration, or severity. A positive correlation was also reported between the presence of renal involvement and pulmonary vascular involvement p=0.04. Gates method showed reduction of the GFR in 54.9% of the systemic sclerosis patients. The formulae used were not as precise as the measured GFR in diagnosing all cases with subclinical renal involvement. Patients with systemic sclerosis should be screened for renal involvement irrespective of disease severity or duration.

Keywords Systemic sclerosis · Glomerular filteration rate · Cockcroft and Gault · Modification of Diet in renal disease equation

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Introduction

Systemic sclerosis is a clinically heterogeneous, systemic disorder characterized by alterations of the microvasculature, disturbances of the immune system and by massive deposition of collagen and other matrix substances in the connective tissue [1]. The incidence of systemic sclerosis (SSc) is between 2.6 and 20 to 28/million/year [2–5]. The overall female/male ratio was reported as 3:1 [2, 6, 7]. The female preponderance is most marked early in adult life (7:1), narrowing toward the fifth decade to 2-3:1 [8]. The average onset of SSc occurs between 40 and 50 years; but in women, it is in the late childbearing years between 30 and 39 [8]. It has been demonstrated that severe organ involvement often occurs early in the course of diffuse SSc which markedly affects survival [9]. Affection of the kidney in patients with systemic sclerosis reflects high morbidity and mortality risks. Clinically, 10-40% is affected but by autopsy, the figure is 80% [10]. The chronic form develops slowly over the years and leads in 50% of affected patients to a moderate reduction of kidney function, often clinically inapparent [11, 12]. The mechanism of renal affection in systemic sclerosis might be either

renal or pre-renal. Renal causes involving reduplication of elastic fibers, sclerosed glomeruli, tubular atrophy, and interstitial fibrosis reflecting the chronic changes of scleroderma represents one form. Pre-renal causes (associated with cardiac and pulmonary arterial involvement, vasculitis of renal artery, vasospastic disorder) as well as drugs. Inflammatory renal disorders can also occur, the main patterns of which are glomerulonephritis, vasculitis, or interstitial nephritis [13–15].

Researchers reported a reduction in the glomerular filteration rate that occurs in patients with SSc in the absence of sclerodermal renal crises [16]. However, examination of records of 544 patients with diffuse systemic sclerosis identified 32% with abnormal renal function but none developed renal disease requiring dialysis over a mean follow-up of 10 years [17], which reflects that chronic kidney disease seems to have a benign prognosis [18].

The cornerstone for diagnosing renal disease is the glomerular filteration rate (GFR) which is influenced by various factors including structural and/or functional kidney disease as well as patient's age, weight, and body surface area. The annual decline of GFR with age is approximately 1 ml/min/1.73 m^2 body surface area (BSA) beginning after the patient reaches 20-30 years of age; furthermore, a BSA of <1.4 m^2 impairs the sensitivity of GFR testing by either the measured or the calculated GFR [19–21]. The gold standard for GFR is inulin clearance, which requires a steady state plasma concentration and urine collection but is too costly and time-consuming for routine clinical practice. ^{51}Cr-EDTA clearance is a widely accepted and accurate substitute yet a very expensive screening tool [22, 23]. Subsequently, other isotope clearance methods have been validated, employing labeled iodothalamate and diethylenetriamine-pentacetic acid (DTPA) [24].

Our aim is to detect subclinical renal impairment in Egyptian patients with systemic sclerosis using the classical Gate's method Tc99mm DTPA [25] for measuring the GFR and correlate the reduction in the GFR to disease severity index. We will use the Cockcroft and Gault formula and the MDRD formula to calculate the GFR [16]. Finally, we are going to compare the results of the sensitivity of the measured to that of the calculated GFR regarding detection of subclinical renal impairment.

Patients and methods

Patients

Consenting patients fulfilling the criteria of the American Rheumatism Association for classification and diagnosis of systemic sclerosis [26] who presented at the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospitals, over a period of 2 years were screened for laboratory evidences of renal impairment by assessing their serum creatinine and blood urea concentrations as well as complete urinalysis. Patients with elevated serum creatinine, elevated serum urea, evidences of urinary tract infection, uncontrolled hypertension, lupus-scleroderma overlap, antiphospholipid syndrome (history of thrombotic events, recurrent abortions, or positive anticardiolipin antibody profile) were excluded from the study. Patients in whom measurement of creatinine and GFR were more than 8 days apart were also excluded. The demographic features of the study group and the medications are displayed in Table 1.

Thirty one age- and sex-matched healthy controls were included for comparison; they included 25 females (80.6%) and six males (19.4%) their ages ranged from 30 to 50 years (median 40 years, mean 40.65±6 years).

All participants gave informed consent for performing the clinical and laboratory requirements of the research. The study was approved by the ethics committee of the Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospitals. All participants were subjected to complete general as well as musculoskeletal clinical examination, full hematology profile, serum albumin, 24-h urine albumin, creatinine clearance; in addition, estimation of disease severity was done in the disease population using disease severity index [9] for assessing skin, joint, vascular as well as internal organ involvement. Serological surveys included antinuclear antibodies, anti-scleroderma-70, as well as reviewing the anticardiolipin antibodies. The required radiographic investigational techniques included X-ray for involved joints, echocardiography, upper gastrointestinal endoscopy, abdominal ultrasonography to assess renal echopattern and sizes as well as plain chest radiographs were performed if were not available. BSA was estimated using the Haycock normogram [27]. GFR in patients and controls was assessed using the Gates method for measurement of GFR using Tc99mDTPA *(25)* and calculated using two formulae; the Cockcroft-Gault formula and the MDRD *(16)*.

Technique

GFR measurement by Gates method [25]

GFR was measured using technicium 99m DTPA. The patient's weight and height are measured. Proper hydration is ensured by asking the patient to drink plenty of water and making sure of adequate urine output. Three to five mCi of Tc-99m DTPA are injected intravenously in a bolus form (1-2 ml).

Serial frames of the posterior view are acquired for 20-30 min immediately after tracer injection. The frame rate is

Table 1 Demographic features of the study group

Descriptive	Range	Mean±SD (median)
Age	19-68 years	43.25±11.28 years (45 years)
Disease duration	1-17 years	6.6±4.8 years (6 years)
Weight	42-104 kg	62.43±14.89 kg (62 kg)
Height	143.50-170 cm	159.75±6.60 cm (160 cm)
Body surface area	1.32-2.14 m^2	1.64±0.18 m^2 (1.6 m^2)
Patients	Number (31)	Percentage
Sex		
Females	27	87.1
Males	4	12.9
Types of systemic sclerosis		
Diffuse	12	38.7
Limited	16	61.3
Polymyositis-scleroderma overlap	3	9.7
Medications	Patients number	Percentage
Calcium channel blockers	20	64.5
Prednisolone	17	54.8
Cyclophosphamide	9	29
Methotrexate	9	29
Antihypertensives	7	16.1
Seldenafil	3	9.7

1-3 s/frame for about 1 min to assess perfusion (perfusion phase), 10-15 s/frame for about 4 min to assess function (function phase); and then, 10-30 s/frame to assess the urinary system (excretion phase). Dynamic acquisition of the data is continued for 6 min. DTPA is taken up by the kidney through glomerular filtration and is not secreted or reabsorbed by the renal tubules. Once it reaches the kidney, about 20% is accumulated, and the remainder flows away. That is, the extraction fraction of DTPA is 20%, a value approximating the filtration fraction. It is filtered through the glomerular membrane. Its high extraction fraction of approximately 50% makes it possible to acquire high-quality images [28].

Serum creatinine concentration: Serum creatinine was measured using a Roche/Hitachi Modular P analytical system with a blanked modification of the Jaffé reaction [29, 30].

Creatinine clearance measurement: creatinine concentration in urine *x* volume of urine per minute serum creatinine concentration

Calculation of the GFR

MDRD formula

GFR was calculated using equation 7 developed in the MDRD study [31]. This formula uses demographic and serum variables but does not require urine collection: GFR=170× [serum creatinine 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). The MDRD formula was developed using non-SI units. The following factors were employed to convert the database SI units to 88.5 urea micromole per liter to serum urea nitrogen milligram per deciliter, multiplied by 2.8; albumin gram per liter to gram per deciliter, divide by 10.

Cockcroft-Gault formula for calculation of creatinine clearance and GFR

Creatinine clearance was calculated using the modified Cockcroft and Gault formula [32]: [creatinine clearance = 1.2×(140−age in year) × weight (kilogram) × 0.85 (if female)] divided by serum creatinine concentration (micromole per liter). Normal reference ranges for creatinine clearance are for males from 55-146 ml/min/1.73 m^2; and for females, 52-134 ml/min/1.73 m^2.

For calculation of the GFR using the Cockcroft-Gault formula

A correction factor of 0.84, proposed by the MDRD study investigators [31] to convert creatinine clearance calculated by the Cockcroft and Gault formula to GFR.

The stratification of chronic kidney disease was performed according to the recommendations of Kidney Dialysis Outcomes and Quality Initiative Stages [33]

Statistical methods

Statistical analyses were performed using SPSS 13.0 statistical package. All continuous variables were expressed as ranges, median, mean ± SD, whereas categorical variables were expressed as frequencies and their percentages. Mann-Whitney *U* test was performed to see the association between continuous variables. Pearson correlation was done for parametric measures; nonparametric correlations were achieved using Spearman's correlation. *P* value of ≤0.05 will be considered as significant.

Results

Forty two systemic sclerosis patients were screened of whom 31 patients only satisfied the conditions required for the study (Table 1). Clinical descriptive data of the study population are represented in Table 2. The Disease Severity Index according to Medsger score [9] ranged from 3 to 16 with a mean of 9.35±3.65, median 8. None of our patients had laboratory evidences of azotemia, pyuria, hematuria, or casts in urine. We had seven patients (22.6%) with mild controlled hypertension on calcium channel blockers; none of the patients were on angiotensin-converting enzyme inhibitors, and one borderline diabetic patient (3.2%) with controlled or diuretics blood sugar (1 year duration, not requiring oral hypoglycemics or insulin and had no clinical or laboratory evidences of nephropathy). All the included patients had normal renal echopattern and sizes (10-12 cm, median 10.5 cm) as evaluated by abdominal ultrasonography. Serum creatinine concentration was within normal ranges in all patients included in the research (ranged from 0.6 to 1 mg for females; 0.6-1.2 mg/dl for males) with a mean of 0.7±0.16 mg/dl and median 0.7mg/dl. Serum albumin was within normal ranges in all patients (3-5 gm/dl) with a mean of 3.8±0.4 mg/dl, urine albumin/24 h ranged from 0 to 0.60 gm/24 h with a mean of 0.28±0.30 gm/24 h, median 0.18 gm/24 h. Serum creatine kinase was normal in all patients. Creatinine clearance ranged from 46 to 146 ml/min with a mean of 84.35±30.40 ml/min, median 75 ml/min. We had only two patients below the reference ranges; one with normal kidney function and serum creatinine and the other patient, having mild reduction in the measured GFR (60-89 ml/min). Because we had two SSc patients who had reduced creatinine clearance, we could not correlate this reduction statistically to other clinical parameters of the study group (Table 3). Autoantibody survey in the study group revealed antinuclear antibodies to be positive in four patients (12.9%), antitopoisomerase-1(antiscleroderma-70) to be positive in seven patients (22.58%); all patients had a negative antiphopholipid profile.

Systemic sclerosis patients under study had a measured GFR that ranged from 38.80±118 ml/min with a mean of 79.24±25.18 ml/min, median 79.77 ml/min, whereas the control group had a measured GFR that ranged from 84 to 140 ml/min with a mean of 107.46±15.50 ml/min, median 101 ml/min. Results revealed a statistically highly significant difference between patients and controls regarding the measured GFR with *p* value 0.001.

Further analysis of the data regarding the reduction in the measured GFR in terms of renal functional impairment according to laboratory reference ranges revealed:

Table 2 Clinical features in SSc patients under study according to Medsger score (2000)

Organ involvement	Number of patients (31)	Percentage
General features (Hb g%)		
Normal Hemoglobin	8	25.8
Anemia	23	74.2
Peripheral vascular disease		
Normal	2	6.5
Peripheral vascular disease	29	93.5
Skin tightness		
Mild	7	22.6
Moderate	16	51.6
Severe	6	19.4
End stage	2	6.5
Finger to palm distance		
0-0.9 cm	12	38.7
1-1.9 cm	1	3.2
2-3.9 cm	10	32.3
3.50	2	6.5
>5 cm	6	19.3
Muscle power		
Normal	18	58.1
Weakness	13	42
Gastrointestinal		
Normal	10	32.3
Esoph hypoperistalisis	21	67.8
Interstitial lung disease		
Normal	8	25.8
Affected	22	71
Pulmonary artery pressure		
Normal	23	74.2
Hypertension	8	25.8
Cardiac involvement		
Normal	25	80.6
Affected	6	19.4

Table 3 Laboratory features of the study group

Laboratory features	Range	Mean ± SD	Median
HB	7.10-15.50 g/dl	11.4±1.6 g/dl	11.4 g/dl
Serum albumin	2.7-5 g/dl	3.9±0.41 g/dl	3.8 g/dl
Serum creatinine	0.6-1.18 mg/l	0.7±0.16 mg/l	0.7 mg/l
Serum urea	11-55 mg/l	28.61±9.7 mg/l	28 mg/l
Creatinine clearance	46-146 ml/min	84.35±30.45 ml/min	75 ml/min
24 h urine albumin	0.00-0.58 g/24 h	0.28±0.30 gm/24 h	0.18g/24 h
GFR	38.80-118.84 ml/min	79.24±25.18 ml/min	79.77 ml/min

A measured GFR within normal (>89 ml/min) was found in 14 patients (45.1%) with normal kidney function and serum creatinine. Reduced GFR was reported in 17 patients (54.9%), it ranged from 60 to 89 ml/min with mild renal impairment in ten patients (32.3%) and ranged from 30-59 ml/min showing moderate functional impairment in seven patients (22.6%); none of our patients had severe renal impairment according to the Gates method for measuring the GFR (Table 4).

Looking for the relation between renal involvement in the study group assessed by the measured GFR and various disease parameters as regards disease pattern, disease duration, patients' age, general features of disease activity, as well as severity of organ involvement results showed that:

In the population of SSc patients who had a reduced measured GFR, we had eight patients with limited systemic sclerosis (25.80%), nine patients (29.03%) with diffuse systemic sclerosis, and one patient (3.2%) with overlap syndrome. Furthermore, no significant difference was found between SSc of the diffuse type where the measured GFR ranged from 38.80 to 72.48 ml/min with a mean of 57.94±13.40 ml/min, median 62.89 ml/min, and those with the limited type where the measured GFR ranged from 41.17 to 79.88 ml/min with a mean of 69.79±17.30 ml/min, median 79.66 ml/min, $p>0.05$ (Table 5).

Comparing means of the measured GFR in the groups of patients with SSc in relation to different clinical features of the disease, we found no statistically significant difference between patients with and without cardiac involvement $p=0.1$, hypertensive and normotensive patients $p=0.4$, patients with interstitial lung disease versus those without $p=0.7$, patients with and without GIT affection $p=0.4$.

Results showed a statistically significant difference between mean GFR measurement in SSc patients with and without pulmonary hypertension $p=0.04$.

The reduction in GFR had no significant correlation with disease duration ($p=0.8$), patient's age ($p=0.28$), general features of active disease ($p=0.1$), the severity of PVD ($p=0.75$), the severity of interstitial lung fibrosis ($p=0.6$), cardiac involvement ($p=0.9$), or GIT involvement ($p=0.5$), Rodnan score ($p=0.3$), muscle affection ($p=0.19$), disease severity judged by Medsger score($p=0.5$), as well as autoantibody profile in the study group (Table 6).

There was also lack of correlation between the different lines of treatment patients are receiving and impairment in renal function in terms of reduced measured GFR: calcium channel blockers ($p=0.4$), steroids ($p=0.3$), cyclophosphamide ($p=0.4$), methotrexate ($p=0.4$), vasodilators ($p=0.2$; Table 7).

However, there was a statistically significant correlation between the presence of a reduction in the measured GFR and presence of pulmonary hypertension in the population under study $p=0.03$.

Calculated GFR using Cockcroft-Gault formula showed impaired renal function in only six out of the 17 patients who had impaired renal function using the measured GFR, with a sensitivity of 35.29% and a specificity of 41.17%. On the other hand, using the MDRD formula, we found that the formula succeeded to detect seven out of the 17 patients with impaired renal function with a sensitivity of 41.17% and a specificity of 41.17%.

Looking for the correlation between the results of the two formulae to that of the measured GFR, we found a statistically significant correlation between the results of the measured GFR and the results of the MDRD ($p<0.05$) with no correlation between the measured GFR and results of the Cockcroft-Gault formula ($p=0.2$)

Discussion

Systemic sclerosis is an autoimmune disease characterized by fibrosis of the skin and internal organs. Renal involvement is a life-threatening complication of SSc which is clinically evident in 10-40% of cases, subclinical renal involvement exceeds this range whereby autopsy up to 80% of patients with SSc were found to have renal affection [28]. Consideration of renal function is essential before prescribing a wide range of therapies as medications might require dose reduction or alteration of dosing interval; cyclophosphamide and methotrexate are good examples

Table 4 Measured GFR in Ssc patients under study

Ranges	Number of patients (31)	Percentage
Normal >89 ml/min	14	45.19
Stage II chronic kidney disease 60-89 ml/min	10	32.3
Stage III 30-59 ml/min	7	22.6
Stage IV 15-29 ml/min.	0	0

[34]. Several researchers have studied renal involvement in systemic sclerosis; however, the prevalence of subclinical renal disease (non scleroderma renal crisis chronic kidney disease) in SSc was not frequently evaluated. [12, 16, 35]

Considering the fact that SSc is an uncommon disease among Egyptian population, many aspects of the disease usually pass underdiagnosed, especially subclinical organ affection. In the current study, we looked for evidences of subclinical renal affection in Egyptian patients with SSc.

Despite that none of our patients had clinical or laboratory evidence of renal functional impairment, except two having decreased creatinine clearance, the classical Gates method for measuring the GFR revealed a reduced GFR with evidences of renal functional impairment in 54.9% of the population under study (32.3% classified as stage II chronic kidney disease and 22.6% classified as stage III chronic kidney disease) with a highly significant difference between patients and controls regarding the measured GFR (p value <0.001). Renal involvement in the study group did not show specific correlation to the type of SSc. The reduction in the GFR had no correlation with disease duration, patient's age, and disease severity. This agrees with what has been reported by previous authors, none of the above mentioned parameters had significant influence on the GFR [35, 36].

However, the current study was the first to demonstrate that the presence of subclinical renal affection evaluated by the measured GFR significantly correlated with the presence of pulmonary vascular affection. This suggests that renovascular involvement might be a contributing factor in these cases and evidences that the main cause of vascular damage in SSc is endothelial injury induced by angiogenetic and angiostatic factors such as endothelin-1,vascular endothelial growth factor, and thrombomoduline, which leads to vascular lesions with generalized microangiopathy and systemic fibrosis [37–40]. Structural vascular damage in systemic sclerosis occurs in many vascular beds and contributes to pulmonary, renal, cardiac, and gastrointestinal complications [39, 40]. Considering the fact that renal involvement in systemic sclerosis might be due to pre-renal causes of which pulmonary arterial involvement might play a role, either through cardiac complications or vasculopathy of the pulmonary artery with an associating renal vasculopathy [41]. And based on what the authors have found in the current research where the presence of subclinical renal affection significantly correlated with the presence of pulmonary arterial involvement in the study group, there were significant reduction in the mean GFR measurement in SSc patients with pulmonary vascular involvement compared to those without. The authors suggest that patients with systemic sclerosis who have pulmonary arterial involvement should have the priority while screening patients by the measured GFR for evidence of renal involvement and because the gold standard for evaluation of pulmonary arterial hypertension is the right heart catheterization rather than echocardiography which is a screening test. Therefore, it is recommended that such investigative technique would be adopted in later studied in addition to renal Doppler studies and renal angiography for better evaluation of such association between renovascular and pulmonary vascular affection in SSC.

In daily clinical practice, performing an isotopic GFR on every patient at each clinic attendance is clearly not a practical proposition because it is considered relatively invasive technique besides financial considerations. Therefore, different formulae have been postulated for facilitating screening of renal functional impairment. Of these formulae, the Cockcroft–Gault formula and MDRD equation have been widely used as indirect estimates of renal function [42]. The precision and reliability of these formulas regarding kidney function are still discussed. In the current research, we aimed at evaluating the benefit of these formulae compared to measured GFR as regards their accuracy in detecting subclinical renal affection in patients with SSc. It was evident in our results that calculation of the GFR using the formulae was a less sensitive screening tool for detecting

Table 5 Comparing results of GFR measurement in patients with diffuse and limited SSc

Pattern of SSc	GFR range	Mean ± SD	Median	Significance
Diffuse (29.03%)	38.80-72.48 ml/min	57.94±13.40 ml/min	62.89 ml/min	0.06
Limited (25.80%)	41.17-79.88 ml/min	69.79±17.30 ml/min	79.66 ml/min	

Table 6 Correlation between the measured GFR and the various clinical and lab features of the study group

Clinical features	*R* value	Significance (two-tailed)
Age	0.3	0.28
Disease duration	0.02	0.89
General features	−0.31	0.12
Skin tightness-Rodnan score	−0.20	0.30
Medzger score (disease severity)	0.12	0.55
Peripheral vascular disease	0.06	0.75
Finger to palm test	0.10	0.60
Interstitial lung disease	0.09	0.64
Pulmonary hypertension	0.38	0.03*
Cardiac affection	0.003	0.98
Gastrointestinal involvement	0.13	0.50
Muscle involvement	0.26	0.19
Hemoglobin	0.27	0.17
MDRD	0.45	0.04*
Cockcroft-Gault	0.24	0.23
Antinuclear antibody	0.10	0.60
Anti-topoisomerase-1	0.23	0.2

*denotes significant positive correlation (*p* value less than 0.05)

early renal impairment in patients with SSc compared to measuring the GFR using the Gate's method. The Cockcroft-Gault formula could detect reduction in the GFR in 35.29% only of those patients who had an actual reduction in the measured GFR also the MDRD detected reduction in the GFR in 41.17% of those with actual reduction in the measured GFR using the Gate's method.

Kingdon and coworkers were the first to evaluate renal functional impairment in patients with systemic sclerosis using both the measured GFR using Cr51 EDTA and the calculated GFR using the above mentioned formulae. They studied 26 patients with SSc median age 58 years, age range 12-80 years, 18 out of 19 patients (94.73%) analyzed with a serum creatinine concentration less than the upper limit of the normal range had a measured GFR outside the normal range. They illustrated that the use of serum creatinine as an index of renal function without a correction factor for sex, age, and muscle mass may be misleading [16]. As renal function declines, the tubular secretion of creatinine increases increasing urine creatinine, this reaches its maximum at serum creatinine 2 mg/dl. This increases falsely the creatinine clearance leading to overestimation of the GFR. Therefore, using laboratory reference ranges without a correction factor for age, sex, and body mass cannot be relied upon [43, 44].

Table 7 Correlation between drugs taken and reduction in GFR

Drugs used	*R* value	Significance
Calcium channel blockers	−0.13	0.4
Prednisone	−0.17	0.3
Cyclophosphamide	0.1	0.4
Methotrexate	−0.1	0.4
Vasodilators	0.2	0.2

This was further confirmed in our study where all the studied patients with SSc had within normal serum creatinine concentrations, yet a reduced GFR with evidences of renal functional impairment was found in 54.9% of them. Furthermore, creatinine clearance in the studied population was within normal ranges for all patients except two patients (46 ml/min) who also happened to have normal serum creatinine with reduced GFR in only one patient range 60-89 ml/min (stage II). The relative contribution of tubular secretion of creatinine and extrarenal elimination of creatinine to the measured creatinine clearance increases with falling GFR which exaggerates the discrepancy between creatinine clearance and measured GFR [19, 45]. Therefore, we cannot rely on serum creatinine measurements for detecting early renal involvement in patients with systemic sclerosis, and still the GFR will be our cornerstone for evaluation.

As regards using the formulae for screening to detect early renal affection, the authors found that the formulae did not detect all affected cases furthermore, 80% of the cases detected by the formulae were having stage III chronic kidney disease. This was also reported in other recent researches where the formulae correctly showed decreased kidney function in stages III and IV only of chronic kidney disease [42] yet, they were not reliable when patients were in end-stage chronic kidney disease especially when using the MDRD equation for which the authors could not find an explanation [46, 47]. This controversy regarding results of the formulae was explained

in recent studies by the fact that the accuracy and extent to which the results of a formula can be extrapolated to a population of interest depends on the population in which any formula was derived. Cockcroft and Gault derived their formula from creatinine measurements in a cohort of patients of whom only 4% were female, which represents a limitation especially in systemic autoimmune diseases in which female population represents the majority of those affected. Extremely small size is as important as female sex. Our study population was predominantly of the female gender as systemic sclerosis is more common in the female population together with consideration of the possible contribution of racial as well as ethnic factors in the study group. This might in fact have contributed to the reliability of the formula in detection of cases of systemic sclerosis patients with impaired kidney function. Accordingly, the MDRD formula is apparently more accurate in detecting reduced GFR in SSc patients with renal impairment, and this was further emphasized in recent studies, where Wielosz and coworkers reported that the MDRD and serum cystatin C levels were more accurate measures of evaluation of the GFR in SSc patients with renal disease than the Cockcroft-Gault formula [48]. However, despite that the Cockcroft–Gault formula and the MDRD equation are widely used as indirect estimates of renal function, researches are directed recently towards revisions of the original formula and incorporating a number of clinical and demographic variables for more reliable results [22, 28, 47].

Conclusion

Impairment of renal function in patients with SSc can occur in the presence of normal serum creatinine.

The measured GFR remains the cornerstone in evaluation of renal function in patients with systemic sclerosis especially the chronic subclinical forms in which serum creatinine and other parameters are normal. SSc patients with pulmonary vascular involvement might be at a greater risk of developing early renal involvement. Calculation of the GFR using the studied formulae was a less reliable method compared to the classic Gates method.

Findings illustrated in this research suggest that a basal GFR should be measured in patients with systemic sclerosis to be followed throughout the disease course. Screening for renal involvement should be irrespective of disease duration or disease severity especially in those with pulmonary vascular affection. Renal Doppler studies and angiography should be considered in SSc patients with reduced measured GFR to rule out early renovascular involvement in these patients. Cardiac catheterization can be used in later studies in conjunction with renal angiography for more detailed understanding of the currently reported association between renovascular and pulmonary vascular involvement in SSC.

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Disclosures None.

References

1. Haustein UF (2002) Systemic sclerosis-scleroderma. Dermatol Online 8(1):3
2. Silman AJ (1997) Scleroderma—demographics and survival. J Rheumatol 24:58–61
3. Altman RD, Medsger TA Jr, Bloch DA, Beat AM (1991) Predictors of survival in systemic sclerosis (scleroderma). Arthritis Rheum 34:403–413
4. Silman AJ, Jannini S, Symmons D, Bacon P (1988) An epidemiological study of scleroderma in the West Midlands. Br J Rheumatol 27:286–290
5. Olschewski H, Ghofrani HA, Walmrathh D (1999) Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med 160:600–607
6. Haustein UF, Albrecht M (1993) Zur Epidemiologie und Klinik der systemischen Sklerodermie. Z Hautkrankh (H+G) 10:651–658
7. Steen VD, Medsger TA Jr (1990) Epidemiology and natural history of systemic sclerosis. Rheum Dis Clin North Am 16:1–10
8. Medsger TA, Masi AT (1971) The epidemiology of systemic sclerosis (scleroderma). Ann Intern Med 74:714–721
9. Steen VD, Medsger TA Jr (2000) Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 11:2437–2444
10. Steen VD (1996) Scleroderma renal crisis. Rheum Dis Clin North Am 22:861–878
11. Steen VD, Medsger TA, Osial TA, Ziegler GL, Shapiro AP, Rodnan GP (1984) Factors predicting development of renal involvement in progressive systemic sclerosis. Am J Med 76:779–786
12. Guerini S, Cavazzana I, Venturelli C, Rozzi M, Turina S, Sottini L, Tardanico R, Franceschini F, Scolari F (2007) Renal involvement in systemic sclerosis. G Ital Nefrol 24(4):295–310
13. Denton CP (2008) Renal manifestations of systemic sclerosis—clinical features and outcome assessment. Rheumatology 47 (Supplement 5):v54–v56
14. Arnaud L, Huart A, Plaisier E et al (2007) ANCA-related crescentic glomerulonephritis in systemic sclerosis: revisiting the 'normotensive scleroderma renal crisis'. Clin Nephrol 68:165–170
15. Kamen DL, Wigley FM, Brown AN (2006) Antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis in scleroderma: a different kind of renal crisis. J Rheumatol 33:1886–1888
16. Kingdon EJ, Knight CJ, Dustan K, Irwin AG, Thomas M, Powis SH, Burns A, Hilson AJW, Black CM (2003) Calculated glomerular filtration rate is a useful screening tool to identify scleroderma patients with renal impairment. Rheumatology 42:26–33
17. Steen VD, Syzd A, Johnson JP et al (2005) Kidney disease other than renal crisis in patients with diffuse scleroderma. J Rheumatol 32:649–655

18. Penn H; Denton C.P. Diagnosis, management and prevention of scleroderma renal disease (2008) Curr Opin Rheumatol 20(6): 692-696
19. Mitch WE, Walser M (1978) A proposed mechanism for reduced creatinine excretion in severe chronic renal failure. Nephron 21:248–254
20. El Nahas AM, Coles GA (1986) Dietary treatment of chronic renal failure: ten unanswered questions. Lancet 1:597–600
21. Wibell L, Bjorsell-Ostling E (1973) Endogenous creatinine clearance in apparently healthy individuals as determined by 24 h ambulatory urine collection. Ups J Med Sci 78:43–47
22. Coresh J, Auguste P (2008) Reliability of GFR formulas based on serum creatinine, with special reference to the MDRD Study equation. Scand J Clin Lab Invest Suppl 241:30–38
23. Chantler C, Garnett ES, Parsons V, Veall N (1969) Glomerular filtration rate measurement in man by the single injection methods using [^{51}Cr] EDTA. Clin Sci 37:169–180
24. Perrone RD, Steinman TI, Beck GJ et al (1990) Utility of radioisotopic filtration markers in chronic renal insufficiency: simultaneous comparison of 125I-iothalamate, 169Yb-DTPA, 99mTc-DTPA, and inulin. The Modification of Diet in Renal Disease Study. Am J Kidney Dis 16:224–35
25. Gates GF (1982) Glomerular filtration rate:Estimation from fractional renal accumulation of Tc-99m DTPA (stannous). AJR 138:565–570
26. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee (1980) Arthritis Rheum 23: 581–590
27. Haycock GB, Schwartz GJ, Wisotsky DH (1978) Geometric method for measuring body surface area: a height–weight formula validated in infants, children, and adults. J Pediatr 93:62–66
28. Yusuke Inoue, Manabu Minami, Kuni Ohtomo. Isotopic scanning for Renal Disease (2004) Kidney Trans 15: 3, 257-264.
29. Bartels H, Bohmer M, Heierli C (1972) Serum creatinine determination without protein precipitation. Clin Chim Acta 37:193–197
30. O'Leary N, Pembroke A, Duggan PF (1992) A simplified procedure for eliminating the negative interference of bilirubin in the Jaffe reaction for creatinine. Clin Chem 38:1749–1751
31. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461–470
32. Gault MH, Longerich LL, Harnett JD, Wesolowski C (1992) Predicting glomerular function from adjusted serum creatinine. Nephron 62:249–256
33. National Kidney Foundation Kidney Disease, Outcome Quality Initiative Advisory Board. Clinical Practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Kidney disease quality initiative: Staging system and action planes for chronic kidney disease. Am J of kidney disease, 2002; 39 (2suppl2): SI-246
34. Steen V.D., Renal involvement in systemic sclerosis (1994) Clin Dermatol. Apr-Jun 12(2):253-258.
35. Gupta R., Bammigatti C., Dinda A.K., Marwaha V., Gupta S. Prevalence of renal involvement in Indian patients with systemic sclerosis (2007). Ind Journ Med Sci 61 (2); 91-96.
36. Desai A, Goldschmidt RA, Kim GC (1990) Sequential development of pulmonary renal syndrome associated with c-ANCA 3 years after development of anti-GBM glomerulonephritis. Neph Dial Tran 22(3):926–929
37. Guiduicci S, Matucci Cerinic M (2009) Vasculogenesis and angiogenesis: vascular damage in systemic sclerosis. Rheumatismo 61(2):81–83
38. Solanilla A, Villeneuve J, Auguste P, Hugues M, Alioum A, Lepreux I et al (2009) the transport of high amounts of vascular endothelial growth factors by blood platelets underlines their potential contribution in systemic sclerosis angiogenesis. Rheumatology (Oxford) 48(9):1036–1044
39. Papaioannou AL, Zakynthinos E, Kostikas K, Kiropoulos T, Koutsokera A, Ziogas A et al (2009) Serum VEGF levels are related to the presence of pulmonary arterial hypertension in systemic sclerosis. BMC Pulm Med 9:9–18
40. Fleming JN, Nash RA, Mahoney WM Jr, Schwartz SM (2009) Curr Rheumatol Rep 11(2):103–110
41. Denton CP, Black CM, Abraham DJ (2006) Mechanisms and consequences of fibrosis in systemic sclerosis. Nat Clin Pract Rheumatol 2:134–144. doi:10.1038/ncprheum0115
42. Vytautas Kuzminskis, Inga Skarupskienė, Inga Arūnė Bumblytė, Žydrūnė Kardauskaitė, Jurgita Uogintaitė. Comparison of methods for evaluating renal function (Data of Kaunas University of Medicine Hospital in 2006). Online article, published May 2007.
43. Perazella M.A., Reilly R.F. Chronic kidney disease: a new classification and staging system (2003) Hospital Physician; 18-22. www.Turner-white.com
44. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
45. Morgan DB, Dillon S, Payne RB (1978) The assessment of glomerular function: creatinine clearance or plasma creatinine? Postgrad Med J 54:302–310
46. Broekroelofs J, Stegeman CA, Navis GJ et al (2000) Creatinine-based estimation of rate of long term renal function loss in lung transplant recipients. Which method is preferable? J Heart Lung Trans 19:256–262
47. Verhave J. C., Balje-Volkers, C. P; Hillege, H. L., DE Zeeuw, D., DE Jong, P. E. The reliability of different formulae to predict creatinine clearance (2003) J Int Med 253(5); 563-573
48. Wielosz E, Dryglewska M, Majdan M (2009 Aug) Antiphospholipid antibodies and kidney involvement in patients with systemic sclerosis. Clin Rheumatol 28(8):881–882