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ORIGINAL ARTICLE

Evaluation of microalbuminuria in patients with systemic sclerosis as an indicator of early renal damage and increased morbidity

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KEYWORDS

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Abstract *Introduction:* Renal involvement and systemic vascular damage have been shown to be significantly affecting prognosis in systemic sclerosis.

Aim of work: Microalbuminuria detection in SSc patients as an indicator of early renal involvement and its correlation with various SSc clinical, laboratory parameters and severity of organ systems' damage assessed by Scleroderma Assessment Questionnaire.

Patients and methods: Forty SSc patients (33 females and 7 males) with mean age of 27.48 ± 12.56 years and mean disease duration of 6.2 ± 4.14 years were included. Twenty-four (60%) had lSSc; 13 (32.5%) had dSSc and 3 (7.5%) patients had SSc sine scleroderma.

Results: Eight (20%) had microalbuminuria and 9 (22.5%) patients had decreased creatinine clearance. Albumin/creatinine ratio was significantly higher among dSSc patients compared to those with lSSc and SSc sine scleroderma ($X^2 = 9.077$; $p = 0.01$). Albumin/creatinine ratio showed significant positive correlations with telangiectasia ($r = 0.322$; $p = 0.04$) and mRodnan's skin score

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($r = 0.352$; $p = 0.026$) and negative correlations with inter-incisor distance ($r = -0.525$; $p = 0.001$) and pleurisy ($r = -0.446$; $p = 0.004$). Albumin/creatinine ratio correlated significantly and positively with IMSS and IDS indices of SAQ ($r = 0.378, 0.32$; $p = 0.016, 0.044$, respectively). SSc patients with microalbuminuria showed significantly higher mean IDS than those without (1.058 vs. 0.631, $p = 0.04$). No statistically significant correlations were found between creatinine clearance and the different demographic, clinical features and the indices of SAQ.

Conclusion: Microalbuminuria compared to creatinine clearance may be a more sensitive indicator of early renal affection and predictor of increased morbidity.

1. Introduction

Systemic sclerosis (SSc) is a generalized disorder of connective tissue which is characterized by thickening and fibrosis of the skin and by distinctive forms of involvement of internal organs; notably the heart, lungs, kidneys and gastrointestinal tract [1].

Renal involvement and systemic vascular damage have been shown to be significantly affecting prognosis in SSc. Survival rates of patients with SSc are critically dependent on the presence and severity of renal involvement. Different types of kidney disease have been described [2].

An increased excretion of total urinary protein is a classical hallmark of renal diseases. Assay of total urinary protein is non-specific and insensitive and the advent of sensitive and specific assay for albumin, the dominant urinary protein in patients with renal glomerular dysfunction, has enabled the detection of abnormalities at an earlier stage of the disease process [3].

It is often difficult to assess damage to the renal and systemic vasculature in SSc patients. Using detailed urinary protein analysis is thought to detect scleroderma renal disease at an early stage and to assess systemic vasculopathy. Abnormal urinary protein excretion is associated with parameters of increased morbidity such as diffuse cutaneous disease and visceral involvement. Systemic sclerosis patients with microalbuminuria have a worse prognosis than those with normal renal function [4]. Normal urinary protein excretion is up to 150 mg/day. Microalbuminuria refers to the excretion of a very small amount of proteins, primarily composed of albumin that could not be detected by routine methods, i.e., dip stick method [5]. According to the American Diabetes Association, microalbuminuria is defined as urinary albumin excretion (UAE) of 30–299 mg/ 24 h or albumin/creatinine ratio of 30–299 μg/mg creatinine [6].

In SSc, the inflammatory process is very mild and organ damage develops often insidiously and slowly. Mostly used diagnostic procedures are not sensitive enough to detect organ damage in the early phase and to notice the minimal change in damage or function over time. Symptoms and subjective patient's complaints are very important in the evaluation of disease status in SSc. Scleroderma Assessment Questionnaire (SAQ) demonstrates the severity of damage of the different organ systems and the degree of change in the severity of affection over time [7].

The objective is microalbuminuria detection in SSc patients and its evaluation as an indicator of early renal involvement and to find out its correlation with the various SSc clinical, laboratory, radiological disease parameters and severity of organ systems' damage assessed by SAQ.

2. Patients and methods

2.1. Study population

Forty SSc patients (33 females and 7 males) with a mean age of 27.48 ± 12.56 years and mean disease duration of 6.2 ± 4.14 years, fulfilling SSc criteria described by *The Subcommittee for Scleroderma Criteria of the American College of Rheumatology* [8], attending the Rheumatology and Rehabilitation Department, Kasr El-Aini Hospitals, Cairo University, comprised the study group.

- SSc patients were subdivided according to the classification subsets of SSc patients, which is based on the extent of skin affection. Twenty-four (60%) had limited SSc; 13 (32.5%) had diffuse SSc [9] and 3 (7.5%) patients had SSc sine scleroderma [10].
- *Exclusion criteria:* Localized forms of scleroderma, various forms of pseudo-scleroderma, SSc patients with associated arterial hypertension, diabetes mellitus, cardiovascular diseases including pulmonary hypertension, heart failure, pre-existing renal disease (e.g., renal agenesis or polycystic kidney disease), urinary tract infection and hematuria. Other conditions that may invalidate urine albumin excretion, e.g., exercise within 24 h, acute febrile illness and pregnancy.

All patients included in the study were subjected to:

(A) Full history taking including Scleroderma Assessment Questionnaire (SAQ) [11].
- SAQ consists of 23 questions divided into 4 subgroups: 4 items related to vascular, 6 items to respiratory, 5 items to gastrointestinal and 8 items to musculoskeletal dysfunctions. Some items are derived from the Systemic Sclerosis Questionnaire (SySQ), with permission of the authors. The range of all indices is from 0 to 3. Answering categories: (A) intensity of symptoms (no = 0, some = 1, moderate = 2, very intensive = 3), (B) frequency of symptoms (never = 0, sometimes = 1, frequently = 2, always = 3) and (C) ability to perform activities (without difficulty = 0, with some difficulty = 1, with much difficulty = 2, not able to do = 3). The Index of Vascular Status (IVS), Index of Respiratory Status (IRS), Index of Gastrointestinal Status (IGS) and Index of Musculoskeletal Status (IMSS) are calculated by dividing the total score for a particular group by the number of questions for

that group. A higher index value indicates more severe damage of a particular organ system. By dividing the total score for the entire questionnaire by the number of questions, the Index of Disease Status (IDS) was obtained.

(B) Thorough general (including interincisor and finger to palm (in flexion) distances in cm [12], cardiopulmonary, abdominal, musculoskeletal and neurological system examinations.

(C) Skin examination including calcinosis, digital lesions and assessment of skin sclerosis severity by modified Rodnan's skin score (mRss) [13].

(D) Vascular system examination including Raynaud's phenomenon, digital pitting scar, digital gangrene and bone resorption.

(E) Laboratory investigations:

- Complete blood picture was done by Cell Dyne 1800. ESR was done by Westergren technique.
- Liver enzymes (AST, *n*: 0–41 U/L and ALT, *n*: 0–41 U/L).
- Kidney functions: serum Creatinine (*n*: 0.32–1.2 mg/dl).
- Muscle enzymes (CPK, *n*: 0–195 U/L and LDH, *n*: 240–480 U/L).
  - All chemical analysis of blood and creatinine in urine were done on Hitachi 917 by a kit purchased from Roche Diagnostic GmbH, D-68298 Mannheim.
- ANAs: positivity and pattern were identified by indirect immunofluorescence (IIF).
- Urinalysis
  - Complete urine analysis (physical appearance, chemical constitutes and microscopic contents).
  - 24 h urinary protein (*n*: up to 0.15 gm/24 h): was assayed by turbidimetry (1 cc of urine + 3 cc of trichloroacetic acid) where turbidity is compared to a standard for detection of macroalbuminuria.
  - Creatinine clearance (*n*: 80–120 ml/min): was calculated using the following equation, where Cx is creatinine clearance, Px is the plasma concentration of the creatinine, Ux is the urinary concentration of creatinine and V is the urine flow rate. It is considered as a measure of glomerular filtration rate.

$$Cx = \frac{Ux \times V}{px}$$

  - Urinary albumin/creatinine ratio: was assayed by Nephelometry BN ProSpec by kits purchased from Siemens HealthCare Diagnostic Products GmbH. Emil-Von-Behring-Str.76.35041 Marburg/Germany, in random spot urine samples. Normal: up to 30 μg/mg creatinine, microalbuminuria: 30–300 μg/mg creatinine and gross proteinuria (macroalbuminuria) > 300 μg/mg creatinine).

(F) Radiological investigations (plain X-ray of the hands and chest and High resolution CT-chest).

- Concerning treatment, corticosteroids were received by 32 (80%) patients (2.5–50 mg/day). Fourteen patients received IV methylprednisone with a cumulative dose ranging from 1–6.5 gm. Methotrexate was received by 22 (55%) patient (7.5–25 mg/week). Thirteen (32.5%) patients received IV cyclophosphamide with a cumulative dose ranging from 3.6–12.6 gm. Eight (20%) patients received azathioprine (100 mg/day). Vasodilators were received by 25 (62.5%) patients.

3. Statistical analysis

All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, USA) version 15 for Microsoft Windows. Data were statistically described in terms of range, mean ± SD, median, frequencies and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples when comparing 2 groups and Kruskal Wallis analysis of variance (ANOVA) test with Mann Whitney U test for independent samples as posthoc multiple 2-group comparisons when comparing more than 2 groups. Correlation between various variables was done using Spearman rank correlation equation for non normal variables. p value < 0.05 was considered statistically significant.

4. Results

The clinical features and laboratory parameters of the study SSc group are shown in Tables 1 and 2.

Complete urine analysis revealed within normal results, none of patients had macroalbuminuria in 24 h urine analysis. Eight (20%) patients had microalbuminuria; 4 (50%) had dSSc, 2 (25%) lSSc and 2 (25%) SSc sine scleroderma patients. Nine (22.5%) patients had decreased creatinine clearance.

ANAs positivity was detected in 35 (87.5%) patients. Twenty-four (68.6%) showed speckled, 7 (20%) nucleolar and 4 (11.4%) homogenous pattern. In addition, five (62.5%) out of eight patients with microalbuminuria showed speckled pattern and 3 (37.5%) showed nucleolar pattern.

No significant correlation was found between albumin/creatinine ratio and demographic (age, sex and disease duration) features. Albumin/creatinine ratio was significantly higher among dSSc patients compared to those with lSSc and SSc sine scleroderma (Pearson's $X^2 = 9.077$ and $p = 0.01$), as shown in Fig. 1. Furthermore, albumin/creatinine ratio showed significant positive correlations with telangiectasia and mRodnan's skin score ($r = 0.322$, 0.352 and $p = 0.04$, 0.026, respectively). Albumin/creatinine ratio had significant negative correlations with inter-incisor distance and pleurisy ($r = -0.525$, -0.446 and $p = 0.001$, 0.004, respectively).

SSc patients with and without microalbuminuria were compared regarding the various demographic and clinical features. There was a significant difference concerning the disease subset (Pearson's $X^2 = 7.067$ and $p = 0.029$), 50% of patients with microalbuminuria had dSSc, 25% had lSSc and 25% had

Table 1 Clinical features of the study SSc group.

Clinical feature	Number of patients (%)
Vascular manifestations	
Raynaud's phenomenon	39 (97.5%)
Digital pitting scars	30 (75%)
Digital gangrene	6 (15%)
Bone resorption	13 (32.5%)
Calcinosis	10 (25%)
Telangiectasia	10 (25%)
GIT manifestations	
Esophageal dysmotility	37 (92.5%)
Flatulence	12 (30%)
Malabsorption	13 (32.5%)
Pulmonary manifestations	
Pleurisy	6 (15%)
Pleural effusion	1 (2.5%)
Interstitial pulmonary fibrosis	22 (55%)
Musculoskeletal manifestations	
Myositis	9 (22.5%)
Myopathy	1 (2.5%)
Arthritis	14 (35%)
Neurological manifestations	
CT syndrome	1 (2.5%)
Peripheral neuropathy (sensory type)	4 (10%)
Cranial nerve involvement	1 (2.5%)
Sicca manifestations	19 (47.5%)
	Range (mean ± SD)
Modified Rodnan's skin score	0–41 (16.53 ± 10.13)
Interincisor distance (cm)	1–5 (3.07 ± 1.002)
Finger to palm (in flexion) distance (cm)	0–9 (1.82 ± 1.69)
Indices of SAQ	
IMSS	0.00–2.25 (0.6 ± 0.68)
IVS	0.00–2.25 (1.2 ± 0.61)
IRS	0.0–2 (0.45 ± 0.48)
IGS	0.0–2.8 (0.88 ± 0.69)
IDS	0.0–2 (0.72 ± 0.49)

SAQ: Scleroderma Assessment Questionnaire; IMSS: index of musculoskeletal status; IVS: index of vascular status; IRS: index of respiratory status; IGS: index of gastrointestinal status; IDS: index of disease status.

Table 2 Laboratory parameters of the study SSc group.

Laboratory parameter	Range (mean ± SD)
ESR (mm/1st hour)	7–110 (39.68 ± 26.26)
Hemoglobin (gm/dl)	9.0–16.1 (12.14 ± 1.53)
WBCs count (1000/cm^3)	3.6–20.1 (8.05 ± 3.35)
Platelet count (1000/cm^3)	169–605 (324.45 ± 99.25)
AST (U/l)	8–125 (29.85 ± 25.25)
ALT (U/l)	6–327 (29.58 ± 52.03)
CPK (U/l)	16–2282 (253.58 ± 486.84)
LDH (U/l)	142–2,08 (471.9 ± 358.301)
Serum creatinine (mg/dl)	0.3–1.0 (0.58 ± 0.18)
Creatinine clearance (ml/min)	45–166 (102.68 ± 30.13)
Albumin/creatinine ratio (μg/mg)	4.7–72.4 (18.81 ± 14.59)
Microalbuminuria (μg/mg creatinine)	32–72.4 (43.78 + 12.94)

ESR: erythrocyte sedimentation rate; WBCs: white blood cells; AST: aspartate transaminase; ALT: alanine transaminase; CPK: creatinine phosphokinase; LDH: lactate dehydrogenase.

SSc sine scleroderma. Furthermore, malabsorption was more prevalent among patients with microalbuminuria (62.5%) compared to those without (25%) (Pearson's $X^2 = 4.103$ and $p = 0.04$).

No significant correlations were found when albumin/creatinine ratio was correlated to the different laboratory parameters. The comparison between SSc patients with and without microalbuminuria regarding the different laboratory parameters revealed no significant difference as well.

Albumin/creatinine ratio correlated significantly and positively with IMSS and IDS indices of SAQ ($r = 0.378$, 0.32 and $p = 0.016$, 0.044, respectively), as shown in Table 3. This was further confirmed by the finding that SSc patients with microalbuminuria showed significantly higher mean IDS than those without (1.058 vs. 0.631, respectively and $p = 0.04$), as shown in Fig. 2.

We failed to find a statistically significant correlation between creatinine clearance and the different demographic and clinical features. SSc patients with normal and those with abnormal creatinine clearance were compared concerning the different demographic and clinical features. Neurological manifestations were significantly more common among patients with abnormal (33.3%) compared to those with normal creatinine clearance (6.5%) (Pearson's $X^2 = 4.61$and $p = 0.03$).

The comparisons between creatinine clearance and the different laboratory parameters could not reveal any statistically significant correlation. Apart from the significant difference in the mean TLC between SSc patients with normal and those with abnormal creatinine clearance, the comparisons concerning the different laboratory parameters failed to reveal any significant difference. SSc patients with impaired creatinine clearance had lower mean TLC compared to those with normal creatinine clearance (5.864/cm^3 vs. 8.684/cm^3 and $p = 0.013$).

There was no significant correlation between creatinine clearance and the different indices of the SAQ. Moreover, the comparison between SSc patients with normal creatinine clearance and those with abnormal creatinine clearance regarding the different indices of the SAQ could not reveal any significant difference.

5. Discussion

The kidney is one of the most clearly affected internal organs that show the complications of vascular insult in SSc [14].

Autopsy studies reveal histological evidence of renal involvement in 60–80% of patients with SSc [15]. In addition, clinical evidence of mild renal involvement including; mild proteinuria, elevated serum creatinine concentration or hypertension, has been detected in 50% of patients [16]. In contrast to the common mild renal dysfunction, scleroderma renal crisis is considered less frequent [14].

Owing to the cumbersome collection of 24 h urine volume and the inaccuracy of the result obtained by the dip stick method as a consequence of the variation of urinary protein concentration according to the urinary volume [17], estimation of albumin/creatinine ratio (μg/mg) on a urine sample is used to accurately measure urinary protein excretion [18]. Moreover, microalbuminuria can detect early renal disease before progression of the condition to structural renal damage and frank macroalbuminuria [19].

Eight (20%) of our SSc patients had microalbuminuria. This coincides with the data demonstrated in the literature where microalbuminuria was detected in 17.9%, 19.04% and

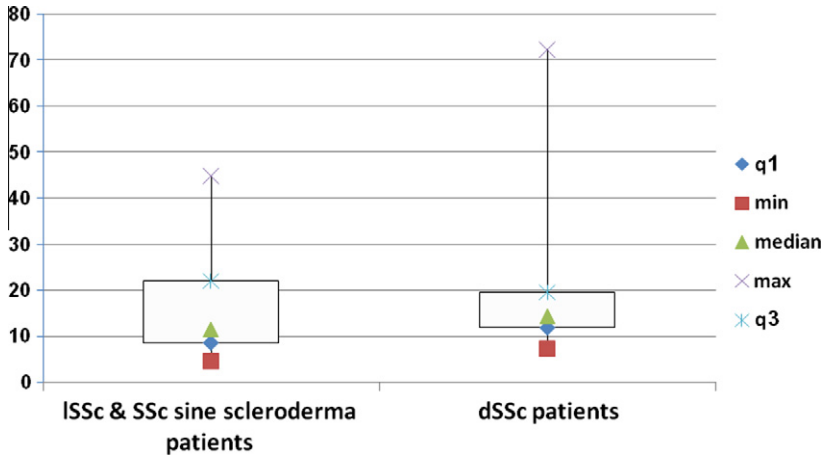

Figure 1 The comparison between patients with dSSc and those with lSSc and SSc sine scleroderma regarding albumin/creatinine ratio.

Table 3 The correlation between albumin/creatinine ratio and the different indices of SAQ.

Indices of SAQ	*r*	*p* Value
IMSS	0.378	0.016
IVS	0.039	0.811
IRS	0.244	0.129
IGS	0.201	0.213
IDS	0.320	0.044

IMSS: index of musculoskeletal status; IVS: index of vascular status; IRS: index of respiratory status; IGS: index of gastrointestinal status; IDS: index of disease status.

17.5% of the study populations, after excluding those with concomitant hypertension and diabetes mellitus [4,15,20].

In disagreement with Seiberlich et al. [4] who found that almost half (45.5%) of SSc patients who had albuminuria in their study were males, we found no significant correlation between the presence of microalbuminuria and gender.

In the present work, albumin/creatinine ratio was not related to patient's age or the disease duration, coinciding with the results of Dawnay et al. [20]. On the contrary, Seiberlich et al. reported that albuminuria was significantly more prevalent in SSc patients whose disease duration was >4 years [4].

In agreement with Seiberlich et al. [4] who found that albuminuria was more prevalent among diffuse subtype, in the current study, albumin/creatinine ratio was significantly higher among dSSc patients compared to those with lSSc and SSc sine scleroderma. Furthermore, we found that albumin/creatinine ratio increases significantly with higher modified Rodnan's skin score and decreased interincisor distance. This coincides with the results of El Sayed et al. who also revealed that patients with microalbuminuria had more extensive skin disease [21].

There was a significant positive correlation between albumin/creatinine ratio and the presence of telangiectasia which can emphasize the association between renal affection and vasculopathy in SSc. In this context, Mohamed et al. detected significant negative correlation between measured GFR and pulmonary hypertension suggesting that SSc patients with PAH are at a greater risk of developing renal involvement [22]. Campo et al. reported strong association between pulmonary hypertension and renal dysfunction [23]. Furthermore, the presence of ANA centromeric pattern, vasculopathy and decreased GFR had been found to be associated [24,25].

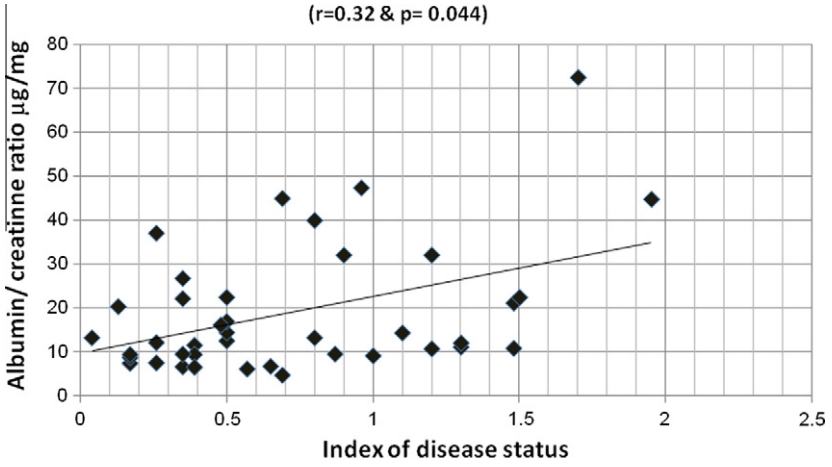

Figure 2 The correlation between albumin/creatinine ratio and IDS.

Albuminuria was reported to be more common among SSc patients with pulmonary involvement [4] and that patients with pulmonary fibrosis were more susceptible to have microalbuminuria [21]. On the other hand, we didn't find a significant correlation between albumin/creatinine ratio and pulmonary manifestations except for a negative correlation with pleurisy. This may be explained by the fact that patients with both interstitial lung disease and pulmonary hypertension were included in the former studies and those with pulmonary hypertension were excluded from our study. Moreover, the negative correlation with pleurisy could be explained by the different pathological processes implicated in the pathogenesis of either of both parameter, i.e., inflammatory process in pleural affection and vascular and fibrotic processes in microalbuminuria.

In this study, malabsorption was more common in SSc patients with microalbuminuria. In agreement, it was revealed that patients with gastrointestinal involvement were at a higher risk of developing albuminuria [4] and hypovolemia secondary to gastrointestinal involvement may also contribute to renal affection in SSc patients [16].

In disagreement with El Sayed et al. [21] who detected a significant positive correlation between the degree of microalbuminuria and serum creatinine level, we could not find a correlation between albumin/creatinine ratio and serum creatinine level. This discrepancy between the studies could be explained by the different characteristics of enrolled SSc patients as 50% of patients in the former study had low baseline GFR. This may highlight the role of microalbuminuria as an early indicator of renal affection before impairment of GFR. In support to our finding, Dawnay et al. demonstrated the value of increased albumin excretion in SSc patients as an indicator of underlying vascular pathology that may also herald the onset of renal disease [20].

Moreover, albumin/creatinine ratio increased significantly with higher IMSS and IDS of SAQ indices and SSc patients with microalbuminuria had significantly higher mean value of IDS compared to those patients without microalbuminuria. In contrast, there was neither a significant correlation between creatinine clearance and the different indices of the SAQ nor a significant difference between SSc patients with normal and those with abnormal creatinine clearance regarding the different indices of the SAQ. This suggests that microalbuminuria may be a predictor of increased morbidity and disease severity rather than just a marker of renal affection.

No significant difference was found between SSc patients with normal and those with abnormal creatinine clearance regarding the different demographic and clinical features except that regarding neurological manifestations which were more prevalent among those with impaired creatinine clearance. The increased prevalence of neurological manifestations among patients with impaired creatinine clearance could be explained by the increased disease severity which is reflected on both the neurological and renal systems. Several studies in the literature had revealed no correlation between creatinine clearance and any of disease subset, patient's age, interstitial lung disease, gastrointestinal tract involvement, modified Rodnan's skin score and muscle affection [22,26,27].

Other causes apart from renal disease can affect creatinine clearance as evidenced by the reduction of baseline GFR in normal individuals with low protein diet [28,29]. The reduction of GFR in our SSc patients without microalbuminuria may be explained by decreased protein intake and/or decreased renal perfusion secondary to gastrointestinal tract involvement with the subsequent reduction of protein and fluid intake.

We can conclude that the evaluation of microalbuminuria compared to creatinine clearance may be a more sensitive indicator of early renal affection in SSc patients with the additional advantage of being a predictor of systemic vasculopathy and increased morbidity of the different organs systems. Subsequently, regular screening of SSc patients for the detection of microalbuminuria is recommended. Microalbuminuric patients should have more frequent follow up visits for early detection systemic organ affection.

Conflict of interest statement

None declared.

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