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Review Article

Renal Involvement in Systemic Sclerosis: An Update

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Abstract
Background: Systemic sclerosis is an immune-mediated rheumatic disease characterized by vascular abnormalities, tissue fibrosis and autoimmune phenomena. ***Summary:*** Renal disease occurring in patients with systemic sclerosis may have a variable clinicopathological picture. The most specific renal condition associated with systemic sclerosis is scleroderma renal crisis, characterized by acute onset of renal failure and severe hypertension. Although the management of scleroderma renal crisis was revolutionized by the introduction of angiotensin-converting enzyme inhibitors, there is still a significant proportion of patients with poor outcomes. Therefore, research on establishing disease markers (clinical, ultrasonographical and serological) and clear diagnostic criteria, which could limit the risk of developing scleroderma renal crisis and facilitate diagnosis of this complication, is ongoing. Other forms of renal involvement in systemic sclerosis include vasculitis, an isolated reduced glomerular filtration rate in systemic sclerosis, antiphospholipid-associated nephropathy, high intrarenal arterial stiffness and proteinuria. ***Key Messages:*** Scleroderma renal crisis is the most specific and life-threatening renal presentation of systemic sclerosis, albeit with declining prevalence. In patients with scleroderma renal crisis, it is mandatory to control blood pressure early with increasing doses of angiotensin-converting enzyme inhibitors, along with other antihypertensive drugs if necessary. There is a strong association between renal involvement and patients' outcomes in systemic sclerosis; consequently, it becomes mandatory to find markers that may be used to identify patients with an especially high risk of scleroderma renal crisis.

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Introduction

Systemic sclerosis (SSc) is a chronic multisystem disease characterized by thickening of the skin and fibrosis of various internal organs [1, 2]. Although the exact pathogenesis of SSc still remains incompletely understood, vasculopathy and dysregulation of the immune system are considered to play a significant role [3].

In SSc one of the most significant, acute consequences of vasospasm and arterial damage is renal involvement. In contrast to pulmonary arterial hypertension, which is characterized by slowly progressive vasculopathy, the vascular changes in renal scleroderma usually develop rapidly due to higher values of systemic blood pressure in comparison to pulmonary pressure [4]. The renal involvement in SSc may remain subclinical until the late stages [5]. Autopsy studies reveal occult renal pathology in 60–80% of SSc patients [6]. Cannon et al. [7] found that up to 50% of asymptomatic patients have clinical markers indicative of renal dysfunction, such as proteinuria, an increased creatinine concentration, or hypertension. Various studies suggest a strong association between renal involvement and worse patient outcomes in SSc [3, 8]. In addition, a multinational SSc inception cohort study found renal crisis to be one of the predictors of early mortality in SSc patients [9].

The most studied form of renal involvement, associated with the most dramatic clinical course, is scleroderma renal crisis (SRC). The other forms of renal involvement include anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, an isolated reduced glomerular filtration rate (GFR) in SSc, antiphospholipid (aPL)-associated nephropathy, high intrarenal arterial stiffness and proteinuria (Fig. 1).

Scleroderma Renal Crisis

The most specific form of renal involvement in SSc is SRC, characterized by acute onset of renal failure and severe hypertension. On presentation, 90% of patients with SRC consistently have blood pressure levels exceeding 150/90 mm Hg and decreased renal function (≥30% reduction in estimated GFR [eGFR]). SRC occurs in 10–15% of patients with diffuse cutaneous SSc (dcSSc) and only rarely (1–2%) in limited cutaneous SSc (lcSSc) [10, 11]. SRC was a predominant cause of death in previous decades [12, 13]; however, in recent years, declining trends have been observed [14]. An analysis of 637 patients with dcSSc with a disease duration <4 years from the European League against Rheumatism Scleroderma Trials and Research (EUSTAR) cohort has shown the prevalence of SRC at an estimated 2.4% [15, 16].

Pathogenesis of SRC

The exact pathogenesis of SRC is still under investigation, but genetic and environmental factors are likely involved. The primary pathogenic process is thought to be injury to endothelial cells resulting in intimal thickening and proliferation of the renal intralobular and arcuate arteries. SRC appears histologically as "onionskin lesions" of the renal interlobular arteries [17]. Antiendothelial cell antibodies, which are capable of inducing endothelial cell apoptosis, have been detected in up to 85% of SSc patients [18]. In addition to structural changes, episodic vasospasm, named "renal Raynaud's phenomenon," contributes to renal hypoperfusion, increased renin release and juxtaglomerular hyperplasia. Hyperreninemia causes vasoconstriction and renal ischemia, which contributes to accelerated hypertension [19–21]. Endothelin-1, a peptide that plays a role in blood vessel constriction, and its receptor ET-B are overexpressed in patients with SRC [22].

Alterations in cellular and humoral immunity may both play a role in SRC pathogenesis [23–25]. SSc has been associated with activation of type 2 helper T lymphocytes, cytokine

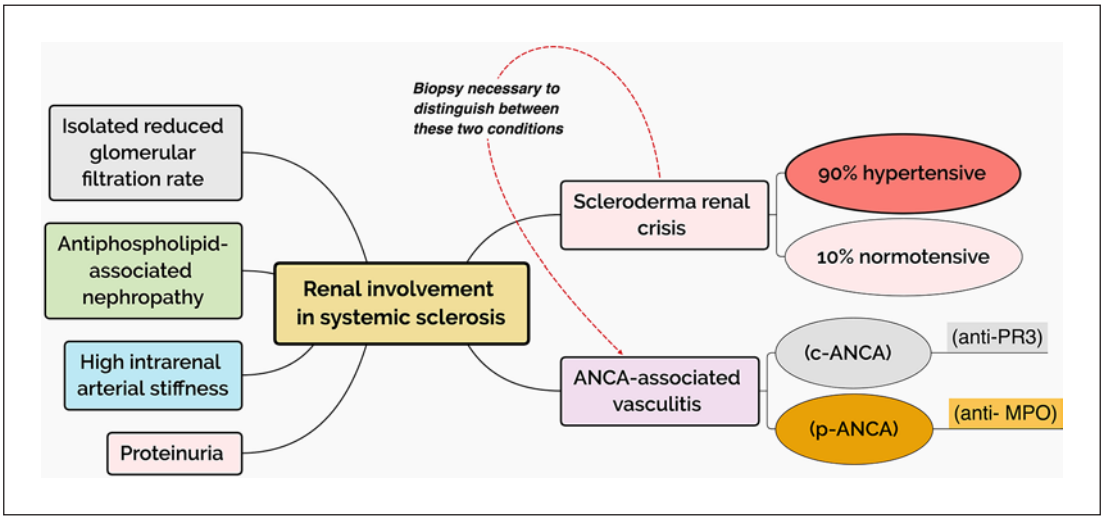

Fig. 1. The spectrum of kidney involvement in systemic sclerosis. c-ANCA, diffuse cytoplasmic staining; anti-PR3, anti-proteinase 3 antibodies; p-ANCA, perinuclear pattern; anti-MPO, anti-myeloperoxidase antibodies.

production and excess collagen accumulation, all of which participate in the development of vasculopathy [26]. The potential pathogenic role of specific autoantibodies is implied by the association between their presence and the development of SRC [27, 28]. Furthermore, the complement degradation product C4d, which is regarded as an immunologic marker of antibody-mediated rejection of renal allografts, was detected in native renal biopsies from a subset of SRC patients [29].

There is a strong relationship between SRC development and specific MHC classes, in particular HLA (human leukocyte antigen)-DRB1*0407 and HLA-DRB1*1304. Additionally, gene screening studies showed an association of SRC with genes in the complement region. Polymorphism in the endothelin ligand receptor axis, but not in the angiotensin-converting enzyme (ACE) axis, has also been associated with an increased risk of SRC [30].

CD147, also known as extracellular matrix metalloproteinase inducer, is a glycosylated membrane protein which belongs to the immunoglobulin superfamily. Yanaba et al. [31] found that an increased concentration of serum soluble CD147 was associated with the presence of SRC. Therefore, CD147 may play a role in the development of SRC, and measurement of circulating soluble CD147 may be a useful biomarker for SRC risk stratification.

Clinical Symptoms of SRC

Patients with SRC may present with headaches, hypertensive retinopathy, encephalopathy, seizures, fever and general malaise. Pulmonary edema is also common, resulting from water and salt retention due to overload and oliguria [32, 33].

Laboratory tests of patients with SRC reveal multiple abnormalities. A rapid increase in serum creatinine concentration and/or microangiopathic hemolytic anemia is associated with severe glomerular damage and with intravascular hemolysis [34]. In addition, the renin concentration is also significantly increased [7]. Urinalysis commonly demonstrates mild proteinuria and hematuria with granular casts visible on microscopy [35]. Markers of endothelial cell perturbation have been observed, including a high concentration of soluble adhesion molecules in the blood (VCAM-1, ICAM-1 and E-selectin) [36].

Ninety-nine experts evaluated a broad list of potential diagnostic criteria in order to identify key aspects of SRC [37], the results of the study were used for the development of classification criteria for SRC (Fig. 2). A consensus was reached regarding the following

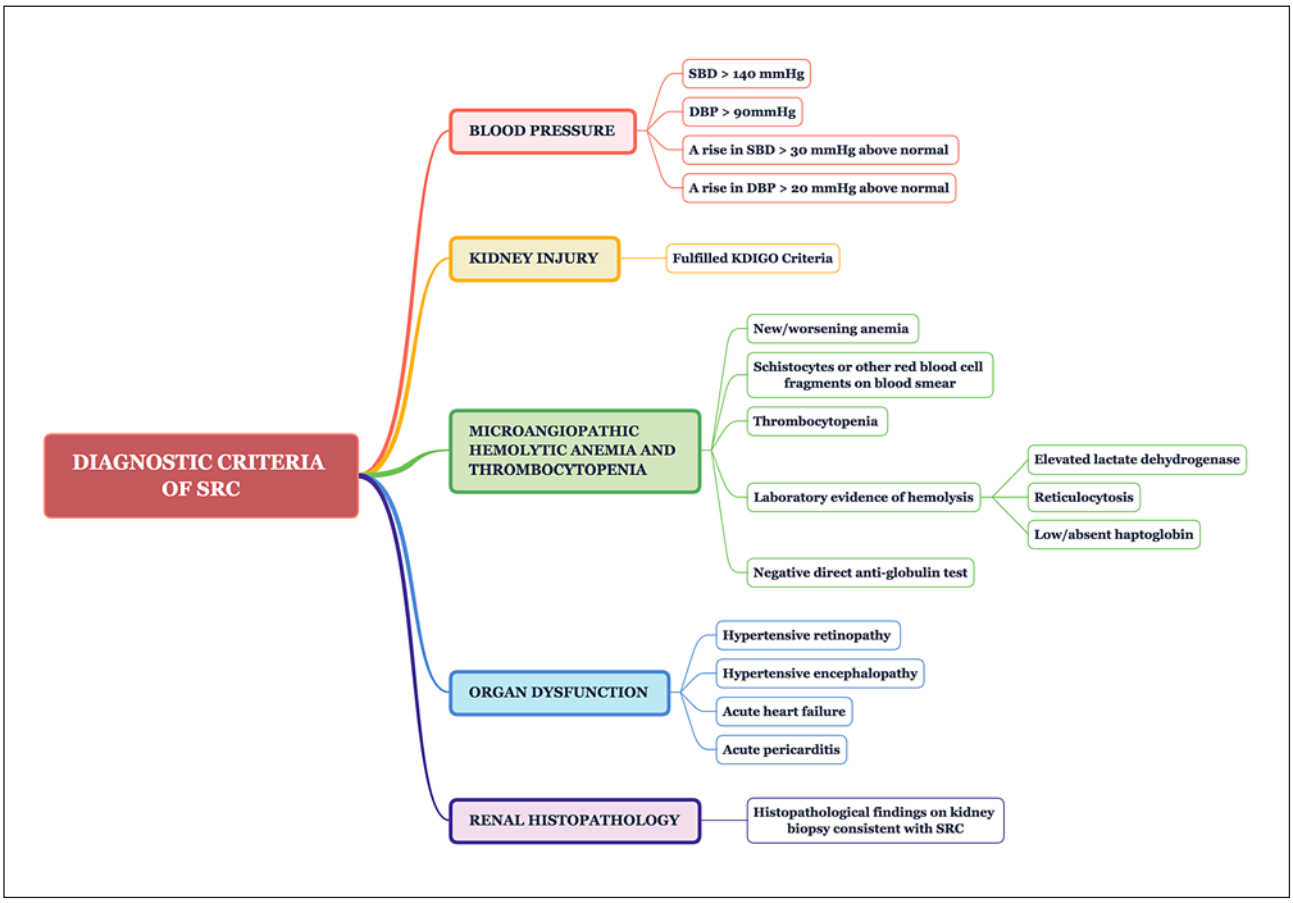

Fig. 2. Proposed diagnostic criteria for scleroderma renal crisis (SRC). SBD, systolic blood pressure (German: "systolischer Blutdruck"); DBP, diastolic blood pressure; KDIGO, Kidney Disease: Improving Global Outcomes.

aspects and may be a useful tool that summarizes valid clinical features of SRC, thus directing the diagnosis.

Blood Pressure. (1) Acute rise in blood pressure defined as one or both of the following: systolic blood pressure >140 mm Hg; diastolic blood pressure >90 mm Hg. (2) A rise in systolic blood pressure >30 mm Hg above normal and/or diastolic blood pressure >20 mm Hg above normal. (3) Blood pressure measurement should be taken twice, separated by at least a 5-min interval. (4) If blood pressure readings are discordant, repeat readings should be obtained until 2 consistent readings are obtained.

Kidney Injury. Acute kidney injury fulfilling Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Microangiopathic Hemolytic Anemia and Thrombocytopenia. (1) New or worsening anemia not due to other causes. (2) Schistocytes or other red blood cell fragments on blood smear. (3) Thrombocytopenia <100,000/μL, confirmed by manual smear. (4) Laboratory evidence of hemolysis: elevated lactate dehydrogenase, reticulocytosis, and/or low/absent haptoglobin. (5) Negative direct antiglobulin test.

Organ Dysfunction. (1) Hypertensive retinopathy confirmed by an ophthalmologist. (2) Hypertensive encephalopathy. (3) Acute heart failure. (4) Acute pericarditis.

Renal Histopathology. Histopathological findings on kidney biopsy consistent with SRC [37].

Table 1. Differential diagnosis of scleroderma renal crisis

ANCA-associated vasculitis
Malignant hypertension
Drug-induced renal injury
Complement dysregulation
Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura
Transplant rejection

The proposed diagnostic criteria for SRC are presented in Figure 2.

Renal biopsy is not recommended in patients with SSc presenting with typical features of SRC, but it plays a key role in cases with atypical presentation or in doubtful cases [38–40]. SSc mostly affects the interlobular arteries, in contrast to hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), which predominantly affect the glomeruli. Malignant hypertension-associated thrombotic microangiopathy may have an appearance identical to that seen in SSc, although this is more often associated with underlying arteriolonephrosclerosis. Clinical history and serological data help to distinguish these etiologies [41]. Table 1 shows the differential diagnosis of SRC.

Risk Factors for SRC Development

Rapidly progressive skin thickening appears to be the main risk factor for SRC, with most dcSSc patients developing SRC within 7.5 months to 4 years of disease onset [10, 11, 42]. According to Moinzadeh et al. [43], development of proteinuria and/or hypertension, as well as positive anti-RNA polymerase III (anti-RNAP III) antibodies are the strongest risk factors for SRC. Terras et al. [44] and Stochmal et al. [45] showed that the presence of anti-RNAP III antibodies in patients with SSc correlates with renal crisis and severe cutaneous involvement. Although an association between SRC and anti-RNAP III antibodies has already been reported in patients with dcSSc, Takada et al. [46] recently reported a case of anti-RNAP III antibody-associated SRC in a patient with lcSSc.

A number of other risk factors have been identified, for example, anemia [42], recent cardiac events, large joint contractures [47], digital pitting scars, myalgia and myopathy [38]. Shimizu et al. [48] reported a case of SRC complicated by thrombotic microangiopathy in a patient with no other risk factors after infection with influenza B virus. In regard to medications, glucocorticoids have been implicated as a major risk factor when used in doses ≥15 mg per day in the preceding 6 months [49]. It is hypothesized that high doses of corticosteroids can promote endothelial dysfunction and inhibit prostacyclin production, which in turn increase ACE activity [50]. Cyclosporin therapy is another risk factor for SRC development [51].

Treatment of SRC and Preventive Measures

The key to management of SRC is early detection and treatment with ACE inhibitors (ACE-I) [52]. The EULAR recommends ACE-I as first-line treatment, and that patients started on steroids should be carefully monitored for the development of SRC [53]. Studies have shown that if the diagnosis of SRC is delayed or if ACE-I are not used aggressively, irreversible kidney damage and death are more likely to occur [34, 54]. Early detection and aggressive treatment are also crucial to prevent other complications associated with SRC, such as hypertension, retinopathy and pulmonary edema [35]. Unfortunately, the data show that over half of SRC cases have a delay in diagnosis, and thus long-term mortality remains significant [55]. If blood pressure control remains suboptimal at the maximum tolerated doses of ACE-I, other antihypertensive drugs (calcium channel blockers as second-line and diuretics or alpha-

blockers as third-line treatment) should be added. Angiotensin II receptor blockers should be used only in patients intolerant to ACE-I [52]. There has also been recent interest in combining ACE-I with endothelin receptor blockers and agents targeting complement component 5 [54]. The target for antihypertensive treatment is to decrease systolic blood pressure by 20 mm Hg and diastolic blood pressure by 10 mm Hg per 24 h to the normal range, avoiding hypotension.

Risk factors for poor outcome in SRC include the following: a serum creatinine concentration >3 mg/dL at presentation, male gender, a delay in initiating antihypertensive treatment, inadequate blood pressure control, congestive heart failure, normotensive SRC, and renal biopsy findings showing (1) arteriolar fibrinoid necrosis, (2) severe glomerular ischemic collapse or (3) severe tubular atrophy and interstitial fibrosis [50].

In terms of preventive measures, regular blood pressure monitoring and seeking early attention when blood pressure suddenly increases [11, 14] are vital. Patients deemed at high risk for SRC may benefit from shorter follow-up intervals with particular focus on subtle changes or abnormalities in proteinuria and eGFR, intensive home blood pressure monitoring (to include 24-h ambulatory blood pressure monitors) and earlier nephrology consultation [56]. Renal function should be assessed regularly via serum creatinine concentration, eGFR and serum renin concentration, as well as via general urine analysis and 24-h proteinuria [57].

There is no evidence at present to support the use of ACE-I prophylactically, although prompt initiation of treatment remains a key point in SRC therapy. New therapeutic options are needed [14, 53].

Plasma exchange, which has been proposed for thrombotic microangiopathy, has not demonstrated efficacy and should not be recommended, with the exception of rare SRC patients who might develop thrombotic microangiopathy associated with anti-ADAMTS-13 antibodies [58]. There are currently no clinical trial data regarding the use of plasma exchange in SRC.

In severe cases of SRC with systemic complement activation and resistant to conventional treatment, eculizumab, the C5 blocker, has recently been proposed as a possible treatment option. Eculizumab is a humanized recombinant monoclonal antibody directed against complement component 5. The drug inhibits the generation of C5a and C5b-9, and thus inhibits lysis and endothelial damage [59]. The rationale for the involvement of the complement system in the pathogenesis of SRC, as well as for the usage of eculizumab, is as follows: an association of hypocomplementemia with SSc and vascular involvement, occurrence of microangiopathic hemolytic anemia in SRC, C5b-9 deposits in capillaries of SSc patients' skin biopsies and C4d deposits in renal peritubular capillaries of SSc patients with a poor renal outcome [60].

Renal Replacement Therapy and Renal Transplantation

Despite treatment, dialysis is still needed in 23% of SRC patients, and permanent dialysis in 41% of SRC patients [10]. Up to half of the cases requiring renal replacement therapy eventually come off dialysis, although this may be between 6 and 24 months after the initial SRC. Renal transplantation offers superior survival in SSc compared with long-term dialysis [61], although it should be emphasized that renal transplantation is not always possible due to the severe multiorgan involvement. In a cohort of 260 patients with SSc who underwent kidney transplantation, the overall 5-year graft survival rate was 56.7% [62]. In a report of the United Network of Organ Sharing, recurrence of disease after transplantation was 6.7% [58]. Based on the finding that cyclosporine may be responsible for acute renal failure in patients with SSc, calcineurin inhibitors are not recommended as immunosuppressants after kidney transplantation [51]. Data from the Australia and New Zealand Dialysis and Transplant (ANZDATA)

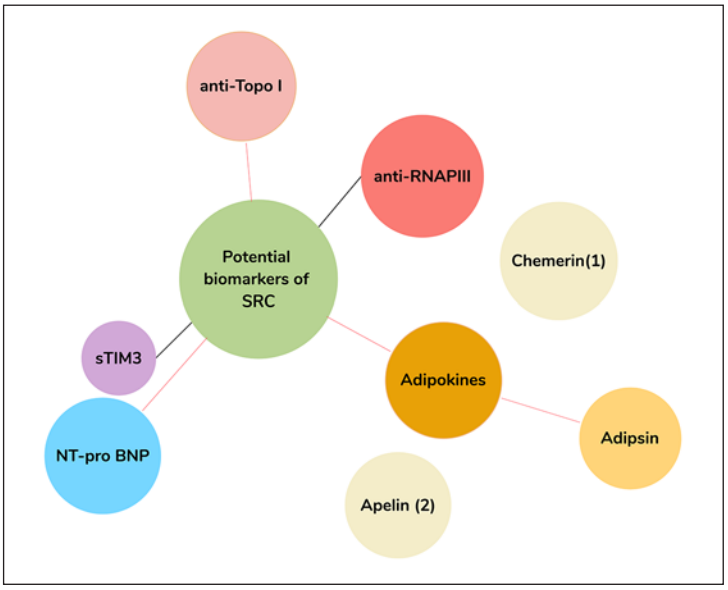

Fig. 3. Potential biomarkers of scleroderma renal crisis (SRC). (1) Promising marker of increased risk of impaired renal function in the early stage of systemic sclerosis; the role in SRC is not established. (2) Inhibits the fibrotic process in numerous organs including the kidneys, secretion in systemic sclerosis is decreased; the role in SRC is not established. anti-Topo I, anti-topoisomerase I; anti-RNAP III, anti-RNA polymerase III antibodies; sTIM3, soluble T-cell immunoglobulin and mucin domain 3; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

registry and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry confirmed that overall survival of SSc patients receiving renal replacement therapy is worse than that of patients with other causes of end-stage renal disease. However, patients with SSc have a higher rate of dialysis-independent renal function recovery [63, 64].

Antinuclear Antibodies Associated with SRC

Autoimmune serology can be used to identify patients at significant risk of SRC. Anti-RNAP III antibodies and anti-topoisomerase I (anti-Topo I/anti-Scl70) have been associated with an increased risk of developing SRC. The anti-centromere antibodies, typically seen in lcSSc, are considered "protective" against renal crisis [65]. A proportion of 16.7–24% of patients with the anti-RNAPIII antibodies develop SRC [44, 66, 67].

An Italian study [68] showed that patients with anti-RNAP I–III antibodies tend to develop SRC early in the course of the disease, while anti-Topo I-positive patients typically develop SRC later. In that study, 100% of the patients who were anti-RNAP I–III positive developed SRC within 18 months from disease onset, and in almost 30% of the patients, SRC was the presenting symptom of the disease. In the anti-Topo I-positive group, the onset of SRC occurred within 18 months of the disease in only 50% of the cases; 23% of the patients developed SRC between 18 and 48 months, and 27% >48 months after the disease onset. All anti-RNAP I–III-positive patients developed hypertensive renal crisis, while in the anti-Topo I group, 40% were diagnosed with the normotensive type of SRC. Patients with anti-Topo I antibodies tended to have higher creatinine levels and a less favorable outcome.

The available data indicate that detecting SSc-specific antibodies with a prognostic value may lead to a better risk stratification.

Other Biomarkers

Chiba et al. [69] found soluble T-cell immunoglobulin and mucin domain 3 (sTIM3) to be more frequently elevated in patients with a history of SRC. Chighizola et al. [70] identified N-terminal prohormone of brain natriuretic peptide (NT-proBNP) as a potentially useful biomarker for risk stratification of renal outcome in SRC, selectively identifying patients likely to require renal replacement therapy.

Table 2. Comparison of hypertensive and normotensive SRC

Hypertensive SRC	Normotensive SRC
90% of SRC cases	10% of SRC cases
BP levels >150/90 mm Hg	Absence of hypertension although BP is often elevated compared to the patient's baseline values; worse renal outcome and higher mortality
Nearly half of patients require renal replacement therapy 6–24 months after SRC	Earlier need for renal replacement therapy
Good response to treatment with ACE-I	ACE-I or dialysis seems to be less effective in this group

SRC, scleroderma renal crisis; BP, blood pressure; ACE-I, angiotensin-converting-enzyme inhibitor.

Recently, adipokines (cell signaling proteins secreted by adipose tissue) have attracted much attention as a cytokine family contributing to the various pathological processes of SSc. Chemerin, one of the adipokines, appears to be a promising marker of increased risk of impaired renal function in the early stage of SSc [71, 72]. Adipsin was suggested to take part in the pathogenesis of SRC due to an alternative pathway of complement activation [60]. Apelin, the secretion of which is decreased in SSc, was reported to inhibit the fibrotic process in numerous organs including the kidneys [73].

Other adipokines have been associated with organ fibrosis in SSc; however, their link with renal involvement is not fully established and requires further investigation (Fig. 3) [74].

Normotensive SRC

In approximately 10% of patients, SRC occurs in the absence of hypertension (normotensive SRC) [75–77]. Relative hypertension may be present, i.e., a significant increase in blood pressure which still remains within the normal range but is elevated compared to the patient's baseline values (e.g., 130/85 mm Hg in a young woman whose baseline value is 100/70 mm Hg) [78]. Absence of elevated blood pressure in SRC may delay its diagnosis and treatment, leading to disease progression. Therefore, any change in blood pressure or any kidney dysfunction should lead to close monitoring and additional tests. Normotensive renal crisis diagnosis is particularly challenging and requires confirmation of progressive azotemia and/or microangiopathic hemolytic anemia with thrombocytopenia. To diagnose normotensive renal crisis, an elevated serum creatinine concentration and at least one of the following should be found: proteinuria, hematuria, thrombocytopenia, hemolysis or hypertensive encephalopathy.

Normotensive SRC is associated with worse prognosis, a higher mortality rate and an earlier need for renal replacement therapy (Table 2) [11, 75, 79, 80]. The poor outcome has been, in part, attributed to subclinical renal injury leading to thrombotic microangiopathy in the setting of delayed diagnosis. Normotensive SRC is more common in patients with cardiac involvement. Based on several case reports, it was hypothesized that cardiac involvement may preclude a hypertensive response and worsen prognosis [76]. However, a study comparing 15 normotensive renal crisis patients with 116 hypertensive SRC patients did not show differences in the prevalence of cardiac involvement [75]. Significant differences that may contribute to a worse prognosis in normotensive SRC are more frequent occurrences of severe anemia, thrombocytopenia and pulmonary hemorrhage [75]. In the study by Helfrich et al. [75], 64% of the normotensive patients received prednisone ≥30 mg/day compared

Table 3. Comparison of SRC and ANCA-associated vasculitis

SRC	ANCA-associated vasculitis
Occurs mainly in dcSSc and only rarely (1–2%) in lcSSc	Occurs mainly in lcSSc
Malignant hypertension	Mild hypertension
Acute onset of renal failure and severe hypertension	Subacute presentation with progressive renal failure
Patients develop SRC within 7.5 months to 4 years of SSc onset	Typically occurs several years after SSc onset
ACE-I as the first-line treatment in SRC	Does not respond to ACE-I
Steroids (≥15 mg/day) are one of the major risk factors	Responsive to steroids

SRC, scleroderma renal crisis; ANCA, antineutrophil cytoplasmic antibody; SSc, systemic sclerosis; dcSSc, diffuse cutaneous SSc; lcSSc, limited cutaneous SSc; ACE-I, angiotensin-converting enzyme inhibitor.

with 16% of the hypertensive patients. Conversely, 52% of the hypertensive but only 7% of the normotensive patients received no corticosteroids.

Despite the lack of clinical studies, ACE-I are often used in normotensive SRC patients, but they seem to be less effective in this group of patients than in hypertensive SRC patients [81].

ANCA-Associated Vasculitis and SSc

ANCA are autoantibodies directed against enzymes localized within primary granules of neutrophils and lysosomes in monocytes and are implicated directly in the pathogenesis of small vessel vasculitis [82]. ANCA-associated vasculitis is rare in SSc, found in up to 9% of patients [83]. ANCA-associated vasculitis is a systemic necrotizing vasculitis of unknown etiology, including granulomatosis with polyangiitis (previously Wegener's granulomatosis), microscopic polyangiitis, renal limited vasculitis, and Churg-Strauss syndrome. Two major patterns of ANCA can be distinguished by indirect immunofluorescence: a diffuse cytoplasmic staining pattern (c-ANCA) mainly associated with anti-proteinase 3 (anti-PR3) antibodies, and a perinuclear pattern (p-ANCA) mainly associated with anti-myeloperoxidase (anti-MPO) antibodies. It has been postulated that scleroderma vasculopathy exacerbates the interaction of ANCA with the endothelium near the vascular pole and neutrophil activation in the glomerulus [53].

Most cases of ANCA-associated vasculitis are described as normotensive renal failure related to anti-MPO crescentic glomerulonephritis [84]. In contrast to classic SRC, the majority of such cases occur in lcSSc rather than dcSSc, and the process has a subacute presentation with progressive renal failure, mild hypertension and proteinuria. ANCA-associated vasculitis, in comparison to SRC, causes renal failure due to mononuclear cell infiltration and vessel wall destruction. These two conditions can only reliably be distinguished by histopathological examination [85]. ANCA-associated vasculitis typically occurs after several years of SSc – compared to SRC, which mainly occurs in the earlier stages of disease [86]. The main differences between SRC and ANCA-associated glomerulonephritis are shown in Table 3. Its diagnosis should be considered in any SSc patient with positive MPO antibodies and renal failure.

Isolated Reduced GFR in SSc

Clinically apparent renal involvement is uncommon in SSc. Many patients with SSc demonstrate less severe complications associated with a decreased GFR. The mechanisms of chronic and slowly progressive renal disease in SSc are still not fully elucidated [87]. Patients with SSc

with normal kidney function develop blood vessel abnormalities in the kidneys which are comparable to those seen in other organs. In most patients this damage is subclinical. Autopsy studies reveal occult renal pathology in 60–80% of patients with SSc, and almost all of these cases involve vascular abnormalities. It seems that renal involvement in SSc is primarily characterized by vascular damage and glomerular hypofiltration, which is quite different from patients with diabetic or hypertensive nephropathy, where hyperfiltration and increased glomerular capillary pressure represent the major causes of progressive renal dysfunction [6]. Impaired renal function may be present in SSc despite a normal serum creatinine concentration as serum creatinine may not be elevated until the GFR is <50% of normal [6].

There is an association between renal dysfunction and pulmonary hypertension. Campo et al. [88] recently evaluated 76 consecutive SSc patients with pulmonary arterial hypertension and found that at the time of diagnosis, 45.6% had renal dysfunction (eGFR <60 mL/min/1.73 m^2), while only 6.5% of them had had a prior episode of renal crisis. Furthermore, eGFR was a strong predictor of survival in this cohort, with eGFR values <60 mL/min/1.73 m^2 associated with a 3-fold increase in mortality. This strong association may be a reflection of pulmonary hypertension and right heart failure contributing to renal dysfunction through fluid retention and neuroendocrine activation.

aPL-Associated Nephropathy

aPL syndrome is characterized by antibodies directed against either phospholipids or plasma proteins bound to anionic phospholipids [89]. The presence of aPL is correlated with a constellation of clinical features including venous and arterial thrombosis, recurrent fetal loss and thrombocytopenia [90]. The prevalence of aPL in SSc varies up to 41% [91, 92]. Although the role of aPL antibodies in the pathogenesis and long-term outcomes of SSc is still unclear, the presence of aPL seems to be correlated with higher involvement of the skin and visceral organs [93, 94]. Wielosz et al. [95] suggest a relationship between kidney involvement and the presence of aPL antibodies in patients with SSc. Positivity for IgG aCL and IgG a-B2GPI in patients with SSc without secondary aPL syndrome seems to be connected with decreased glomerular filtration [95].

High Intrarenal Arterial Stiffness

Intrarenal vascular stiffness is measured via the renal vascular resistive index; using this method, a surge in arterial stiffness has been documented in SSc patients [96]. Doppler indices of intrarenal stiffness were previously also utilized as markers for prediction of new digital ulcer occurrence in SSc [97]. Additionally, it has been suggested that renal vascular stiffness parameters are increased in SSc patients with the presence of anti-RNAP III antibodies, which are a known risk factor for SRC development [98]. To date, little has been studied on the significance of the observed increase in intrarenal arterial stiffness in terms of patients' outcomes in long-term observation. Rosato et al. [99] observed renal function in SSc patients in a well-designed prospective trial with a mean follow-up of 4 years using several organ function assessment measures. In accordance with previous studies [96–99], the authors demonstrated increased intrarenal stiffness parameters in Doppler ultrasonography within the study group. During follow-up, all of the patients, except for 6 individuals in whom SRC occurred, had preserved normal renal function despite increased intrarenal stiffness. An important observation was that no significant differences in renal Doppler and serological parameters were observed between patients with renal complications (in whom SRC

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Table 4. Renal manifestations of SSc

Renal dysfunction in SSc	Risk factors	Management
SRC	Diffuse skin disease Rapidly progressive skin disease Large joint contractures Prednisolone at a dose >15 mg/day <4 years since scleroderma onset Presence of anti-RNA polymerase antibody Proteinuria Anemia Recent cardiac events Digital pitting scars Myalgias and myopathy Cyclosporin therapy HLA-DRB1*0407 and HLA-DRB1*1304 High serum CD147 levels	ACE-I are the initial choice of therapy Monitoring BP several times per day with a target of <130/90 mm Hg Other antihypertensive medications (e.g., calcium channel blockers) as needed In case of severe renal failure and/or end-stage renal disease, consider dialysis as required Consider renal transplantation in dialysis-dependent eligible patients (usually within 2 years) No evidence to support prophylactic use of ACE-I In cases with dramatic clinical and histological severity, and in those that do not respond to conventional treatment, eculizumab has recently been proposed
Normotensive SRC	Cardiac involvement Previous treatment with glucocorticoid Absence of elevated BP may delay treatment, leading to disease progression	Earlier need for renal replacement therapy ACE-I or dialysis seems to be less effective in this group
ANCA-associated vasculitis MPO-ANCA	The majority of such cases occur with limited cutaneous SSc Typically occurs after several years of SSc Drugs, e.g., side effect of D-penicillamine treatment	Does not respond to ACE-I Initiate treatment with intravenous cyclophosphamide and corticosteroids Followed by maintenance therapy with azathioprine, methotrexate or mycophenolate Biopsy to distinguish ANCA-associated vasculitis from SRC
Isolated reduced GFR in SSc	Vasculopathy	Vasodilator therapy
Antiphospholipid-associated nephropathy	IgG aCL IgG a-B2GPI	Anticoagulants
Microalbuminuria and proteinuria	Disease duration >4 years Elevation of systolic BP	ACE-I Proteinuria >1 g/day – renal biopsy recommended
Penicillamine-associated renal disease	Up to 20% of patients treated with D-penicillamine develop membranous glomerulopathy with proteinuria	Discontinue D-penicillamine In more severe cases, steroids, plasmapheresis and immunosuppression have been required

SRC, scleroderma renal crisis; SSc, systemic sclerosis; ACE-I, angiotensin-converting enzyme inhibitor; BP, blood pressure; HLA, human leukocyte antigen; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; GFR, glomerular filtration rate.

Table 5. Summary of key points

– SRC is the most frequent renal complication of SSc
– SRC is associated with a high risk of fatal outcome
– The key management of SRC is early detection and treatment with ACE-I
– The use of ACE-I at SSc diagnosis is associated with an increased risk of SRC
– High blood pressure is a common presenting feature of SRC
– Patients with SRC may be normotensive at presentation; this group has a poorer prognosis and higher mortality than the group of patients with hypertensive SRC
– Anti-topoisomerase I and anti-RNA polymerase III antibodies are associated with an increased risk of developing SRC
– ANCA-associated vasculitis in SSc does not respond to ACE-I but is responsive to steroids; histopathology is often required to exclude SRC
– Mild chronic renal insufficiency in SSc may result from vasculopathy and is probably underrecognized

SRC, scleroderma renal crisis; SSc, systemic sclerosis; ACE-I, angiotensin-converting enzyme inhibitors.

occurred) and those without renal complications. Doppler indices of intrarenal stiffness were significantly elevated in patients with digital ulcers. The study concluded that asymptomatic renal vasculopathy was present in SSc patients, but it did not seem to be associated with accelerated deterioration of renal function during follow-up [99].

Proteinuria in SSc

Increased excretion of urinary total protein is a classic marker of renal disease. Proteinuria and albuminuria are useful markers of vasculopathy and are known to be independent predictors of cardiovascular morbidity and mortality in patients with other vasculopathic diseases, such as diabetes and hypertension [100, 101]. Vascular kidney damage can be detected at an early stage by increased permeability of proteins passing the glomerular filtration barrier.

Seiberlich et al. [102] analyzed urine albumin, urine total protein and urine electrophoresis to assess protein excretion in 80 SSc patients and 18 healthy age- and gender-matched controls, all with normal GFRs. Increased total protein excretion was detected in 17.5% of SSc patients, and albuminuria was identified in 25%. Albuminuria correlated with disease duration >4 years and elevation of systolic blood pressure, suggesting it may be reflective of chronic vascular injury [102].

Proteinuria >1 g/day in SSc is uncommon and suggests an underlying glomerular disorder. In the context of serological features of lupus, significant proteinuria should be verified by renal biopsy [55].

In regard to SSc, epidemiological studies have identified proteinuria as a risk factor for increased mortality [102–104]. In patients with SSc and proteinuria, initiation of ACE-I therapy resulted in a significant decrease in urine protein excretion [105].

Conclusions

Renal involvement in patients with SSc may have a variable clinicopathological course (Table 4). The spectrum of kidney involvement includes the following: asymptomatic reduction of the GFR, ANCA-associated vasculitis, an isolated reduced GFR in scleroderma,

aPL-associated nephropathy, high intrarenal arterial stiffness and proteinuria. SRC is the most specific and life-threatening renal presentation of SSc; however, in recent years, declining frequencies have been observed.

In patients with established SRC, it is mandatory to control blood pressure early with increasing doses of ACE-I, along with other antihypertensive drugs if necessary. The lack of specific diagnostic criteria for SRC is an ongoing problem. A consensus of experts evaluated a broad list of potential diagnostic items in order to identify the key aspects of SRC.

Autoimmune serology – anti-RNAP III antibodies and anti-Topo I – can be used to identify patients with a higher risk of SRC. sTIM3 was also found to be frequently elevated in patients with a history of SRC. NT-proBNP has been proposed as a potentially useful biomarker in risk stratification of renal outcome in SRC, identifying patients in whom renal replacement therapy is more likely to be required. Recently, adipokines have attracted much attention as potential new biomarkers due to their contribution to the various pathological processes in SSc. There is a strong association between renal involvement and patients' outcomes in SSc. Consequently, it seems mandatory to find markers that may be used to identify patients with an especially high risk of SRC. The key points are summarized in Table 5.

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Author Contributions

All authors conceived the manuscript and collected the literature; M.C., M.S. and L.R. drafted the manuscript; J.M. and J.M.R. provided a critical review of the nephrology part; all authors edited and approved the final version of the manuscript.

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