Kidney involvement in systemic sclerosis

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Summary

Kidney involvement in systemic sclerosis (SSc) is primarily manifested by scleroderma renal crisis (SRC). Formerly, it was the most severe complication in scleroderma and was the most frequent cause of death in these patients. More than 30 years ago, with the development of angiotensin converting enzyme (ACE) inhibitors, SRC became a very treatable complication of scleroderma. Although there are still many patients who do not survive and have poor outcomes, early diagnosis of renal crisis and prompt therapeutic intervention can achieve excellent outcomes. Renal abnormalities independent of renal crisis have been noted, but can usually be attributed to other problems. Further understanding of the pathogenesis of renal disease in scleroderma may lead to additional improvement in the therapy of renal crisis and perhaps the disease in general. This chapter reviews the pathogenesis, clinical setting, and therapy of this serious complication of SSc.

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Definition

Scleroderma renal crisis is defined as the new onset of accelerated arterial hypertension and/or rapidly progressive oliguric renal failure during the course of SSc. One should not assume that non-malignant hypertension alone without azotemia or other renal abnormalities is renal crisis. Likewise, urine abnormalities and/or mild azotemia in a scleroderma patient are likely to have...
other explanations and should not be considered SRC. There are some differences between the criteria used to define SRC in different studies and this may in part account for some of the different outcomes that are reported. There has now been a general consensus about the clinical criteria that define SRC and these are summarized in box 1 [1].

Pathogenesis of scleroderma renal crisis

The pathogenesis of renal events in SSc remains incompletely understood, but the acute episode seems to evolve from a series of insults to the kidney (figure 7). The primary process, similar to that seen in vessels in other organs, is injury to the endothelial cells, which results in intimal thickening and proliferation of intralobular and arcuate arteries. Inflammatory cells, including lymphocytes and other mononuclear cells, are conspicuously absent in the pathologic examination of these arteries. The thickened abnormal vessel wall allows platelet aggregation and adhesion to occur. Release of platelet factors increases vascular permeability and may participate in the production of increased collagen and fibrin deposition contributing to the luminal narrowing.

The narrowed arterial vessels are the primary cause of decreased renal perfusion, particularly cortical blood flow. Episodic vasospasm, or what has been called “renal Raynaud’s” phenomenon, was carefully demonstrated in early classic studies by Cannon et al. although its significance is unclear [2]. These vascular abnormalities have been documented in asymptomatic patients but measurements of blood flow including newer techniques using color flow Doppler sonography have been unsuccessful at predicting renal crisis. The resistance index (RI), a measure of renal blood flow, was abnormal in scleroderma patients and correlated with “renal” involvement but NOT renal crisis [3] and disease duration [4] It improved in patients without renal disease with intravenous prostacyclin (Iloprost) and angiotensin converting enzyme inhibitors but not calcium channel blockers [5]. This technique does measure renal blood flow but there must be something more than just decreased blood flow that triggers the acute episode of renal crisis. Decreased blood flow leads to decreased perfusion of the juxtaglomerular apparatus, which causes hyperplasia of the juxtaglomerular apparatus [6]. At the time of renal crisis, patients have marked elevation in peripheral levels of renin, which strongly supports the primary role of the renin-angiotensin system mediating the hypertension. Also, the dramatic improvement in hypertension following nephrectomy and the striking response to angiotensin converting enzyme inhibitors demonstrates the importance of renin derived from the kidney in the pathogenesis of renal crisis [2].

Kovalchik et al. found hyperreninemia and an exaggerated renin response to a cold pressor test in some patients without clinical evidence of SRC. These patients also had marked vascular changes on renal biopsy [7]. However, prior to the actual onset of renal crisis, hyperreninemia is uncommon [8] and when detected, it is not predictive of SRC. Hyperreninemia plays a major role in the pathogenesis of SRC. However, it is not known what triggers the acute release of the hyperreninemia, which leads to the onset of malignant hypertension and rapid progression of renal failure.

Vascular changes are present in patients without renal crisis and, like plasma renin activity, do not predict the development of SRC [7,9]. Kidney biopsies from diffuse scleroderma patients without renal abnormalities show vessels with the typical intimal thickening and thickening that are seen in patients with renal crisis. A case control autopsy series documented that even limited cutaneous scleroderma patients, who very rarely get renal crisis, had thickened vessels compared to the non-scleroderma controls [9]. Thickening of the vessels and the degree of luminal occlusion were not correlated with age, disease duration, or last serum creatinine. However, patients with renal crisis had the most severe intimal proliferation. Vascular changes are frequently present in scleroderma patients, but additional factors beyond the vascular changes must be present to trigger the acute crisis event.

The precipitation of SRC could result from situations in which renal blood flow is further compromised. Cardiac dysfunction that decreases renal perfusion, i.e., large pericardial effusions, arrhythmias, or congestive heart failure, have preceded SRC in some patients [8,10], but they also can be the result of a hyperreninemic state [11]. Pregnancy, with its alterations in blood volume and flow, has been reported to precipitate renal crisis [12] but our extensive experience with scleroderma in pregnancy suggests that the association of renal crisis is primarily with early diffuse scleroderma and not with pregnancy [13]. Sepsis and dehydration causing hypotension could contribute to the problem, but in most patients, there is not an obvious precipitating cause.

Drugs, which can decrease renal perfusion such as non-steroidal anti-inflammatory agents, calcium channel blockers or ACE inhibitors, have not been associated with increased frequency of renal crisis and in fact a recent study suggested that calcium channel blockers decreased the frequency of renal crisis [14]. However, other drugs, which do cause vasospasm, have been

Box 1
Definition of renal crisis
In the course of a scleroderma patient:
• new onset accelerated arterial hypertension and/or
• rapidly progressive oliguric renal failure
• new hypertension without azotemia, non-progressive increase in creatinine or urine abnormalities are NOT renal crisis
associated with renal crisis including cocaine [15], cyclosporine [16] and tacrolimus [17].

Corticosteroids have long been implicated in the development of SRC [18,19]. However, since patients who are most likely to receive steroids are those with early inflammatory disease, they are the same patients who are at greatest risk for SRC. A significant association of antecedent high dose (> 40 mg) prednisone or high dose pulse methylprednisolone therapy [20] was noted in patients who had normotensive SRC. Also, a case control study of patients with renal crisis compared to other high risk patients, found a significant association of high dose prednisone (> 15 mg prednisone) and renal crisis in the 6 months prior to renal crisis [21]. Several other recent studies from Italy [14] and France [22] and a recent meta-analysis [23] describing the complications of steroid treatment in scleroderma patients confirmed this strong association with high dose prednisone and renal crisis. The exact pathogenic relationship is not known, but corticosteroids can alter endothelial function and they inhibit prostacyclin production, increasing ACE activity and there may be unknown other ways they contribute to the pathogenesis of SRC.

More recently, endothelial cell activation has been suggested to play a potential role in the development or progression of renal crisis. Increased levels of endothelin-1 [24], soluble vascular adhesion molecules (s-VCAM-1) and soluble E-selectin [25] have been shown to be associated with renal crisis. Mouthon et al. carefully studied endothelin-1 immunohistochemically in 14 kidneys of scleroderma patients with renal crisis and compared them to 26 kidneys from patients with other diseases, which might simulate renal crisis including thrombotic microangiopathy, cyclosporine toxicity, and hemolytic uremic syndrome [26]. Only in the scleroderma patients with renal crisis was endothelin-1 (ET-1) overexpressed in both the glomeruli and the arterioles. There was some staining in arterioles in some of the other kidney diseases and in the glomeruli in hemolytic uremic syndrome. Penn et al. also found that ET-1 and both endothelin A and endothelin B receptor expression was increased in SRC biopsies [27]. In addition, polymorphism in the endothelin ligand receptor axis [28] but not the ACE axis [29] have been associated with scleroderma. Although there is no evidence that autoantibodies play a role in the pathogenesis of SRC, the striking dichotomy between the frequency of SRC in patients with anti-centromere antibody (< 1 %) and those with anti-RNA polymerase III (33 %) is very intriguing [30]. It is also extremely curious that there are also very strong and unique associations of gastric antral vascular ectasia [31] and cancer [32] with RNA polymerase III antibody. Hopefully in the future, we will be able to determine what role this antibody plays in these very different manifestations all occurring in diffuse scleroderma patients.

**Renal pathology**

Renal biopsy is particularly important in patients where there is any uncertainty about the diagnosis. If anything is atypical in
the presentation, the patient or the course, it is important to confirm diagnosis and rule out other etiologies of kidney pathology. Pathologic changes of “scleroderma kidney” are very similar to those observed in other forms of malignant hypertension. Microscopic changes are characteristically seen in the small interlobular and arcuate arteries. Fibrinoid necrosis may be present either in arterial walls or in a subintimal location in small arteries and arterioles. The resulting intimal thickening in interlobular arteries leads to narrowing and often total obliteration of the lumen. Intramural fibrin deposition or fibrin thrombi have been noted, as in other forms of malignant hypertension, but can also be seen in scleroderma patients who are not hypertensive. Adventitial and peri-adventitial fibrosis, which is seen in SRC, is rarely noted in non-sclerodermatous malignant hypertension, making them helpful distinguishing features between the two entities. Large arteries may be normal or may show more typical atherosclerotic changes consistent with the patient’s age.

Glomerular changes are variable and include thickening and collapse of capillary loops and other ischemic changes. Juxtaglomerular cell hyperplasia is not specific to SSc but is consistent with the marked hyperreninemia characteristic of SRC [6]. It is most prominent when arterial narrowing is severe. Tubules appear to be secondarily affected by vascular insufficiency from arterial luminal occlusion. Immunoglobulins (chiefly IgM) and complement components (C3) are non-specifically deposited in small renal arteries, but discrete electron-dense deposits consistent with immune complexes are absent. The non-specificity of these findings is attributed to the gross disruption of vascular integrity and increased permeability rather than immune injury.

Several recent studies have looked at renal biopsies to determine if they are helpful in predicting outcome. Batal et al. studied 17 SRC patients who were all treated with ACE inhibitors including 7 who had good recovery of renal function [33]. The percentage of thrombosed vessels and increased peritubular capillary C4d staining were most strongly associated with non-recovery of function. Penn et al. also looked at different pathologic changes and found that acute changes of mucoid intimal thickening in arteries and fibrinoid necrosis in arterioles were associated with a poorer renal outcome [34]. Interestingly, they found that the chronic damage index that normally predicts long-term outcome in many renal pathologies does not appear to do so in SRC. Renal biopsy can thus provide useful prognostic information.

**Epidemiology**

Renal crisis occurs in approximately 10% of the entire scleroderma population and 20–25% in patients with diffuse scleroderma, but is quite variable from country to country dependent on how many diffuse scleroderma patients with early disease are included in the study. In a recent study from the large European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) group, it was present in only 5% of diffuse scleroderma patients [35]. However, this was a prevalence study of patients with a mean disease duration of more than 7 years. Additionally, the strong association of RNA polymerase III with renal crisis is also contributing to this difference, particularly since the frequency of this antibody within scleroderma is on the low side in many European countries. Some feel that the incidence of renal crisis has decreased since ACE inhibitors have been available. Although calcium channel blockers and d-penicillamine have been associated with a decreased occurrence of renal crisis [14,21,36], it is most likely that aggressive early treatment with ACE inhibitors has affected our ability to accurately diagnose this once fatal complication of scleroderma. There is no evidence that ACE inhibitors prevent renal crisis. Recent series have shown that 20 to 57% of patients who developed renal crisis were taking ACE inhibitors [22,34].

Renal crisis is most often encountered early in the course of the disease, with 75% of SRC cases occurring less than 4 years after the first symptom attributable to scleroderma [8]. However, late occurrences, even 20 years after disease onset, have been seen. Early studies showed that African-American patients are 3 times as likely as Caucasians to develop SRC, and (proportionately) males are more frequently affected than females [37] although more recent studies were not able to confirm these findings.

**Factors predicting SRC**

The characteristics of a typical patient are well recognized from several cohort studies. Many of these features or laboratory characteristics (box 2) can be identified before the development of a renal crisis and therefore careful baseline assessment of all scleroderma cases for risk of crisis is essential. Patients with a greatly increased risk to develop this complication must be followed extremely closely for any hints of renal crisis.

**Box 2**

Factors that occur prior to SRC that may be predictive for future SRC

- Diffuse cutaneous skin involvement
- Early disease with symptoms < 4 years
- Rapid progression of skin thickening
- Anti-RNA polymerase III antibody
- New cardiac events:
  - pericardial effusion
  - congestive heart failure and/or arrhythmias
- New anemia
- Antecedent high dose corticosteroid (> 15 mg prednisone daily)
Patients with diffuse cutaneous scleroderma with skin thickening on the proximal extremities and/or the trunk are at greatest risk for SRC, with 20 to 25% of this patient subgroup getting SRC [38]. Only 1% of patients with limited cutaneous scleroderma (previously termed the CREST syndrome) that have long-standing skin changes restricted to distal extremities ever develop renal crisis. There are even fewer cases of renal crisis documented in limited scleroderma patients with anti-centromere antibody [39,40]. Interestingly, there have been several cases of a malignant hypertension associated with anti-centromere antibody in Japanese patients without scleroderma [41,39,42]. Thus, the vast majority of SRC cases (75–80%) occur in patients with obvious diffuse cutaneous changes. The rapid progression of skin thickening has also been shown to be a good predictor of SRC, but this is likely because of the association with anti-RNA polymerase III, which has the most severe skin involvement [8,30].

Another 15 to 20% of SRC cases occur in patients who are destined to develop typical diffuse scleroderma, although they may only have minimal or even no skin changes at the time of the diagnosis of renal crisis. It is not infrequent for this type of patient with such minimal cutaneous and systemic findings to have the diagnosis of renal crisis made only at the time of kidney biopsy [43–45]. There are several distinguishing features that are helpful to identify those patients who are likely to evolve to diffuse cutaneous disease (box 3). These patients almost always have a short duration of symptoms, often less than 1 year. Polyarthritis/arthralgias, puffy or swollen hands and legs, and carpal tunnel syndrome is a common complex of symptoms in patients with early diffuse scleroderma. Although Raynaud’s phenomenon eventually is almost universally found in scleroderma, its absence in early diffuse scleroderma is not uncommon and particularly with the RNA polymerase III antibody which is the most common antibody seen in SRC [30]. The presence of palpable tendon friction rubs, which occur in 65% of diffuse scleroderma patients, is an extremely helpful and is predictive of diffuse scleroderma even prior to the development of diffuse cutaneous skin involvement [46]. Less than 5% of limited scleroderma patients ever have tendon rubs. Patients without known scleroderma who present with new isolated malignant hypertension should be carefully questioned for the presence of the aforementioned set of symptoms.

Autoantibodies are very helpful in predicting SRC. Anti-nuclear antibodies by immunofluorescence are seen in 95% of scleroderma so, their presence may be helpful in determining whether a malignant hypertension patient could possibly have scleroderma. However, the newer, commonly used method of a direct ANA using a multiplex assay is only positive in 60% of scleroderma patients and does not recognize the RNA polymerase III antibody [47]. Anti-RNA polymerase III (POL III) (using a commercially available ELISA assay) is a scleroderma specific antibody that is seen almost exclusively in diffuse scleroderma, and 24 to 33% of patients with this antibody develop SRC [48,49]. There are strong HLA genetic associations with POL III [50,51] and thus, the frequency of this antibody vary from country to country. This may be the primary reason for the differences in the frequency of renal crisis reported in different studies. The frequency of this antibody in scleroderma in several European and Asian countries ranges from 6 to 9%, so, it is not surprising that they have a low frequency of renal crisis particularly compared to the United States where the frequency is of RNA polymerase III is more than 20% [48]. Renal crisis occurs in only 10% of patients with anti-topoisomerase antibody patients, where it is a marker for diffuse cutaneous disease but not renal crisis [38]. The anti-centromere antibody, the antibody seen in classic limited scleroderma (or CREST syndrome) is a protective factor for renal crisis [42]. All patients with early diffuse scleroderma should monitor their own blood pressures regularly and notify their physicians immediately when their blood pressure is increased.

Antecedent hypertension is not usually present prior to SRC. Most often, there is a very acute onset of markedly elevated blood pressure. Normal blood pressures have been documented within 24 hour prior to the onset of SRC hypertension [37]. Marked elevation of plasma renin is the hallmark of acute SRC. Often it is 10 times normal and occasionally reaches 100 times normal. Because the use of ACE inhibitors interferes with the renin assay and results are often not available for weeks, this important finding is rarely used in the diagnosis or management of SRC. In isolation, an abnormal urinalysis or increased serum creatinine does not predict SRC. Such findings can usually be attributed to other causes or are only transient [7,8,52,53]. Several non-renal abnormalities may precede SRC. Asymptomatic pericardial effusion, congestive heart failure, and/or

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**Box 3**

**Rheumatic disease symptoms which would suggest scleroderma as the etiology of malignant hypertension in patients without the firm diagnosis of scleroderma**

- Recent onset of Raynaud’s (although this may be absent at time of renal crisis)
- Swollen stiff hands/fingers suggestive of arthritis
- Carpal tunnel syndrome
- Swollen lower legs without any obvious etiology
- Tendon friction rubs and pain over distal extremity tendons
- New onset of fatigue, weight loss, joint pains, weakness
- Positive anti-nuclear antibody
- Some skin thickening even if it confined to the distal extremities
- Diagnosis of “CREST” syndrome in a patient with < 18 months of symptoms.
arrhythmias may antedate renal crisis [8, 10]. New anaemia, an uncommon manifestation of scleroderma, can be an early clue to renal crisis, particularly when microangiopathic hemolysis and thrombocytopenia are present. Prior use of high dose corticosteroid frequently precedes the development of SRC, particularly normotensive SRC [20]. A case control study matched 106 patients with renal crisis to other scleroderma patients based on features that would be associated with increased risks for renal crisis or the use of steroids [21]. Sex, disease subset, disease duration, extent of skin thickening, the presence of tendon friction rubs and inflammatory myopathy were similar in both groups. Patients who received high dose prednisone (>15 mg/day) were 3 times more likely to develop renal crisis in the next 6 months. High dose steroids should be used with great caution and very close monitoring in patients with early diffuse scleroderma. Unfortunately, recent series from Italy and France have continued to see this association of high dose steroids with renal crisis [14,54].

**Clinical presentation**

Patients may complain of severe headache, blurred vision, or other encephalopathic symptoms with the onset of accelerated hypertension. Seizures may be an early finding, but fortunately, education of patients, early diagnosis and intervention with effective therapy has decreased the frequency of these events. Otherwise, the symptoms are non-specific: increased fatigue, headache, dyspnea or just not feeling well. High-risk patient must be taught to take these symptoms seriously and should check their own blood pressure if these symptoms occur. Most patients have striking elevations of blood pressure at the onset of SRC. Ninety percent have blood pressure levels greater than 150/90 mmHg, and 30 % have diastolic recordings greater than 120 mmHg. Only 10 % of cases have a “normal” blood pressure. An increase of 20 mmHg in a blood pressure reading may be significantly high for that particular patient, and yet, may still remain in the normal range (95/60 to 140/85). This can represent renal crisis. Any change in blood pressure should lead to further testing and close monitoring. Normotensive renal crisis requires the presence of other features, primarily rapidly progressive unexplained azotemia and/or microangiopathic hemolytic anemia with thrombocytopenia. Pulmonary hemorrhagic is a rare life-threatening problem, which has occurred in several of these patients [20,55]. It complicates the diagnosis and is a poor prognostic sign. In some situations, SRC symptoms are confused with other illnesses. Several cases of thrombotic thrombocytopenic purpura (TTP) have been reported in scleroderma patients, but it is unclear whether it was an isolated coexistent disease or just a different interpretation of SRC [56,57]. A review of the 8 cases of TTP and scleroderma in the literature found that there were few differences between the patient subsets. Although a few “responded” to plasmapheresis, most were also treated with ACE inhibitors [58]. Fever and hemorrhagic manifestations were the only findings that were different. New research in the pathophysiology of TTP has led to the observation that vWF-cleaving protease activity is decreased or deficient in TTP [59]. A pilot study did not find abnormalities of the vWF-cleaving protease activity in 10 SRC patients. If a diagnosis of TTP is made in a scleroderma patient, an ACE inhibitor should be used in conjunction with TTP treatment.

**Laboratory findings**

The serum creatinine is usually elevated and rises rapidly during the initial event. Although a slower increase of serum creatinine can occur over days to weeks, it is much more likely to increase by 0.5 to 1.0 mg/dL creatinine per day. It is important to recognize that even after anti-hypertensive therapy has effectively controlled blood pressure the serum creatinine may continue to rise. The issue of whether the ACE inhibitor itself contributes to such increases is often raised, but in that setting, I have not seen any patient who had significant improvement in serum creatinine after stopping the ACE inhibitor. Unfortunately, there are still situations where the serum creatinine continues to rise and the patient develops renal failure in spite of adequate control of the blood pressure with ACE inhibitors. In these circumstances, the addition of corticosteroids, immunosuppressive therapy or plasmapheresis are never helpful for classic scleroderma renal crisis. Routine urinalysis shows proteinuria (not usually exceeding 2 g/24 h), microscopic hematuria (5–100 rbc/hpl), and often granular casts. Microangiopathic hemolytic anemia, which is characterized by normochromic, fragmented red blood cells, shistocytes, reticulocytosis, and thrombocytopenia, occurs in almost half of patients with SRC. The platelet count is rarely lower than 20,000/mm³ and its improvement is often the first sign of adequate response to therapy even though the serum creatinine is continuing to increase. Patients are not usually symptomatic from this process, except that the anaemia may precipitate congestive heart failure. Patients with SRC often present with congestive heart failure, serious ventricular arrhythmias (even cardiac arrest), or large pericardial effusions [8,10]. This is primarily from the stress of the hypertension on the heart, effects of hyperreninemia, and from fluid overload secondary to oliguric renal failure, although some patients with very severe disease may also have primary scleroderma myocardial involvement contributing to these problems. Severe pulmonary hypertension secondary to the malignant systemic hypertension has also been seen but has a different course than the more frequent chronic pulmonary hypertension seen in limited scleroderma patients. Even if patients have both renal crisis and pulmonary hypertension, it is uncommon for it to occur simultaneously and it is more likely that either the pulmonary hypertension is related to
cardiac issues from the renal crisis, or renal failure is secondary to cardiac failure from the pulmonary hypertension [60,61]. Prompt control of the blood pressure usually improves these cardiac problems.

**Treatment**

The vicious cycle of decreased blood flow, ischemia, hyperreninemia, hypertension, and further vasoconstriction almost invariably resulted in a fatal outcome prior to the availability of ACE inhibitors. In those days, only a small minority of SRC patients (< 10%) survived more than 3 months. In the late 1970s, there were several reports of survival with very aggressive approach in controlling the blood pressure and dialysis. However, persistent, uncontrollable hypertension, hyperreninemia and resultant congestive heart failure made management even with dialysis very difficult. For a time, bilateral nephrectomy was performed to eliminate the hyperreninemia. This allowed the blood pressure, heart failure, and dialysis to be managed more successfully [37,62,63].

In the late 1970s, the first ACE inhibitors were experimentally used in scleroderma renal crisis [64,65]. These drugs work by acting as competitive inhibitors of the conversion of angiotensin I to angiotensin II. Inhibition of angiotensin II production promptly lowers blood pressure in scleroderma patients. Although angiotensin I and renin continue to accumulate, they are not biologically active and do not affect blood pressure. These drugs also proteolyze bradykinins, which, as potent vasodilators, potentially could have a role in the hypotensive effect of these agents as well. Survival was dramatically improved compared to the pre-captopril time. However, not all patients’ blood pressure responds promptly to the ACE inhibitor, and in some cases, renal failure is not prevented [66]. The initial level of creatinine at the start of therapy played a pivotal role in the final outcome. In one study, starting an ACE inhibitor when the serum creatinine was greater than 3 mg/dL or not controlling the blood pressure within 3 days were associated with a bad outcome [67]. Males, older age, and presence of congestive heart failure were additional risk factors associated with a bad outcome. Recent studies have shown similar frequencies of “good” and “bad” outcomes [22,34].

An ACE inhibitor should be continued even while the patient is on dialysis, since so many patients have the potential of improvement in their renal function after renal crisis. Hyperreninemia may be an ongoing process causing further damage to kidneys and heart, preventing kidney recovery and possibly causing congestive heart failure, so, it is important to continue to use an ACE inhibitor even if it is only a small dose on nondialysis days. Since there is a real possibility and hope for the return of adequate renal function and subsequent discontinuation of dialysis, plans for renal transplant should be kept on hold until at least 12 months have passed without return of kidney function. Recurrences of SRC have been rarely reported following renal transplant [68]. This may be from persistent hyperreninemia from the native kidney, particularly if the transplant was done within a short time of the renal crisis as was the case in 2 of the 5 cases reported by Pham. Overall renal transplant improved survival in scleroderma compared to those who remained on dialysis [69]. A review of outcomes of 50 kidney transplants in rare diseases from the United Network for Organ Sharing registry from 1987 to 1996 showed some decrease in graft and overall survival in scleroderma patients compared to those with analgesic nephropathy and diabetes but not as good as would be expected for transplants in patients without systemic diseases [68].

Management of normotensive renal crisis is also with ACE inhibitors even though these patients do not have significant increases in the blood pressure, the drugs can be lifesaving during acute SRC. Even in small doses, they can reverse the process if given early enough in the course. Thus, it is very important to strongly consider SRC in the setting of patients with early diffuse scleroderma who have renal insufficiency or other suggestions of renal crisis even in the absence of malignant hypertension. A renal biopsy should be strongly considered if it is not clear what is going on.

There is no difference in the outcome of patients treated with the second line ACE inhibitors compared to captopril. However, since captopril has a shorter half-life, it allows more flexibility in management of blood pressure early in the course of treatment. If the blood pressure is not adequately controlled with maximum amounts of an ACE inhibitor alone, other anti-hypertensive agents can be added. One should strive for a blood pressure of 120/70–80 mmHg. If the serum creatinine continues to rise even though the blood pressure is controlled, do NOT assume that the ACE inhibitor is “not working” or is contributing to the deterioration. Although this may occur in other settings, stopping the ACE inhibitor during renal crisis never improves renal function.

As for other agents, clinical experience with angiotensin receptor blockers and direct renin inhibitors is very limited and is variable, but many chose to add these drugs to the ACE inhibitor [70,71]. Any other anti-hypertensive can be added to control the blood pressure, although beta-blockers can aggravate Raynaud’s. More recently, because of the recent findings of marked increases in endothelin-1 in the serum and kidney of patients with scleroderma renal crisis [26], endothelin receptor blockers have been piloted in patients with renal crisis [27].

**Prognosis**

The use of ACE inhibitors has dramatically changed the survival of patients with SRC. Prior to the availability of these drugs, patients almost always died. Only 10% survived the first year. The long term outcome of 145 cases of SRC seen at the University of Pittsburgh who were treated with ACE inhibitors showed that 61% had a good outcome as defined by not
requiring or only requiring temporary dialysis [72]. Their long-term outcome was excellent with a 10-year survival from renal crisis of 90%, which was comparable to diffuse scleroderma patients without renal crisis. Fifty-five of the 145 patients never required dialysis. Their serum creatinine peaked at 3.8 mg/dL and slowly decreased. Seven years after renal crisis, these patients' mean serum creatinine was 1.8 mg/dL. None of them went on to develop chronic renal failure. There were 62 patients who required dialysis during the acute renal crisis episode, but more than half (n = 34) were successfully able to discontinue dialysis 3 to 18 months (mean 8 months) later. The mean serum creatinine 6 years later in these patients was 2.2 mg/dL. Only 2 of them later developed slowly progressive renal failure and went back on dialysis (4%).

There were 28 (19%) patients who had an early death, a mean of 3 months after SRC along with the 28 (19%) who had permanent dialysis had a bad prognosis. Patients on permanent dialysis did not survive as well as non-scleroderma patients, so the survival of this group was very poor. This group included patients who were older, male, with cardiac involvement and had a higher serum creatinine at the start of treatment. Interestingly, a lower peak blood pressure was associated with a worse outcome [72].

Unfortunately, recent reviews of renal crisis throughout the world have not shown any further improvement in the survival of patients with renal crisis with 5-year survivals ranging from 50 to 70% [22,34,54,73,74]. Similar risk factors for bad outcomes have been seen in these studies, including males, older age and lower blood pressure for most of these studies. However, a new bad outcome predictor factor of prior exposure to ACE inhibitors was noted by both Penn and Teixeira. Although they did not reach a statistical significance in the individual studies, combining the 2 studies, there was a significant association. A recent international prospective observational cohort study was able to show the worse prognosis for patients who were on an ACE at the time of diagnosis of renal crisis. In an adjusted analysis, exposure to ACE inhibitors prior to the onset of SRC was associated with an increased risk of death (hazard ratio 2.42, 95% CI 1.02, 5.75, \( P < 0.05 \)) [74]. It is likely that although these agents are very good at treating renal crisis they do NOT prevent it and perhaps because they may blunt the onset of renal crisis, they turn it into a more chronic, less treatable and harder to identify problem.

Summary

Renal crisis occurs in systemic sclerosis patients with rapidly progressive diffuse cutaneous thickening early in their disease. SRC is characterized by malignant hypertension, hyperreninemia, azotemia, microangiopathic hemolytic anemia, and renal failure. This complication was almost uniformly fatal, but in most cases, it can now be successfully treated with ACE inhibitors. This therapy has improved survival, reduced the requirement for dialysis, and often allowed for the discontinuation of dialysis 6 to 18 months later. Prompt diagnosis and early, aggressive initiation of therapy with ACE inhibitors will result in the most optimal outcome.

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