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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 1*). 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 proliferation 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 creatinine or urine abnormalities are NOT renal crisis