Long-Term Outcomes of Scleroderma Renal Crisis

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Background: **Although scleroderma renal crisis, a complication of systemic sclerosis, can be treated with angiotensin-converting enzyme (ACE) inhibitors, its long-term outcomes are not known.**

Objective: **To determine outcomes, natural history, and risk factors in patients with systemic sclerosis and scleroderma renal crisis.**

Design: **Prospective observational cohort study.**

Setting: **University program specializing in scleroderma.**

Patients: **145 patients with scleroderma renal crisis who received ACE inhibitors and 662 patients with scleroderma who did not have renal crisis.**

Measurements: **Among patients with renal crisis, the four outcomes studied were no dialysis, temporary dialysis, permanent dialysis, and early death. Demographic, clinical, and laboratory data were compared to identify risk factors for specific outcomes. Follow-up was 5 to 10 years.**

Results: **61% of patients with renal crisis had good outcomes (55 received no dialysis, and 34 received temporary dialysis); only 4 of these (4%) progressed to chronic renal failure and permanent dialysis. More than half of the patients who initially required dialysis could discontinue it 3 to 18 months later. Survival of patients in the good outcome group was similar to that of patients with diffuse scleroderma who did not have renal crisis. Some patients (39%) had bad outcomes (permanent dialysis or early death).**

Conclusions: **Renal crisis can be effectively managed when hypertension is aggressively controlled with ACE inhibitors. Patients should continue taking ACE inhibitors even after beginning dialysis in hopes of discontinuing dialysis.**

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Scleroderma renal crisis (1) is defined as the new onset of severe hypertension associated with a rapid increase in serum creatinine concentration, microangiopathic hemolytic anemia, or both. Outcomes of this disorder, a once-fatal complication of scleroderma, have dramatically improved with the use of angiotensin-converting enzyme (ACE) inhibitors (1). We examined short- and long-term outcomes of renal crisis in patients taking these medications.

METHODS

We examined all patients with systemic sclerosis (2) who were seen at the University of Pittsburgh (Pittsburgh, Pennsylvania) between 1979 and 1996. Of 807 patients with diffuse scleroderma, 145 experienced renal crisis and received ACE inhibitors; these 145 patients made up the study sample. None of the other 662 patients had an unexplained serum creatinine concentration greater than 177 μmol/L (2 mg/dL). We collected a standardized set of baseline data and then followed patients prospectively (accountability, 95%). Follow-up clinical data were obtained at regular intervals (3–5). Each patient's treatment was determined by his or her physician.

We examined long-term outcomes and divided the 145 patients with renal crisis into four categories (1): no dialysis (those who did not require dialysis in the first year after renal crisis), temporary dialysis (those who received dialysis and later discontinued it for at least 1 year), permanent dialysis (those who required permanent dialysis), and early death (those who died within 6 months of renal crisis). We determined the methods and complications of dialysis and compared the frequency of complications per patient-year of dialysis with the frequency reported for other dialysis recipients in the literature (6, 7). Data analysis included descriptive statistics and analyses for between-group comparisons. We used the log-rank method to analyze survival from time of diagnosis of renal crisis to death.

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RESULTS

At the time of renal crisis, 75% of patients had had scleroderma symptoms for less than 4 years (median, 2.4 years). The mean age of all patients was 50 years. Seventy-five percent of patients were women, and 92% were white. Most patients (88%) had diffuse scleroderma with skin thickening proximal to the elbows or on the trunk. Eighteen patients with less extensive skin disease had features

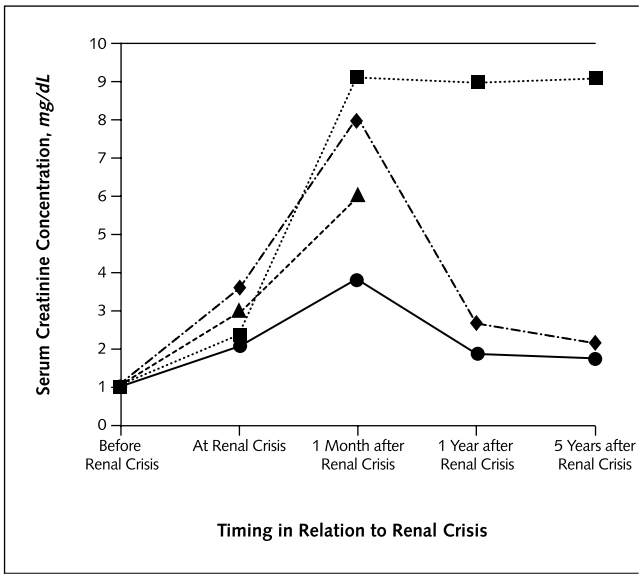
suggestive of diffuse scleroderma, including early disease, tendon friction rubs or antibodies, anti-topoisomerase I antibody, and anti-RNA polymerase III antibody (2, 3, 5, 8). Only 4 patients had limited cutaneous scleroderma, no patients had anticentromere antibodies, and 4% of patients had antiribonucleoprotein antibody. Eighty-five percent of patients had new diastolic hypertension (mean peak blood pressure, 178/102 mm Hg), 90% had an abnormal initial serum creatinine concentration (mean, 248 μmol/L [2.8 mg/dL]), and 45% had microangiopathic hemolytic anemia.

Outcomes of Scleroderma Renal Crisis

Figure 1 shows the outcome data for the 145 patients with renal crisis who received ACE inhibitors. No dialysis and temporary dialysis were considered good outcomes, and permanent dialysis and early death were considered bad outcomes. In the 55 patients who did not receive dialysis (38%), serum creatinine concentration peaked at 336 μmol/L (3.8 mg/dL) and decreased to 159 μmol/L (1.8 mg/dL) 7.1 years later. Seventy-eight percent of patients in this group had creatinine concentrations less than 265 μmol/L (3 mg/dL) at diagnosis. Only 2 (4%) had slow deterioration of renal function that required dialysis 4 and 6 years later, respectively. All 55 patients continued taking ACE inhibitors; however, in 1 patient, malignant hypertension and renal failure recurred despite continuing captopril. Several patients later had successful pregnancies (9).

Thirty-four patients (23%) received temporary dialysis, which was discontinued after 2 to 18 months (mean, 8 months). The mean serum creatinine concentration was 239 μmol/L (2.7 mg/dL) when dialysis was discontinued and decreased to 194 μmol/L (2.2 mg/dL) 6.1 years later. All 34 patients continued taking ACE inhibitors, although 1 nonadherent patient later returned to dialysis. Of the 32 patients (3 from the good outcome group, 1 from the temporary dialysis group, and 28 from the permanent dialysis group) who received permanent dialysis (19%), 9 had chronic peritoneal dialysis and 23 had hemodialysis. Six patients who received kidney transplants after 4 or more years of dialysis have continued taking ACE inhibitors without recurrence of renal crisis. Initial blood pressure, serum creatinine concentration, choice of ACE inhibitors, and need for additional antihypertensive medication were similar in both dialysis groups. Serum creatinine concentration increased more slowly in the permanent dialysis group. All patients in the temporary dialysis group but only 75% of those in the permanent dialysis group continued taking ACE inhibitors while receiving dialysis.

Figure 1. **Relation of serum creatinine concentration to time of renal crisis in 145 patients with systemic sclerosis.**



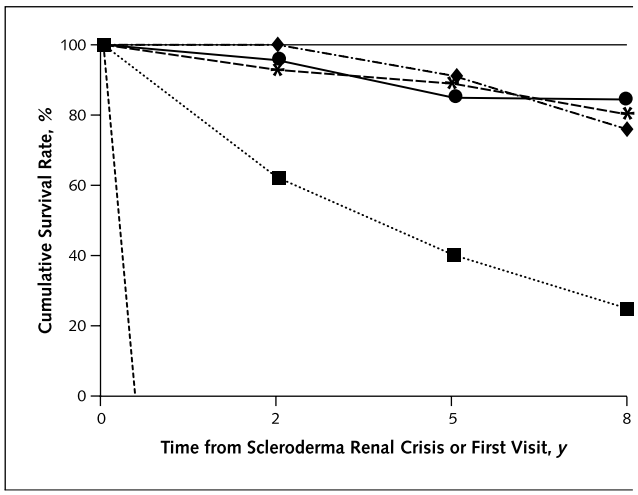
The solid line indicates those who did not receive dialysis ($n = 51$), the dotted line indicates those who received permanent dialysis ($n = 25$), the dashed line indicates those who died early ($n = 23$), and the dashed and dotted line indicates those who received temporary dialysis ($n = 34$). Patients who did not have a late follow-up measurement of creatinine were excluded. To convert mg/dL to μmol/L, multiply by 88.4.

Twenty-eight patients died early (19%), a mean of 3 months after renal crisis. Patients in this group were more frequently male (33% vs. 16% in other groups), were significantly older (54 years vs. 46 years), and had a higher initial serum creatinine concentration. Sixty-four percent required dialysis. Patients in this group were more likely to have scleroderma myocardial disease (43% vs. 5%) than those in the no dialysis or temporary dialysis groups. Multiorgan failure (involving the heart, gastrointestinal tract, and lungs), infection, and problems with dialysis were the most common causes of death.

Survival

Survival of patients in the no dialysis and temporary dialysis groups was similar to that of the 662 patients who had diffuse scleroderma without renal crisis. The 5-year cumulative survival rate was 90%, and the 8-year cumulative survival rate was 80% to 85% (**Figure 2**). Treatment with D-penicillamine and methotrexate was significantly

Figure 2. **Cumulative survival rate for patients with different outcomes after scleroderma renal crisis and patients with diffuse scleroderma who did not have renal crisis.**



The solid line indicates those who did not receive dialysis ($n = 55$), the dotted line indicates those who received permanent dialysis ($n = 28$), the small dashed line indicates those who died early ($n = 28$), the dashed and dotted line indicates those who received temporary dialysis ($n = 34$), and the large dashed line indicates those who did not have renal crisis ($n = 662$).

less common in patients with renal crisis than in those without.

Complications of Dialysis

Patients with scleroderma renal failure had dialysis-related complications that were similar to those of other patients with renal failure. Of patients for whom we had adequate information to determine complications, 70% of the 33 patients who received hemodialysis had central catheters. Patients with scleroderma and those without had similar rates of thrombosis of access grafts; some patients with scleroderma had functioning arteriovenous grafts for up to 10 years. Severe ischemia and gangrene did not occur. Only 1 patient, an elderly woman with previous severe Raynaud phenomenon, experienced acute onset of new severe digital-tip ulcers, which eventually led to the removal of the graft. The rate of hemodialysis complications per patient-year (6) ranged from 0.44 per patient-year in the permanent dialysis group to 0.58 per patient-year in the temporary dialysis group. These findings are similar to those seen in patients without scleroderma who were receiving hemodialysis (6).

Only 14 patients received peritoneal dialysis, which was usually long-term and ambulatory. Four other patients did not have adequate clearance to use this type of dialysis. Patients with scleroderma who received peritoneal dialysis had the same type and frequency of catheter infections, catheter obstruction, and peritonitis as patients in a previous study who received peritoneal dialysis but did not have scleroderma (7).

DISCUSSION

The use of ACE inhibitors has dramatically improved outcomes and survival in patients with scleroderma renal crisis (1). However, if diagnosis of renal crisis is delayed or if ACE inhibitors are not used aggressively, irreversible kidney damage and death can still occur. Our study confirms that patients with early diffuse scleroderma are at greatest risk for developing scleroderma renal crisis and should be encouraged to monitor their own blood pressure. Some patients in renal crisis present without the Raynaud phenomenon or skin thickening but usually have swollen hands or legs, fatigue, arthralgia, carpal tunnel syndrome, palpable tendon friction rubs, or anti-topoisomerase antibody (2–5, 8, 10); these findings should lead physicians to suspect the disorder. A new antibody, anti-RNA polymerase III, is highly specific for scleroderma, and renal crisis occurs in 25% to 33% of patients who have it (8, 11); however, it is not yet commercially available. Anticentromere antibodies are extremely uncommon.

The patients in our study had the classic presentation of renal crisis: severe hypertension and a rapidly increasing serum creatinine concentration. During 10 years of follow-up, we did not observe asymptomatic, silent development of renal failure (12). On the basis of our findings, we believe that ACE inhibitor therapy should be started as soon as scleroderma renal crisis is diagnosed. The best outcome—no dialysis—was achieved in patients who began taking ACE inhibitors when their creatinine concentration was less than 265 μmol/L (3 mg/dL). It is important to note that fewer than 5% of patients who initially did not require dialysis needed it later. Because we have not seen any patient in renal crisis improve after stopping ACE inhibitor therapy, we think that such therapy should be continued even if the serum creatinine concentration increases after blood pressure has been controlled. Of the 62 patients receiving dialysis, 55% were able to permanently discontinue it. Although the relationship was not statistically significant, continued use of ACE inhibitors may have con-

tributed to this result. Therefore, we believe that patients should continue to receive at least a small dose of ACE inhibitors indefinitely if there is any chance for additional improvement in kidney function.

We found that management of dialysis in patients with scleroderma renal crisis was not as difficult as has been described elsewhere (13). Only one of our patients experienced major vascular compromise. Peritoneal dialysis was generally well tolerated, and some patients preferred it (7). Patients who never required dialysis and those who were able to discontinue it had excellent long-term outcomes, similar to those of patients who had diffuse scleroderma without renal crisis. These patients continued taking ACE inhibitors, and their serum creatinine concentrations continued to improve slowly over time. Only 4 of the 89 patients with good outcomes (4%) later required permanent dialysis. Renal crisis, however, continues to be associated with many early deaths. Patients who die tend to have multiorgan involvement, often including scleroderma heart disease.

In summary, we found that prompt, aggressive treatment with ACE inhibitors greatly decreased the need for dialysis in a cohort of patients with scleroderma renal crisis. More than 50% of patients who initially required dialysis were able to discontinue it permanently. Patients who required no or only temporary dialysis rarely developed renal failure at a later date. The survival of patients who required no dialysis or only temporary dialysis was as good as that of patients who had diffuse scleroderma without renal crisis. We strongly recommend that patients with early diffuse scleroderma be closely monitored for new onset of hypertension and that they subsequently receive aggressive, continuous treatment with ACE inhibitors.

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