Renal manifestations of systemic sclerosis—clinical features and outcome assessment

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Renal manifestations occur frequently in scleroderma (SSc). Commonest is a reduction in renal function due to chronic disease but most clinically important is the scleroderma renal crisis (SRC). This life-threatening complication occurs in up to 15% of the cases of dcSSc. Mortality is reduced by use of angiotensin converting enzyme (ACE) inhibitors. Renal outcome can be assessed by quantifying renal function, measuring proteinuria, exploring the frequency of renal crisis episodes and through assessment of renal outcome following SRC—such as frequency and duration of dialysis, or recovery of renal function.

Key words: Scleroderma, Renal crisis, Incidence, Biopsy, Treatment, Endothelin-1.

Introduction

Renal complications are common in scleroderma (SSc) although they are not always clinically significant. Compared with other disease manifestations it is a major advantage in renal assessment in SSc that renal function can be quantitative as there are a large number of easily measurable variables. These are listed in Table 1. However, interpretation of the significance of individual measurements is less clear. In assessing scleroderma renal disease the most important end-point is reasonably considered to be scleroderma renal crisis (SRC); however, this is confounded by the absence of an adequately clear definition. In addition, renal involvement due to more than one pathology is often present and it has been shown that asymptomatic chronic kidney disease is often present in SSc.

Overview of renal involvement in SSc

Scleroderma renal crisis

SRC occurs in 10–15% of the patients with dcSSc and only vary rarely (1–2%) in lcSSc [1, 2]. Most cases occur within the first 12 months of the disease and in up to a quarter of patients with SRC, the diagnosis of SSc is made at the time of the renal presentation. Typically, patients present with accelerated hypertension and progressive renal impairment. End-organ damage can result in encephalopathy with generalized seizures or flash pulmonary edema. Microangiopathic anaemia is common, and disseminated intravascular coagulation may develop (Table 2). Approximately two-thirds of the cases of SRC require renal replacement therapy [1]. Of these, half eventually recover sufficiently to discontinue dialysis. This can occur for up to 24 months, and so decisions about renal transplantation should be postponed until that time. The possibility for delayed renal recovery distinguishes SRC from other causes of end-stage renal failure. Historically, SRC was the commonest form of scleroderma-associated death [3]. Dramatically improved outcomes in the short-term are achieved with the use of angiotensin converting enzyme (ACE) inhibitors as routine therapy for established SRC. It remains unclear whether these or related drugs, such as angiotensin receptor blockers (ARBs), are effective in preventing or abrogating SRC. Corticosteroids, along with cyclosporin [4], have been implicated as precipitants of SRC [5, 6].

Management of renal crisis in SSc

In all cases, hospital admission and prompt initiation of ACE inhibitor (e.g. captopril or once-daily agents as oral therapy) as cornerstone of therapy is recommended. Dose should be increased daily to achieve a systolic blood pressure reduction of 10–20 mmHg/24 h, even if there is continued deterioration in renal function, which can be followed by daily creatinine clearance or calculated glomerular filtration rate (GFR). Patients are routinely given continuous low-dose prostacyclin that may help control blood pressure and has potentially beneficial effects on renal blood flow [7], endothelial cell function and production of pro-inflammatory or profibrotic factors [8]. This is currently without formal confirmation of benefit. Additional antihypertensive agents may be useful including combinations of ARB and ACE inhibitors or calcium channel blockers, nitrates (especially if pulmonary oedema) or other vasodilator agents such as doxazosin. Care must be taken to monitor cardiac function closely. Vasodilatation may be associated with relative hypovolaemia. SVR monitoring using an oesophageal Doppler probe can be used and offers an alternative to more invasive monitoring such as pulmonary arterial balloon catheter.

Although improved by treatment, outcome of SRC remains inadequate. Early mortality approaches 10% and up to half of the patients need dialysis. This may be temporary, with up to half of the cases needing renal replacement therapy eventually coming off dialysis although this may be between 6 and 24 months after the initial SRC. For this reason, even though allografts appear no less successful in SSc than in SLE, final decisions should not be made until at least 2 yrs after the renal crisis. There is firm evidence that renal transplant offers superior survival in SSc compared with long-term dialysis [9]. Almost all cases of suspected SRC managed in our unit have renal biopsy, which may provide prognostic information and also confirms the diagnosis. A number of cases of SSc with inflammatory glomerular pathology have been identified and these require potentially very different treatment to classical SRC.

Other forms of renal involvement in SSc

Several patterns of renal pathology are recognized in patients with SSc: almost all involve vascular abnormalities. Apart from SRC described above, many patients demonstrate less severe renal complications, probably associated with reduced renal blood flow and the consequent reduction in GFR. The mechanism of this slowly progressive form of chronic renal disease is unclear.

Other acute renal complications may occur, especially in overlap syndromes with lupus nephritis. There may be serological clues that a patient is evolving within the CTD spectrum that asymptomatic chronic kidney disease is often present in SSc.
Renal manifestations of SSc

Levels of cytokines, growth factors and oxidant stress as markers of scleroderma renal disease

In the research arena, there are many potential measures of renal pathophysiology that can be assessing serum, plasma and urine. These include mediators of fibrosis such as TGF-β and connective tissue growth factor (CTGF), vascular markers such as soluble vascular cell adhesion molecule-1 (sVCAM-1) [12, 13], markers of prostacyclin synthesis such as isoprostanes, and peptides such as ET-1 that may have broader roles in pathogenesis. At present, soluble markers are of interest in research protocols rather than for routine management. Similarly, there is evidence of up-regulation of a number of key vascular and fibrotic markers in renal biopsy specimens. The association of SRC with increased plasma concentration of ET-1 [14] as well as up-regulation of ET-1 and endothelin receptors in renal biopsy samples [15] suggests that endothelin receptor antagonists (ETRAs) may be of value in SRC, perhaps as an adjunct to conventional therapy. This is being explored in clinical trials, although the potential role of endothelin in renal homeostasis may be relevant. It is noteworthy that renal dysfunction is not regarded as a significant side-effect of licensed ETRAs such as bosentan or sitaxentan that are in current use for pulmonary arterial hypertension. The sporadic nature of SRC may be explained by association with anti-RNA polymerase antibodies [16], which in turn have genetic association with genetic polymorphisms in endothelin receptor subtypes [17].

Renal biopsy analysis

Although renal biopsy is often performed in SSc cases it is not likely to be useful as an end-point for clinical studies. In SRC, it is of value to perform a biopsy to confirm diagnosis and assess the extent of acute markers of vascular injury that associate with outcome. In addition, biopsies provide valuable opportunities to explore expression and activity of key potential mediators or markers of renal damage (see above). In cases where there is diagnostic uncertainty such as those with co-existent clinical or serological features of SLE or vasculitis, it is essential that cases of significant renal impairment are biopsied to determine the presence of inflammatory glomerular disease that may require additional or different management to that of hypertensive renal crisis. Likewise, any cases of renal impairment or significant proteinuria in the absence of hypertension require consideration for renal biopsy. One possibility in this case is a normotensive SRC, a subset of SRC with especially poor outcome. Interestingly, in a recent series examining biopsy changes in SRC, chronic renal scarring did not seem important but the presence of acute vascular injury predicted poor outcome [1].

### Table 1. Potential outcome measures for renal disease in scleroderma

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Renal function assessment</td>
<td></td>
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<tr>
<td>Isotope GFR</td>
<td>Gold standard assessment is isotope</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Low cost but full collection may be difficult.</td>
</tr>
<tr>
<td>eGFR</td>
<td>Good correlation with other measures.</td>
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<tr>
<td>Serum creatinine</td>
<td>Low sensitivity for change and confounded by</td>
</tr>
<tr>
<td>Urinary protein excretion</td>
<td>Significant proteinuria suggests renal</td>
</tr>
<tr>
<td>Renal blood flow assessment</td>
<td>Doppler assessment feasible as a research</td>
</tr>
<tr>
<td>Vascular markers</td>
<td>ET-1, VCAM-1 and other markers of vascular</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td></td>
</tr>
<tr>
<td>Renal crisis frequency</td>
<td>Low frequency and in 20% of the cases</td>
</tr>
<tr>
<td>Renal biopsy</td>
<td>Useful to differentiate other pathology and</td>
</tr>
<tr>
<td>Dialysis requirement</td>
<td>Frequency and duration of dialysis</td>
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### Table 2. Key features of scleroderma renal crisis

SRC is a clinical syndrome of acute renal failure and accelerated hypertension in the presence of SSc.

**Risk factors**
- Recent-onset diffuse scleroderma
- Active, progressive skin disease
- Tendon friction rubs
- Anaemia
- New cardiac events
- Steroid use (>15 mg prednisolone/day)
- Presence of anti-RNA polymerase III

**Key clinical features**
- Patients with SRC will typically have an acute or sub-acute presentation with fluid overload and/or symptoms of end-organ complications of hypertension.
- New onset hypertension (>90%)
- Acute renal failure
- Hypertensive retinopathy (>60%)
- Pulmonary oedema (>50%)
- Encephalopathy (20%)
- Seizures (10%)

### titre of an associated anti-dsDNA antibody

It has been suggested that ANCA reactivity may predict unusual renal complications of SSc, such as glomerulonephritis and renal vasculitis [10]. Some of these changes occur in SSc patients treated with d-penicillamine. Indolent chronic renal involvement, characterized by a slow decrease in GFR accompanied by proteinuria, has been described in SSc [11].

### Renal function assessment in SSc

Measurement of GFR is central to the determination of renal blood flow and intrinsic renal damage. Although isotope GFR is considered the gold standard it is also possible to assess renal function by creatinine clearance or estimated GFR. The latter takes account of size and surface area and several different formulae are available. It has been demonstrated in SSc that the modification of diet in renal disease (MDRD) formula correlates well with other estimates and with GFR measured by creatinine clearance, and thus is probably the test of choice for non-invasive monitoring of renal function.

### Measurement and significance of proteinuria

Simple measures of renal function are helpful in assessing the presence of clinically significant renal disease and have an important place in clinical practice. However, the significance of borderline abnormalities and value for predicting future clinically important events is much less clear. Protein:creatinine ratio is a more convenient measure of proteinuria than 24 h excretion as it can be performed on a single urine sample. The significance of change in response to therapy is uncertain.

Markers of tubular proteinuria have been examined in one small study. There was a high frequency of proteinuria but this did not correlate with renal function as assessed by the MDRD formula to estimate GFR. Likewise, there were a significant number of cases demonstrating glomerular proteinuria and microalbuminuria. This may be of clinical significance but prospective studies are necessary.
Renal blood flow assessment

There have been several studies exploring the use of Doppler angiology to assess renal blood flow. These have included some interventional studies that have shown, for example, improved renal blood flow after prostacyclin infusion. For this reason such non-invasive tests may have a useful place in the evaluation of specific renal cases. Such approaches are far from applicable to routine assessment at present.

Methodologies for clinical studies that evaluate renal involvement in SSc

Design of studies to evaluate treatments that could affect renal disease in SSc is complicated by the fact that much renal involvement is not of immediate clinical significance and the relative rarity of SRC, which makes it a challenge to evaluate, in a prospective cohort of patients. To overcome this other study designs have been used. The first studies that explored the efficacy of ACE inhibitors in treatment of SRC used case-control design and suggested a dramatic benefit, making subsequent conventional placebo-controlled studies unethical. Other information has come from cohorts of patients examined in other clinical trials such as the D-penicillamine study or from retrospective data collection in well-characterized groups of patients [5]. However, such approaches have significant limitations. In the future, it may be possible to perform prospective randomized studies that look into preventative strategies. This has been suggested although it is unclear whether case enrichment would be needed to ensure an adequate event frequency. For example, restricting cases to early dcSSc may be appropriate or focusing on cases that carry the anti-RNA polymerase III autoantibody, which is strongly associated with SRC. Perhaps the most robust end-point for SRC study is the frequency of such events according to consensus criteria.

Outlook

Even today, the long-term mortality after SRC remains poor, especially if chronic dialysis is needed. This may reflect co-morbidity in a subgroup of patients with active or extensive SSc but emphasizes that this is an important complication. In the future, the main points that need to be addressed in research are whether additional vasoactive mediators may be targeted in a way that further improves outcome, what the significance of renal impairment in SSc is and whether treatments may prevent the development of SRC and so be used prophylactically in high-risk cases [18].

Rheumatology key messages

- SRC, interstitial fibrosis and glomerulonephritis all occur in scleroderma.
- SRC requires prompt diagnosis and treatment with ACE inhibitors.
- Renal biopsy confirms diagnosis and provides critical insight into pathogenesis.
- Endothelin is a logical potential target for therapy in renal scleroderma.

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References