Full Reviews

Treatment of renal sarcoidosis: is there a guideline? Overview of the different treatment options

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Abstract

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology characterized by the presence of noncaseating granulomas. It may affect any organ including the kidney. A disordered calcium metabolism is most often responsible for the development of renal failure. Granulomatous interstitial nephritis is the most typical histological finding, but it rarely leads to renal insufficiency. Since development of renal insufficiency in sarcoidosis is uncommon, we lack large (randomized) trials concerning the treatment of this disorder. We gather most information from case reports and small series. Our knowledge of pulmonary sarcoidosis is more comprehensive. It is, however, impossible to treat renal manifestations identically because some of the drugs used in pulmonary sarcoidosis are nephrotoxic. Moreover, renal sarcoidosis is a specific entity with its own characteristics and response to therapy. A guideline for treatment is currently missing. Based on a review of the literature, we present an overview of the different treatment options to promote a more uniform and scrutinized approach of this disease. Hypercalcaemia and hypercalciuria can be treated with corticosteroids, (hydroxy)chloroquine or ketoconazole. Preventive measures play a supportive role. In granulomatous interstitial nephritis, glucocorticoids are the standard of care. In patients with failure of or a contraindication to corticosteroids or in those patients who need a high maintenance dose of corticosteroids, azathioprine or mycophenolate mofetil can be used. TNF-alpha inhibitors are useful in case of steroid-resistant sarcoidosis or in patients who develop severe steroid toxicity. With increasing insight in the pathogenesis of sarcoidosis, other immunosuppressive drugs have been proposed, but more research is necessary before their routine use can be advocated.

Keywords: kidney, sarcoidosis, treatment

Introduction

Sarcoidosis is a multisystem inflammatory disease characterized by the presence of noncaseating epitheloid granulomas [1]. At early stages, an accumulation of activated T cells and macrophages is observed at sites of ongoing inflammation. These activated cells release chemo-attractants and growth factors, which leads to granuloma formation. These granulomas can resolve without sequelae or result in the development of fibrosis [2]. The aetiology of the disease is yet to be discovered. It is possibly triggered by an unknown environmental factor (infection? toxicity?) in people with a genetic predisposition [3].

The disease typically presents in young and middle-aged adults. It has a benign course with spontaneous resolution in up to two-thirds of cases. However, in one-third a chronic disorder develops leading to significant organ impairment [4]. Sarcoidosis may affect any organ, but most commonly it involves the lungs, lymph nodes, skin and eyes [4, 5]. The incidence of renal involvement remains unclear. In autopsy studies a granulomatous infiltrate is found in the kidneys in up to 23% and even up to 48% in small series of biopsy findings [6, 7].

Even though sarcoidosis is a well-known disease, its renal manifestations remain elusive and evidence regarding diagnosis and treatment is scarce. Despite difficulties due to limited patient numbers, future randomized controlled trials are warranted. In this review, we will describe the available data on the renal manifestations of sarcoidosis, its diagnosis and treatment options.
METHODS

We conducted a systematic literature search of the Medline database. The search terms used were ‘kidney, sarcoidosis and treatment’. We excluded studies published as abstracts only and restricted to those published in English and French. We excluded articles on the treatment of extrarenal sarcoidosis. The reference list of the identified relevant studies was manually searched for additional citations.

RENAL MANIFESTATIONS

Sarcoidosis is associated with a broad spectrum of renal manifestations, as we discuss here in detail. The most important cause of renal dysfunction is a disordered calcium metabolism [5–9]. Interstitial granulomatous nephritis is the most typical histological finding, but development of renal insufficiency is unusual. Finally, there is a wide range of glomerulopathies associated with sarcoidosis. Different types of renal sarcoidosis have also been reported to coexist [1, 10, 11].

Hypercalcaemia and/or hypercalciuria

Hypercalcaemia presents in 10–17% of patients with sarcoidosis, hypercalciuria in 40–62% of patients [1]. These features may fluctuate with disease activity or a patient’s total UV light exposure [6].

In sarcoidosis and other granulomatous disorders, 1-alpha hydroxylase is synthetized by granulomas and activated macrophages. This enzyme activity is responsible for the increase in 1,25-dihydroxy vitamin D and is resistant to normal negative feedback mechanisms [1, 5, 7]. As a result, 1,25-dihydroxy vitamin D levels in sarcoidosis are directly related to the availability of its substrate, 25-hydroxy vitamin D. 1,25-dihydroxy vitamin D augments the gastro-intestinal calcium absorption, stimulates the osteoclast activity and bony reabsorption and increases renal tubular calcium reabsorption. The net result is an increase in plasma calcium and thus hypercalcaemia. Additionally, the rise in 1,25-dihydroxy vitamin D causes a suppression of parathyroid hormone (PTH) by a direct as well as an indirect mechanism by producing hypercalcaemia. This decreased PTH synthesis along with an increased renal calcium load results in the development of hypercalciuria [1, 3, 6, 11].

A disordered calcium homeostasis is responsible for the development of renal dysfunction by several different mechanisms. Hypercalcaemia promotes a decrease in glomerular filtration rate by vasoconstriction of the afferent arteriole. Second, it inhibits sodium-potassium ATP-ase leading to urinary sodium wasting with polyuria and dehydration. Third, urinary concentration is impaired by a decreased sensitivity to anti-diuretic hormone. Finally, acute tubular necrosis may result from intracellular calcium overload and tubular obstruction by calcium precipitates. Hypercalciuria predisposes to nephrolithiasis and obstructive uropathy. Untreated, chronic hypercalcaemia and hypercalciuria causes a progressive tubulo-interstitial inflammation with associated calcium deposits leading to nephrocalcinosis, which is the leading cause of chronic kidney disease in sarcoidosis [3, 6, 11]. In the acute phase, the consequences of hypercalcaemia and hypercalciuria are reversible. Once fibrotic lesions have developed due to longstanding disease, the damage is irreversible [11].

Granulomatous interstitial nephritis

Granulomatous interstitial nephritis is the most common renal lesion seen on biopsy. It can present either as acute or chronic renal failure [1, 11]. The true incidence is unknown, but in autopsy studies of patients with sarcoidosis, a granulomatous infiltrate is found in the kidneys in 7–23%, although many remained clinically silent [6, 7]. In several small series of biopsy findings a much greater frequency of kidney involvement is suggested. Renal abnormalities were reported in 10–48% of patients with chronic sarcoidosis [12, 13].

Glomerular disease

Glomerular involvement in sarcoidosis is rare, although a variety of different lesions have been described including membranous nephropathy, focal segmental sclerosis, mesangioproliferative glomerulonephritis, IgA nephropathy and crescentic glomerulonephritis [3, 14, 15]. There is no clinical or histological characteristic that distinguishes sarcoid-associated glomerulopathy from the primary form. It is unclear whether therapy should be tailored to the specific glomerulopathy or should be identical to the treatment of granulomatous interstitial nephritis (Figure 2) [11].

Tubular dysfunction

Tubular dysfunction is frequently associated with hypercalcaemia and granulomatous interstitial nephritis. It may present as isolated proximal or distal tubular acidosis, Fanconi syndrome, urinary concentration deficits or metabolic alkalosis [6].

Obstructive and vascular uropathy

Obstructive uropathy is usually due to nephrolithiasis and this can be the first manifestation of the disease. Retropertitoneal fibrosis, retroperitoneal lymph nodes and ureteral, urethral or bladder obstruction by sarcoid involvement can also cause obstructive disease [3, 6].

Granulomatous angiitis is a rare complication of sarcoidosis and can involve the renal artery. It is often accompanied by arterial hypertension [11].

DIAGNOSIS

The diagnosis of renal sarcoidosis is made by exclusion. Whenever the diagnosis is clinically suspected, a histopathological confirmation should be attempted. Sarcoidosis is a systemic granulomatous disease and the diagnosis usually requires the demonstration of typical lesions in more than one organ system [9]. Although sarcoid-related granulomatous interstitial nephritis is often accompanied by systemic manifestations, isolated renal sarcoidosis is an accepted entity [6, 7]. It can also be the early manifestation of a systemic disease. In case of isolated renal disease, a heightened vigilance is warranted to exclude other reasons of granulomatous inflammation [6]. Granulomatous conditions that can mimic renal sarcoidosis
include allergic reactions due to medication use (e.g. beta-lactam antibiotics, nonsteroidal anti-inflammatory drugs), infections (e.g. tuberculosis), neoplasia and autoimmune disorders (e.g. granulomatosis with polyangiitis) [14, 16–18]. The absence of characteristic kidney biopsy findings does not exclude the diagnosis as renal sarcoidosis can be focal in nature and characteristic lesions can easily be missed in biopsy [10, 16].

The urinary manifestations of renal sarcoidosis are not specific either. Granulomatous interstitial nephritis is often associated with mild proteinuria and more rarely with aseptic pyuria and microscopic haematuria. In glomerular disease, more overt proteinuria or the presence of red cell casts is more typical. Importantly, a blank urine sediment does not exclude renal involvement [10]. As hypercalciuria is a frequent finding in patients with sarcoidosis [1], the measurement of urinary calcium excretion may help in establishing the diagnosis of renal sarcoidosis.

Serum angiotensin converting enzyme is often elevated, as is the case in extrarenal sarcoidosis. The enzyme is produced by epitheloid cells, multinucleated giant cells and macrophages within granulomas, but it is nonspecific and has limited sensitivity. It can be elevated in other granulomatous disorders and even in non-granulomatous diseases as diabetes and end-stage renal disease of varying causes. Considering its poor specificity, it has a limited role in the diagnosis of sarcoidosis, but can be used as a marker for disease activity and response to treatment [6, 11, 17].

**TREATMENT**

Treatment is always required for renal, cardiac, ocular and neurologic manifestations of sarcoidosis, given the substantial risk of end-organ damage [4, 19]. We gather most information from case reports and small series. Much more is known about the more prevalent pulmonary sarcoidosis. It is, however, impossible to extrapolate these findings to renal sarcoidosis. First, some drugs used in pulmonary disease are nephrotoxic, which precludes liberal use in case of renal involvement. Second, renal sarcoidosis is a specific entity with its own characteristics and response to treatment. Until now, a guideline for treatment is lacking. Based on a review of the existing literature we present an overview of the different treatment options (Figure 1).

**Treatment of hypercalcaemia and hypercalciuria**

As mentioned earlier, hypercalcaemia promotes dehydration. In general, patients with severe (>3.5 mmol/L) or symptomatic hypercalcaemia require intravenous saline hydration as initial therapy [20]. The specific treatment is aimed at treatment of the underlying disorder. Glucocorticoids are the first choice as they diminish the amount and activity of granulomas, block the activity of 1-alpha hydroxylase in macrophages and diminish the absorption of calcium [3]. Most authors recommend a starting dose of 0.3–0.5 mg per kg once daily [1]. Recommendations on maintenance dose and duration of treatment have not been established. Demetriou et al. [21] proposed a prednisone taper to a maintenance dose of 5–10 mg once daily and a total duration of treatment of at least 12 months. Chloroquine is an alternative to corticosteroids. The optimal dose is unknown, but a daily dosage of 250–500 mg is most often used. Retinal toxicity is the major concern. Hydroxychloroquine is supposed to be slightly less effective, but carries less risk of retinopathy. Recommended daily dosing is 200–400 mg. The effect of these agents is less predictable and slower than treatment with corticosteroids [1, 3, 19, 21]. Ketoconazole in a daily dose of 600–800 mg is an alternative as well and corrects hypercalcaemia by inhibiting the production of 1,25-dihydroxy vitamin D. Hepatic toxicity is the major limiting side effect [21].

Preventive measures such as a low dietary intake of calcium, vitamin D and oxalate as well as the limitation of sunlight exposure play an additional supportive role. Thiazide use should be avoided given the substantial risk of aggravating hypercalcaemia [3, 6, 21] (Figure 2).

<table>
<thead>
<tr>
<th>Hypercalcaemia and hypercalciuria in sarcoidosis</th>
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<tbody>
<tr>
<td><strong>Intravenous saline hydration</strong></td>
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<tr>
<td>- Severe (&gt; 3.5 mmol/L) or symptomatic hypercalcaemia</td>
</tr>
<tr>
<td><strong>Standard of care: glucocorticoids</strong></td>
</tr>
<tr>
<td>- Starting dose: 0.3 – 0.5 mg/kg/d</td>
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<tr>
<td>- Maintenance dose: 5 – 10 mg/d</td>
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<tr>
<td>- Total duration of treatment: at least 12 months</td>
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<tr>
<td><strong>Alternatives</strong></td>
</tr>
<tr>
<td>- Chloroquine</td>
</tr>
<tr>
<td>- Dose: 250 – 500 mg/d</td>
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<tr>
<td>- Hydroxychloroquine</td>
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<td>- Dose: 200 – 400 mg/d</td>
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<td>- Ketoconazole</td>
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<tr>
<td>- Dose: 600 – 800 mg/d</td>
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<tr>
<td><strong>Preventive measures</strong></td>
</tr>
<tr>
<td>- Limit sunlight exposure</td>
</tr>
<tr>
<td>- Low dietary intake of calcium, vitamin D and oxalate</td>
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<tr>
<td>- Avoid thiazide use</td>
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**FIGURE 1:** Suggested treatment of hypercalcaemia and hypercalciuria in sarcoidosis.
Treatment of granulomatous interstitial nephritis

Glucocorticoids. Glucocorticoids remain the cornerstone of treatment despite its adverse effect profile. However, there is no standardized protocol for doses or duration. The response to therapy was best noted in the study of Mahévas [10] and the study of Rajakariar [7]. Both were retrospective series of patients with sarcoid-related granulomatous nephritis treated with prednisone. As shown in Table 1, most patients had an impressive treatment response, but relapses were frequent.

Most authors recommend starting with an initial dose of 0.5–1 mg per kg oral prednisone once daily depending on the severity of the disease [1, 4, 6, 7, 10, 11, 19]. The highest dose regimen is warranted in case of major organ impairment, to increase the likelihood of a complete response. A dose of 0.5 mg per kg once daily is often sufficient in case of milder disease [19]. In the study of Mahévas, 10 patients received intravenous pulse methylprednisolone. Five of them (50%) had an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m² according to the Modification of Diet in Renal Disease (MDRD) formula at the end of follow-up, compared with 27.7% of the patients treated with oral steroids (n = 36). Although there was a tendency to have a better renal outcome when treated with intravenous methylprednisolone, the difference regarding the response to conventional corticosteroid treatment was not significant [10].

The initial dose should be maintained for 4 weeks, to allow improvement and/or stabilization of renal function. As stated in the study of Mahévas, the long-term renal response to treatment is related to the response at 4 weeks, suggesting that granulomatous interstitial nephritis is mostly rapidly responsive to treatment and remains stable with ongoing treatment [10]. Patients with a poor response after 1 month tend to have a worse renal outcome and are more susceptible to relapse [6, 10]. After 4 weeks of treatment, the dose can be tapered by 5 mg each week [7] until a daily dose of 5–10 mg is reached. The goal is to find the smallest possible dose avoiding relapse. When corticosteroids are tapered too brisk, there is an increased risk of relapse. In that case, the dose should be augmented to the last effective dose [19] and continued for a subsequent 4 weeks. If there is no improvement after 4 weeks, the glucocorticoids are augmented to the initial dose. Subsequent tapering should be more gradual than the taper that led to the relapse. In some patients it is impossible to taper the glucocorticoids adequately. Given the many side effects of a prolonged treatment with high-dose glucocorticoids, a steroid-sparing agent (azathioprine or mycophenolate mofetil) can be added aiming at subsequently reducing the glucocorticoid dose [6, 10].

It is difficult to establish the ideal duration of maintenance therapy. Relapses are frequent following withdrawal of
treatment. Given the insidious nature of renal sarcoidosis, these relapses are often difficult to diagnose. They can lead to a further deterioration of renal function, which may irreversibly progress to end-stage renal disease. A total treatment duration of 18–24 months seems necessary to be effective and to prevent relapse [1, 3, 10]. Lifelong treatment with low-dose glucocorticoids may be required for a minority of patients who suffer frequent relapses, although some authors advocate an indefinite treatment for all patients [7]. There are, however, important side effects from long-term steroid use, which need to be balanced against the risk of progression to end-stage renal disease [7].

Most patients respond to treatment, but a full recovery of renal function is rare. There seems to be an inverse relationship between the response to treatment and the initial degree of interstitial fibrosis. Other histological parameters (presence of epitheloid granulomas, tubular atrophy, etc.) have no proven predictive value. It is important to initiate therapy as soon as possible to prevent worsening of fibrosis [10].

As mentioned earlier, corticosteroids have many well-known side effects, the most important of which are diabetes, hypertension, osteoporosis and central obesity [22]. Osteoporosis is particularly difficult to prevent because the supplementation of calcium and vitamin D in a patient with sarcoidosis heralds a risk of aggravating or inducing hypercalcaemia and/or hypercalciuria. When renal insufficiency is mild to moderate, adding a bisphosphonate can help prevent the development of osteoporosis and its complications [2, 19, 23, 24]. Furthermore, bisphosphonates have an additional calcium lowering effect [25]. However, treatment with bisphosphonates, especially when used in high dose for a prolonged duration, can be nephrotoxic [26]. Pamidronate can lead to collapsing focal segmental glomerulosclerosis, and can also cause severe tubulointerstitial nephritis [26, 27]. A variety of other bisphosphonates are associated with toxic acute tubular necrosis [26]. In the setting of renal sarcoidosis, it is important to consider this in the differential diagnosis of a decreased kidney function.

Azathioprine and mycophenolate mofetil. Azathioprine and mycophenolate mofetil are immunosuppressive drugs, which can be used as steroid-sparing agents or in patients with failure or a contraindication to corticosteroids. We propose to start treatment with these drugs only after at least 1 month of treatment with glucocorticoids, since this time is needed to allow improvement or stabilization of renal function.

Azathioprine should be given in a daily dose of 2 mg per kg, mycophenolate mofetil in a dosage of 1 g, twice a day [1, 10, 19, 28]. The evidence in support of these second-line agents is very limited. Benefit has only been reported in small case series [10, 28]. Mahévas reported three patients with a renal relapse in whom azathioprine (n = 1) and mycophenolate mofetil (n = 2) were used and allowed a sustainable control of renal function while reducing the steroid level below 5 mg daily for two patients and 12 mg daily for one patient. No severe adverse events relative to the immunosuppressive therapy were reported [10]. Moudgil reported a case of a 15-year-old boy who presented with severe renal failure (eGFR 10.3 mL/min/1.73 m²) due to renal limited sarcoidosis [28]. After 3 months of corticosteroid therapy, there was an impressive improvement in kidney function (eGFR 68.5 mL/min/1.73 m²). However, the child developed significant side effects (e.g. weight gain, fasting hyperglycaemia). Because of these steroid side effects, a treatment with mycophenolate mofetil 500 mg twice daily was started. The dose was increased to 1000 mg twice daily over the next 2 months and the prednisone was tapered and finally discontinued after 4 months. Treatment with mycophenolate mofetil led to a further improvement of kidney function, which remained stable during the course of the treatment. After 1 year of treatment, the estimated glomerular filtration rate was 80.8 mL/min/1.73 m² according to the MDRD formula [24]. Le Benerais also mentioned the use of azathioprine and mycophenolate mofetil in steroid-resistant patients, but his series did not include such patients [1].

Methotrexate. Methotrexate is an important agent in the treatment of extrarenal sarcoidosis where it can be used as an alternative to corticosteroids or as a steroid-sparing agent [2, 4, 19]. Even though low-dose methotrexate is not nephrotoxic, the use of methotrexate in renal sarcoidosis is not recommended because its excretion is almost exclusively via the kidneys. In case of renal impairment, there is a substantial risk of accumulation of this drug and major side effects may develop [29].

TNF-alpha inhibitors. Tumour necrosis factor is thought to be a major player in sarcoidosis through its role in the maintenance of granuloma formation [30]. Therefore, inhibition of TNF-alpha has been postulated as a treatment strategy in case of steroid-resistant sarcoidosis. It should only be used when at least one other immunosuppressive agent has been tried or in patients who have developed severe steroid toxicity [19].

Table 1. Comparison of clinical series of sarcoidosis-related granulomatous interstitial nephritis treated with corticosteroids

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<tr>
<td>Number of patients</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td>Mean age at onset (years)</td>
<td>47 (±?)</td>
<td>44 (±15)</td>
</tr>
<tr>
<td>Mean eGFR at the time of diagnosis (mL/min/1.73 m², MDRD)</td>
<td>20.5 (±19)</td>
<td>26.8 (±14)</td>
</tr>
<tr>
<td>Initial dose of prednisone (mg/kg/day)</td>
<td>0.5–1</td>
<td>0.5</td>
</tr>
<tr>
<td>Prednisone taper (mg/w)</td>
<td>?</td>
<td>5</td>
</tr>
<tr>
<td>Maintenance dose (mg)</td>
<td>?</td>
<td>5–7.5</td>
</tr>
<tr>
<td>Mean eGFR after 1 month of treatment (mL/min/1.73 m², MDRD)</td>
<td>44 (±24.7)</td>
<td>?</td>
</tr>
<tr>
<td>Mean eGFR after 1 year of treatment (mL/min/1.73 m², MDRD)</td>
<td>47 (±19.9)</td>
<td>49.6 (±5.2)</td>
</tr>
<tr>
<td>Risk of relapse (%)</td>
<td>36</td>
<td>35</td>
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careful work-up is mandatory before starting this type of treatment because this type of drug has many significant side effects and its use may increase the risk of serious infectious complications (such as reactivation of latent tuberculosis) [29].

Infliximab was effective albeit in case reports [31–33]. It is usually given in a dose of 3–5 mg per kg at Week 0, 2 and 6 followed by 3–5 mg per kg every 6–8 weeks thereafter [30]. Thumfart described the case of a 13-year-old boy presenting with acute renal failure (eGFR 19 mL/min/1.73 m²) caused by a sarcoid-associated granulomatous interstitial nephritis [29]. The kidney function improved initially with corticosteroids (eGFR 37 mL/min/m²), but later the patient showed signs of severe steroid toxicity and progressive renal failure (eGFR 20 mL/min/m²). Monthly treatment with infliximab was started, which led to a steady improvement of renal function (eGFR 36 mL/min/m² at 4 months after initiation of infliximab). Mubashir presented the case of a 57-year-old male with acute renal failure due to granulomatous interstitial nephritis [32]. There was a good response to treatment with high-dose corticosteroids. However, relapses were frequent and the patient suffered from steroid toxicity. Treatment with infliximab was instituted and resulted in a steady improvement of renal function despite steroid taper.

Adalimumab could be an interesting alternative for patients intolerant of infliximab, but more outcome data are needed before its use can be advocated [19]. Etanercept seems to have no beneficial effect in patients with sarcoidosis, as in other granulomatous diseases [4, 19].

Kidney transplantation. End-stage renal disease secondary to sarcoidosis is uncommon. The current knowledge about renal transplantation in patients with sarcoidosis is scarce. It is, however, an interesting option given the fact that the disease generally occurs in young and middle-aged adults. Recently, Aouizerate et al. [34] published the first series of 18 patients who underwent renal transplantation for sarcoidosis in a French multicentre study. The authors concluded that renal transplantation can be carried out safely in patients with sarcoidosis with excellent graft and patient survival. However, a relatively high rate of renal recurrence (17%) after transplantation was reported in most cases occurring shortly after transplantation and with negative effect on graft function. The long-term effects of recurrence on graft survival remain elusive. A short delay between the last episode of sarcoidosis and renal transplantation is a risk factor for recurrence [34].

Experimental therapy. Following the incremental knowledge of the role of cytokines in the pathogenesis of sarcoidosis, other immunosuppressive drugs including thalidomide, pentoxifylline and rituximab have been proposed as steroid-sparing agents, but more research is needed before their use in renal sarcoidosis can be advocated.

**SUMMARY**

Renal involvement is rare in sarcoidosis. When it occurs, treatment is always required given the substantial risk of the development of renal failure. A disordered calcium metabolism is the most important cause of renal failure. Granulomatous interstitial nephritis is the most typical histological finding. A guideline for treatment is currently lacking. Based on a literature review, we present a detailed overview of the different treatment options, to promote a more uniform approach to the treatment of this disorder.

**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**

A look at the upper heart chamber: the left atrium in chronic kidney disease

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ABSTRACT

Altered left ventricular (LV) mass and function are classical hallmarks of cardiomyopathy in chronic kidney disease (CKD). The left atrium (LA), a heart chamber exquisitely sensitive to volume overload and diastolic function, is an independent predictor of death and adverse cardiovascular (CV) events in high-risk patients such as those with hypertension and/or with heart failure. In this review we focus on the relationship of LA size with LV diastolic function, and the association between LA enlargement and CV and renal outcomes in patients with CKD, including patients with end-stage renal disease. Increased LA size emerges as a powerful predictor of mortality and major adverse CV events in both end-stage and early CKD, and some studies also show a close association between enlarged LA and renal disease progression. Secondary analyses of clinical trials suggest that the LA has the potential to be elected as a surrogate end point in CKD patients but the issue remains to be tested in specifically designed clinical studies.

Keywords: cardiomyopathy, CKD, clinical outcome, diastolic function, left atrium

INTRODUCTION

Cardiomyopathy, which is defined in anatomical terms as left ventricular hypertrophy (LVH) or as a functional alteration in left ventricular (LV) systolic and/or diastolic function, is the most prevalent cardiovascular (CV) disorder in chronic kidney disease (CKD). The left atrium (LA), a heart chamber exquisitely sensitive to volume overload and diastolic function, is an independent predictor of death and adverse cardiovascular (CV) events in high-risk patients such as those with hypertension and/or with heart failure. In this review we focus on the relationship of LA size with LV diastolic function, and the association between LA enlargement and CV and renal outcomes in patients with CKD, including patients with end-stage renal disease. Increased LA size emerges as a powerful predictor of mortality and major adverse CV events in both end-stage and early CKD, and some studies also show a close association between enlarged LA and renal disease progression. Secondary analyses of clinical trials suggest that the LA has the potential to be elected as a surrogate end point in CKD patients but the issue remains to be tested in specifically designed clinical studies.