

# Renal disease in primary Sjögren's syndrome

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## Introduction

Primary Sjögren's syndrome (SS) is an autoimmune disease characterised by inflammation in the lacrimal and salivary glands. The kidneys may also be involved in SS, reflected by e.g. tubulointerstitial nephritis (TIN) and/or distal renal tubular acidosis (dRTA), the latter often associated with hypocitraturia. TIN as well as dRTA are risk factors for the development of urolithiasis.

## Distal renal tubular acidosis (dRTA)

Normally most bicarbonate is reabsorbed in the proximal tubuli, and hydrogen ions are secreted in the distal nephron. Renal tubular acidosis is characterised by a reduced ability to acidify the urine. In distal (type 1) renal tubular acidosis (dRTA), hydrogen secretion in the distal nephron is deficient. In proximal (type 2) renal tubular acidosis, the reabsorption of bicarbonate is impaired in the proximal tubule. Type 3 renal tubular acidosis is characterised by a defect in the distal nephron in addition to bicarbonaturia, and type 4 renal tubular acidosis by low urinary pH, hyperchloremic acidosis and hyperkalemia.

Several etio-pathogenetic factors can be involved in dRTA, for instance inherited defects, autoimmune diseases, drugs, toxins, and various tubulointerstitial diseases. In dRTA urinary pH is always high (above 5.5) and serum potassium is normal or reduced. Patients with complete dRTA have metabolic acidosis (low blood-Base Excess) in contrast to patients with incomplete dRTA (normal blood-Base Excess). In the latter condition, the inability to acidify the urine is recognised only during induced acidosis, e.g. by an oral ammonium chloride loading test. Note that this test can be inconvenient to the patient by causing nausea.

In children, dRTA can be manifested as growth retardation and metabolic emergency with hypokalemic paralysis. In adults, symptoms from renal stones and nephrocalcinosis are more common, but osteomalacia may also occur.

## Renal tubular dysfunction in primary Sjögren's syndrome

Tubulointerstitial inflammation in the kidneys is often associated with tubular dysfunction. *Proximal tubular dysfunction* can be characterised by renal glucosuria, proximal renal tubular acidosis, and aminoaciduria. However, these abnormalities are uncommon in SS (1,2). *Distal tubular dysfunction* can include distal renal tubular acidosis (dRTA), high or low values of serum potassium, salt wasting or decreased urine concentrating ability.

*dRTA* has been reported in 15-33% of SS patients (2). We investigated a group consisting of SS patients with an established diagnosis of dRTA/urolithiasis as well as SS patients who had previously not been evaluated with respect to dRTA or urolithiasis. dRTA was present in 18 of 27 patients (67%), of whom 3 had complete dRTA (1).

*The maximal urine concentrating ability* is decreased in 12-82% in SS (the great variations may be due to different patient selections and different methods used). A method using DDAVP (Minirin®) given subcutaneously or intranasally gives reliable results, and age related reference values should be used.

*Hypocitraturia.* Citrate is normally reabsorbed in the proximal tubuli. Metabolic acidosis is one important factor in the pathogenesis of reduced citrate excretion and explains the association between dRTA and hypocitraturia. Reduced citrate excretion (below 1.69 mmol/24h) is a risk factor for calcium stone formation. Hypocitraturia was found in 20 of 27 SS patients in one study (1).

*Decreased tubular reabsorption of phosphate*, as measured with TRP%, is common (67%) but the clinical significance is unclear (1).

*Tubular proteinuria* is characterised by leakage of medium sized molecules. To estimate this, measurement of urinary alfa-1-microglobulin has advantages over beta-2-microglobulin. *Tubular enzymuria* can be assessed with several tubular enzymes, such as NAG (n-acetyl-beta-D-glucosaminidase). Abnormal leakage of alfa-1-microglobulin was found in 46% and of NAG in 29% in one study of SS patients (1). Most patients with tubular proteinuria or enzymuria had a decreased glomerular filtration rate (GFR) probably reflecting a more severe renal injury (1).

*The pathogenetic mechanisms* of dRTA and TIN in SS are not well understood. TIN often occurs in association with dRTA (2), but SS patients can sometimes have dRTA and normal renal histopathology (1,3). Antibodies from mothers with SS causing transient tubular dysfunction in fetuses have been reported (4). In three interesting case reports the tubular membrane-associated enzyme H-ATPase was missing in patients with SS and dRTA. H-ATPase is essential for proton excretion into the urine in the distal nephron, and lack of this enzyme could possibly explain dRTA in these patients (5).

### **Tubular tests as indicators of renal disease in primary Sjögren's syndrome**

In patients with tubulointerstitial nephritis, proteinuria is usually insignificant and the urine sediment findings are often non-specific. A sensitive biochemical marker of renal disease should indicate renal dysfunction before glomerular filtration starts to decline. Abnormal values of urine NAG and urine alpha-1-microglobulin are mostly found in patients with a decreased GFR, whereas urine citrate, TRP%, dRTA and the maximal urine concentrating ability are more useful as early markers of renal disease. The specificity of decreased TRP% is low, making it difficult to use as an indicator of renal disease. Impaired urine concentrating ability is not so frequent as dRTA or hypocitraturia in our material (1). Determination of citrate in the urine is easy for the patient and gives reliable results. Therefore, 24-hour urine citrate is recommended for screening of renal disease in SS patients. In the absence of complete dRTA, ammonium chloride loading is probably still necessary to confirm renal disease in patients with SS. Renal biopsy should be considered in patients with decreased glomerular filtration rate.

### **Glomerular filtration in primary Sjögren's syndrome**

GFR is measured most accurately with Cr EDTA or Iohexol clearance. 24-hour creatinine clearance and plasma concentration of creatinine give less reliable estimates.

At least 27 patients with a 24-hour creatinine clearance below 50 ml/min (4-49 ml/min) have been described in 14 different papers. Three of these patients were dialysis-dependent (6). Retrospectively, Vitali et al (7) found two among 104 SS patients with 24-hour endogenous creatinine clearance values of 41 and 60 ml/min. We investigated 27 SS patients with Cr-EDTA clearance and 33% of them had a lower GFR than normal (8). It is important to emphasise that most SS patients with impaired GFR have only a slight to moderate impairment of GFR.

### **Factors related to decreased GFR**

GFR has mostly been attributed to TIN (3,6), although glomerulonephritis has been demonstrated in a few patients with SS (9,10). In one study, five patients with SS and decreased GFR had TIN, and when the histopathological findings were quantified the GFR values were inversely related to the extent of the tubulointerstitial lesions (11).

*dRTA*. In a group of 27 SS patients we found dRTA in 8 of 9 patients with decreased GFR. However, the mean values of GFR did not differ between those who had dRTA and those who were without dRTA, speaking against dRTA as a cause of decreased GFR (8). Probably TIN and dRTA are just two associated conditions.

*Urolithiasis and upper urinary tract infection (UTI)*. Besides reflecting tubulointerstitial nephritis, dRTA can also be a risk factor for the development of urolithiasis. This, together with upper UTI, can cause secondary ipsilateral renal dysfunction. In our study 3 of 9 patients with a decreased GFR had no history of urolithiasis. Furthermore, mean values of Cr-EDTA clearance did not differ between stone formers and others (mean 67 v. 70 ml/min) (8). Five SS patients with nephrocalcinosis have been reported, and only two of these patients had a decreased creatinine clearance (24 and 34 ml/min) (12). Thus, urolithiasis and upper UTI are not essential for decreased GFR, but they may contribute in some patients.

### **Treatment and prognosis of patients with decreased GFR**

In one study, seven patients were investigated with Cr-EDTA clearance test on several occasions. Four patients were treated with sodium bicarbonate, and GFR increased or remained stable in three. In the three patients given immune suppressive therapy, GFR increased (8). In different case reports renal disease in SS has been treated with glucocorticoids (2,6) or cyclophosphamide (13). Patients with a slight to moderate decrease of GFR probably do not need immune suppressive therapy, providing GFR is stable.

### **Renal histopathological findings**

Chronic tubulointerstitial nephritis (TIN), defined by presence of mononuclear interstitial inflammation and varying degrees of interstitial fibrosis and tubular atrophy in the absence of atherosclerotic lesions, is the most common finding in patients with primary Sjögren's syndrome (3,10). Glomerulonephritis has been reported in a few patients (9,10).

The interstitial inflammation in TIN is focal in most cases and always combined with diffusely distributed inflammatory cells. The inflammatory cells consist of small lymphocytes, plasma cells and monocytes. Proliferative lesions are usually not seen in the glomeruli, but sclerotic lesions can be found in the glomeruli. The percentage of sclerotic glomeruli is usually out of proportion to the vascular changes, and the tubulointerstitial lesions seem to be the primary event that secondarily affects the glomeruli (11).

*Differential diagnostic considerations.* The histopathological findings of SS-associated TIN differ from nephrosclerotic lesions or TIN induced by infection or drugs - i.e. no constant tubulitis or infiltration of eosinophils or polymorphonuclear leukocytes. However, the histopathology is not specific enough to allow the exclusion of other causes of TIN, and the histopathological findings must be correlated to clinical data, including history of infection, drugs, hypertension, hereditary and metabolic diseases.

### **Risk factors of calcium stone formation in primary Sjögren's syndrome**

In an unselected population of stone formers, calcium oxalate is the most common constituent in kidney stones. In patients with dRTA, however, pure calcium phosphate stones are frequently found. Calcium stone formation is a dynamic process. Solutions that are concentrated enough to make a crystal grow are termed supersaturated. Urine saturation is influenced by ion strength, complex formation and urine pH. Even in small concentrations, some constituents of the urine have an ability to inhibit crystallisation of calcium salts, e.g. citrate and magnesium. Among calcium stone formers, an increased excretion of calcium and oxalate and a decreased excretion of citrate have been reported.

In our group of 27 patients with SS, 16 patients had no history of urolithiasis, and 11 patients had formed at least one stone (14).

*dRTA* was found in all stone formers, but also in 7 of 16 non-stone formers.

*Hypocitraturia* is usually present in patients with dRTA (15), a finding confirmed in our SS patients; 15 of 18 patients with dRTA had hypocitraturia. The mean urinary excretion, however, did not differ between non-stone formers and stone formers (1.76 v. 1.43 mmol/24h).

*Calcium* excretion was significantly higher in the stone formers (3.14 v. 5.16 mmol/24h), and hypercalciuria has been reported in between 3 and 36% of dRTA patients without SS (16). In a group of stone formers with SS and dRTA, hypercalciuria was considered the most important risk factor for calcium stone formation in 4 of 5 patients (12).

We found no differences between stone formers and non-stone formers in their urinary excretion of *magnesium*, *oxalate* or *phosphate*.

In conclusion, other urine abnormalities besides dRTA and hypocitraturia might increase the risk of developing urinary calculi in patients with SS (14).

### **Stone recurrence preventive therapy in patients with SS and dRTA**

The urine composition of patients with SS, dRTA and urolithiasis is similar to that of other stone patients with dRTA, and the recurrence preventive therapy can be designed as for these patients. As stone preventive therapy can be very efficient it is important to search for biochemical risk factors of urolithiasis in SS patients with kidney stones.

*Potassium citrate* (Renapur<sup>®</sup>, Urocit-K<sup>®</sup>) efficiently inhibits new stone formation, causes an increase in urinary citrate and a decrease in urinary calcium in patients with dRTA and urolithiasis (17). Although efficient as stone prevention therapy, *sodium bicarbonate* has been claimed to be inefficient in restoring urinary citrate excretion in patients with dRTA and hypocitraturia. In most studies, however, urine citrate increased when a sufficiently large dose was given (15). *Thiazides* can be given if hypercalciuria does not respond to alkali.

### **Urolithiasis and dRTA preceding primary Sjögren´s syndrome**

The pathogenesis of dRTA in stone patients is thought to be immune-mediated in about 25% (16), and SS is commonly diagnosed in these patients.

At the Department of Nephrology, University Hospital of Linköping, all patients with urolithiasis and dRTA, but without sicca symptoms at the presentation of urolithiasis, were investigated with respect to autoantibodies and subjective and objective signs of SS. Anti-SS-A antibodies were detected in 8 of 10, ANA in 4 of 10, and a diagnosis of SS or possible SS was established in 7 of 10 dRTA patients. In no instance were anti-DNA antibodies recorded, and none of the patients fulfilled the criteria for having SLE (18). Patients with SS and dRTA usually have isolated tubulointerstitial nephritis, whereas this histopathological finding is claimed to be uncommon in SLE (19). Subjective sicca symptoms subsequently presented 1-48 years after the presentation of urolithiasis (18).

Renal disease preceding the onset of classical manifestations of SS has also been reported by Tu et al (3). At least six patients with dRTA and *objective* signs of SS, but *without subjective* sicca symptoms have been reported. Thus, SS can be diagnosed in dRTA patients even in the absence of subjective sicca symptoms.

### **Autoantibodies and primary Sjögren´s syndrome in kidney stone patients with hypocitraturia**

Hypocitraturia and dRTA are common in patients with SS. The problem can be approached from another perspective: how common are autoantibodies and autoimmune diseases such as SS in hypocitraturic stone formers?

In 197 hypocitraturic stone patients we found IgG-ANA in 18% of 67 female and in 1.5% of 130 male patients. Of the women 16% had anti-SS-A antibodies, whereas no man had these autoanti-

bodies. Four of 14 evaluated hypocitraturic women with anti-SS-A antibodies or ANA fulfilled the criteria for SS or possible SS (20).

In conclusion, a Sjögren-related renal disease characterised by urolithiasis and/or dRTA and antibodies to SS-A, with or without subjective sicca symptoms, may exist. It is also possible that autoimmune factors are important in some hypocitraturic stone patients whether dRTA is present or not.

As dRTA is mostly associated with tubulointerstitial nephritis in patients with SS, anti-SS-A antibodies should be analysed also in patients with tubulointerstitial nephritis of unknown etiology.

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