Pss renal involvement and treatment

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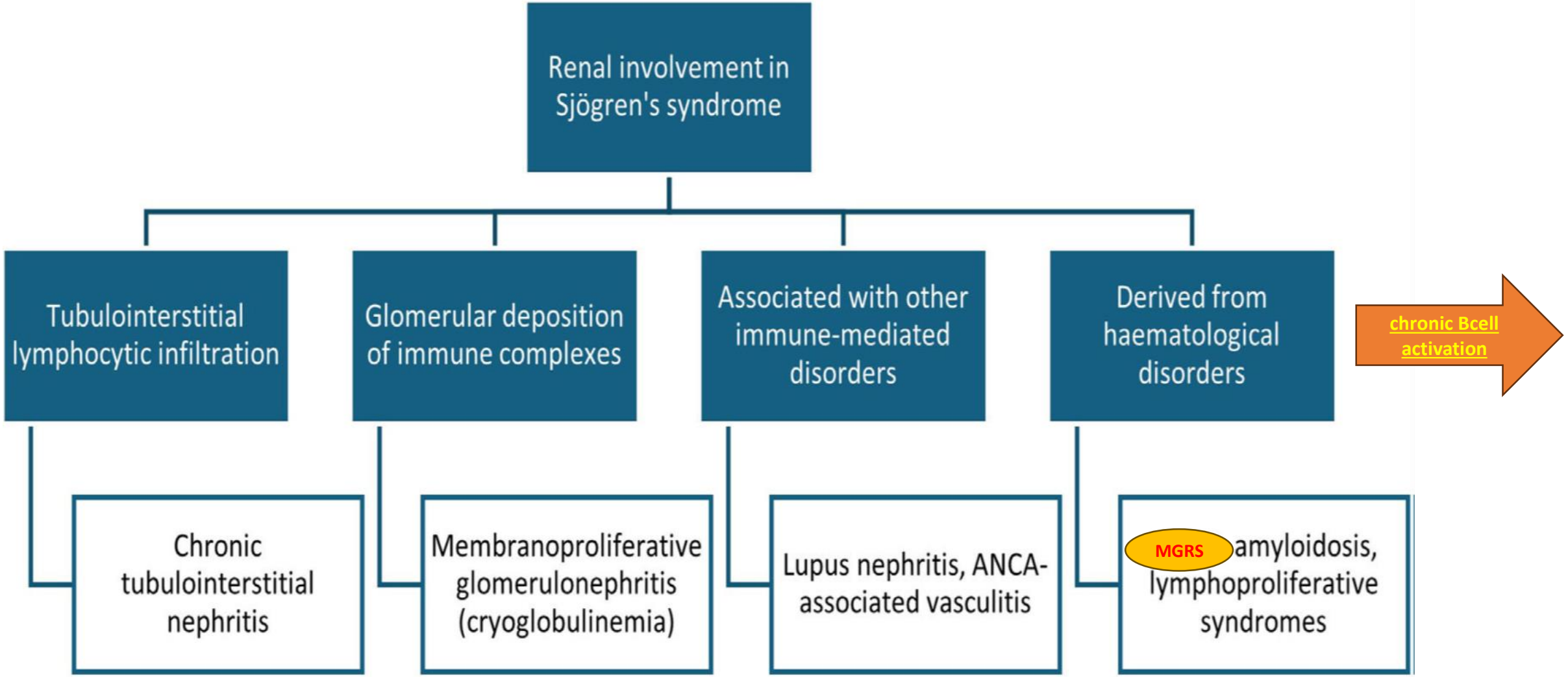
- Sjögren's syndrome (SS) is an autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands. **Approximately half of the patients will present with systemic symptoms.**
- patients with pSS exhibit extraglandular manifestations that affect many organs,including the lungs, skin, joints, nervous system and kidneys.
- Renal involvement is one of the systemic complication.
- The prevalence of renal involvement in pSS varies according to ethnicity and the definition of renal involvement. **Prevalence is about 1% in large retrospective registries, between 4 and 9% in most European studies, and 30% or higher in Indian and Chinese studies.**

❑**Disparities in diagnostic criteria**

❑**Ethnicity**

❑**Environmental factors may account for the observed variability**

❑**And discrepancies in the definition of kidney involvement.**



Classically, two types of renal manifestations are distinguished in SS: tubulointerstitial nephritis and immune complex deposition glomerulopathy.

Nefrologia 45 (2025) 501341

SEROLOGICAL FINDINGS

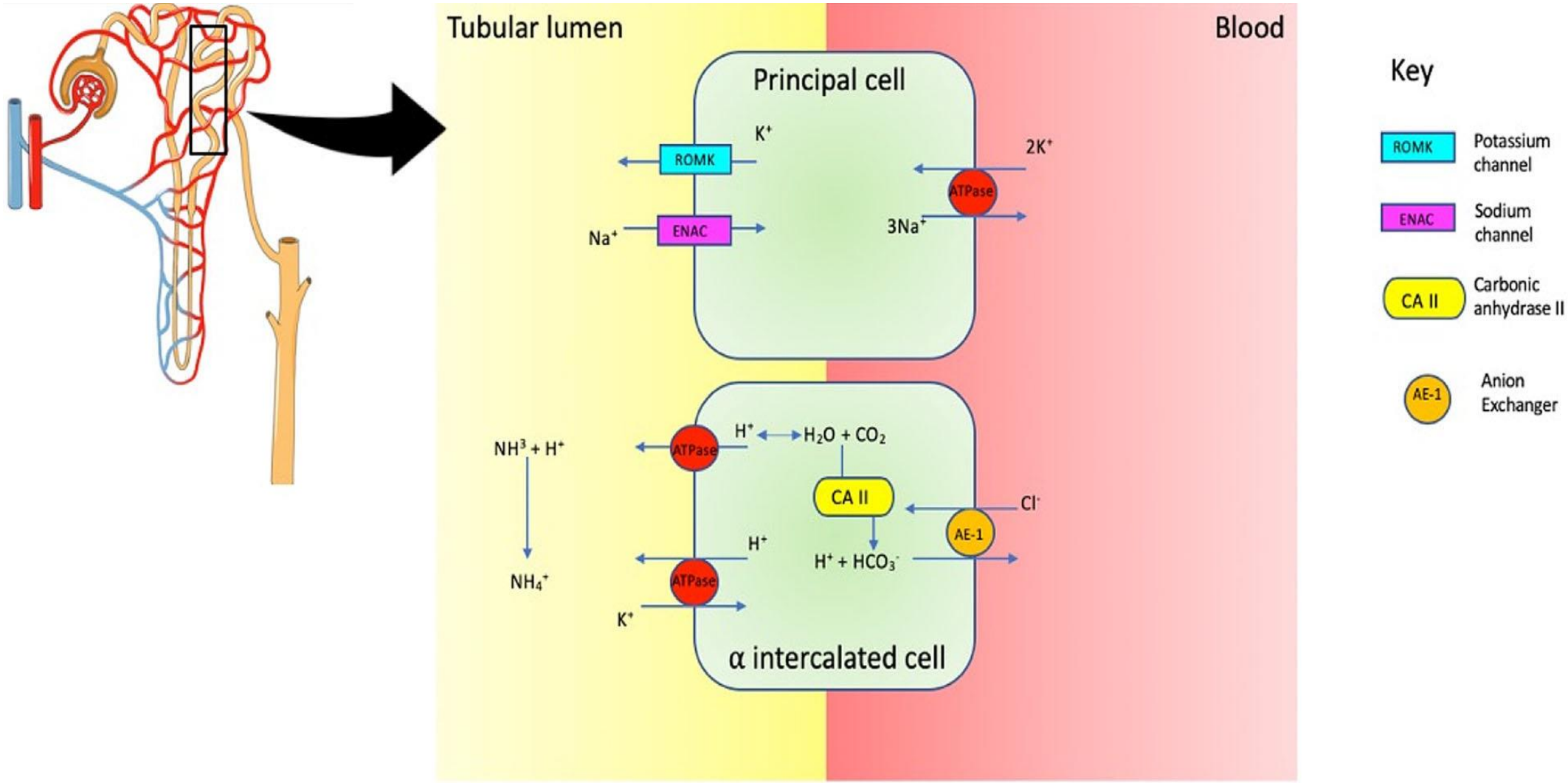
- Patients with pSS and kidney disease have comparable incidences of ANA, anti-La/Ro and rheumatoid factor to those without kidney disease.
- Hypergammaglobulinaemia is associated with distal renal tubular acidosis(dRTA).
- whilst low C3, levels and cryoglobulins are associated with GN.

Rheumatol Ther (2021) 8:63–80

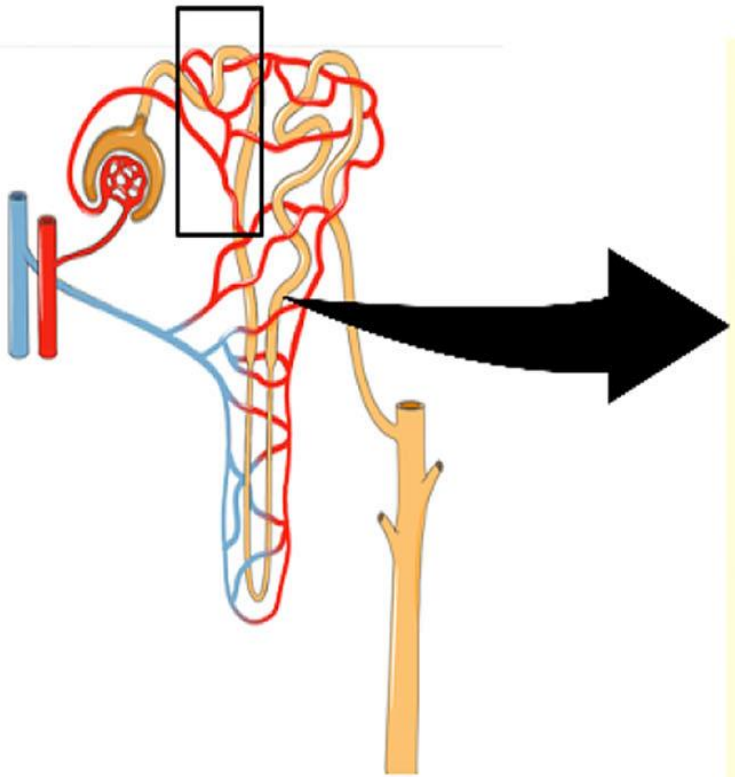
SPECTRUM OF KIDNEY DISEASE

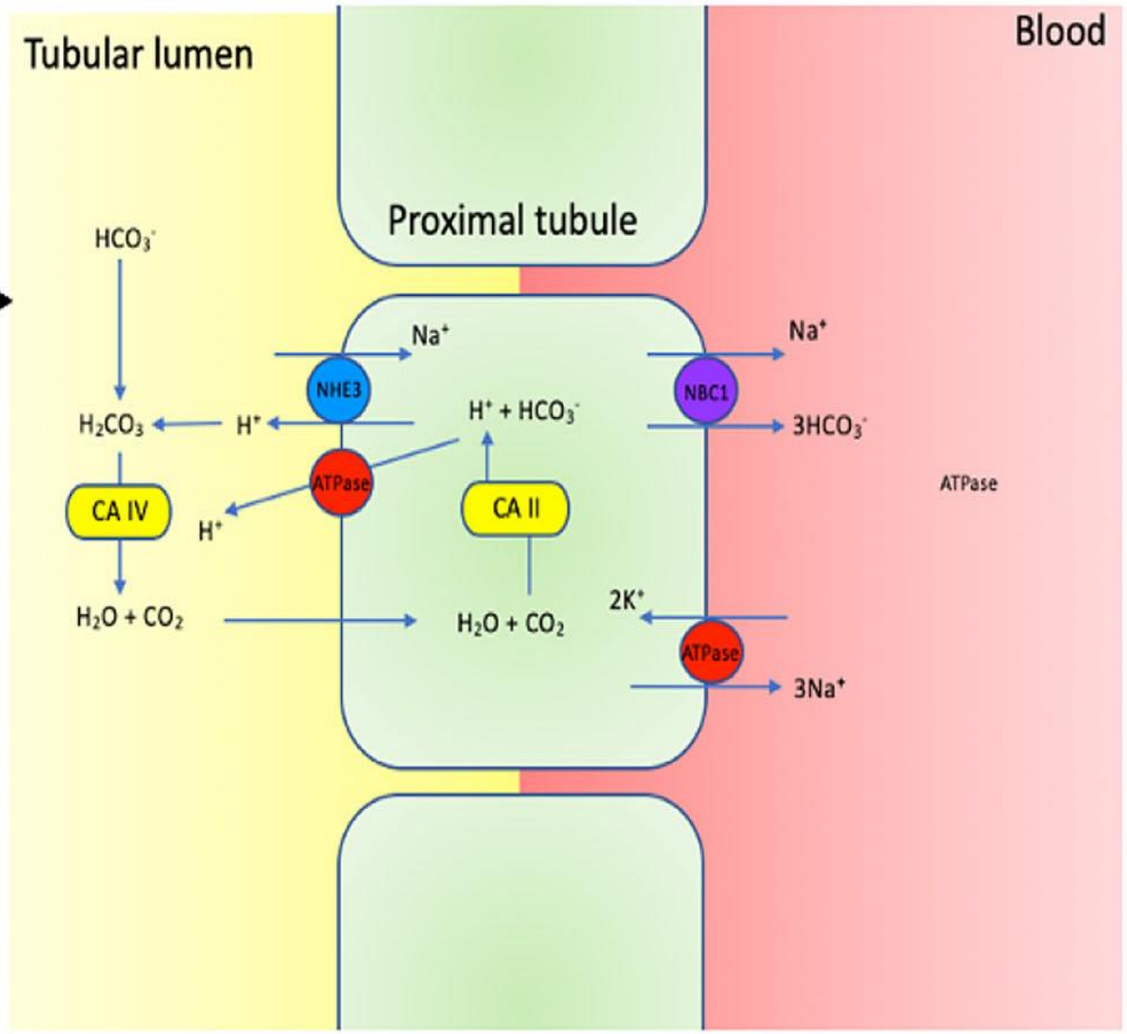
- **Tubular Dysfunction**:Renal tubular dysfunction can present in several ways, including hypokalaemia in association with renal tubular acidosis, Fanconi syndrome,Bartter syndrome, Gitelman syndrome and nephrogenic diabetes insipidus.
- **Hypokalaemia** is a common finding in pSS, occurring in 30–47% of patients with kidney disease .Hypokalaemia is usually asymptomatic but rarely presents as paralysis or respiratory arrest .Hypokalaemia occurs secondary to urinary potassium wasting in distal renal tubular acidosis (dRTA).
- **The incidence of dRTA** in pSS varies widely, and is quoted as between 5 and 70% in published series. All patients with hypokalaemia and pSS who underwent kidney biopsy were found to have TIN.

- dRTA occurs when there is inadequate hydrogen ion excretion in the distal nephron. Complete dRTA is characterized by normal anion gap metabolic acidosis, urinepH\5.5, and is often associated with hypokalaemia. The underlying mechanism by which SS leads to dRTA is unclear. H-ATPase pumps are absent in immunohistochemical analysis ofkidney tissue, and autoantibodies directed against carbonic anhydrase II (carbonic anhydrase deficiency results in dRTA) are found inpatients with pSS. dRTA may also be incomplete, with normal serum bicarbonate levels (distal acidification defect is insufficient to cause overt acidosis).



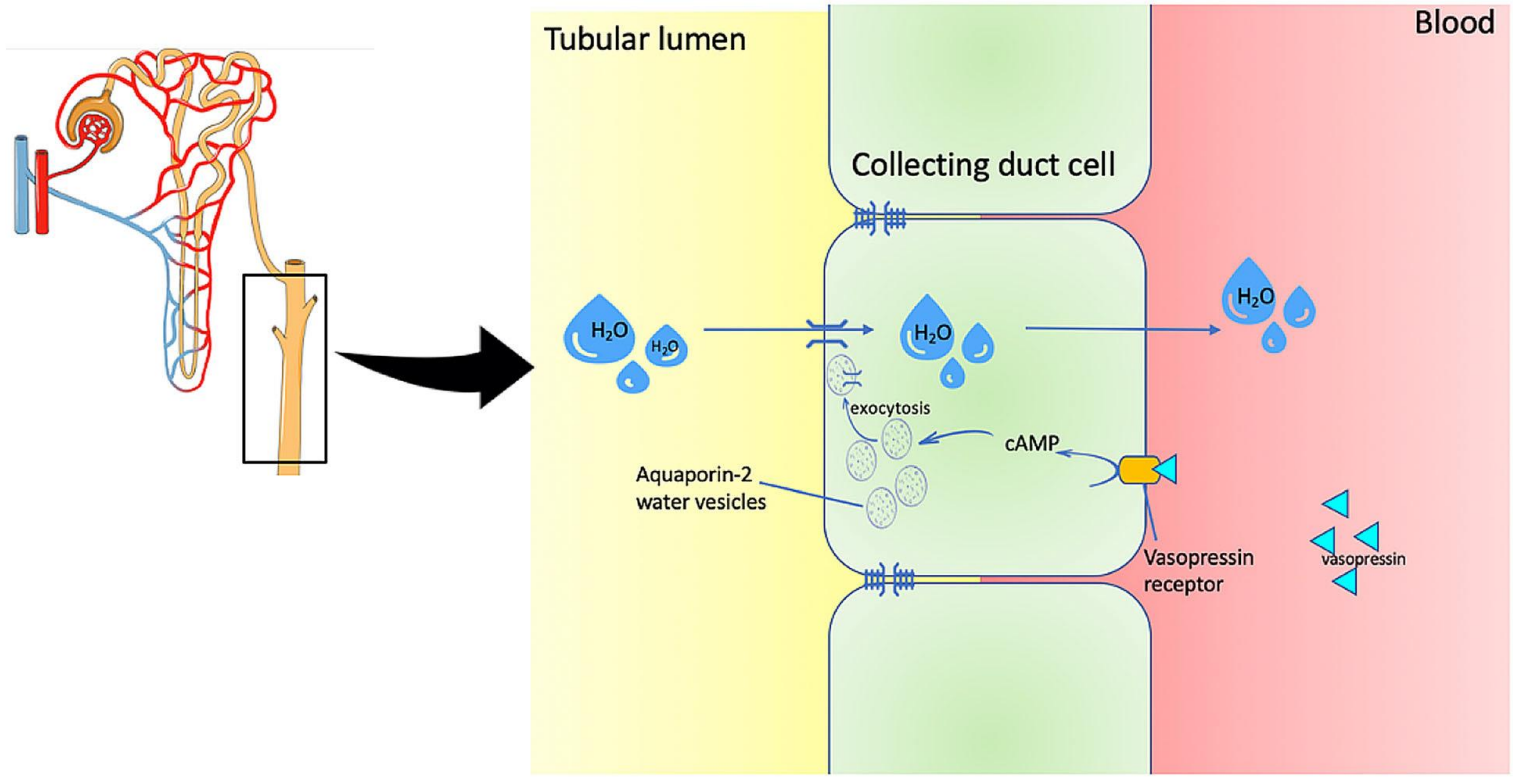
Rarely (* 3%), the proximal segment of the tubule can also be affected in pSS, leading to Fanconi syndrome (proximal tubular acidosis)





- Other acquired tubular defects such as Gitelman and Bartter syndromes rarely occur in pSS.
- Nephrogenic Diabetes Insipidus:In an Italian cohort, a quarter of pSS patients had a urine concentrating defect and in Chinese 38%.

- **Nephrolithiasis:14–25% of patients with pSS have stone disease**, **with nearly all patients experiencing renal colic**. **TIN is the predominant histological finding inpatients with renal colic and radiological features of nephrolithiasis.**



Tubulointerstitial Nephritis

- Lymphocytic infiltration leading to acute or chronic TIN is the principal kidney manifestation in pSS .About 75%-85% of pSS patients undergoing a kidney biopsy will have TIN.
- It is thought that infiltration in the renal tubules is primarily by CD4 T lymphocytes, similar to the pathophysiological process in salivary glands . CD8 T cells and plasma cell infiltration can also be present. In 10% of cases, B cells are the predominant cell type . Granulomas, though infrequently seen, suggest the presence of sarcoidosis.
- The manifestation of TIN is variable. Patients can present with **tubular dysfunction** as described, but also **acute kidney injury (AKI) or a slow progressive deterioration in kidney function**.**TIN may remain undiagnosed due to its indolent clinical course; interstitial inflammation is often accompanied by fibrosis and tubular atrophy on renal biopsy .**
- **TIN can occur prior to the onset of sicca symptoms, so pSS should be considered in patients with TIN and hypokalaemia.**

Glomerular Disease

- Glomerular involvement is less common than tubular disease in pSS. AKI, rapidly progressive GN with nephritic syndrome, CKD, and nephrotic syndrome can occur.
- Membranoproliferative glomerulonephritis **(MPGN)** is the most frequently reported glomerular lesion. In pSS, the mechanism of glomerular lesions(MPGN) is thought to be related to immune complex deposition, C4 consumption due to activation of the classical complement pathway, and cryoglobulinemia. It is associated with cryoglobulinemic vasculitis in more than half of the cases.
- Other glomerular diseases have also been reported, such as **minimal change disease**, **IgA nephropathy, focal segmental glomerulosclerosis, membranous nephropathy, fibrillary GN and vasculitis.**It **is possible that, rather being than features of the pSS disease process itself, these other glomerular lesions coexist with pSS.**
- Antineutrophil cytoplasmicantibodies (ANCA) are prevalent in 6–7% of patients with pSS (anti-MPO).

- Studies in populations with different ethnicities have shown some inconsistencies. For instance, glomerular lesions appear less common in Asian patients, occurring in just 14%(18/130) in a Chinese cohort .In contrast, early/mild glomerular changes were seen in35% (n = 6/17) of an Indian population ,whilst 29% (n = 7/24), 36% (n = 9/25) and 49%(n = 17/35) of patients in American, Scottish and Greek series, respectively, had histological evidence of GN .
- **MPGN was the predominant glomerular lesion in all studies.**
- Itis difficult to know if these variations represent true discrepancies in the disease across **ethnicity and geographical cohorts or differences in perceptions of indication for kidney biopsy in different countries.**

KIDNEY DISEASE AND SJÖGREN'S – SCREENING

Check for symptoms related to kidney involvement (oedema, nephrotic/nephritic syndrome, bone pain, muscular weakness, polyuria and polydipsia)

Urinary testing should include urinalysis with pH (blood, protein, glucose) and urine protein to creatinine ratio, consider urinary electrolytes if anomalies detected

Serum tests include creatinine/eGFR, urea and electrolytes, phosphate, urate and bicarbonate

Perform renal tract ultrasound to identify nephrocalcinosis/obstructive uropathies and, when the patient has nephrolithiasis

In patients with suspected GN, testing for cryoglobulins, immunoglobins, paraproteins and complements is recommended

Consider referral to nephrology especially in severe electrolyte imbalance and/or deteriorating kidney function

Discuss kidney biopsy

- **It is suggested that screening for all patients should include yearly urinalysis and serum creatinine.**
- **Furthermore, serum electrolytes should be measured in all patients at least yearly in order to detect disturbances due to TIN presenting as RTA. These should not be limited to measurements of sodium and potassium but should include chloride and bicarbonate. This will allow detection of hyperchloremic metabolic acidosis and potential hypokalemia.**
- **In that subset of patients in whom abnormalities of renal function are detected, testing should be performed at least twice a year, and may need to be more frequent (should be guided by the individual patient).**
- For patients with stable CKD and eGFR between 30 and 60 ml/min/1.73 m2, we recommend six-monthly screening.
- **CKD stage 4 and 5 (eGFR\30 ml/min/1.73 m2) is best managed with a multidisciplinary approach that includes nephrology physicians.**
- **Renal echography should be similarly performed twice a year if hypercalciuria is present, to rule out nephrolithiasis.**

- Frontiers in Immunology September 2020 | Volume 11 | Article 562101

The ESSDAI score classifies kidney disease activity

- A kidney biopsy is not mandatory; however, if performed, histology directs the activity score.
- Urinalysis (proteinuria, haematuria and urinary pH osmolality, proteinuria, creatininuria, calciuria, citraturia, urinary sediment, and culture should be performed.) together with serum tests(creatinine and electrolytes, including phosphate, urate and bicarbonate) are required to monitor activity.
- urinary analysis of pH, Patients with **RTA are scored as low in the absence of kidney failure or glomerular involvement (proteinuria, haematuria)**.**If present, the score is moderate .**
- **Glomerular disease is recorded as low, moderate or high depending on the degree of proteinuria(\1, 1–1.5 and[1.5 g/day, respectively).**

Kidney biopsy

- Generally, a kidney biopsy should be undertaken when the histological findings will alter management and influence treatment.
- patients with pSS who have preserved renal excretory function and tubular abnormalities such as hypokalemia, the underlying pathology is presumed to be TIN, and kidney biopsy is not usually undertaken .
- Kidney biopsy should be considered when there is AKI and/or urinary abnormalities.

Treatment

- Treatment of kidney disease associated with pSS is very much dependent upon the disease process.
- In patients with dRTA, treatment is largely supportive and involves correction of acidosis and hypokalaemia with bicarbonate and potassium supplements. Immunosuppressive therapy to reduce inflammation and the development of fibrosis may be initiated in certain circumstances.
- Immunosuppressive treatment options are disease specific but may include corticosteroids, antiproliferative agents, calcineurin inhibitors, cyclophosphamide and B-cell depletion therapy.

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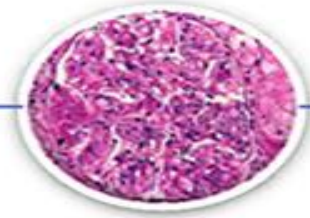
RENAL INVOLVEMENT



Tubular involvement

Glomerulonephritis

Rule out ANCA, SLE

Mild ESSDAI

1st-line	Symptomatic*	4

No response

Moderate ESSDAI

1st-line	GC (0.5)	4
2nd-line	Oral ID**	4

No response

High ESSDAI

1st-line	GC (0.5-1)	4
2nd-line	RTX*** or CyC	4
Rescue	Pex****	4

*Symptomatic: correction of the metabolic acidosis/K levels

**no head-to-head comparisons (consider Aza, CyA, MMF)

***Cryo vasculitis

****Life-threatening cryo vasculitis

Tubulointerstitial Nephritis

- **Corticosteroids** are the preferred choice of treatment in TIN.
- Other treatment options are considered in patients who are intolerant of steroids or those with refractory disease.
- **MMF** inhibits the proliferation of B and T lymphocytes—key players in the lymphocyte-rich infiltration associated with pSS. In a case series of patients with TIN in pSS, MMF yielded a significant improvement in kidney function.The optimal dose of MMF is unknown, but doses of 1–3 g daily were used in the study. Alow or short weaning course of corticosteroids in addition to MMF was the favoured regime.
- **Rituximab**, a monoclonal anti-CD20 antibody, is increasingly used in both systemic and kidney conditions. Interest in rituximab and pSS originates from the role of B cells in the disease pathogenesis, **When rituximab was used, it was primarily to treat worsening sicca symptoms rather than kidney disease. Rituximab is infrequently required in TIN and is more likely to be used in glomerular disease. In a case of TIN with recurrent kidney stones secondary to dRTA, rituximab improved excretory renal function and corrected the tubular defect.**

Glomerular Disease

- A patient with glomerular disease is likely to require more than one immune therapy .
- The choice of immunosuppressive agent in pSS associated glomerular disease varies amongst clinicians.
- A combination of corticosteroid with an antiproliferative/alkylating agent or rituximab are reasonable treatment options that are dictated by the glomerular lesion and clinical judgement.
- **Half of patients require at least three immune agents; corticosteroid, MMF and rituximab were the most frequent combination.** Cyclophosphamide in combination with corticosteroids is also used.
- **Rituximab appears to have a role in cryoglobulinaemia**. Rituximab plus corticosteroid with or without antiproliferative/alkylating agent, is preferred in noninfectious cryoglobulinaemia associated with pSS .A large French multicenter study (CryoVas) of noninfectious cryoglobulinaemic vasculitis showed that rituximab plus corticosteroid combination therapy was superior to either corticosteroid monotherapy or corticosteroid in combination with an alkylating agent .Patients with pSS represented a quarter of the cohort in this study.
- **Plasmapheresis** is considered in refractory autoimmune diseases, including pSS ,but **is reserved for life-threatening indications such as thrombotic thrombocytopenic purpura or vasculitis with pulmonary involvement.**

PROGNOSIS

- 10–30% of such patients present with chronically reduced renal function.
- Based on biopsy series, 10–20% of patients with pSS and kidney disease develop ESKD.
- In Kidder et al. although the 3-year renal survival was 92% in both (TIN and GN) groups,3-year patient survival was less in the GN group(66%) than the TIN group (100%).

TABLE 1 | Summary of most relevant findings from recent studies on kidney disease in pSS.

Author	Patient number	Country	Year	Factors positively associated with kidney disease	Factors inversely associated with kidney disease	Serum and urine biomarkers
Zhao et al.	483	China	2015	Anti-SSA, RF		
Yang et al.	103	China	2018	Steroids treatment	ILD, xerostomia, xerophthalmia, hyperIgG	
James et al.	839	United Kingdom	2018			Serum free light chains, β2-microglobulin
Zeron et al.	10007	Worldwide (7,289 Europeans)	2019	Asian ethnicity, southern countries, young age at diagnosis	Whites, Hispanics and African Americans; Northern countries, older age at diagnosis	
Luo et al.	434	China	2019	LSGB+, low C3, hypoalbuminemia, anemia	Xerophthalmia, anti-SSA	
Luo et al.	1002	China	2019	Prealbumin, anti-scl-70, RF, ENA, anti-SSB, anti-SM, urea, creatinine, cystatin C, α_1-MG, serum β_2-microglobulin, anemia, low C3	Anti-SSA	Combination of serum creatinine and urine α_1-MG

Asian ethnicity were also at considerably higher risk of developing renal disease (10.2% compared with 3.8% in Whites, 2.2% in Hispanics and 1.4% in African Americans)

Zhao, Yang, and Luo considered in their analyses the most common clinical and laboratory features which can be altered in pSS. James et al. considered markers of B-cell activation (BAFF, FLC, and β2M). Zeron et al. considered epidemiological factors and latitude in their study.

Take home message

- ❑The diversity of symptoms and heterogeneity of kidney disease in pSS makes diagnosis challenging.
- ❑It is also difficult to institute an effective screening program.
- ❑Regular screening is required to detect and prevent chronic kidney disease.
- ❑Although TIN carries a better prognosis, optimal management is unknown.
- ❑Glomerular disease is more aggressive and usually requires immunosuppressive therapy.
- ❑Around 5%-11%will develop lymphoma.(Renal involvement is important risk especially GN).
  Scientific Reports | (2025) 15:4211 | https://doi.org/10.1038/s41598-025-88368-8 nature
- ❑20% of patients with SS have monoclonal gammopathy of uncertain significance (MGUS), which is associated with a higher prevalence of hypergammaglobulinemia, cryoglobulinemia, and hematological malignancies. The coexistence of SS and MGUS presents a worse prognosis, so periodic serum immunoelectrophoresisis recommended in patients with SS.


Thank you