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INTEGRATED STUDY MASTER'S THESIS

Kidney Injury in Patients with Sjögren's Syndrome

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Summary

Sjögren's syndrome (SS) is a systemic chronic autoimmune disease that primarily affects exocrine glands, leading to sicca symptoms such as dry mouth and dry eyes.

However, SS can also present in extraglandular manifestations, including renal involvement, which is less common but can significantly impact patient outcomes.

This thesis explores the pathophysiology, clinical manifestations, diagnosis, treatment, and prognosis of kidney injury in primary Sjögren's syndrome (pSS).

The most common renal complication in pSS is tubulointerstitial nephritis (TIN), a process that results from lymphocytic infiltration of the renal interstitium and could lead to distal renal tubular acidosis (dRTA). Less frequently, glomerulonephritis (GN) occurs due to immune complex deposits, leading to proteinuria, hematuria, and a severe decline in kidney function.

The diagnosis of renal involvement in pSS is challenging due to limited data and the diversity on the clinical picture of the patient. The essential methods for detecting renal injury are urinalysis, serological tests, and biopsy. The histopathological findings in TIN include lymphocytic infiltration and interstitial fibrosis, whereas GN is characterized by immune complex deposits in the glomeruli.

The management of renal injury in pSS depends on the disease severity. Starting from symptomatic management, such as potassium and bicarbonate supplementation, as first line treatment to glucocorticoids, immunosuppressants and in more severe cases plasma exchange.

Prognosis varies; TIN generally follows a benign course, whereas GN is associated with worse prognosis and increased risk of lymphoma.

Renal involvement presents significant diagnostic and therapeutic challenges. This thesis highlights the need for early detection to preserve kidney function, standardized diagnostic criteria and novel treatment strategies to improve patient outcomes.

Keywords:

Sjögren's Syndrome, Primary Sjögren's Syndrome, Kidney Injury, Autoimmune disease, Extra glandular Symptoms, Sicca, Renal Injury, Renal involvement, Glomerulonephritis, Tubular Interstitial Nephritis, Chronic Kidney Disease, Renal Injury, Lymphoma, Distal Renal Tubular Acidosis.

Introduction:

Sjögren's syndrome (SS) is a chronic autoimmune systematic disease, primarily characterized by inflammation of exocrine glands, leading to progressive dysfunction of salivary and lacrimal glands.

This results in sicca symptoms, such as dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca). [1]

The disease is classified into primary Sjögren's syndrome (pSS) and secondary Sjögren's syndrome, which is associated with other autoimmune disorders such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).

SS majorly affects women, with a female-to-male ratio of approximately 9:1, and is typically diagnosed around the age of 50 years. [2]

While the exact etiology of pSS remains unknown, its pathogenesis involves lymphocytic infiltration of exocrine glands, leading to immune-mediated destruction.

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[1] Schafer. SICCA (More than dryness) [Internet]. Sjögrens Advocate . 2024 [cited 2025 Feb 5]. Available from: https://www.sjogrensadvocate.com/sicca2

[2] Carsons SE, Patel BC. Sjogren Syndrome. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431049/

Although SS primarily affects exocrine glands, it is a systemic disease that can involve multiple organ systems, including the skin, gastrointestinal tract, lungs, musculoskeletal system, nervous system, and kidneys.

Among these, renal involvement in pSS is a significant but often underrecognized complication that can impact patients' quality of life and long-term prognosis.

Renal manifestations in pSS are relatively rare but can have severe clinical implications.

The most common renal complication is tubulointerstitial nephritis (TIN), which can lead to renal tubular acidosis (RTA) and electrolyte imbalances, primarily hypokalemia.

In more severe cases, glomerulonephritis can occur, which may lead to chronic kidney disease (CKD) and progressive loss of renal function.

Despite these risks, renal complications in pSS are often overlooked, leading to delayed diagnosis and treatment.

PSS is a rare and often misdiagnosed disease, with limited large-scale studies on renal involvement. Although noteworthy progress has been made in understanding the systemic complications of pSS, renal manifestations remain under-researched, particularly in terms of pathophysiology, early detection, and optimal management strategies. [3]

This study is relevant because early recognition and timely intervention in renal complications can prevent long-term kidney damage and improve patient outcomes.

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[3] Negrini S, Emmi G, Greco M, Borro M, Sardanelli F, Murdaca G, Indiveri F, Puppo F. Sjögren's syndrome: a systemic autoimmune disease. Clin Exp Med. 2022 Feb;22(1):9-25. doi: 10.1007/s10238-021-00728-6. Epub 2021 Jun 7. PMID: 34100160; PMCID: PMC8863725.

Literature Review:

This study examines kidney involvement in primary Sjögren's syndrome by reviewing recent research published in the past decade. While pSS is primarily known for its exocrine gland dysfunction, renal complications such as TIN and, less commonly, GN have been increasingly recognized.

Research on early biomarkers and predictive factors for renal involvement remains limited.

A key challenge in studying renal disease in pSS is the lack of standardized criteria. While the American College of Rheumatism/ European League Against Rheumatism (ACR/EULAR) classification helps identify pSS, it does not specifically address renal complications, leading to underdiagnosis.

Despite progress, gaps remain in understanding the early detection and pathophysiology of kidney disease in pSS. This review underscores the need for further research of predictive biomarkers, targeted therapies, and standardized diagnostic approaches to improve patient outcomes.

Methods:

In this study, I conducted a literature review to examine kidney injury in pSS. The primary databases used for sourcing relevant articles were PubMed and Science Direct. The selection criteria focused on articles that specifically addressed renal injury in pSS, aligning with the central theme of this thesis.

To ensure a comprehensive and systematic approach, I used the following key search terms in different combinations: ''Sjögren's Syndrome'', ''renal injury'', ''kidney disease'', ''extra glandular manifestations'', nephropathy in pSS'', ''renal injury in pSS'' and ''pathophysiology of pSS''. Filters were applied to prioritize peer-reviewed and recent articles (published withing the last 20 years), with an emphasis on studies discussing clinical manifestations, histopathology, and treatment options.

In addition to kidney-specific studies, I also considered broader reviews on the pathophysiology of Sjögren's syndrome. A particularly valuable source was an article from *Archives of Medical Research,* which provided insights into potential viral triggers in pSS.

Beyond renal manifestations, I explored articles covering other extra glandular manifestations of pSS, including neurological complications, to provide a more holistic understanding of the disease.

A unique source was Musculoskeletal, a database frequently utilized by students and lecturers. This resource contributed information on Jaccoud's arthropathy and its potential connection to PSS.

For patient perspectives, I incorporated information from Sjögren's Advocate, a blog written by a specialist doctor in PSS. Although this source is not a peer-reviewed journal, it offers clinically accurate yet accessible explanations of Sicca Symptoms, making it a valuable educational tool for both healthcare professionals and patients. The decision to include this source was based on its ability to bridge the gap between scientific knowledge and patient understanding.

The core references for the kidney-related aspects of pSS include an article from PubMed titled *Renal Disease in pSS* and a study from *the American Journal of Kidney Diseases- Atlas of Renal Pathology,* both of which provide detailed insights into renal pathology in pSS. To supplement histopathological details, I used Pathology Outlines, a well-known pathology database, to quickly access relevant kidney histology findings.

Since pSS research is well-established in Sweden, I incorporated Swedish sources due to their relevance and my fluency in the language. These include:

- Internetmedicin (a database maintained by Swedish doctors)
- DIVA-Portal (a repository of Swedish university theses, referenced primarily for exocrine manifestations)
- Tandläkartidningen (a Swedish dental newspaper, consulted for Sjögren's-related oral health discussions)

Limitations

While this study aimed to include a wide range of literature on renal injury in PSS, there are some inherent limitations:

- Publication Bias: Studies with positive findings are more likely to be published, which could skew the representation of data.
- Limited access: Some potentially relevant articles were behind paywalls and could not be accessed.
- Non-Standardized Terminology: Differences in terminology (e.g., ‘’renal involvement’’ vs ‘’renal disease’’) may have led to the exclusion of some relevant studies.
- Language Constraints: Although I included Swedish sources, I primarily reviewed English-language literature, which may have led to the omission of significant findings published in other languages.
- Reliance on Secondary data: As this is a literature review, no new experimental or clinical data were generated, limiting the scope of original findings.

However, by utilizing a combination of peer-reviewed journal articles, clinical databases, and expert-authored patient resources, this methodology ensures a comprehensive yet focused examination of kidney injury in PSS. Despite some limitations, the selected sources provide a robust foundation for understanding renal manifestations in Sjögren’s Syndrome and their implications for patient care.

Research Results:

Introduction:

PSS is a chronic autoimmune disorder primarily affecting the exocrine glands, leading to dryness of the eyes and mouth due to lymphocytic infiltration. In addition to glandular dysfunction, the disease manifests various extra glandular complications, including arthritis, myalgia, and fatigue, as well as systemic involvement of multiple organs, including the kidneys.

Although renal disease is less common compared to other systemic complications of Sjögren's syndrome, it remains a significant concern. The primary renal manifestations include TIN, RTA, nephrolithiasis (kidney stones), and GN. Among these, TIN is the most frequently observed renal complication, often leading to distal renal tubular acidosis (dRTA). While GN can occur, it is relatively rare in this patient population.

The reason renal disease in pSS is an issue of concern is due to the impact of patient morbidity and long-term renal function outcomes.

Renal injury in pSS leads to electrolyte imbalances, nephrocalcinosis and kidney stones. If left undiagnosed or untreated, chronic tubular dysfunction can contribute to progressive renal damage and chronic kidney disease (CKD). Additionally, glomerulonephritis may lead to proteinuria and even nephrotic syndrome in some cases, further complicating disease management.

Studying renal involvement in pSS is crucial for several reasons like early diagnosis and prevention, optimizing treatment strategies, reducing disease burden, and advancing research.

Pathophysiology SS:

The etiology of SS remains incompletely understood. While genetic predisposition plays a role, particularly in the presence of anti-SSA (Ro) and anti-SSB (La) antibodies, it is speculated-but

not yet fully proven- that certain viral infections may act as triggers for disease onset. [4] For example, one of the viruses found in lacrimal, saliva and salivary gland biopsies was Epstein-Barr virus (EBV). [5]

A key feature in the pathogenesis of pSS is dysregulated immune activation, with type I interferons (IFNs) and B-cell activating factor (BAFF) being central signaling molecules. The disease is characterized by an autoimmune attack on exocrine glands, primarily the salivary and lacrimal glands, by infiltrating lymphocytes. This process leads to chronic inflammation, tissue damage, and loss of glandular function, resulting in the hallmark SICCA symptoms (dry eyes and dry mouth).

Immune dysregulation and autoantibody production:

pSS is classified as an autoimmune disorder, wherein the immune system mistakenly targets exocrine glands. The disease can occur in two forms:

- Primary PSS (SICCA syndrome)- Occurring in isolation
- Secondary PSS- Associated with other autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or systemic sclerosis.

A key immunological feature of pSS is the production of nuclear autoantibodies, specifically anti-SSA (Ro) and anti-SSB (La). Pathogenesis involves:

1. Release of nuclear components from damaged or apoptotic cells.
2. Activation of helper T-cells, which stimulate B cells.

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[4] Heller Asmussen K. Reumatoid Artrit och Sjögrens syndrom. Vetenskap och klinik. [Internet]. 2012; Available from: https://www.tandlakartidningen.se/wp-content/uploads/2012/02/s-76-81-Asmussen.pdf

[5] Lendrem D, Mitchell S, McMeekin P, Bowman S, Price E, Pease CT, Emery P, Andrews J, Lanyon P, Hunter J, Gupta M, Bombardieri M, Sutcliffe N, Pitzalis C, McLaren J, Cooper A, Regan M, Giles I, Isenberg D, Vadivelu S, Coady D, Dasgupta B, McHugh N, Young-Min S, Moots R, Gendi N, Akil M, Griffiths B, Ng WF; UK primary Sjögren's Syndrome Registry. Health-related utility values of patients with primary Sjögren's syndrome and its predictors. Ann Rheum Dis. 2014 Jul;73(7):1362-8. doi: 10.1136/annrheumdis-2012-202863. Epub 2013 Jun 12. PMID: 23761688.

3. B-cell proliferation and autoantibody production, specifically targeting ribonucleoproteins SS-A and SS-B.

Lymphocytic Infiltration and Tissue Damage:

Following autoantibody production, both T-cells and autoantibodies enter systemic circulation and infiltrate exocrine glands. Activated T-cells release cytokines, which recruit additional immune cells, amplifying the inflammatory response. The persistent lymphocytic infiltration leads to:

- Glandular tissue destruction and fibrosis, replacing normal secretory tissue.
- Progressive loss of secretory cells, resulting in severe glandular dysfunction.
- Involvement of other organ systems, occurring in approximately one-third of patients.

Systemic complications and lymphoma risk:

Beyond glandular dysfunction, systemic manifestations can affect multiple organs, including the kidneys lungs, nervous system, and vasculature. Patients with chronic inflammation are at increased risk (5-10%) of developing B-cell lymphomas, most commonly mucosa-associated lymphoid tissue (MALT) lymphoma. The persistent polyclonal B-cell activation in pSS may lead to the formation of cryoglobulins, contributing to systemic vasculitis and kidney involvement.

The triggers for B-cell proliferation remain unclear, though hypotheses suggest that viral infections or chronic immune activation induce the expression of HLA-DR molecules on exocrine glandular and renal epithelium. In cases where uncontrolled B-cell proliferation persists, it may lead to malignant transformation and lymphoma development in 2-9% patients. [6]

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[6] García-Carrasco M, Fuentes-Alexandro S, Escárcega RO, Salgado G, Riebeling C, Cervera R. Pathophysiology of Sjögren's syndrome. Archives of Medical Research. 2006 Nov;37(8):921–32. doi:10.1016/j.arcmed.2006.08.002

Organs involved in pSS:

Exocrine symptoms:

The most common exocrine manifestations of Sjögren's syndrome are ocular and oral dryness. Reduced salivary secretion can result in dysphagia, altered taste sensation, and a burning or painful sensation in the oral cavity. Patients frequently report difficulty swallowing dry foods and an inability to speak for extended periods without consuming fluids.[7]

Ocular manifestations:

Ocular dryness leads to irritation and a foreign body sensation, often described as a feeling of sand in the eyes. Additionally, patients may experience photosensitivity and ocular pain. Prolonged dryness can progress to keratoconjunctivitis sicca, characterized by inflammation and potential ulceration of the cornea and conjunctive inflammation and ulceration of the cornea and the conjunctiva.

In severe cases, complications such as corneal perforation may occur, which can result in permanent vision loss.

Oral Manifestations:

Reduced salivary glands functions leads xerostomia (dry mouth), which is a hallmark symptom of Sjögren's syndrome. Histopathological findings typically reveal diffuse fibrosis in cases of salivary gland dysfunction, whereas the presence of nodules may indicate a neoplastic process rather than Sjögren's syndrome.

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[7] Karlstads Universitet, Raad H. Oral Hälsa vid Sjögrens Syndrom. [Internet] DIVA PORTAL. [updated Apr 2018; cited Feb 2025]. Available from: https://www.diva-portal.org/smash/get/diva2:1204054/FULLTEXT01.pdf

Other prominent oral symptoms include loss of taste, fissuring of the taste, mucosal atrophy, dysphagia, and tooth decay. Xerostomia also predisposes patients to opportunistic infections such as oral candidiasis. In severe cases, inflammation of the salivary glands can lead to parotid gland swelling, which may be clinically evident.

Other exocrine manifestations:

Other manifestations of pSS include generalized dryness affecting the skin, characterized by cutaneous xerosis. Dryness in the respiratory tract leads to persistent hoarseness and chronic non-productive cough. Vaginal dryness may lead to dyspareunia, significantly impacting the patient's quality of life. In severe cases, persistent dryness of the airways can result in mucosal ulceration and difficulties in phonation, leading to impaired speech. [8] Diminished secretion of the exocrine glands of the digestive tract may involve pancreas and stomach, causing pancreatic dysfunction and hypochlorhydria, respectively. [9]

Systemic manifestation:

SS is a systemic chronic autoimmune disorder. Except from dryness like mentioned before, a systemic disease can occur, involving any organs and leading to a variegated clinical manifestation.

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[8] Olsson P. Primärt Sjögrens syndrom [Internet]. Internetmedicin; n.d. [cited 2025 Feb 4]. Available from: https://www.internetmedicin.se/reumatologi/primart-sjogrens-syndrom#diagnostik-och-utredning

[9] Lendrem D, Mitchell S, McMeekin P, Bowman S, Price E, Pease CT, Emery P, Andrews J, Lanyon P, Hunter J, Gupta M, Bombardieri M, Sutcliffe N, Pitzalis C, McLaren J, Cooper A, Regan M, Giles I, Isenberg D, Vadivelu S, Coady D, Dasgupta B, McHugh N, Young-Min S, Moots R, Gendi N, Akil M, Griffiths B, Ng WF; UK primary Sjögren's Syndrome Registry. Health-related utility values of patients with primary Sjögren's syndrome and its predictors. Ann Rheum Dis. 2014 Jul;73(7):1362-8. doi: 10.1136/annrheumdis-2012-202863. Epub 2013 Jun 12. PMID: 23761688.

The quality of life of pSS patients is jeopardized due to the high degree of fatigue, depression, anxiety and decreased physical activity. According to life-quality scoring studies, pSS was comparable to SLE and RA which are seen as more aggressive autoimmune disorders. [10]

General constitutional symptoms:

This manifestation is present in 70-80% of patients, significantly impacting their quality of life- Other non-specific manifestations of pSS include sleep disturbances, anxiety, depression, and widespread pain. Studies suggest that this subgroup of patients exhibit lower levels of autoantibodies, which can complicate diagnosis. Furthermore, the overlap of symptoms with conditions such as menopause, diabetes, hypothyroidism, fibromyalgia poses additional diagnostic challenges particularly in female patients. [11]

Musculoskeletal manifestation

Arthritis in SS is typically non-erosive synovitis, primarily affecting the metacarpophalangeal (MCP) joints, though it can also involve the knees, ankles, shoulders, and metatarsophalangeal

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[10] Lendrem D, Mitchell S, McMeekin P, Bowman S, Price E, Pease CT, Emery P, Andrews J, Lanyon P, Hunter J, Gupta M, Bombardieri M, Sutcliffe N, Pitzalis C, McLaren J, Cooper A, Regan M, Giles I, Isenberg D, Vadivelu S, Coady D, Dasgupta B, McHugh N, Young-Min S, Moots R, Gendi N, Akil M, Griffiths B, Ng WF; UK primary Sjögren's Syndrome Registry. Health-related utility values of patients with primary Sjögren's syndrome and its predictors. Ann Rheum Dis. 2014 Jul;73(7):1362-8. doi: 10.1136/annrheumdis-2012-202863. Epub 2013 Jun 12. PMID: 23761688.

[11] Negrini, S., Emmi, G., Greco, M. *et al.* Sjögren's syndrome: a systemic autoimmune disease. *Clin Exp Med* **22**, 9–25 (2022). https://doi.org/10.1007/s10238-021-00728-6

joints. A study by Fauchais et al. reported that articular involvement was the initial symptom in 17% of the patients.[12]

Many SS patients experience joint-related symptoms, particularly in the small joints, with some developing morning stiffness and arthritis. Erosive arthritis is uncommon and may suggest an overlapping syndrome with rheumatoid arthritis (RA). In rare cases, joint deformities, such as Jaccoud's arthropathy, can occur in pSS. [13]

However, the prevalence of arthritis, degenerative spinal disease, and tendon disorders in SS patients does not appear to be higher than in the general population.

Some SS patients experience muscle pain, while others may develop generalized pain meeting the diagnostic criteria for fibromyalgia. [14]

Dermatological manifestation

Except for xerosis, which is the most common cutaneous manifestations, annular erythema and cutaneous vasculitis are also frequently observed in pSS patients. Those are often linked to anti-Ro/SS-A and anti-La/SS-B autoantibodies.

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[12] Rozis M, Vlamis J, Vasiliadis E, Mavragani C, Pneumaticos S, Evangelopoulos DS. Musculoskeletal Manifestations in Sjogren's Syndrome: An Orthopedic Point of View. J Clin Med. 2021 Apr 8;10(8):1574. doi: 10.3390/jcm10081574. PMID: 33917955; PMCID: PMC8068384.

[13] Musculoskeletal Key. Jaccoud's arthropathy [Internet]. [cited 2025 Feb 5]. Available from: https://musculoskeletalkey.com/jaccouds-arthropathy/

[14] Olsson P. Primärt Sjögrens syndrom [Internet]. Internetmedicin; n.d. [cited 2025 Feb 4]. Available from: https://www.internetmedicin.se/reumatologi/primart-sjogrens-syndrom#diagnostik-och-utredning

Raynaud's phenomenon occurs in 10-20% of patients, typically preceding sicca symptoms but with a milder course than in systemic sclerosis. [15]

Respiratory tract manifestation

Pulmonary involvement occurs in 9-24% of SS patients, though subclinical abnormalities are detected in up to 75% via pulmonary function tests, bronchioalveolar lavage and computed tomography.

Upper airway dryness can lead to nasal crusting, epistaxis, and rhinosinusitis, while thick mucus at the vocal cords may cause chronic hoarseness. Xerotrachea affects nearly 50% of patients, leading to a chronic non-productive cough.

Additionally, airway dryness increases the risk of atelectasis, bronchiectasis, and recurrent respiratory infections. [16]

Bronchiolitis, particularly follicular bronchiolitis, is the most common distal airway manifestation in SS. Interstitial lung diseases (ILDs), such as non-specific interstitial pneumonia (NSIP) (the most frequent pattern), organizing pneumonia, lymphocytic interstitial pneumonia, and cryptogenic organizing pneumonia, are also observed.

Clinically, ILDs present with cough and dyspnea, while high-resolution CT findings, restrictive ventilatory defects and reduced DLCO on PFTs support the diagnosis.

Other respiratory complications include amyloidosis, BALT lymphomas, thromboembolic disease, pulmonary arterial hypertension, and pleural disease.[17]

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[15] Negrini, S., Emmi, G., Greco, M. *et al.* Sjögren's syndrome: a systemic autoimmune disease. *Clin Exp Med* **22**, 9–25 (2022). https://doi.org/10.1007/s10238-021-00728-6

[16] Stojan G, Baer AN, Danoff SK. Pulmonary manifestations of Sjögren's syndrome. Curr Allergy Asthma Rep. 2013 Aug;13(4):354-60. doi: 10.1007/s11882-013-0357-9. PMID: 23797265; PMCID: PMC4393654.

[17] Stojan G, Baer AN, Danoff SK. Pulmonary manifestations of Sjögren's syndrome. Curr Allergy Asthma Rep. 2013 Aug;13(4):354-60. doi: 10.1007/s11882-013-0357-9. PMID: 23797265; PMCID: PMC4393654.

Nervous system manifestation

According to John Hopkins Sjögren's Center, neurological involvement of PSS may include Myelitis, optic neuritis, which can mimic multiple sclerosis (MS). [18]

Other common neurological manifestations include polyneuropathy, presenting as paresthesia, decreased sensation and pain.

In SS, small nerve fibers are often affected, making diagnosis challenging with standard nerve conduction tests, which primarily assess large nerve fibers. A more effective method for detecting small-fiber pathology is a skin biopsy, which evaluates small sensory nerve fibers innervating the skin.

Symptoms of small-fiber neuropathy include pain, burning and prickling sensations, often without muscle weakness. [19]

SS can also cause autonomic neuropathy, leading to symptoms such as dizziness upon standing, hypo or hyperhidrosis and early satiety. Additionally, trigeminal, and glossopharyngeal neuralgia can occur, with trigeminal neuropathy coexisting in up to 20% if cases. [20]

Hematology and lymphoma development in SS

Cytopenia's, similar to those seen in systemic lupus erythematosus (SLE), are common in SS but are generally less severe and rarely require treatment.

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[18] Birnbaum, J. Neurologic Complications. Johns Hopkins Sjögren's Center. [Date Unknown] (cited 2025 Feb 04) Available from: https://www.hopkinssjogrens.org/disease-information/sjogrens-disease/neurologic-complications/

[19] Perzyńska-Mazan J, Maślińska M, Gasik R. Neurological manifestations of primary Sjögren's syndrome. Reumatologia. 2018;56(2):99-105. doi: 10.5114/reum.2018.75521. Epub 2018 May 9. PMID: 29853725; PMCID: PMC5974632.

[20] Olsson P. Primärt Sjögrens syndrom [Internet]. Internetmedicin; n.d. [cited 2025 Feb 4]. Available from: https://www.internetmedicin.se/reumatologi/primart-sjogrens-syndrom#diagnostik-och-utredning

One of the most serious complications of SS is lymphoma, particularly non- Hodgkins lymphoma (NHL). SS patients have a 15-20% higher risk of developing NHL compared to the general population, with a 5-10% lifetime risk.

Symptoms suggestive of lymphoma include parotid swelling, purpura, or other vasculitis, cytopenia, polyneuropathy, glomerulonephritis, low level of SSA/SSB antibodies and decreased complement C3-C4. Patients presenting with these features should be classified as high-risk and are often identifiable early in the disease course. [21]

Kidney manifestation

Finally, and most important for this thesis, is the renal involvement in SS. The main renal pathologies observed in SS patients include tubulointerstitial nephritis (TIN), renal tubular acidosis (RTA), Fanconi's syndrome, diabetes insipidus and glomerulonephritis.

Among these, TIN is the most common, while glomerulonephritis, though less frequent, is associated with a worse prognosis. Each of these conditions will be explored in detail throughout this thesis. [22]

[21] (Ibid.)

[22] (Ibid.)

Kidney Injury in Sjögren's Syndrome

Prevalence of Kidney Injury in pSS

The reported prevalence of kidney involvement in pSS varies significantly across studies. This variability can be attributed to differences in diagnostic criteria, study designs, and definitions of renal involvement.

Earlier studies have used the 2002 American -European Consensus Group (AECG) criteria, while more recent research relies on the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria, which have become the most used in clinical studies.

According to a review by Mariette et al. (2015), the prevalence of renal involvement in pSS ranges from 1% to 33% worldwide, with significant geographic and ethnic variations.

In most European studies, the prevalence is estimated to be between 4% and 7%, while certain ethnic groups appear to have higher prevalence.

Prospective studies that systematically screen for renal tubular dysfunction suggest a higher prevalence of kidney abnormalities, particularly subclinical tubular dysfunction.

However, not all tubular abnormalities have clinical significance, which limits the practical implications of such findings.

Histopathological studies reveal much lower prevalence of biopsy-confirmed kidney disease in pSS since kidney biopsies are not routinely performed unless significant renal dysfunction is present.

A long-term retrospective study by Maripuri et al. (2014) found that out of 7276 pSS patients, only 0.3% (n=24) underwent renal biopsy over a 30-year period.

Importantly, despite the potential for renal involvement, studies suggest that patients with pSS do not have an increased risk of developing end-stage renal disease (ESRD) compared to the general

population. This indicates that while kidney involvement is relatively common, it is often mild and rarely progresses to severe renal impairment. [23]

Pathophysiology

Autoimmune lymphocytic infiltration

Kidney involvement in pSS is primarily driven by chronic autoimmune inflammation, affecting the renal tubules and interstitium more than the glomeruli.

One of the main pathological processes is the autoimmune lymphocytic infiltration which leads to TIN.

This is characterized by infiltration of CD4+ T cells, B cells, and plasma cells into the renal tubules and interstitial space. The resulting chronic inflammation damages the distal tubules, impairing their ability to excrete acid and reabsorb electrolytes.

The key consequences of this process include distal renal tubular acidosis (dRTA), leading to metabolic acidosis, hypokalemia and nephrocalcinosis. Over time, persistent inflammation contributes to tubular atrophy, interstitial fibrosis, and the progression to CKD.

Autoantibody-mediated injury

Another pathology mechanism is the autoantibody-mediated injury (Anti-Ro (SS-A) and anti-La (SS-B). These autoantibodies are present in 70-90% of pSS but their direct role in kidney injury is unclear. Other autoantibodies are the Anti-Carbonic Anhydrase II (CA-II), these are found in pSS patients with dRTA and impair hydrogen ion secretion by blocking carbonic anhydrase in distal tubules, causing metabolic acidosis.

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[23] Aiyegbusi O, McGregor L, McGeoch L, Kipgen D, Geddes CC, Stevens KI. Renal Disease in Primary Sjögren's Syndrome. Rheumatol Ther. 2021 Mar;8(1):63-80. doi: 10.1007/s40744-020-00264-x. Epub 2020 Dec 24. PMID: 33367966; PMCID: PMC7991017.

The role of cryoglobulins is that they create deposits in the kidney, leading to cryoglobulinemic glomerulonephritis, causing proteinuria and hematuria.

Rheumatoid factor (RF) plays a role as well in immune complex deposition, leading to glomerular inflammation in some cases.

Immune-complex mediated

Unlike TIN, glomerular disease is less common in pSS. When present, it is usually immune-complex mediated and associated with low complement levels (C3, C4) and cryoglobulinemia. The two main histological patterns observed in pSS-related glomerular diseases are membranoproliferative glomerulonephritis (MPGN) due to cryoglobulin deposition and mesangial glomerulonephritis. Both conditions lead to proteinuria, hematuria and in severe cases CKD. [24]

Chronic immune activation

PSS is associated with chronic immune activation, leading to excessive production of pro-inflammatory cytokines like Interferon-gamma (IFN-y) which activate macrophages and promote tissue damage and Tumor Necrosis Factor-alpha (TNF-a) that leads to fibrosis and tubular dysfunction. Interleukin-6 (IL-6) increases cell activation and contributes to autoantibody production. B-cell activating factor (BAFF) supports B-cell survival, enhancing autoantibody formation. The consequence of chronic immune activation is that persistent inflammation leads to fibrosis, tubular atrophy, and loss of renal function, progressing potentially to CKD. [25]

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[24] Aiyegbusi, O., McGregor, L., McGeoch, L. *et al.* Renal Disease in Primary Sjögren's Syndrome. *Rheumatol Ther* **8**, 63–80 (2021). https://doi.org/10.1007/s40744-020-00264-x

[25] Davis D. PathologyOutlines.com. [Updated 2020) Sjögren syndrome – kidney pathology [Internet]. PathologyOutlines.com; [cited 2025 Feb 7]. Available from: https://www.pathologyoutlines.com/topic/kidneysjogrensyndrome.html

Clinical features and Diagnosis of Renal Injury in Sjögren's Syndrome

Symptoms and Clinical presentation:

Tubulointerstitial nephritis

TIN is the hallmark of kidney injury in pSS, primarily affects the renal tubules. This results in significant disturbances in renal function, particularly in acid-base balance and electrolyte homeostasis. The key consequence of TIN is dRTA. Clinically, this manifests fatigue, muscle weakness and cramps, primarily due to hypokalemia. [26] In severe cases, hypokalemic paralysis can occur. [27] Patients may also develop non-anion gap metabolic acidosis, as the kidneys fail to maintain proper acid-base balance. Over time, the chronic acid accumulation leads to nephrocalcinosis and kidney stone formation as well as hypercalciuria, while defective urine acidification can result in polyuria and polydipsia, sometimes mimicking nephrogenic diabetes insipidus.

TIN also contributes to electrolyte imbalances, except from hypokalemia, it can lead to hyperchloremic metabolic acidosis leading to fatigue and bone pain, as the body attempts to buffer excess acid by mobilizing calcium from the bones. [28]

Glomerulonephritis

Although the prevalence of GN is lower than TIN, it can still present with various clinical manifestations. The most common signs of GN in PSS are proteinuria and hematuria. Patient may

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[26] Bhandari J, Thada PK, Rout P, et al. Tubulointerstitial Nephritis. [Updated 2024 May 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557537/

[27] Gündüz E, Zengin Y, Dursun R, İçer M, Güllü MN, Durgun HM. Hypokalemic Periodic Paralysis Due To Distal Renal Tubular Acidosis. EUR J GEN MED. 2015;12(2):164-6. https://doi.org/10.15197/sabad.1.12.33

[28] Bhandari J, Thada PK, Rout P, et al. Tubulointerstitial Nephritis. [Updated 2024 May 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557537/

complain of foamy urine, this due to the loss of protein in the urine, peripheral swelling due to protein loss. Another clinical finding is hypertension, which can develop in cases with significant renal impairment. [29]

Chronic Kidney Disease

In advanced cases, CKD can be one of the complications. Clinical findings may be progressive decline in kidney function, marked by elevated creatinine levels and a reduced eGFR. Patients complains may involve fatigue, general weakness, loss of appetite and nausea, itching and dry skin, as well as edema in the legs, face or even lungs in case of late stage disease. [30]

Diagnostic methods

Diagnostic approach, ACR/EULAR-criteria

In general, there are no diagnostic criteria for pSS making the diagnosis of the disease challenging.

The diagnosis is set by the clinician based on the clinical picture, laboratory findings and other objective measurement methods. There are classification criteria, but this is particularly used for research purposes. Some new criteria are made from 2016, so called ACR/EULAR- criteria for pSS.

To make a diagnosis of SS, following criteria must be met:

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[29] Keskinyan VS, Lattanza B, Reid-Adam J. Glomerulonephritis. Pediatr Rev. 2023 Sep 1;44(9):498-512. doi: 10.1542/pir.2021-005259. PMID: 37653138.

[30] Saeed, A. Njursvikt, hos vuxna- primär handläggning [Internet]. Internetmedicin; [2024 May 07]. [cited 2025 Feb 22]. Available from: https://www.internetmedicin.se/njurmedicin/njursvikt-hos-vuxna-primar-handlaggning

I. Ocular Symptoms (at least one)	**II. Oral Symptoms** (at least one)	**III. Ocular Signs** (at least one)	**IV. Histopathology**	**V. Oral signs** (at least one)	**VI. Autoantibodies** (at least one)
Symptoms of dry eyes for at least 3 months.	Symptoms of dry mouth for at least 3 months.	Abnormal Schirmer's test (w/o anesthesia; ≤mm/5 min)	Lip biopsy showing focal lymphocytic sialadenitis (focus score ≥1 per 4mm2)	Unstimulated whole salivary flow (≤1.5 ml in 15 min)	Anti-SSA (Ro) or Anti-SSB (La), or both.
A foreign body sensation in the eyes.	Recurrent or persistently swollen salivary glands.	+ Vital dye staining of the eye surface.		Abnormal parotic sialography.	
Use of artificial tears 3 or more times/day.	Need for liquids to swallow dry foods.			Abnormal salivary scintigraphy.	

<u>For a pSS diagnosis:</u>

- Any 4 of the 6 criteria must include either item IV (histopathology) or VI (autoantibodies).
- Any 4 of the 4 objective criteria (III, IV, V, VI)

Exclusion criteria
Past head and neck radiation treatment.
HCV
AIDS
Pre-existing lymphoma.
Sarcoidosis
Graft versus host disease
Current use of anticholinergic drugs

Table 1. EULAR [31]

This together with EULARs Sjögren's Syndrome Disease Activity Index (ESSDAI) is a key table to identify the degree of disease and to personalize the treatment.

Domain [Weight]	Activity level	Description
Constitutional [3] *Exclusion of fever of infectious origin and voluntary weight loss*	No = 0	Absence of the following symptoms
	Low = 1	Mild or intermittent fever (37.5°-38.5°C) / night sweats and/or involuntary weight loss of 5 to 10% of body weight
	Moderate = 2	Severe fever (>38.5°C) / night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy [4] *Exclusion of infection*	No = 0	Absence of the following features
	Low = 1	Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region
	Moderate = 2	Lymphadenopathy ≥ 2 cm in any nodal region or ≥ 3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 3	Current malignant B-cell proliferative disorder
Glandular [2] *Exclusion of stone or infection*	No = 0	Absence of glandular swelling
	Low =1	Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular or lachrymal swelling
	Moderate = 2	Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling
Articular [2] *Exclusion of osteoarthritis*	No = 0	Absence of currently active articular involvement
	Low = 1	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate = 2	1 to 5 (of 28 total count) synovitis
	High = 3	≥ 6 (of 28 total count) synovitis
Cutaneous [3] *Rate as "No activity" stable long-lasting features related to damage*	No = 0	Absence of currently active cutaneous involvement
	Low =1	Erythema multiforma
	Moderate = 2	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 3	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary [5] *Rate as "No activity" stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use etc.)*	No =0	Absence of currently active pulmonary involvement
	Low = 1	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: No breathlessness and normal lung function test.
	Moderate = 2	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (N or abnormal lung function tests restricted to: 70% >DL_{CO}≥ 40% or 80%>FVC≥60%
	High = 3	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III,

Table 2 . The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): Domain and item definitions and weights.

[31] Vitali C, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61:554-558

EULAR Sjögren's syndrome disease activity index: Development of a consensus systemic disease activity index for primary Sjögren's syndrome - Scientific Figure on ResearchGate. Available *from: https://www.researchgate.net/figure/The-EULAR-Sjoegrens-Syndrome-Disease-Activity-Index-ESSDAI-Domain-and-item-definitions_tbl1_44389348 [accessed 11 Mar 2025]* [32]

Specifically, for pSS with kidney involvement we need to have in mind the different possible pathologies that can affect patients and thereafter analyze the findings. The symptoms related to kidney dysfunction are muscle weakness, fatigue, metabolic acidosis, edema, hematuria, or proteinuria.

Urinalysis

Urinalysis is a fundamental tool in assessing kidney function and provides valuable insight into renal involvement in pSS. It serves as a non-invasive yet essential diagnostic method for detecting and monitoring renal complications.

Proteinuria is an indication of kidney injury, this injury can be in the glomerulus, which is the filtering structure, or in the tubules (tubules are the structures responsible for reabsorbing filtered salts, water, and acids from the blood filtration). [33]

Hematuria is another important finding in urinalysis. It is often associated with glomerular disease but may also originate from pathology in the collecting system or bladder, such as nephrolithiasis or tumor. The presence of white blood cells or casts suggests TIN, while an inappropriately high urine pH may indicate dRTA.

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[32] *EULAR Sjögren's syndrome disease activity index: Development of a consensus systemic disease activity index for primary Sjögren's syndrome - Scientific Figure on ResearchGate.* Available *from: https://www.researchgate.net/figure/The-EULAR-Sjoegrens-Syndrome-Disease-Activity-Index-ESSDAI-Domain-and-item-definitions_tbl1_44389348 [accessed 11 Mar 2025]*

[33] Johns Hopkins Sjögren's Center. Blood and urine tests [Internet]. Baltimore (MD): Johns Hopkins University; [cited 2025 Feb 7]. Available from: https://www.hopkinssjogrens.org/disease-information/diagnosis-sjogrens-disease/blood-and-urine-tests/

TIN, the most prevalent renal manifestations in Pss, due to the inflammation of renal interstitium surrounding the tubules, in urinalysis is reflected by a low specific gravity, proteinuria, and in cases of dRTA, an abnormally high urine Ph.

Though glomerulonephritis is less common in Pss, it remains a significant cause of renal involvement. When present, it is typically associated with proteinuria and may be accompanied by dysmorphic RBC, WBC, or cellular cast, depending on the underlying pathology.

Cryoglobulinemic glomerulonephritis, a more severe but less frequent manifestation, may present with nephrotic-range proteinuria, microscopic hematuria, and active urinary sediment, indicating significant glomerular injury.

Rapidly progressive GN with nephritic syndrome can occur, this will cause hematuria and proteinuria, typically <3g/day, accompanied by AKI, oliguria, and hypertension. Nephrotic syndrome can occur as well, by contrast, this will show heavy proteinuria (>3g/day), hypoalbuminemia (<30g/L) and peripheral edema.[34]

Serology

Blood tests play a crucial role in evaluating renal involvement in Pss. Basic laboratory tests include:

- **Electrolytes**: To detect hypokalemia, hyperchloremic metabolic acidosis (characteristic or RTA), commonly seen in pSS-related kidney injury.
- **Serum creatinine and eGFR**: Help assess overall kidney function and detect progressive renal impairment.

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[34] Aiyegbusi O, McGregor L, McGeoch L, Kipgen D, Geddes CC, Stevens KI. Renal Disease in Primary Sjögren's Syndrome. Rheumatol Ther. 2021 Mar;8(1):63-80. doi: 10.1007/s40744-020-00264-x. Epub 2020 Dec 24. PMID: 33367966; PMCID: PMC7991017.

- **Autoantibodies:** Detection of anti-Ro/SSA and anti-La/SSB antibodies supports the diagnosis of pSS and correlates with the disease activity.
- **Complement levels C3, C4**: Low levels may indicate immune complex-mediated glomerulonephritis, particularly in cases of cryoglobulinemic glomerulonephritis, which is associated with worse prognosis.
- **Other immune tests:** Cryoglobulins, RF and serum immunoglobulins, may be useful in identifying patients at higher risk of immune complex deposition and glomerular injury. [35]

Imaging

Imaging studies are highly valued, renal ultrasound helps to identify structural abnormalities like nephrolithiasis, small, scarred kidney and may help to exclude other pathologies of obstructive origin, especially in patients presenting with renal colic and acute kidney injury.

If there is an indication, CR of MRI is possible, this can aim to detect renal stones, nephrocalcinosis.

Biopsy

Biopsy in cases of pSS is rarely required and not all cases are suitable for biopsy, however the indications for biopsy are rapidly progressive kidney dysfunction, proteinuria >1g/day, active urine sediment and systemic vasculitis [36]

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[35] Johns Hopkins Sjögren's Center. Blood and urine tests [Internet]. Baltimore (MD): Johns Hopkins University; [cited 2025 Feb 7]. Available from: https://www.hopkinssjogrens.org/disease-information/diagnosis-sjogrens-disease/blood-and-urine-tests/

[36] Aiyegbusi O, McGregor L, McGeoch L, Kipgen D, Geddes CC, Stevens KI. Renal Disease in Primary Sjögren's Syndrome. Rheumatol Ther. 2021 Mar;8(1):63-80. doi: 10.1007/s40744-020-00264-x. Epub 2020 Dec 24. PMID: 33367966; PMCID: PMC7991017

Renal biopsy is the gold standard for diagnosing the type and severity of kidney injury in pSS when there is a significant renal dysfunction, proteinuria >1g/day, hematuria of unclear etiology.

The findings in tubulointerstitial nephritis are lymphocytic infiltration, mainly by T-cells, in the interstitium, tubular atrophy and interstitial fibrosis. 75% of the patients with TIN will have CD4+ cells and/or CD8+. Less commonly, on the other hand, in 10% of the cases, B-cells are prominent. TIN is the most prevalent finding in patients with renal colic and that shows radiological features of nephrolithiasis, although it remains still undiagnosed due to the indolent course of disease.[37]

On the other hand, in cases of glomerulonephritis, immune complexes will be seen in the glomeruli, for instance IgA, IgG, complement deposition in cryoglobulinemia or MPGN and proliferative changes in the glomerular capillary loops.

Histopathological features

Extra glandular disease varies around up to 20% of the patients. According to European studies renal involvement is present in 5-14%, whereas in a Chinese study 30%. [38] The clinical manifestations vary among the patients. Symptoms usually occur after 2-7 years after diagnosis of pSS as escalating low-grade proteinuria and slowly decreasing kidney function due to chronic or acute interstitial nephritis. Some patients can show dRTA, less common proximal renal tubular acidosis with full-blown Fanconi syndrome, with glycosuria, aminoaciduria, and low-level tubular proteinuria.

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[37] ibid

[38] François, H., Mariette, X. Renal involvement in primary Sjögren syndrome. *Nat Rev Nephrol* **12**, 82–93 (2016). https://doi.org/10.1038/nrneph.2015.174

PSS patients usually undergo immunosuppressive treatment to manage the symptoms of the disease, although the glomerular filtration rate is preserved long term in patients with chronic interstitial nephritis.

According to AJKD Atlas of Renal pathology, of patients with pSS undergoing kidney biopsy, tubulointerstitial nephritis is present in 67% of patients undergoing renal biopsy. 5-30% have cryoglobulinemic glomerulonephritis because of ongoing polyclonal B-cell stimulation. This pathological feature relates to worse prognosis in the form of decreased renal and overall survival.

On the other hand, light microscopy may show acute interstitial nephritis with lymphoplasmacytic infiltrate and edema or chronic interstitial nephritis with similar infiltration of cells, together with interstitial fibrosis and tubular atrophy.

The infiltration is of CD4/CD8 T-cells, B-cells, and plasma cells with scattered tubulitis.

In normal cases, glomeruli are unaffected unless there is concomitant cryoglobulinemic glomerulonephritis- if this is the case proliferative changes will be seen, with periodic acid-Schiff positive cryo-plugs.[39]

Again, in cases of cryoglobulinemic glomerulonephritis show cryoglobulin deposit, mostly IgM dominant with clonal shift with mesangium and capillary walls involved, in immunofluorescence microscopy.

On the other hand, on electron microscopy and glomerulonephritis, mesangial and subendothelial deposits with short curvilinear substructure are seen.

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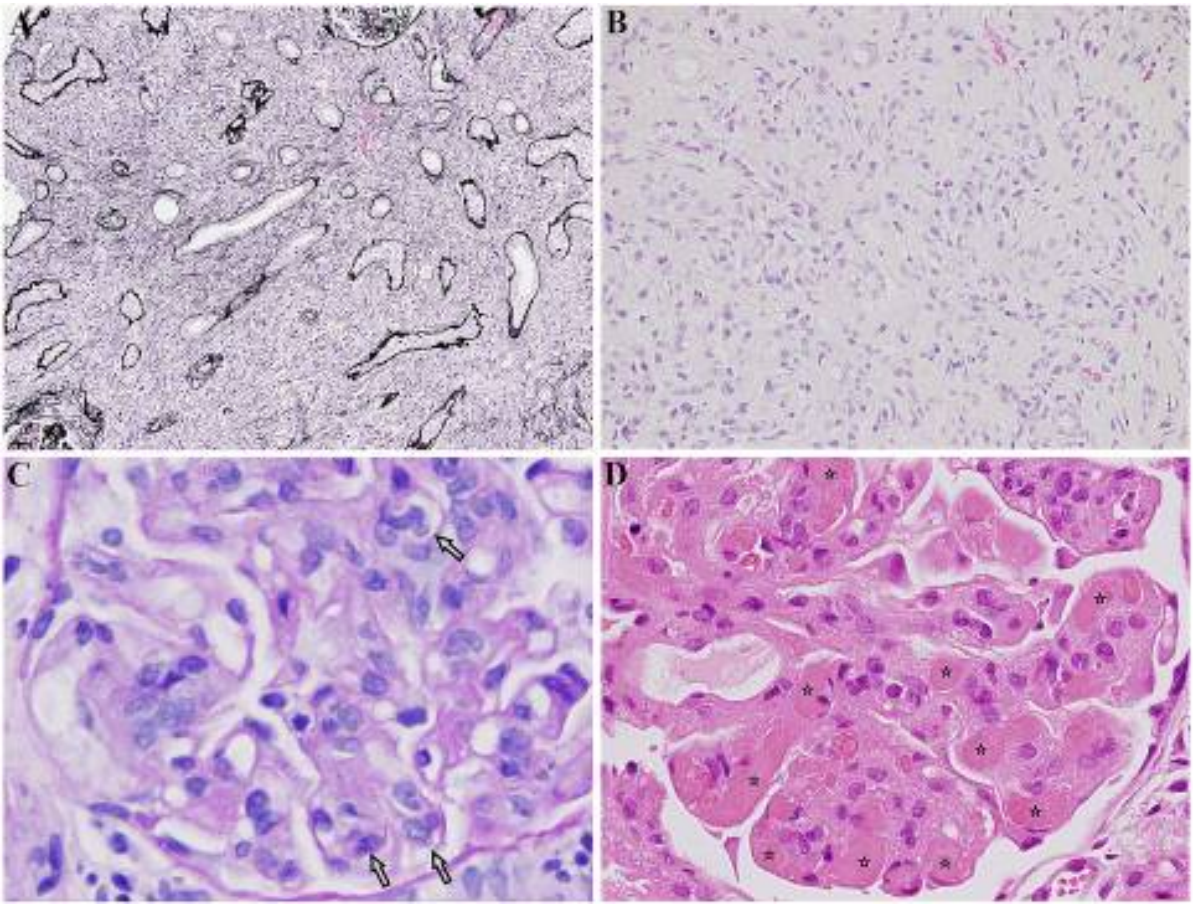
[39] *AJKD* Atlas of Renal Pathology: Kidney Disease in Primary Sjögren Syndrome
Fogo, Agnes B. et al. American Journal of Kidney Diseases, Volume 69, Issue 6, e29 - e30

In general, tubulointerstitial nephritis do not implicate any changes in EM or Immunofluorescence microscopy, only in LM. [40]



A) Picture shows IgG4-related TIN. Tubules are separated by expansile interstitial fibrosis and inflammation. This image was originally used in Kidder et al. [41]

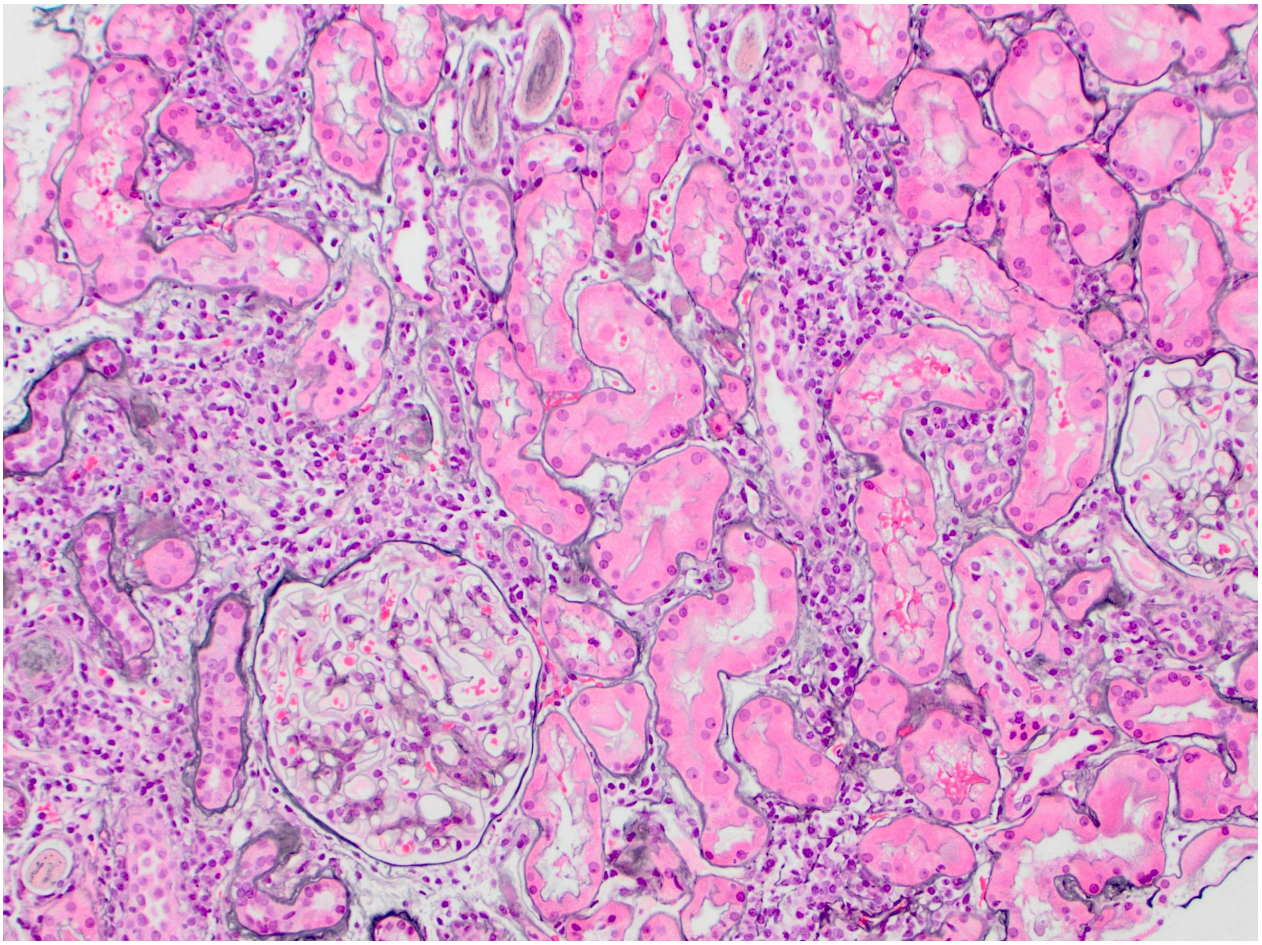
[40] *AJKD* Atlas of Renal Pathology: Kidney Disease in Primary Sjögren Syndrome Fogo, Agnes B. et al.American Journal of Kidney Diseases, Volume 69, Issue 6, e29 - e30

[41] Kidder D, Rutherford E, Kipgen D, Fleming S, Geddes C, Stewart GA. Kidney biopsy findings in primary Sjögren syndrome. Nephrol Dial Transplant. 2015;30(8):1363–1369. doi: 10.1093/ndt/gfv042.

B) IgG4-related TIN: interstitial storiform fibrosis and inflammation. This image was originally used in Kidder et al. [42]

C) Membranoproliferative GN in SS: glomerulus shows intracapillary hypercellularity. This image was originally used in Kidder et al.

D) Cryoglobulinemic glomerulonephritis in SS: glomerulus containing several hyaline thrombi, ‘’cryoplugs’’ (indicated by stars), in capillaries. This image was originally used in Kidder et al.[43]



[42] Ibid.

[43] Ibid.

Image E) Plasma cell rich TIN, Jones stain. Contributed by Nicole K. Andeen, M.D, Pathology Outlines. [44]

Management and Treatment

TIN follows a benign course in patients with pSS patients when identified early. It typically causes mild deterioration of kidney function, often reflected as a slight elevation in serum creatinine. In most cases, this does not require treatment, and progression to ESRD is uncommon.

When renal dysfunction is suspected in a pSS patient, a kidney biopsy is performed to confirm the underlying pathology. If the biopsy reveals TIN, corticosteroid therapy is initiated, which generally leads to an improvement in kidney function within a few weeks, provided that irreversible scarring has not yet occurred.

In case of RTA, urine becomes more alkaline due to inability to excrete acids in the urine due to kidney tubule dysfunction, as the blood becomes more acidic. This imbalance may present muscle weakness due to hypokalemia or loin pain resulting from kidney stone formation. Treatment depends on disease severity; potassium supplementation is required in cases of significant hypokalemia, while alkaline agents such as sodium bicarbonate are used to correct metabolic acidosis and prevent renal stone formation.

Although glomerular involvement is rare, when present, it is usually due to immune complex deposition. This may result in progressive renal impairment, and in severe cases kidney failure. Kidney biopsy is necessary to assess the extent of glomerular damage. If GN is confirmed, treatment consists of corticosteroids and immunosuppressive agents, such as cyclophosphamide,

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[44] Davis D. Sjögren syndrome. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/kidneysjogrensyndrome.html. Accessed March 3rd, 2025.

mycophenolate mofetil or rituximab, to mitigate immune-mediated damage and preserve kidney function. [45],[46]

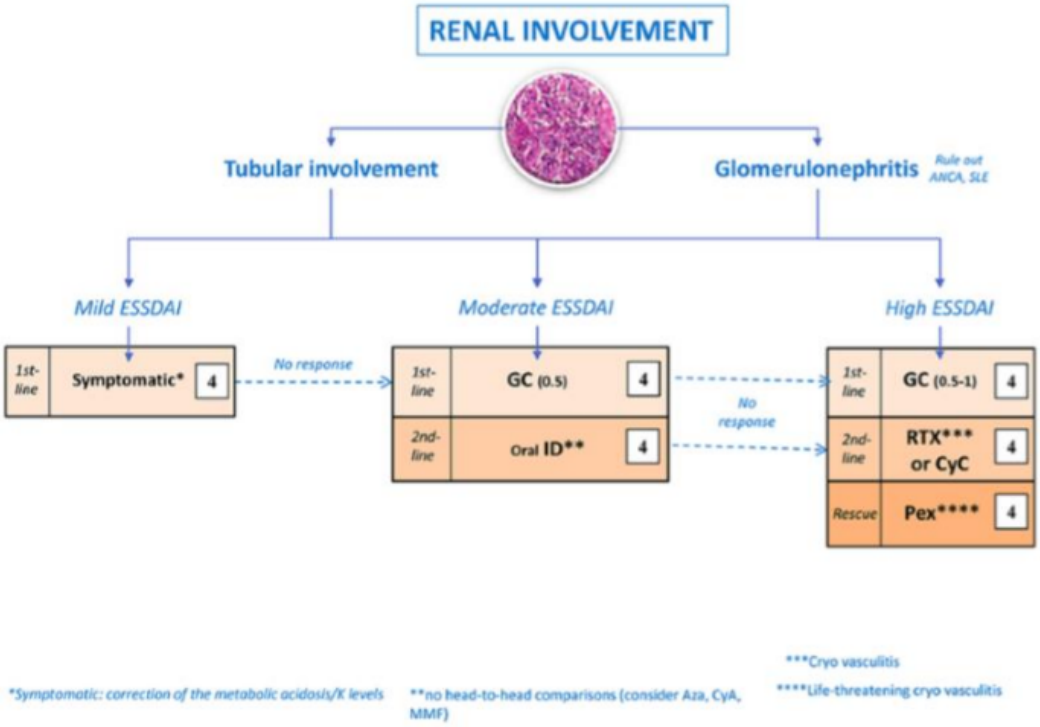

Figure 2. Rugiene, R. SISTEMINE SKLEROZE. Presented at; 2023; Medical Faculty, Rheumatology, Vilnius University Hospital Santaros Clinic. [47]

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[45] Hal Scofield, R., and others, 'The Internal Organs in Sjögren's', in Daniel J. Wallace (ed.), *The Sjögren's Book*, 5th edn (New York, 2022; online edn, Oxford Academic, 19 May 2022), https://doi.org/10.1093/oso/9780197502112.003.0014, accessed 3 Mar. 2025.

[46] Wallace, Daniel J., 'Management of Kidney-Associated Involvement in Sjögren's', in Daniel J. Wallace (ed.), *The Sjögren's Book*, 5th edn (New York, 2022; online edn, Oxford Academic, 19 May 2022), https://doi.org/10.1093/oso/9780197502112.003.0039, accessed 3 Mar. 2025.

[47] Rugiene, R. SISTEMINE SKLEROZE. Presented at; 2023; Medical Faculty, Rheumatology, Vilnius University Hospital Santaros Clinic.

According to Figure 2, the management of renal involvement in pSS depends on the ESSDAI score. In cases of tubular involvement, the first line treatment should be symptomatic management, including the correction of potassium levels and metabolic acidosis. However, if the disease course is moderate or if the symptomatic treatment proves insufficient, glucocorticoid therapy is indicated as the first line treatment, while oral immunosuppressants such as rituximab are considered second line options.

In cases of GN, it is essential to rule out ANCA and SLE. If GN is confirmed, or if there is no response to the treatment for moderate ESSDAI, the disease is classified as high ESSDAI. In such cases, the first line treatment should be glucocorticoids, followed by rituximab or cyclophosphamide as second line options. In refractory cases, plasma exchange may be considered as a rescue therapy.

In addition to these established treatments, novel therapeutic agents targeting B-cell activating factor (BAFF) have shown promise. However, their clinical use remains relatively new, and further research is needed to fully establish their efficacy. [48]

Prognosis and Long-term outcomes

TIN is generally associated with milder manifestations and better prognosis compared to membranoproliferative glomerulonephritis (MPGN). However, it can often go undetected, leading to progression to CKD if not identified early.

[48] Rugiene, R. SISTEMINE SKLEROZE. Presented at; 2023; Medical Faculty, Rheumatology, Vilnius University Hospital Santaros Clinic. Available from https://2023.emokymai.vu.lt/pluginfile.php/157034/mod_resource/content/1/SSD_SjS_lecture.pdf [Accessed 11 Mar 2025]

In contrast, glomerular disease is typically more symptomatic, making it more likely to be diagnosed and treated at an earlier stage. [49]

GN is linked to a higher risk of severe renal impairment and progression to ESRD if left untreated. Additionally, PSS patients with GN are at higher risk of developing lymphoma which is associated with poorer survival rates compared to those with TIN.

A cohort study*, Clinically Significant Renal Involvement in Primary Sjögren's Syndrome*: *Clinical presentation and outcome,* analyzed 715 patients who met the American-European Consensus Group (AECG) criteria for pSS. Kaplan-Meier analysis was used to compare mortality rates between patients with and without renal involvement.

The study found that 35 of the 715 patients (4.9%) had clinically significant renal involvement. The cumulative follow-up time after the diagnosis of renal dysfunction was 252.2 person-years. All patients were women, with a median age at diagnosis of 52 years (range 25-76 years). The median disease duration was 11 years (interquartile range 8-18 years).

Among the 35 patients with renal disease:

- 17 patients had GN alone.
- 13 patients had TIN alone.
- 5 patients developed both pathologies and were categorized in the GN group.
- 2 patients with pSS with renal declined to undergo a renal biopsy.

Of the 22 patients with GN, renal biopsy findings in 21 included.

- Membranoproliferative GN in 10 patients.
- Mesangial GN in 7 patients.

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[49] Goules AV, Tatouli IP, Moutsopoulos HM, Tzioufas AG. Clinically significant renal involvement in primary Sjögren's syndrome: clinical presentation and outcome. Arthritis Rheum. 2013 Nov;65(11):2945-53. doi: 10.1002/art.38100 . PMID: 24166794 .

- Membranous GN in 2 patients.
- Segmental glomerulosclerosis in 1 patient.
- Proliferative GN in 1 patient.

In 12 of 13 patients with TIN alone, histological examination revealed lymphocytic infiltration of the interstitium, and tubules were inspected.

Nineteen of the 35 patients had already been identified in 1998 and 16 additional patients diagnosed between 1998 and 2012 were included in this study.

Outcomes:

- 9 patients died (25.7%)
- 9 developed non-Hodgkin's lymphomas.
- 11 developed CRF, of whom 4 required hemodialysis.

The estimated incidence rates per 100 person-years were:

- 3.6 for lymphoma.
- 4.4 for CRF.
- 1.6, for hemodialysis.

Among the nine reported

- Three were due to lymphoma.
- Two were due to cardiac arrest related to hemodialysis or CRF.
- One died of infection.
- One of stroke.
- One of cerebral hemorrhage.
- One had an unknown cause of death.

The estimated 5-year overall survival rate after renal diagnosis was 85% (0.85). After adjusting for age, type of renal involvement, lymphoma and the need for hemodialysis, lymphoma remained the only significant predictor of poor survival. [50]

Discussion

Kidney injury in pSS remains an underdiagnosed but clinically significant complication. The primary pathology, TIN, is driven by chronic lymphocytic infiltration, leading to impaired renal function and metabolic disturbances. A secondary but important manifestation is GN, which, although less common, is associated with immune-complex deposition and a worse prognosis.

The findings suggest that autoimmune lymphocytic infiltration predominantly affects the tubulointerstitium, leading to dRTA, metabolic acidosis, hypokalemia and nephrocalcinosis. The presence of carbonic anhydrase II antibodies further supports an autoimmune mechanism disrupting acid-base homeostasis. Glomerular involvement, though less frequent, is often mediated by immune complexes, as seen in cryoglobulinemic GN and membranoproliferative GN, both of which can contribute to significant proteinuria and hematuria.

Chronic immune activation in pSS, characterized by excessive cytokine production, plays a vital role in disease progression. IFN-y promotes macrophage activation and tissue damage, while TNF-a and IL-6 contribute to fibrosis and autoantibody production. This chronic inflammatory state leads to progressive kidney dysfunction, with some patients advancing to CKD.

Despite the well-established renal manifestations of pSS, diagnosis remains challenging due to the absence of standardized criteria. ACR/EULAR criteria provide a structured approach to

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[50] Goules AV, Tatouli IP, Moutsopoulos HM, Tzioufas AG. Clinically significant renal involvement in primary Sjögren's syndrome: clinical presentation and outcome. Arthritis Rheum. [Internet] 2013 Nov [Cited 9 March 2025] ;65(11):2945-53. Available from: doi: 10.1002/art.38100. PMID: 24166794.

identifying pSS, but renal involvement often necessitates additional diagnostic measures, including urinalysis, serological markers, imaging, and, in certain cases, renal biopsy.

The study findings align with previous research, indicating that TIN is the most prevalent form of kidney injury in pSS, often manifesting as low-specific gravity urine, proteinuria, and inappropriately high urine pH due to dRTA. While GN is rarer, its presence warrants immediate investigation due to its association with worse renal outcomes.

Treatment strategies are primarily tailored to the underlying renal pathology. In cases of TIN, corticosteroid therapy remains the mainstay of treatment, leading to improved renal function in most patients. In contrast, GN often necessitates immunosuppressive therapy with agents such as cyclophosphamide, mycophenolate mofetil, or rituximab. Supportive measures, including potassium citrate for dRTA and hydration, play a crucial role in preventing CKD progression.

Prognosis varies depending on the type and severity of renal involvement. TIN generally follows a benign course if detected early, while GN is linked to more severe renal impairment and a higher risk of progression to ESRD. Furthermore, patients with renal involvement are at an increased risk of developing non-Hodgkin's lymphoma, which significantly impacts overall survival.

A cohort study analyzing 715 patients with pSS found that renal involvement was present in 4.9% of cases, with GN accounting for the majority of severe renal dysfunction. Notably, the estimated five-year survival rate post-renal diagnosis was 85%, with lymphoma emerging as a key predictor of poor diagnosis. These findings highlight the importance of early recognition and intervention to mitigate long-term complications.

Conclusion

Renal involvement in pSS is a significant but often underrecognized complication with variable clinical manifestations. While TIN is the most common renal pathology, GN poses a greater risk for severe renal impairment and systemic complications. Early diagnosis and appropriate

management are critical in preserving kidney function and improving patient outcomes. Further research is needed to refine diagnostic criteria and explore targeted therapies that address the underlying immune dysregulation in pSS-associated kidney disease.

Future research should focus on identifying novel biomarkers that can predict renal involvement in pSS before clinical symptoms appear. Additional studies are needed to further elucidate the pathogenic role of specific autoantibodies in kidney dysfunction.

Investigating targeted biologic therapies, such as B-cell depleting agents, could provide new avenues for treatment. Large-scale, long-term studies examining the progression patterns of renal involvement and its impact on overall morbidity and mortality will be essential.

Furthermore, exploring genetic predisposition and epigenetic modifications may help clarify the underlying mechanisms contributing to kidney involvement in pSS. Personalized medicine approaches, based on immune profiling and disease phenotypes, could lead to more tailored treatment strategies.

Lastly, investigating the association between pSS-related kidney disease and increased risks for cardiovascular disease, infections, and malignancies will provide a broader understanding of the systemic impact of renal involvement in pSS.

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