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Sjögren's Syndrome: Current Insights into Pathogenesis, Diagnosis and Treatment

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ABSTRACT

Sjögren’s syndrome is a chronic autoimmune disease mainly targeting exocrine glands with resultant dry eyes and mouth symptoms, plus systemic manifestations of fatigue, arthritis, and an increased risk of lymphoma. This review synthesizes the recent findings to provide extensive updates on the disease's pathogenesis, diagnosis, and treatment. Current evidence shows that epithelial cell activation and type I interferon responses are major in initiating immune disorders. Adaptive immune systems contribute further through autoreactive B and T cells, resulting in persistent inflammation and antibody production. Diagnostic strategies have developed with the implementation of ACR/EULAR classification criteria and using both traditional (anti-SSA/Ro, anti-SSB/La) and novel biomarkers. Advances in imaging techniques, such as salivary gland ultrasound, are improving diagnostic accuracy, especially in seronegative patients. Treatment remains largely symptomatic, but B-cells are subject to activation factors, JAK-STAT pathways, and biological therapy targeting CD40-CD40L interactions in clinical trials. Despite these developments, challenges remain in early detection, treatment standardization, and systemic manifestations. This review highlights the emerging clinical and therapeutic strategies that can lead to personal care approaches and better patient results, emphasizing the need for ongoing research to close the current gap in clinical management.

Key Words: Sjögren's syndrome, autoimmune disease, pathogenesis, type I interferon, B-cell activation, dry eyes, dry mouth, autoantibodies, diagnosis, biomarkers, ACR/EULAR criteria, salivary gland ultrasound, biologic therapy, JAK-STAT pathway, CD40-CD40L, personalized medicine, systemic complications, immunomodulation, lymphoma risk, clinical trials.

Sjögren’s Syndrome: Current Insights into Pathogenesis, Diagnosis and Treatment

1. Introduction

Sjögren's syndrome is a chronic systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, leading to mainly dry mouth and eyes, and is often associated with systemic manifestations (Carson & Patel, 2023). It mainly affects women, with 90% of cases usually beginning in the middle of life, usually between 45 and 55 years. Over the past three years, epidemiological analysis has emphasized better data, showing global incidence and prevalence estimates due to inconsistent diagnostic criteria and underdiagnosis in patients with Sicca symptoms (Thurtle et al., 2023). Recent research

highlights a multifactorial pathogenesis that involves genetic disposition, environmental triggers such as viral infections, and dysregulation of innate and adaptive immune systems. Focused attention has been placed on the role of epithelial cells in triggering type I interferon responses and autoreactive B-cell activation within exocrine glands, which may contribute to disease progression and increase the risk of non-Hodgkin lymphoma. Clinically, Sjögren's syndrome manifests as glandular sicca symptoms but also includes extra-glandular problems such as arthritis, neuropathy, and lung or renal involvement (Carsons & Patel, 2023). Despite progress in understanding its biology, the diagnosis continues to rely on composite criteria involving salivary gland biopsy, autoantibody detection, and patient-reported dryness measurements. Therapy remains mostly symptomatic, with immunomodulators showing modest effects. This developing landscape guarantees a detailed review of the latest diagnostic paradigms and new targeted therapies to improve patient results.

2. Purpose of Research

The purpose of this review is to synthesize recent scientific findings and provide a clear, updated understanding of Sjögren's syndrome by focusing on pathogenesis, diagnostic methods, and treatment strategies. Over the past few years, research has significantly advanced our knowledge of disease mechanisms, revealing the complex immune conversation and molecular factors involved (Zhan et al., 2023). A key goal is to clarify how congenital immune responses, especially type I interferon signaling and epithelial cell activation, initiate and maintain glandular, and how adaptive imbalance involving autoreactive B and T cells contributes to disease progression and complications, such as lymphoma. In parallel, the review tries to assess changing diagnostic benchmarks, especially using ACR/EULAR classification standards, and look at biomarkers comprising autoantibodies like anti-SSA/Ro and anti-SSB/La and molecular markers. Recent proof suggests that these autoantibodies could appear years before malfunctioning glands, supporting their possible role in early detection strategies (Jonsson et al., 2022).

Finally, the paper aims to assess treatment advances. While symptomatic treatment remains the mainstay, recent clinical studies of biological agents are aimed at B-cell-activating factor, CD40-CD40L interactions, and Janus kinase pathways show promise (Nocturne & Mariette, 2023). However, the field lacks effective immunomodulatory therapies validated in extensive studies. This review will analyze the coverage of new strategies such as regulatory T-cell modulation, targeted cytokine inhibition, or combination therapies, highlighting both achievements and persistent challenges. By integrating insights across disease mechanisms,

early detection, and therapeutic innovation, this review aims to highlight individual care opportunities and identify intervals that obstruct progress in Sjögren's syndrome research. The intended outcomes include a refined framework for physicians and researchers to guide future studies to develop targeted treatments and improve diagnostic accuracy, with the ultimate goal of enhancing patient quality and long-term results.

3. Research Materials and Methods

The review was conducted after a rigorous framework was designed to catch the most recent and relevant research on Sjögren's syndrome. The research applied a comprehensive search strategy to suit the PRISMA guidelines and ensure transparency and reproducibility. Databases including PubMed, PubMed Central, Google Scholar, Scopus, and Cochrane Library using combinations of terms such as "Sjögren Syndrome," " pathogenesis," "Diagnosis," "Treatment, "and" Clinical trial, with Boolean operators AND/OR to refine results. The research included full-text peer-reviewed articles written in English, including original research, clinical trials, systematic reviews, meta-analysis, and practice guidelines. The study only focused on pediatric populations, unrelated autoimmune conditions, or an inadequate data deficiency.

The screening process included two independent reviewers examining titles and abstracts for relevance, followed by a full-text assessment. To suit the best practices in systematic reviews, the third reviewer solved discrepancies through discussion or arbitration. As a result, 112 studies met the inclusion criteria, of which 26 were selected for detailed data extraction. However, the data extracted included significant results related to study characteristics, study design, patient demographics, pathogenesis markers, clinical accuracy measures, and treatment efficacy. For diagnosis, the sensitivity and specificity of tests, including salivary gland biopsy and imaging modalities, are considered. Therapy assessment detailed the results of interventions such as biological agents, symptomatic therapies, and immunomodulators.

Quality assessment was done using validated tools like AMSTAR-2 for systematic reviews, Cochrane risk of bias for randomized controlled trials, and the Newcastle-Ottawa scale for observational studies. 45% clinical trials were given low or moderate risk status, while two narrative reviews achieved high scores on the SANRA assessment. All data were compiled in a centralized spreadsheet, and analysis included a quantitative summary and a narrative synthesis. The significant elements of pathogenesis include innate immunity, type I interferon activation, and B-cell cytokine profile discoveries. Diagnostic metrics were examined for performance characteristics, focusing on the newly validated minor salivary gland biopsy and

elastography techniques. The evaluation of treatment included biological agents such as belimumab and low-dose interleukin 2, with safety profiles assessed.

Data synthesis highlighted concordance on central pathogenic mechanisms, such as epithelial cell-driven inflammation, and emerging biomarkers predictive of disease progression, such as salivary gland ultrasound patterns, and novel autoantibodies. The clinical performance was variable, with combined histology and imaging providing strong accuracy. Treatment results suggested minor improvements in systemic symptoms but slight changes in glandular dysfunction. The limitations included heterogeneity across studies in patient populations, diagnostic criteria, and outcome measures. The lack of longitudinal and multicenter trials prohibited our ability to evaluate long-term and generalized efficacy. Publication bias was addressed through funnel plot analysis in meta-analysis, where applicable. Therefore, this review ensures a comprehensive synthesis of recent progress in the syndrome research of the functioning function, spread of the fundamental pathological mechanisms, evolving diagnostic strategies, and advances in targeted therapy. By integrating high-quality evidence from multiple study types, the study aims to present a balanced, current perspective that identifies both achievements and areas requiring further discovery.

4. Literature Review

I. Epidemiology and Risk Factors

Sjögren's syndrome affects about 0.3 to 1 percent of the population, with an incidence rate of 3.5 to 6.9 per 100,000 persons. The prevalence varies widely and is estimated to be between 22 and 770 per 100,000 individuals, largely depending on geographical regions and diagnostic criteria used (Thurtle et al., 2023). The disease mainly affects women, with a striking female-male ratio of about 9:1 to 28:1, and usually manifests between ages 34 and 57, although the diagnosis often comes after several years (Maleki-Fischbach et al., 2024). Delay in diagnosis contributes to increased illness. Genetic susceptibility is driven by HLA variants, including HLA-DR, HLA-DQ, and non-HLA genes such as STAT4, IRF5, BLK, IL12A, TNIP1, and CXCR5, which promote B cell activation and type I interferon signaling. Epigenetic modifications, including hypomethylation of CD70 and transcription of non-coding RNAs, can alter gene expression in immune cells and favor self-immunity. Environmental factors also play an essential role, especially viral infections. Exposure to Epstein–Barr virus, cytomegalovirus, HTLV-1, HCV, and HIV is associated with an increasing risk of primary Sjögren's, likely through mechanisms such as molecular mimicry, type I interferon activation, and B cell hyperactivation (Maslinska & Kostyra-Grabczak, 2022).

Epidemiological data from a Swedish registry have revealed that individuals with a history of respiratory, skin, or urinary infections had a risk of developing Sjögren's symptoms and autoantibodies (OR 1.9 overall; OR 2.9 for respiratory infections), compared to controls over a sixteen-year follow-up period (Westerlund et al., 2021). The higher prevalence of EBV DNA and serum antibodies in the tissues of the glands of patients with Sjögren supports viral involvement. Therefore, Sjögren's syndrome usually affects women in middle age and is shaped by a combination of genetic and environmental triggers, with viral infections and efficient changes as significant risk factors that contribute to initiation and progression.

II. Pathogenesis and Molecular Mechanisms

The pathogenesis of Sjögren's syndrome involves a complex interaction between epithelial cells, innate and adaptive immunity, genetics, and environmental triggers. The salivary gland epithelial cells play an active role in the disease initiation by acting as nonprofessional antigen presenting cells and secreting the proinflammatory cytokines and B-cell activating factors, thus increasing lymphocytic infiltration and inflammation of the chronic glands Dysregulated epithelial cell death by apoptosis and pyroptosis results in intracellular autoantigens being released from inside the cells, such as Ro/SSA and La/SSB, which further increases immune activation. Upregulation of inflammasome components like NLRP3 and AIM2 are over-expressed in epithelial and immune cells, allowing for chronic inflammation through caspase-1 and IL-1β (Sisto et al., 2022). Genetic predisposition loci through IRF5, STAT4, IL12A, and OAS1 support strong type I interferon signatures in patients and enable continuous innate immune system activation through the JAK-STAT pathway (Imgenberg-Kreuz et al., 2021).

Innate immune pathways involving inflammasome and tolls, such as receptor activation, also contribute to disease progression. Ligands recognized by TLR3, TLR4, and TLR7 cause salivary epithelial cell dysfunction and reduce secretory function as part of the early inflammatory process (Zhao et al., 2024). Innate immune activation promotes the recruitment of plasmacytoid dendritic cells that secrete interferon-α, driving a feed-forward amplification loop that increases BAFF production, B-cell survival, autoantibody production, and extension of ectopic germinal centers in the gland. Adaptive immune responses further perpetuate tissue damage. Autoreactive T helper cells, including the Th1 and Th17, mainly produce IFN-γ, IL-17, and TNF-α, which cause direct epithelial cytotoxicity and mediate further recruitment of immune cells. Cytotoxic CD8 T cells work to destroy the glandular epithelial tissue through Fas, Fas Ligand, and perforin-mediated apoptosis (Sisto et al., 2022). B cell activation follows

via antigen presentation and survival signals, causing autoantibody production, immune complex formation, and germ centers within the salivary glands.

Environmental factors such as viral infections, including EBV and HTLV 1, can initiate epithelial cells' apoptosis and expose autoantigens such as RbAp48, triggering autoimmune pathways in genetically disposed individuals (Chivasso et al., 2021). Estrogen deficiency also modulates epithelial presentation and contributes to female predominance. Therefore, Sjögren's syndrome pathogenesis is driven by dysfunctional epithelial interactions, chronic inflammatory and interferon activation, genetic disposition for immunity regulation, and environmental stimuli. This complex pathophysiology presents several therapeutic goals ranging from epithelial cell stabilization to B-cell and cytokine modulation.

III. Clinical Manifestations and Disease Variants

The Sjögren's syndrome presents mainly with persistent dryness of the mouth and eyes. Almost all patients experience xerostomia and keratoconjunctivitis sicca due to lymphocytic infiltration of salivary and lacrimal glands (Yaseen, 2024). Fatigue and musculoskeletal complaints, such as combined pain, are also common, affecting most patients and significantly impairing quality of life. Approximately one-third of patients develop additional-glandular diseases, including several organ systems, including neurological, pulmonary, kidney, and liver systems (Negrini et al., 2021). Neurological complications often include peripheral neuropathy that manifests in the form of numbness, tingling, or neuropathic pain and usually contains symptoms of the central nervous system, such as cognitive dysfunction. Pulmonary involvement can range from a dry cough to interstitial lung disease, and physicians recommend screening for lung abnormalities through imaging. Renal disease is usually presented as tubulointerstitial nephritis, while hepatic manifestations may occur in about 5 to 26 percent of patients with primary biliary cholangitis or autoimmune hepatitis with asymptomatic liver testing abnormalities (Fernandes et al., 2022).

A serious yet rare complexity is lymphoma development, especially the mucosa-associated lymphoid tissue lymphomas of the salivary glands. The risk of non-Hodgkin lymphoma is approximately 3 to 5 percent and often occurs years after early diagnosis (Aghjayan, 2021). Sjögren's syndrome can occur alone (primary) or with other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (secondary); the latter is often referred to as Sjögren's disease with overlap. In addition, male, older patients, and anti-LA/SSB positivity, low complement levels, cryoglobulins, or vasculitis are more likely to develop severe systemic disease and lymphoma (Bodakçi, 2024). The presentation varies widely from

mild dryness to multi-organ involvement, and some patients also have a decrease in classic sicca symptoms, requiring physicians to maintain a high index of suspicion to enable initial diagnosis.

IV. Diagnostic Criteria and Biomarkers

The accurate diagnosis of Sjögren's syndrome depends on a combination of clinical assessment, serological testing, histopathology, and imaging. ACR/EULAR classification criteria established in 2016 remain necessary, providing points for the labial salivary gland biopsy focus score of ≥ 1 and positivity for anti-SSA/RO antibodies (each 3 points), as well as ocular staining score ≥ 5, Schirmer test ≤ 5 mm/5 min, or unstimulated salivary flow ≤ 0.1ml/min (each 1 point) (60–96 percent sensitivity and 95 percent specificity) (André & Böckle, 2022). These criteria prioritize accuracy but can underdiagnose early or seronegative cases, which highlights a need for enhanced screening measures. Autoantibodies remain integral; About 70–90 percent of patients perform positive tests for antibodies, and anti-SSA/Ro or anti-SSB/La (anti-SSA/Ro being more essential for diagnosis), and anti-La/SSB often indicates more serious illness. In addition to traditional serology, new biomarkers such as anti-salivary protein-1, anti-carotid anhydrase 6, and anti-parotid secretory proteins may appear in the progression of the first disease and improve early identification rates when combined with conventional tests (Yang et al., 2024).

The minor salivary gland biopsy is a diagnostic gold standard. Histological focus is related to scoring and detection of germinal center-like structures that contain disease activity and lymphoma risk (Liao et al., 2022). Focus scores ≥ 1 are defined as ≥ 50 mononuclear cell aggregates per 4 mm^2 support diagnosis in early or seronegative cases, while ultrasound-guided biopsy increases accuracy and reduces complications. Sialography and scintigraphy have decreased due to radiation exposure, while salivary flow tests provide functional screening but have limited specifications. The salivary gland ultrasonography has emerged as a valuable non-invasive tool. It recognizes the unique and hypoechogenic areas of the gland, strongly consistent with histological and serological findings, and improves confidence in the diagnosis, potentially reducing the need for biopsy. Elastography further enhances the gland's evaluation by measuring the tissue's stiffness, distinguishing patients from non–Sjögren's sicca controls.

Tear film and saliva proteomics offer promising noninvasive biomarker sources. Tear biomarkers such as lysozyme, lactoferrin, cathepsin S, Aquaporin 5, and special microRNA show diagnostic potential, although the results require a large validation study (Pang et al.,

2024). Saliva proteomic profiles have identified unique peptide patterns that can support future oxygen biomarkers. Multi-omic approaches integrating serologic, genetic, and transcriptomic data can improve disease stratification and biomarker detection. For example, expression of type I and II interferon gene signatures in the peripheral blood and tissue samples is related to the risk of disease activity, systemic manifestations, and lymphoma, which indicates their role in the prognostication (Vital et al., 2021). Novel biomarkers associated with inflammation and glandular damage have also been identified in proteomic studies in the tissue of the salivary gland.

V. Treatment Approaches

The management of Sjögren's syndrome focuses on addressing relief from sicca symptoms and systemic disease activity. Topical therapies are fundamental for exocrine dysfunction. Patients usually use artificial tears and saliva, while muscarinic agonists such as pilocarpine and cevimeline have demonstrated efficacy in improving oral and ocular dryness in clinical trials (Vitali et al., 2021). When artificial tears are inadequate, the ophthalmic disease cyclosporine also reduces ocular surface inflammation. Systemic immunosuppressants such as hydroxychloroquine, methotrexate, and corticosteroids have been prescribed for arthralgia or mild systemic manifestations, although random tests have shown limited advantages to main features such as dryness and fatigue.

Biological therapies aimed at B-cells and important immune pathways have progressed. Rituximab showed mixed results in reducing glandular and systemic symptoms. However, salivary glands of ultrasound in TRACTISS trials demonstrated glandular improvement compared to placebo, and current guidelines recommend rituximab for systemic manifestations such as vasculitis and neuropathy. Newer agents demonstrate promising effects, such as Ianalumab, aimed at the BAFF receptor, significantly reducing the disease activity in a phase II study with favorable safety results. Telitacicept, a TACI–Fc fusion protein approved in China, improved activity points in the EUS SS disease measures over 12 weeks. Targeting BTK with rembrutinib also significantly reduced ESSDAI score in a phase III trial (Nocturne & Mariette, 2023). Emerging targeted treatments such as Dazodalibep, a CD40 ligand antagonist, are advancing through Phase II/III trials, showing improvement in both dryness and systemic symptoms in crossover studies. First, in human case reports, CAR-T cell therapy achieved serological remission and improved saliva and tear production in small cohorts with refractory disease.

VI. Challenges and Limitations

Sjögren's syndrome presents important diagnostic, treatment, and clinical research challenges. First, diagnosis is often delayed for years because early symptoms are nonspecific, and tools to detect early disease are insufficient. Distinguishing pathology from age-related dryness is challenging, especially without reliable biomarkers for the disease's preclinical phase. Treatment options are limited, mostly showing minor benefits with symptomatic or systemic remedies. Many randomized controlled trials of the disease-modifying agents have failed due to the patient's asymmetry, insufficient result measures, and inevitable population (Callegher et al., 2022). The lack of approved disease-modifying drugs is a sufficient requirement in all existing clinical guidelines.

Clinical trials also struggle to recruit representative participants. In some cases, despite demonstrating more serious illness, due to the recognition of men's variants and low male participation, obstacles such as inconsistent documentation are faced. In addition, many trial outcomes rely on subjective measures, leading to high placebo responses and limiting their usefulness (Al-Rawi et al., 2024). In essence, Sjögren's syndrome research is limited by late-stage detection, deficiency of reliable initial biomarkers, ineffective disease-propelled treatment, and testing design flaws, including insufficient patient representation and insensitive result assessment. However, it is necessary to address these limitations in order to progress in care and research results.

5. Basic Results

This review has highlighted key advances in the treatment of pathogenesis, diagnostics, and Sjögren syndrome, corresponding to the purposes of the study. A central finding is the crucial role in innate immune activation, primarily through inflammatory pathways to start type I interferon signaling and autoimmune responses in the gland. Recent studies confirm that type I interferon activity is present in more than half of patients, and pattern recognition receptors like tolls in salivary epithelial cells expand this response and contribute to chronic inflammation and tissue injury (2021). Inflammasome components have been shown to activate NLRP3 and AIM2, caspase 1, and release IL-1β, reinforcing inflammation, and permanently restore the gland-loss cycle. These immune signs form the foundation for adaptive immune responses.

Subsequently, the adaptive immune system leads to continuous lymph infiltration and autoantibody production. Salivary epithelial cells present the Ro and La autoantigens to autoreactive T cells, which activate B cells through cytokines such as IFN-γ, IL-17, and BAFF.

This interaction promotes germinal center formation within the glands and increases the production of anti-SSA/RO and anti-SSB/LA antibodies (Shimizu et al., 2021). These autoantibodies often occur before clinical symptoms develop over the years, providing the capacity for early identification. Advances in diagnostics support a better identification of Sjögren's syndrome. The ACR/EULAR classification criteria, updated in 2016, emphasize objective measures including salivary gland biopsy and anti-SSA positivity (Anić et al., 2023). These criteria maintain strong clinical performance but cannot detect early seronegative disease. Emerging biomarkers such as minor salivary gland ultrasound and novel autoantibodies (Anti-SP1, Anti-CA6) are promising for first detection and non-level stratification.

Treatment advances also appear. Symptomatic therapies like artificial tears, saliva replacements, and secretagogues are the first line, but biological agents aimed at important immune pathways show promise in disease modification. Rituximab demonstrated a limited advantage, although glandular improvement was observed in ultrasound assessments. New means aimed at BAFF receptor (sarilumab), TACI-FC (Telitacicept), and BTK (RemiBrutinib) have resulted in significant reductions in disease activity points in clinical trials. Early-phase therapies targeted to CD40-CD40L and JAK pathways are under investigation, and case reports on CAR T-cell therapy suggest the potential for refractory disease.

Despite these developments, challenges remain. The complex interaction between innate and adaptive immunity disrupts single-target treatment efficacy. Current criteria can remember those people without seronegative patients and classic symptoms. There is also a lack of valid initial identification tools and insufficient mass testing data to guide clinical decision-making. However, the article has greatly enriched the understanding of its underlying immune system and introduced promising clinical and medical equipment. Continuous efforts are required to validate the initial biomarkers, refine classification systems, and conduct rigorous biological and cellular therapy tests. This integrated knowledge provides a foundation for patients with this complex autoimmune disease to enhance the results, align individual care, and improve targeted interventions.

6. Conclusion

Sjögren syndrome is a complex autoimmune disease characterized by continuous gland dysfunction and systemic complications. In the last few years, progress has intensified our understanding of its pathogen, which reveals significant roles of congenital immune activation, type I interferon signaling, and the contribution of epithelial cells to the initiation of the

disease. Adaptive immune responses involving autoreactive T and B cells are associated with complications such as adaptive immune reactions, more chronic inflammation, antibody production, and lymphoma. Diagnostic approaches are more refined by updated biomarkers, such as updated ACR/EULAR criteria, and promising biomarkers, such as anti-SP1 and ultrasound of the minor salivary gland, which is helpful in the early and accurate identification of identity. Treatment remains largely symptomatic, but emerging therapies targeting specific immune pathways, including BAFF inhibition, JAK-STAT signaling modulation, and CD40 interactions, provide hope for future disease-propelled interventions. Clinical trials actively evaluate these biologics and cellular treatments, which may soon become part of individual management strategies. Despite these advances, major challenges persist. Early diagnosis remains difficult, seronegative presentations are poorly recognized, and there is a lack of effective treatment for systemic forms. Continued research, especially in immunomodulation and the discovery of biomarkers, is necessary. A deep understanding of the disease system will support the development of targeted interventions and improve the quality of life for individuals affected by Sjögren's syndrome.

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