

## OCULAR AND ORAL MANIFESTATIONS OF PRIMARY SJÖGREN'S SYNDROME: AN INTERDISCIPLINARY PERSPECTIVE

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### Abstract

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized by exocrine gland dysfunction, particularly affecting the salivary and lacrimal glands. Clinically, this results in xerostomia and keratoconjunctivitis sicca, two hallmark symptoms that significantly impair patients' quality of life. Beyond dryness, pSS encompasses a wide spectrum of oro-ocular manifestations, including mucosal atrophy, dental caries, candidiasis, and ocular surface inflammation. These symptoms reflect the shared pathophysiological mechanisms of glandular epithelial injury and immune-mediated inflammation. Accurate diagnosis requires a multidisciplinary approach, combining clinical observation with objective tests such as salivary flow measurement, ocular surface staining, and labial gland biopsy. Recent research has identified promising biomarkers, such as cathepsin S, SIGLEC1, and interferon signatures, which may improve early detection and guide personalized therapy. Integrated evaluation by dental, ophthalmological, and rheumatological specialists enhances diagnostic accuracy and facilitates individualized treatment strategies. This review provides a comprehensive overview of the oral and ocular involvement in pSS, highlighting clinical correlations, diagnostic tools, and emerging molecular insights. By addressing pSS from an interdisciplinary angle, we aim to support earlier diagnosis and better management of this underrecognized yet impactful autoimmune condition.

**Keywords:** Sjögren's syndrome, xerostomia, keratoconjunctivitis sicca, autoimmunity, oral dryness, interdisciplinary diagnosis

### Introduction

Sjögren's syndrome (SS) is a chronic, systemic autoimmune disease characterized primarily by lymphocytic infiltration and dysfunction of exocrine glands, particularly the salivary and lacrimal glands. This glandular impairment leads to two hallmark clinical manifestations: xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes), significantly impacting patients' quality of life. Beyond glandular involvement, SS may present with a variety of extraglandular complications, including articular, pulmonary, renal, and neurological manifestations, positioning the disease as a

true systemic condition rather than a localized exocrinopathy [1-4].

The prevalence of primary SS (pSS) is estimated to range between 0.1–0.6% globally, with a strong female predominance and peak onset typically in the fourth to sixth decade of life [5,6]. Secondary SS can occur in association with other autoimmune disorders such as systemic lupus erythematosus or rheumatoid arthritis. The disease spectrum is broad and often underestimated, especially in patients presenting solely with non-specific symptoms such as fatigue, ocular irritation, or oral discomfort [3,4,7].

Diagnosis remains complex due to the heterogeneous presentation of symptoms and the lack of a single definitive test. As a result, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed updated classification criteria in 2016, which rely on objective findings from salivary gland biopsy, serologic autoantibody profiles (anti-Ro/SSA), and ocular and oral functional assessments [2]. These criteria aim to improve diagnostic sensitivity and specificity, especially in early or atypical cases.

While most studies have traditionally approached SS through the lens of rheumatology, recent research has highlighted the critical need for interdisciplinary collaboration, particularly between ophthalmologists and dental specialists [9]. The oral and ocular symptoms often appear concurrently and may provide early clues to systemic autoimmunity. Moreover, the severity of dryness symptoms is not only physically debilitating but also correlates with broader immunological activity and disease burden [1, 4].

This review aims to synthesize current knowledge on the ocular and oral manifestations of primary SS, emphasizing the shared immunopathogenic mechanisms, clinical evaluation strategies, and the importance of an integrated diagnostic approach. By bridging the gap between specialties, clinicians can enhance early detection, targeted management, and ultimately, patient outcomes in this complex autoimmune disorder.

### **Patophyiology Sjögren's syndrome**

Sjögren's syndrome is a systemic autoimmune condition in which dysregulated immune responses predominantly target the salivary and lacrimal glands, leading to chronic inflammation, fibrosis, and secretory dysfunction. Initially, it is assumed that an external trigger or an alteration of the glandular epithelium causes the activation of antigen-presenting cells and the release of pro-inflammatory signals. Subsequently, T and B lymphocyte infiltration favors a perpetual autoimmune process, with the formation of periductal foci and the destructuring of glandular architecture [3,8-10].

Type I INTERFERON (IFN-I) plays a central role in activating innate immunity and is present in the peripheral gene expression of most patients with pSS. IFN-I stimulates molecules such as BAFF (B-cell activating factor), which supports the survival of autoreactive B cells. Also, the expression of the SIGLEC1 molecule (CD169), a marker of IFN-induced activation, was correlated with the severity of extraglandular manifestations [11-17].

The peripheral transcriptomic profile showed an increased expression of genes activated by interferon and inflammatory pathways, being investigated as a tool to predict disease activity [33]. All these abnormalities contribute to the progressive destruction of the acinar and ductal epithelium in the lacrimal and salivary glands, reflected histologically by dense lymphocyte foci (focal score  $\geq 1$ ) and clinically by the appearance of xerostomia and keratoconjunctivitis sicca [18-23].

In addition to the classic autoantibodies (anti-Ro/SSA and anti-La/SSB), emerging biomarkers have been

described, such as cathepsin S – detected in tears and associated with the severity of dry eye –, Flt3 ligand – linked to the risk of lymphoma –, as well as beta2-microglobulin and immunoglobulin free light chains – correlated with systemic disease activity [24-30]. MicroRNA dysregulations, such as decreased miR-146a expression, contribute to the loss of

autoregulation of the inflammatory response [28].

Thus, SS pathophysiology involves a complex interaction between innate immunity, adaptive autoimmune mechanisms, and an extensive network of biomarkers being validated, which can contribute to both diagnosis and evaluation of individualized prognosis.

**Table 1.** Common oral and ocular manifestations in primary Sjögren’s syndrome [3-10].

| <i>System Affected</i> | <i>Clinical Manifestation</i>        | <i>Description</i>  |
|------------------------|--------------------------------------|---|
| <i>Oral</i>            | Xerostomia                           | Dry mouth sensation due to salivary gland hypofunction            |
| <i>Oral</i>            | Dysphagia and burning mouth          | Difficulty swallowing; burning sensation of the tongue and mucosa |
| <i>Oral</i>            | Dental caries and candidiasis        | High caries incidence, frequent oral fungal infections            |
| <i>Ocular</i>          | Keratoconjunctivitis sicca (dry eye) | Gritty, burning eyes due to reduced tear secretion                |
| <i>Ocular</i>          | Photophobia and blurred vision       | Sensitivity to light; unstable tear film affects visual acuity    |
| <i>Ocular</i>          | Superficial punctate keratitis       | Epithelial damage caused by tear film instability                 |

Table 1 summarizes the key clinical features of oral and ocular involvement in primary Sjögren’s syndrome. Salivary and lacrimal gland dysfunction leads to characteristic symptoms such as dry mouth, increased caries, and dry eye disease. Recognizing these coexisting signs is critical for early diagnosis and interdisciplinary patient management.

### **Ophthalmological manifestations in Sjögren's syndrome**

Eye damage is one of the earliest and most common clinical manifestations in Sjögren's Syndrome, characterized mainly by keratoconjunctivitis sicca, resulting from hyposecretion of the lacrimal glands. The

underlying mechanism involves the progressive destruction of the lacrimal acinar epithelium under the influence of lymphocyte infiltrate and the autoimmune process, leading to reduced basal tear film secretion and ocular surface instability [3, 10, 12].

Common symptoms include a feeling of sand in the eyes, photophobia, eye redness, irritation, decreased visual acuity, and eye strain. They can vary in intensity, and their severity does not always correlate with the objectively measured level of tear secretion [17]. In the long term, chronic inflammatory changes can lead to corneal damage, punctate epitheliitis, epithelial defects, corneal ulcer, infections, or even

corneal perforation in severe untreated cases [1].

The diagnosis of eye damage is based on a combination of subjective symptoms and objective tests. Among the most used are the Schirmer I test (for measuring tear secretion), the OSS score (Ocular Staining Score) with fluorescein and lysamine green, as well as the tear film tear time (BUT) tests. OSS scores  $\geq 5$  or Schirmer test  $\leq 5$  mm/5 min are included in the ACR/EULAR criteria for pSS classification [2, 14, 24].

In the assessment of severity, a standardized approach is recommended, as proposed by the TFOS DEWS II guidelines, which integrate clinical parameters, patient-reported symptoms, and objective signs of lacrimal dysfunction [12]. Furthermore, the increased expression of some ocular biomarkers, such as cathepsin S in tears, has been correlated with the severity of lacrimal gland damage and chronic ocular inflammation [26].

Recent studies have shown that eye damage can occur even in the absence of obvious oral dryness, often representing the first symptom of the disease. In some cases, extraglandular ocular manifestations such as uveitis, scleritis or optic neuropathy may also occur, which are more common in active systemic forms of pSS [1, 8].

The impact of eye damage on quality of life is significant, affecting daily activities such as reading, driving or working on the computer. Persistent discomfort and instability of vision can have important psychological consequences and contribute to the patient's overall functional deterioration [13, 15, 17]. Therefore, early identification of ocular symptoms and close collaboration with the

ophthalmologist are essential for diagnosis, monitoring and the establishment of local (artificial tears, topical anti-inflammatory drugs) or systemic treatment, depending on the severity of the case.

### **Oral manifestations in Sjögren's syndrome**

The oral manifestations of Sjögren's syndrome are an essential pillar of the clinical picture, being among the earliest and most persistent symptoms of the disease. Xerostomia, the subjective sensation of dry mouth – is caused by lymphocyte infiltration of the major and minor salivary glands, with the destruction of acinar cells and severe decrease in salivary flow [3, 9, 19]. Patients may complain of difficulty chewing, swallowing, speaking, oral burning sensation, halitosis, and a persistent metallic taste. Over time, hyposalivation leads to imbalances in the oral microbiome, decreased pH and loss of the protective function of saliva, favoring the appearance of rampant caries, periodontal disease and recurrent fungal infections, especially with *Candida albicans* [9, 18, 21].

Associated mucosal lesions may include fissures in the commissia, diffuse erythema, ulcerations, lingual atrophy or pseudo-leukoplakia hyperplasia. Hypertrophy or sensitivity of the parotid glands may also occur, sometimes with episodes of recurrent or chronic sialadenitis [3, 19].

The objective evaluation of salivary function involves the measurement of the non-stimulated salivary flow (values  $< 0.1$  mL/min being suggestive), the oral mucosal staining test, as well as the biopsy of the minor salivary glands in the labial mucosa,

considered standard in the pSS classification [2, 24].

The impact on oral health is significant: the rate of tooth decay is greatly increased, as is the need for prosthetic restorations or surgery. In parallel, patients may develop chronic dysphagia, difficulties in prosthetic adaptation and decreased quality of life [18, 22].

Symptomatic treatment involves the use of artificial saliva, salivary stimulants (pilocarpine, cevimelin), maintaining strict oral hygiene and local or systemic antifungal treatment, depending on the severity. The role of the dentist is essential both in the early diagnosis and in the long-term management of patients with SS, especially in forms with marked glandular involvement [9, 22].

**Table 2.** Diagnostic tools for primary Sjögren’s syndrome: oral and ocular perspectives [15-22].

| <i>Diagnostic area</i> | <i>Method</i>  | <i>Purpose/use</i>                                  |
|------------------------|--|---|
| <i>Oral</i>            | Unstimulated whole saliva flow rate                    | Quantifies salivary gland hypofunction              |
| <i>Oral</i>            | Labial salivary gland biopsy                           | Assesses lymphocytic infiltration (focus score)     |
| <i>Oral</i>            | Sialometry and sialography                             | Evaluate ductal architecture and secretion dynamics |
| <i>Ocular</i>          | Schirmer test  | Measures aqueous tear production                    |
| <i>Ocular</i>          | Ocular surface staining (fluorescein, lissamine green) | Assesses epithelial damage and dryness severity     |
| <i>Ocular</i>          | Tear break-up time (TBUT)                              | Evaluates tear film stability                       |

Table 2 outlines key diagnostic tools used to evaluate oral and ocular involvement in primary Sjögren’s syndrome, including objective tests for salivary and tear gland function, as well as histopathological and imaging techniques.

**Oro-ocular clinical correlations and interdisciplinary evaluation**

Sjögren's syndrome is distinguished by a clinical picture in which ocular and oral manifestations coexist frequently, evolve in parallel and may represent the first indications of a systemic autoimmune process. The combined dysfunction of the salivary and lacrimal glands reflects the exocrine nature of the disease, but also the

common pathological substrate – immune-mediated inflammation and lymphocytic infiltration of the glandular epithelium [3, 9].

Symptoms such as dry eyes, dry mouth, foreign body sensation, burning mouth and difficulty swallowing are often present simultaneously and contribute to a significant reduction in patients' quality of life. Clinical evaluations have shown that the severity of keratoconjunctivitis sicca correlates with the degree of hyposalivation and alteration of the composition of tears and saliva, which supports the hypothesis of a unitary systemic inflammatory response [9, 13].

An essential aspect in early diagnosis and monitoring the evolution of the disease is the collaboration between rheumatologist, ophthalmologist and dentist. Interdisciplinary assessments allow for a more precise approach and early therapeutic intervention. Studies have shown that multidisciplinary teams can more effectively identify cases at risk of extraglandular complications, compared to isolated evaluation within a single specialty [9, 14].

Commonly used objective tests – Schirmer's test, OSS score, salivary flow measurement, focal salivary gland biopsy score – complement each other and provide an integrated picture of disease severity. Moreover, the combination of these evaluations with the analysis of biomarkers in biological fluids (tears, saliva, blood) can guide the selection of patients for personalized therapies and for inclusion in clinical trials [13, 22].

The importance of communication between specialties is special not only for diagnosis, but also for chronic monitoring of patients. Ophthalmologists can be the first to suspect pSS in the face of refractory keratoconjunctivitis, and dentists can recognize early signs of xerostomia, mucosal changes, or atypical caries. Without an integrated approach, diagnosis can be delayed for years, with consequences for glandular function and the risk of systemic complications.

### **Emerging biomarkers and therapeutic directions**

Over the past decade, research in the field of Sjögren's syndrome has focused on identifying biomarkers that can improve early diagnosis, stratification of patients,

and monitoring of response to treatment. Due to the clinical variability of the disease and the lack of a single pathognomonic marker, the focus has shifted to integrated molecular profiles combining immunological, proteomic and transcriptomic parameters [25, 26, 33].

In the ocular sphere, a promising marker is cathepsin S, detectable in tears. This lysosomal protease is involved in the regulation of inflammation and antigenic expression, and studies have shown a correlation between increased levels of cathepsin S and the severity of keratoconjunctivitis sicca in pSS [26]. In parallel, increased expression of the SIGLEC1 molecule (CD169) on monocytes was associated with extraglandular forms of the disease, suggesting a potential biomarker of systemic activity [27].

At the systemic level, the type I interferon profile (IFN signature) is present in most patients with pSS and reflects chronic activation of innate immunity. This IFN signature correlates with the expression BAFF (B-cell activating factor), important in the maturation and survival of autoreactive B cells [31-33]. Other serum markers such as beta2-microglobulin, free immunoglobulin light chains or the Fms-like tyrosine kinase 3 (Flt3L) ligand – the latter associated with lymphoma risk – contribute to the identification of patients with increased systemic activity or risk of complications [29, 30].

Emerging biomarkers and therapeutic directions in dentistry and oral medicine are increasingly shaped by advances in orthodontic materials, better understanding of post-extraction inflammatory complications, novel perspectives in tonsillolith management, the

application of bioresorbable scaffolds in regenerative therapies, the identification of behavioral factors influencing dentin sensitivity, and the development of biocompatible biomaterials for pre-implant bone reconstruction [34-39].

In terms of therapeutic strategies, emerging approaches include inhibitors of the interferon pathway, anti-BAFF agents (belimumab), cell therapies and targeted immunomodulators. Regenerative therapies such as growth factors and topically applied biological preparations (bioactive artificial tears, synthetic saliva with anti-inflammatory compounds) are also explored to control local symptoms [3, 8].

The integration of these biomarkers into clinical practice could allow personalized medicine in the future, with treatments adapted to the patient's molecular profile, anticipating the risk of severe complications and optimizing the therapeutic response. In addition, the correlation of tear and salivary biomarkers with clinical data could significantly improve the predictive value of interdisciplinary assessment.

In the dental context, recent research on biomaterials and regenerative therapies has gained particular relevance for patients with Sjögren's syndrome, who frequently experience oral complications such as severe caries, mucosal atrophy, and alveolar bone loss due to chronic hyposalivation. The use of bioresorbable materials, regenerative scaffolds, and biocompatible biomaterials for pre-implant bone reconstruction offers new possibilities for restoring damaged oral structures. Moreover, studies addressing dentin hypersensitivity and oral hygiene behaviors contribute to developing preventive

strategies tailored to the specific needs of patients with xerostomia and glandular dysfunction.

Thus, advances in modern dental materials and tissue regeneration integrate naturally into the interdisciplinary management of Sjögren's syndrome, providing a complementary perspective alongside systemic immunological therapies.

### Conclusions

Primary Sjögren's syndrome is an autoimmune disorder with a pluristructural clinical expression, in which the involvement of the salivary and lacrimal glands is the central element of the diagnosis, as well as the functional burden felt by the patient. The direct relationship between xerostomia and keratoconjunctivitis sicca reflects a common pathogenesis, governed by chronic inflammatory processes, specific autoantibodies, and systemic molecular disturbances.

The importance of interdisciplinary assessment, which integrates clinical, paraclinical, and molecular data from the dental, ophthalmological, and rheumatological spheres, becomes essential for early diagnosis, effective symptom control, and prevention of extraglandular complications. Recent studies highlight the potential of ocular and salivary biomarkers (such as cathepsin S, SIGLEC1, and interferon type I expression) in risk stratification and in guiding therapeutic decisions.

In a clinical context where patients may initially present with either chronic eye discomfort or oral dryness, effective collaboration among the ophthalmologist,

dentist, and rheumatologist is not only beneficial but also imperative. Early identification of the syndrome, supported by modern diagnostic technologies and emerging biomarkers, can significantly improve the functional prognosis and quality of life of patients.

Sjögren's syndrome must be viewed through an integrative lens, which includes

oro-ocular manifestations not only as simple peripheral symptoms, but as essential landmarks in a complex systemic disease. This approach opens up perspectives for the development of interdisciplinary clinical protocols and for the personalization of treatment based on the individual immunological profile.

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