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SJÖGREN'S SYNDROME & ITS EFFECTS ON ORAL HEALTH

A Project Submitted to

The College of Dentistry, Ashur University in Partial Fulfillment for the Bachelor of Dental Surgery

By

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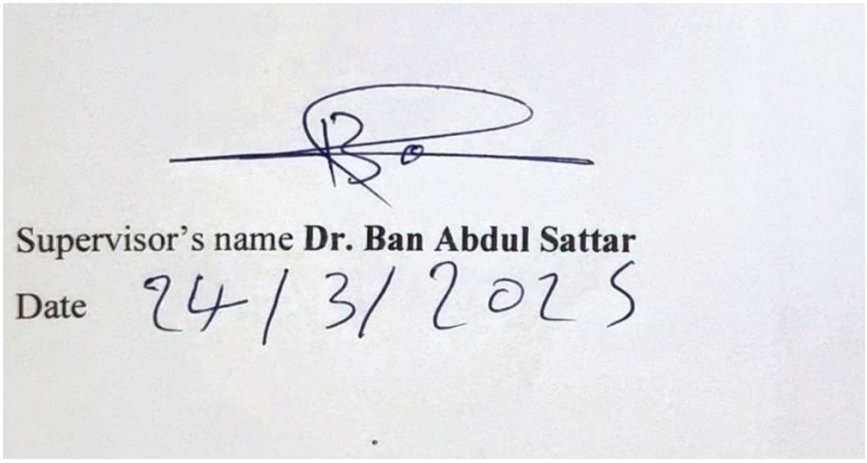
Certification of the Supervisor

I certify that this project entitled " **Sjögren's Syndrome & Its Effects on Oral Health**" was prepared by the fifth-year students **Tia Ammar Fouad** and **Duha Abd Ali Hafith** under my supervision at the College of Dentistry/Ashur University in partial fulfilment of the graduation requirements for the Bachelor Degree in Dentistry.



Dedication

This work is dedicated to all individuals living with Sjögren's syndrome, those who battle its challenges with resilience, strength and unwavering hope. May this research contribute, even in a small way, to a future of better understanding, care, and breakthroughs. You are seen, you are heard and you are never alone ♥.

Acknowledgement

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List of Abbreviations

SS: Sjögren's Syndrome

pSS: primary Sjögren's Syndrome

sSS: secondary Sjögren's Syndrome

SLE: Systemic Lupus Erythematosus

RA: Rheumatoid Arthritis

EULAR: The European Alliance of Associations for Rheumatology Sjögren's Syndrome

ESSPRI: EULAR Sjögren's Syndrome Patient-Reported Index

ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index

EBV: Epstein–Barr virus

HCV: Hepatitis C Virus

HHV-6: Human Herpesvirus 6

HIV: Human Immunodeficiency Virus

RF: Rheumatoid Factor

ANA: Antinuclear Antibody

NLRP3: NOD-like receptor protein 3

IL: Interleukins

AD: Autoimmune Disease

PM: Particular Matter

MHC: Major Histocompatibility Complex

HLA: Human Leukocyte Antigens

GWAS: Genome-wide association studies

SNP: Single Nucleotide Polymorphisms

TFH: Follicular Helper T

TLR: Toll-Like Receptors

NF-κB: Nuclear Factor Kappa B

$CD8^+$ T: Cytotoxic T lymphocytes, or CTLs

CNS: Central Nervous System

PNS: Peripheral Nervous System

MALT: Mucosa Associated Lymphoid Tissue

IgA: Immunoglobulins

PROs: Patient Reported Outcomes

VAS: Visual Analog Scale

PGA: Patient Global Assessment

OTC: Over The Counter

LFA-1: Lymphocyte Function Associated Antigen 1

NSAID: Non-Steroidal Anti-Inflammatory Drugs

DMARD: Disease-Modifying Antirheumatic Drugs

BAFF: B-cell activating factor

Introduction

Sjögren's syndrome is a chronic, systemic autoimmune disease that happens when the immune system attacks healthy tissues, when normally, the immune system protects the body from infection and disease **(Melko K, 2017).**

It primarily affects the salivary glands in the oral cavity and the lacrimal glands in the eyes. As a systemic disease, Sjogren's syndrome can involve virtually any organ system, leading to extremely pleomorphic clinical manifestations whose characteristics and severity may vary greatly from one patient to another **(Cartee Dl, et al., 2015) (Generali E, et al., 2017)**. Specific oral manifestations associated with Sjögren disease may include increased risk of caries, gingivitis, oral ulcers, fungal infections, enlarged salivary glands, glossitis and others **(Azuma N, et al., 2021) (Šijan Gobeljić M, et al., 2020).**

Primary Sjögren disease is diagnosed when it is the only autoimmune disease present, and secondary Sjögren disease is diagnosed when there is at least one other concomitant autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, or dermatomyositis) **(Generali E, et al., 2017) (Mariette X, et al., 2018).**

The disorder most often affects women, and the range of onset is around third to fifth decade but could also affect children and adolescents **(Eleanor Thurtle, et al., 2023).** The reasons for this remains unknown, but research suggests that it's triggered by a combination of genetic, environmental and, possibly, hormonal factors **(Generali E, at al., 2017) (Igoe A, 2013).** Treatment for Sjögren disease is primarily supportive/palliative, as there is no cure at the time **(Berman N, et al., 2019).**

Aims of the study

- Understand the disease and recognize the clinical features of this condition.
- Evaluate the oral health of patients with primary Sjögren's syndrome.
- Assess relationship between the quality of life related to oral health and salivary flow rate, oral and periodontal status, disease activity, and damage.
- Organize referral for specialist care and manage the oral health of these patients.

Review of Literature

1.Disease Description

Sjögren's Syndrome (SS) owes its eponym to the Swedish ophthalmologist Henrik Samuel Conrad Sjögren (1899–1986) that firstly correlated the triad of keratoconjunctivitis sicca, xerostomia and polyarthritis. In 1933 Henrik Sjögren first described a group of women whose chronic arthritis was accompanied by dry eyes and dry mouth **(M Ghafoor, 2011).** To commemorate Professor Sjögren's contribution and raise awareness of the disease, scientists from various countries have decided to designate 23 July (Dr. Sjögren's birthday) as 'World Sjögren's Day' in 2010 **(Sjögren's Foundation, 2024).**

SS is a systemic chronic autoimmune disorder characterized by salivary and lacrimal glands immune-mediated damage, leading to dryness of the mouth (xerostomia) and eyes (xerophthalmia). Besides, dryness may affect other mucosal surfaces such as airways, digestive tract and vagina, resulting in the clinical picture of "sicca syndrome" or "sicca complex" **(Lendrem D, et al., 2014).** Along with symptoms of extensive dryness, other serious complications include severe fatigue, chronic pain, neuropathies, and lymphomas. Sjögren's can also cause dysfunction of organs such as nasal passages, reproductive system, skin, gastrointestinal system, blood vessels, lungs, liver, kidney, pancreas, and the central nervous system **(Generali E, et al., 2017).**

This condition may occur in isolation or in association with organ-specific autoimmune diseases, such as thyroiditis or primary biliary cirrhosis or cholangitis, in which case the disease is referred to as primary Sjögren's syndrome (pSS). In contrast, the term secondary Sjögren's syndrome (sSS) has been used when the disease occurs in association with another systemic autoimmune disease, such as

rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, or dermatomyositis **(Shiboski CH, et al., 2017).**

Concerning the impact of SS on quality of life, the disease negatively affects patient daily activity due to the high prevalence of fatigue, depression, anxiety and decreased physical performances **(Y.Cui, L. Xia, et al., 2018) (Y. Cui, L. Li, et al., 2018)**. A recent study demonstrated that health-related quality of life scores of SS patients was comparable to those observed in other diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) that are generally considered more aggressive autoimmune disorders **(Lendrem D, et al., 2014).**

2. Epidemiology

Sjögren has been reported worldwide in adults and more rarely in children. The disorder, has a marked predilection for women and similar to SLE, the female-male ratio is approximately 9:1. The disease usually presents in middle age but may occur in children as well as the elderly **(Kiadaliri AA, et al., 2018) (Alani H, et al., 2018).**

Results from 62 studies suggest that women and those in older age groups have the highest incidence and prevalence of Sjögren's, and that age at symptom onset and diagnosis ranges between 34-57 years and 40-67 years, respectively **(Eleanor Thurtle, et al., 2023).**

Although it can occur at any age, most patients are between the third and fifth decades of life. In children is much rarer, maintaining the predominance in women, although in a lower proportion, with an average age of onset of the disease between 9.4 and 10.7 years, being girls younger at the age of diagnosis. Unlike adults, there is a lower incidence of dryness symptoms, but a higher incidence of mumps, lymphadenopathy, and systemic symptoms **(Carlos Andrés, et al., 2023).**

The reasons for sex differences in autoimmune diseases could include genetic and hormonal differences **(Brandt JE, et al. 2015),** but may also include differences in presenting symptoms **(Ramirez Sepulveda JI, et al., 2017),** and sex-related differences in healthcare-seeking behavior **(Thompson AE, et al., 2016),** leading to a possible under-diagnosis in males and greater awareness among health care providers for primary Sjögren's in females. Results also suggest that for both sexes, incidence and prevalence increase with age **(Maciel G, et al., 2017).**

Given the multi-system involvement and considerable impact of the disease on the physical and mental health of affected patients, this finding is significant as the ageing global population could confer an increase in the overall healthcare burden of primary Sjögren's **(Chang AY, et al., 2019).**

The female predominance and average age at symptom onset of primary Sjögren's have important implications, as both disease manifestations and potential commencement of therapy are likely to overlap with the window of childbearing potential for women. Primary Sjögren's has been associated with a range of gynaecologic and obstetric complications, including: vaginal dryness, increased risk of sub-fertility/infertility, foetal complications (especially neonatal lupus and congenital heart block) and foetal loss **(Gupta S, et al., 2017) (Upala S, et al., 2016).** Furthermore, some systemic therapies for primary Sjögren's such as hydroxychloroquine and methotrexate have been shown to carry teratogenic risk Therefore, prompt diagnosis and considered management of primary Sjögren's is especially important for improving pregnancy-related outcomes for women of childbearing potential **(Huybrechts KF, et al., 2021).**

In particular, the age at onset of primary Sjögren's overlaps with the ages of childbearing and employment, meaning that poor disease control carries both health-related and economic-burden for society **(Rodrigues KC, et al., 2021) (Westerlund A, et al., 2021).**

The systemic phenotype of primary Sjögren syndrome is strongly influenced by personal factors (e.g. age, gender, ethnicity, place of residence, according to an analysis by the Sjögren Big Data Consortium, a five-continent multicenter registry, of a cohort that included 10,007 patients (9352 females, mean age 53 years) with recorded European League Against Rheumatism's Sjögren Syndrome (EULAR-SS) Disease Activity Index (ESSDAI) scores available **(Brito-Zerón, et al., 2020).** Findings were as follows **(Sriya K Ranatunga, 2023)**:

- Males had a higher mean ESSDAI than females (8.1 vs 6.0, respectively).
- Patients diagnosed at < 35 years had a higher mean ESSDAI than those diagnosed at > 65 years (6.7 vs 5.6).
- By ethnicity, the highest global ESSDAI scores were reported in blacks/African Americans (6.7), followed by whites (6.5), Asians (5.4), and Hispanics (4.8).
- Black/African-American patients showed the highest frequencies in the lymphadenopathy, articular, peripheral and central nervous system, and biological domains.
- White patients showed the highest frequencies in the glandular, cutaneous, and muscular domains.
- Asian patients showed the highest frequencies in the pulmonary, renal, and hematological domains.
- Hispanic patients showed the highest frequencies in the constitutional domain.
- Systemic activity and disease activity was higher in patients from southern countries.

3. Pathogenesis

Similarly to other autoimmune diseases, the etiology of SS is unknown **(Bombardieri M, et al., 2020)**, but it's likely a multifactorial process involving genetic susceptibility and environmental triggers that lead to an abnormal immune response **(Tian Y, et al., 2021)**. With inflammatory infiltration, with mononuclear cells affecting primarily the exocrine glands, epithelium damage, and hyperreactivity of B cells with autoantibodies against ribonucleoproteins: anti-SSA/Ro and anti-SSB/La production **(Parisis D, et al., 2020).**

Primary Sjögren's syndrome is a prototypic autoimmune disorder, management of which has long suffered from a lack of knowledge of the underlying pathophysiological mechanisms. By unraveling the intricate mechanisms by which immune cells infiltrate and damage the salivary glands, specific targets for immunotherapy can be identified to offer more personalized treatment options for patients **(Ting Zhao, et al., 2023).**

3.1. Environmental factors

To date, it is widely accepted that exposure to specific environmental factors in susceptible individuals may play a crucial role, thus, leading to the dysregulation of pathway **(Lessard CJ, et al. 2013).**

3.1.1. Microbes

Environmental factors, including viral infections, lead to the development of the autoimmune reaction by essentially causing a breakdown of autotolerance, which triggers the production of autoantibodies and the development of specific clinical phenomena. Viruses influence the immunity through mechanisms of molecular mimicry, generation of superantigens, apoptosis, necrosis, clearance deficiency, and bystander activation **(Smatti MK, et al., 2019) (Bjork A, et al., 2020).**

In many rheumatic diseases, the influence of viral infections is considered as a potential triggering factor for the activation of an autoimmune process. Several viruses are suggested to have an effect on autoimmunity, among them are Epstein–Barr virus (EBV) and human herpes virus-6 (HHV-6), hepatitis C (HCV) and B (HBV) viruses, enteroviruses, influenza A virus, human immunodeficiency virus (HIV), or viruses of Flaviviridae family (e.g., Zika and dengue viruses) **(Smatti MK, et al., 2019).**

3.1.2. Vaccines

There are some studies dealing with the possible onset of SS after vaccine exposure. The administration of the hepatitis B vaccine has been associated with the development of clinical (dry mouth, dry eyes, arthralgia, fatigue) and laboratory (rheumatoid factor (RF), antinuclear antibodies (ANAs), and anti-Ro/SSA antibodies) features of SS. In this specific case, lip biopsy also confirmed the presence of inflammatory cells infiltrates **(Bjork A, et al., 2020)**. However, also other vaccines have been suspected of causing SS, including the H1N1 vaccine. The case of a patient who developed a complete sicca syndrome 3 months after vaccine delivery has been reported. RF, ANA, and anti-Ro/SSA antibodies tested positive and a gland biopsy was compatible with SS **(Toussirot E, et al., 2020).**

Adjuvants may act by inducing the production of cytokines and chemokines involved in priming, expansion, and polarization of the immune response. Aluminum, one of the most commonly used adjuvants, is able to trigger the activation of NLRP3 inflammasome signaling, leading to the production of proinflammatory cytokines (interleukin (IL) 1b, IL-18) via caspase 1 activation **(Eisenbarth SC, et al., 2008).**

The recently updated EULAR recommendations state that influenza and pneumococcal vaccination should be strongly considered for a majority of patients

with autoimmune inflammatory rheumatic diseases, whilst live-attenuated vaccines may be considered with caution **(Furer V, et al., 2020).**

3.1.3. Silicone

In 2003, the case of a male dental technician who developed SS was diagnosed according to a positive serology and lip biopsy after silicone exposure was illustrated. In a previous report in 1997, another case dealing with a dental technician who developed sicca syndrome after silicone exposure has been described **(S. Colafrancesco, et al., 2016)**. More recently, in 2015, a case of a 34-year-old female patient who had a history of leukopenia, dry mouth, dry eyes, and cyanosis of her fingers that began soon after she underwent silicone breast implantation has been diagnosed with SS **(Akyol L, 2015).**

It has been suggested that silicone-triggered chronic inflammation, leading to a polyclonal B-cell activation with local production of cytokines, can result in full-blown SS **(S. Colafrancesco, et al., 2016)**. The B-cell oligoclonal and monoclonal expansion in infiltrated glands can in turn result in the development of a lymphoid malignancy. Although the transition from a chronic inflammatory condition to malignant lymphoma is a poorly understood multistep process, there is increasing evidence that chronic antigenic stimulation by an exoantigen or autoantigens plays an essential role in the development of SS-associated lymphoproliferation **(Ramos-Casals M, et al., 2005).**

3.1.4. Stress & Environmental Pollution

It was recently shown that before disease onset, patients with SS experience high psychological stress after major negative life events without developing satisfactory adaptive coping strategies to confront their stressful life changes. Indeed, stressful life events prior to disease onset have been proposed as a risk factor for autoimmune

diseases **(Porcelli B, et al., 2016).** Also, patients with non-apneic sleep disorder have been associated with a higher risk for developing ADs **(Hsiao YH, et al., 2015)**.

The relationship between SS and pollution has been addressed in different studies. Epidemiological analyses have associated air particulate matter (PM) inhalation with a decline in lung function and increased morbidity and mortality caused by cardiorespiratory diseases, particularly in susceptible populations.

In a study on mouse model of SS that was exposed to intranasal instillation either with saline (control) or residual oil fly ash solution (1mg/ kg body weight), mouse showed lymphocytic peribronchial infiltrates. Severe lesions of cellular infiltration in the alveoli and a greater decrease in the alveolar space was observed **(Ferraro S, et al., 2015)**. In a recent study from Calgary (Alberta, Canada) it was found that the odds of acquiring an AD are increased with fine particulate levels (PM 2.5) **(Bernatsky S, et al., 2015).**

In another study that aimed at evidencing any difference between occupational exposure to organic solvents and the risk of developing SS, it was found that a number of substances could contribute to the pathogenesis of the disease. Significantly increased odds rations were observed for dichloromethane, perchlorethylene, chlorinated solvents, benzene, toluene, white spirit, and aromatic solvents **(Chaigne B, et al., 2015).**

3.2. Hormones

Many hormonal changes occur during puberty, especially with testosterone and estrogen, influencing sex-specific bodily changes. Alterations are also seen in the immune system, with notable changes in the abundance of T-cell subsets, monocytes and B-cells. Sex hormones have been shown to directly impact immune cell function, leading them to regulate many autoimmune diseases **(Qianfan Yang, et al., 2023).**

In a study with 2,680 female Sjögren's syndrome patients, lower estrogen levels were associated with disease onset. It has been suggested that elevated estrogen levels prevent the development of Sjögren's syndrome **(McCoy SS, et al., 2020).**

Testosterone can suppress some immune-related genes such as cathepsin S in lacrimal glands from female mouse models of Sjögren's syndrome. Cathepsin S is a lysosomal acidic protease highly expressed in lymphocytes and other MHCII-positive cells and is thought to play a role in the adaptive immune response **(Nakajima T, et al., 2016).**

The overexpression of Cathepsin S has been associated with various diseases, including arthritis, cancer, and cardiovascular disease. In Sjögren – prone mice, testosterone has been shown to lower the expression of cathepsin S and additional immune associated genes, resulting in decrease in disease severity **(Morthen MK, et al., 2019)**.

Post-pubertal males have significantly different hormone levels than females. Interestingly, males have much lower estrogen levels than females, however they don't have as high prevalence in Sjögren's syndrome. From a testosterone perspective, higher testosterone prevents expression of cathepsin S and protects males from Sjogren's syndrome **(Conteduca G, et al., 2018)**. On the other hand, females are not equipped with higher testosterone to compensate for the disadvantage from estrogen. Combining estrogen and testosterone effects on the onset of Sjögren's syndrome, sex hormones greatly orchestrate the immune system functionality post-puberty. Since the sexual dimorphism in hormones arise from puberty, Sjögren's syndrome pathogenesis may also begin there **(Qianfan Yang, et al., 2023).**

3.3. Genetic factors

Genetic factors are supposed to play an important role in SS pathogenesis **(Conteduca G, et al., 2018).** Familial association studies showed that about one-third of SS patients have a relative with another connective tissue disease A large study in Taiwanese population confirmed previous observations showing that first-degree relatives of SS patients had an increased risk of SS development as well as of other autoimmune disorders **(Nezos A, et al., 2015).** Of interest, siblings of affected individuals demonstrated the highest relative risk for SS development compared to other first-degree relatives (parents and offsprings), implying both genetic influences and shared environmental exposures as contributory factors to disease development **(Kuo CF, et al., 2015).**

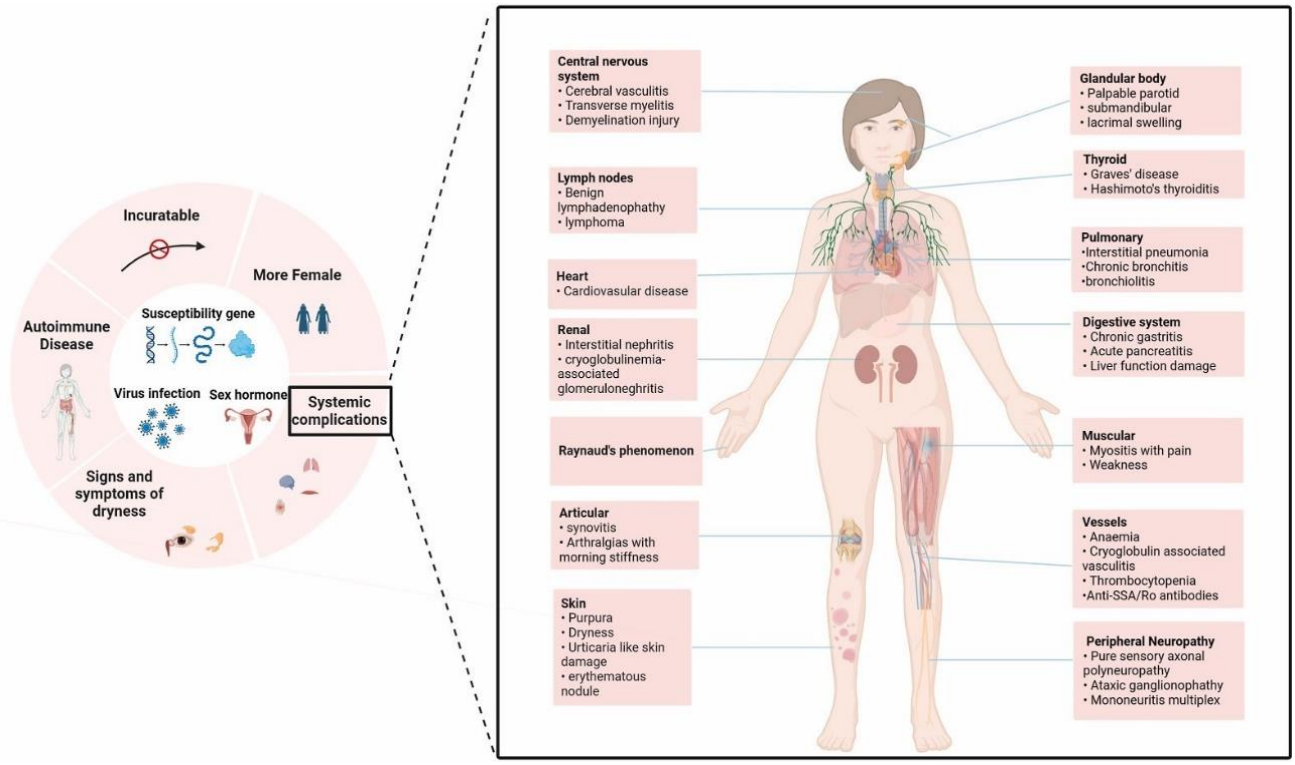

Fig. 1. General features, risk factors and systemic complications of Sjögren's syndrome.

Genetic, viral, and hormonal factors are essential in inducing SS. The extra-glandular manifestations mainly include active synovitis, severe leukocytopenia, interstitial pneumonia, autoimmune cytopenia, Raynaud's phenomenon, lymphadenopathy, cutaneous vasculitis, renal disease, neurological involvement, and myositis. Interstitial lung disease is the most common pulmonary complication in SS. Non- Hodgkin's lymphoma is a severe complication of SS and could worsen disease prognosis. In severe cases, the extra-glandular manifestations of SS may be life-threatening **(Ting Zhao, et al., 2024).**

Various factors have been hypothesized to contribute to SS development, Among these, the Human Leukocyte Antigen (HLA) genes account for the most significant genetic predisposition to SS **(Imgenberg-Kreuz, 2021).**

The epithelial expression of *HLA-DP* or *-DQ*, rather than *-DR*, may be a prerequisite for the autoimmune process underlying SS to develop in genetically susceptible individuals. Moreover, the association between *HLA* and SS is limited to patients with anti-SSA and anti-SSB antibodies. *HLA* is not associated with SS in patients without these auto-antibodies. Strong associations with anti-Ro/SSA and anti-La/SSB have been found in patients carrying *DRB1*03* and *DQB1*02* alleles or those heterozygous for *DQw1* and *DQw2* **(Ting Zhao, et al., 2024).**

A recent study identified ten Sjögren's genetic susceptibility loci in the largest Genome-wide association studies (GWAS) to date of Sjögren's of European ancestry, nearly doubling the total number of identified genetic risk loci from 12 to 22. Although this list lags far behind the >120 risk loci identified for SLE or RA, the Sjögren-SNPs (Single-nucleotide polymorphism) yielded similar Polygenic risk score calculations to SLE and RA, suggesting that this GWAS accounts for a substantial portion of Sjögren's heritability **(Bhuwan Khatri, et al., 2022).**

3.4. Epithelial cells

The exocrine glands of SS patients have an inflammatory microenvironment rich in various proinflammatory cytokines and other factors that can induce an activation status to the surrounding epithelia. Salivary gland epithelial cells can be abnormally activated when stimulated by virus infections or type I interferon, producing chemokines that promote the aggregation of lymphocytes and their focal distribution around the gland ducts **(Ting Zhao, et al., 2024).** Salivary gland epithelial cells can actively secrete cytokines such as BAFF, IL-21, and IL-7 and promote the proliferation and activation of B lymphocytes and TFH cells **(E.K. Kapsogeorgou,**

et al., 2020), Meanwhile, salivary gland epithelial cells are crucial as antigen-presenting cells, which express MHC class II molecules and co-stimulatory molecules on the cell surface, effectively interacting with T lymphocytes to drive T cell activation, In addition to that, apoptosis also serves as a significant source for releasing autoantigens. Increasing the level of epithelial cell apoptosis can trigger the production of anti-SSA and anti-SSB antibodies **(S. Katsiougiannis, et al., 2015).**

The disruption of the salivary gland epithelium in SS is influenced by critical signaling pathways such as the Toll-like receptor (TLR) and nuclear transcription factor kappa B (NF-κB) signaling, as well as interferons pathways. Studies have confirmed that the increased vulnerability of SS salivary gland epithelial cells to the injurious effect of TLR-3 ligation **(G.M. Verstappen, et al., 2021).** Herein, epithelial cells are actively involved in initiating and driving the autoimmune response in multiple ways, although the underlying cause of its persistent abnormality remains a mystery.

3.5. Immune Cells

In patients with SS, the exocrine glands are infiltrated by various immune cells. T-cell subpopulations play essential roles in SS-related autoimmunity through orchestrating complex immune responses. T helper type 1 (Th1) and T helper type 17 (Th17) cells penetrate the gland in the early stage of the disease, producing inflammatory factors that lead to epithelial cell damage and maintaining the inflammatory response **(W. Chen, et al., 2021).** The process of infiltration of TFH and B cells occurs in the late stage of the disease, with TFH promoting B cell differentiation and antibody production **(M. Akiyama, et al., 2023)**. Regulatory T cells (Tregs) might play a role in maintaining immune balance and regulating the loss of self-tolerance mechanisms in SS **(V.G. Blinova, et al., 2023).**

Studies have identified the distinctive phenotype and possible pathogenic impact of $CD8^+$ T cells in SS and their contribution to acinar injury in exocrine glands. While It has been confirmed that interleukin (IL)-17-producing $CD4^-CD8^-$ T cells undergo expansion in peripheral blood and infiltrate salivary glands in patients with SS, peripheral $CD4^+CD8^+$ double-positive T cells may have a protective role in SS **(Ting Zhao, et al., 2024).** Almost half of the infiltrating B cells in the peripheral stroma of the glandular lobules of salivary gland tissue are fully differentiated plasma cells **(J. Li, et al., 2023).**

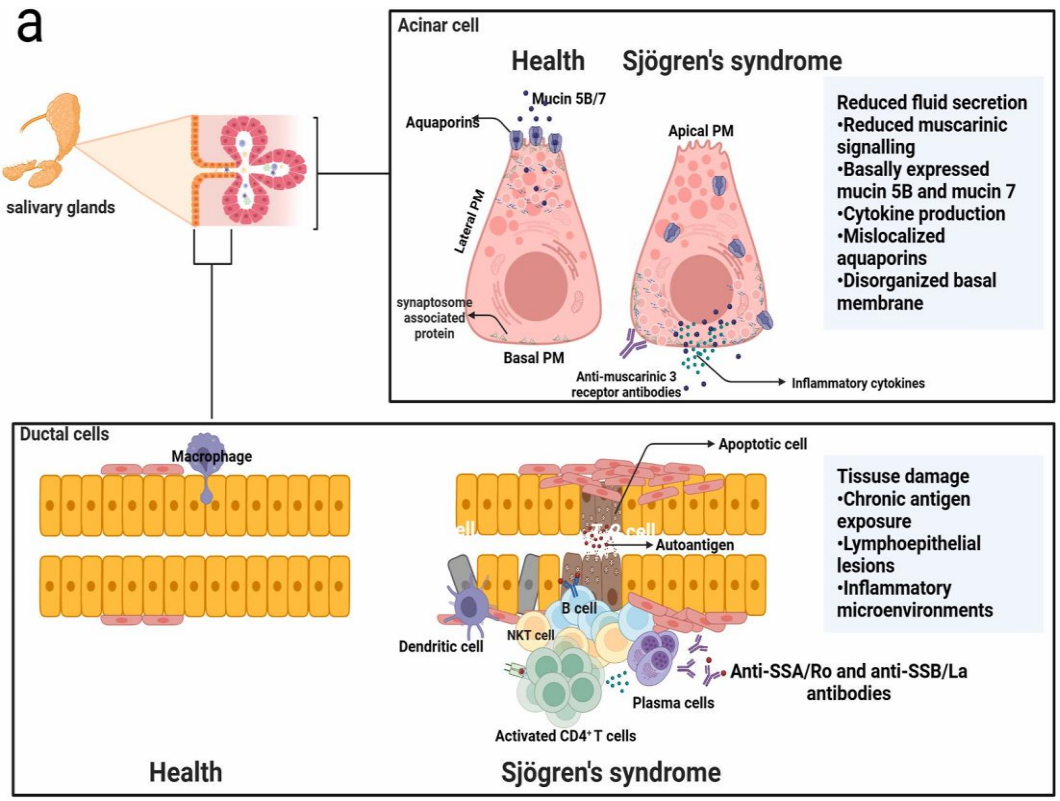

Fig. 2.1. The complex pathogenesis of Sjögren's syndrome

Altered glandular homeostasis precedes the onset of inflammation, contributing to secretory dysfunction in patients with SS. In individuals with SS, acinar cells tend to have multiple defects. The expression of different AQPs is altered, and the ability of these channels to respond to muscarinic stimuli is significantly impaired. Aberrant localization of fusion receptors involved in regulated exocytosis has been observed in the salivary glands of SS patients. The ductal epithelium may be affected during SS development because of various pathogenic events such as activation of innate immune pathways, epithelial cell apoptosis, and senescence. Multiple factors could cause chronic antigen exposure, leading to the formation of lymphoepithelial lesions. **(Ting Zhao, et al., 2024).**

The hyperactivation of B lymphocytes in patients with Sjögren's disease results in the production of many circulating autoantibodies. Traditional biomarkers include anti-Sjögren's disease-related antigens A and B (anti-SSA/Ro and anti-SS-B/La) antibodies, antinuclear antibody (ANA), and rheumatoid factor (RF). Anti-SSA/Ro antibodies are present in nearly 75% of patients with Sjögren's disease and play a key role in diagnosis **(Mehrnaz M-Fischbach, et al., 2024).**

A significant amount of auto-antibodies produced by plasma cells binds to auto-antigens released by damaged host cells, enhancing tissue damage and gland dysfunction. Macrophages -innate immune cells widely present in the glandular tissues of patients with SS- have a bidirectional relationship with the inflammatory microenvironment, which makes them a potential therapeutic target for SS **(Y. Zong, et al., 2023)**. The pathogenesis of aqueous-deficient dry eye is driven by the concerted action of monocytes/macrophages and infiltrating lymphocytes. In addition, natural killer T-like cells infiltrate the labial salivary glands of patients with SS, putatively playing a role in its pathogenesis **(Ting Zhao, et al., 2024).**

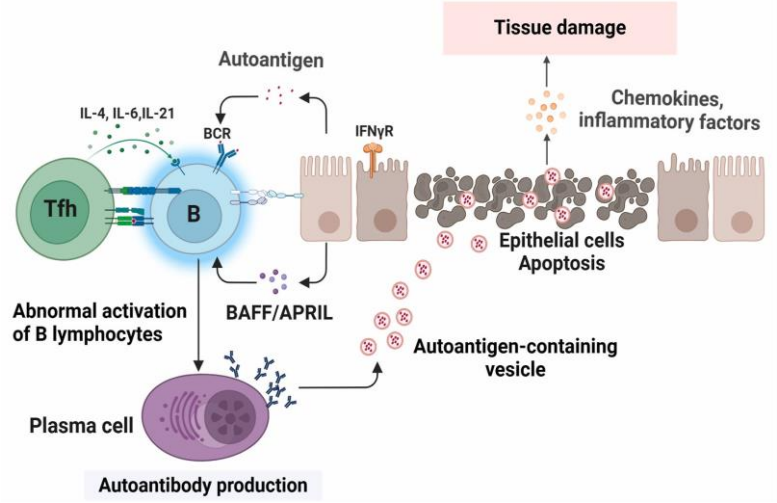

Fig. 2.2. The complex pathogenesis of Sjögren·s syndrome

During immune cell activation, pro-inflammatory factors are released, leading to sustained and persistent inflammatory responses, amplifying tissue damage, and causing progressive functional damage to affected organs. TFH cells secrete cytokines to drive B cell proliferation, leading to the differentiation of B cells into plasma cells and the production of numerous autoantibodies, thus further advancing the progression of SS. The activated infiltrated immune cells are considered to form a complex signaling network with salivary gland cells, leading to impaired secretion. **(Ting Zhao, et al., 2024).**

4. Clinical Manifestations

The clinical spectrum of SS is very heterogeneous and is operatively classified into glandular and extraglandular manifestations, which are not mutually exclusive **(Carlos Andrés RJ., et al., 2023).**

4.1. General Manifestations

4.1.1. General constitutional symptoms

Fatigue is reported by about 70–80% of SS patients, and it often has a negative impact on their quality of life. Other non-specific general symptoms are sleep disorders, anxiety, depression and chronic widespread pain **(Simone Negrini, et al., 2022).**

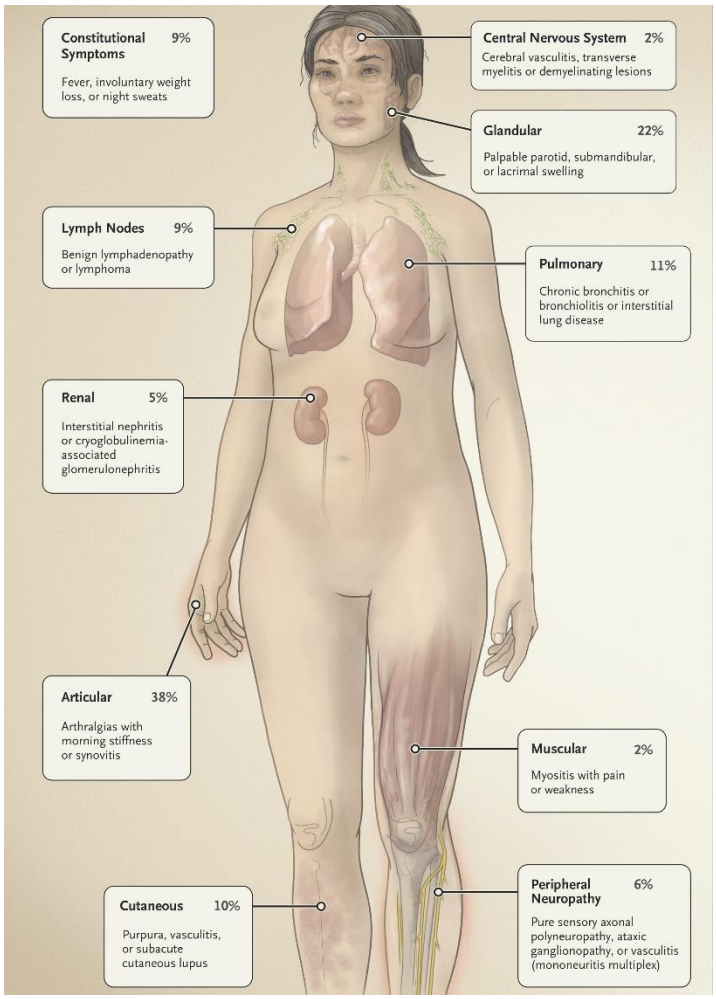

Fig.3. Systemic Manifestations of Primary Sjögren's Syndrome. (Mariette X, et al., 2018).

4.1.2. Exocrine glandular manifestations

The involvement of the exocrine glands in patients with SS is manifested mainly by hyposecretion, mediated by glandular disorders involved in the pathophysiology of the disease **(Carlos Andrés RJ., et al., 2023).**

Lachrymal gland dysfunction causes qualitative and quantitative abnormalities of the tear film, thus leading to ocular surface chronic inflammation. Dry eye syndrome, also known as keratoconjunctivitis sicca, may cause a wide spectrum of signs and symptoms characterized by photosensitivity, erythema, itching or foreign body sensation, early breakage of the tear layer and lesions in the ocular epithelium **(Kuklinski E, et al., 2017).** Likewise, it increases the probability of corneal ulcers, uveitis and scleritis; in moderate to severe cases, optic neuritis and filamentary keratitis may occur, being the latter an entity in which protein fibers and mucous material adhere to the corneal surface, aggravating the dry eye symptoms **(G. Cafaro, et al., 2019).**

Nasal dryness has also been described in 30% of the diagnosed patients, manifested by nasal crusts that cause recurrent epistaxis as well as changes in smell and respiratory mechanics, which increase xerostomia when breathing with the mouth open while sleeping **(Carlos Andrés RJ., et al., 2023).**

Xerosis or dry skin is another frequent condition, found in 66% of patients with SS. It’s associated with specific signs such as inelastic, rough and desquamative skin, associated with hyposecretion of the sweat glands. whereas reduced vaginal secretion leads to dyspareunia and local discomfort **(Simone Negrini, et al., 2022).**

4.1.3. Musculoskeletal manifestations

Musculoskeletal involvement, comprehending myalgia, arthralgia and morning stiffness are present in the majority of SS patients **(Leone MC, et al., 2017)**. The frequency of joint pain without inflammatory signs (arthralgia) is reported up to 75% of patients, whereas overt inflammatory joint disease (arthritis) is less frequent and can be observed in approximately 10% of SS patients. The large majority of SS-related arthritis is non-erosive, while synovitis and bone erosions are characteristic features of secondary SS associated with RA **(Simone Negrini, et al., 2022).**

In SS patients, true myositis is rare, while myalgias and/or muscle weakness are relatively frequent and can be secondary to fibromyalgia or hypokalemia, respectively **(Choi BY, et al., 2016).**

4.1.4. Vascular and Dermatological manifestations

Besides xerosis (skin dryness), which is the most common cutaneous manifestation of SS, other manifestations of skin involvement are relatively frequent. Annular erythema is a non-scarring, not–atrophy-producing, dermatosis characterized by annular polycyclic lesions typically occurring in photo-exposed areas and it's characterized by a wide elevated border and a central pallor area **(Ramos-Casals M, Brito-Zeron P., 2015).** Cutaneous vasculitic lesions are mostly represented by palpable purpura, most commonly distributed over the lower limbs, but other clinical entities such as cutaneous ulcers, urticarial vasculitis or skin nodules have been reported **(F.B. Vivino, et al., 2019).**

SS-related annular erythema is strongly associated with the positivity of anti-Ro/SSA and/or anti-La/SSB autoantibodies as patients with vasculitis present a high prevalence of anti-Ro/SSA and/or anti-La/SSB antibodies and about one-third of them has a positive cryoglobulin test **(Ramos-Casals M, Brito-Zeron P., 2015).** Raynaud phenomenon is a clinical manifestation in which artery spasms cause

reduced blood flow with paleness, cyanosis and even gangrenous change, it's reported in 10–20% of SS patients, and in the majority of the cases, it precedes the onset of sicca symptoms **(Brito-Zeron P, et al., 2016) (Wigley FM, 2016).**

4.1.5. Respiratory tract manifestations

The respiratory compromise found in SS ranges from the involvement of the upper respiratory tract to the small airways. Upper airways dryness can promote nasal crusting, epistaxis and rhinosinusitis. Thick mucus at vocal cords may cause chronic hoarseness and approximately 50% of SS patients complain chronic non-productive cough resulting from tracheal dryness (xerotrachea) **(Simone Negrini, et al., 2022).**

Moreover, airway dryness predisposes SS patients to atelectasis, bronchiectasis and recurrent episodes of respiratory tract infections **(Stojan G, et al., 2013).**

4.1.6. Gastrointestinal manifestations

Studies suggest that up to 80% of SS patients may experience some degree of dysphagia, with negative consequences on their quality of life. Dysphagia may derive from the combination of xerostomia and/or esophageal dysmotility **(Popov Y, et al.,2013).**

Heartburn, chronic cough, chest pain or upper abdominal pain are typical GERD symptoms. GERD is common in the general population (about 20%) but is more common and often more severe in Sjögren's. Patients can often manage this with lifestyle interventions; others may need medications **(Virginia FM Trevisani, et al., 2022).** Dysautonomia and small fiber neuropathy may cause abnormal esophageal motility, abdominal discomfort occurs in up to 37% of patients with SS, constipation in up to 23%, diarrhea in up to 9%, and iron deficiency anemia due to malabsorption in up to 5% **(Virginia FM Trevisani, et al., 2022).**

4.1.7. Renal manifestations

Chronic tubulointerstitial nephritis and renal tubular acidosis have been described as the most frequent forms of renal disease in SS, however, in the majority of cases they start in a subtle manner or asymptomatically **(J. Luo, et al., 2019).**

The symptoms at the level of the bladder can be manifested with dysuria, pollakiuria, nocturia and urgency; if there is no urinary tract infection, the symptoms may be secondary to interstitial cystitis; these symptoms are 20 times more frequent in patients with SS than in the general population **(Carlos Andrés RJ., et al., 2023).**

4.1.8. Nervous System manifestations

The prevalence of neurological involvement in SS is approximately 20%, involving the peripheral nervous system (PNS) more frequently than the central nervous system (CNS) **(F.B. Vivino, et al., 2019)**, with pure sensory neuropathies and axonal sensorimotor polyneuropathies the most common manifestations, therefore, SS should be considered as a differential diagnosis among patients presenting with these neurological entities **(Cafaro G, et al., 2021).** Sensory ataxic neuropathy is related to a dorsal root ganglionitis characterized by T-cell infiltration and loss of neuronal cells of the dorsal root ganglia. Clinically, patients display loss of kinesthesia and proprioception leading to sensory ataxia, difficulty with fine motor movements, unsteady gait and reduced or absent reflexes **(Gwathmey KG, 2021).**

Among CNS disturbances, cognitive dysfunction and sleep disorders are commonly observed among SS patients. Headaches that may present in pSS are tension headaches, migraines and cluster headaches. These conditions contribute to worsen overall patient's quality of life **(Simone Negrini, et al., 2022) (Patel P, et al., 2025).**

Other manifestations such as transient hemiparesis, optic neuritis, seizures, ataxia, parkinsonism, aseptic meningoencephalitis, various forms of acute and chronic myelopathy, vasculitis, lymphomas, affective disorders have been reported **(F.B. Vivino, et al., 2019).**

4.1.9. Lymphoma

B cell lymphoma is one of the most severe complications of SS, approximately 5% of SS patients develop lymphoma. Recent studies suggest that patients with primary Sjögren's disease have a four- to sevenfold higher risk of non-Hodgkin's lymphoma compared with the general population **(Mehrnaz M-Fischbach, et al., 2024) (Ahn JK, et al., 2020).**

Non-Hodgkin's lymphoma occurs in approximately 2–9% of patients with primary Sjögren's disease, with the mucosa-associated lymphoid tissue (MALT) subtype accounting for approximately two-thirds of cases **(Mehrnaz M-Fischbach, et al., 2024).**

Lymphomas often develop in organs where the disease is active, and salivary glands are the most frequent sites. The main clinical predictive factors are persistent swelling of salivary glands, lymphadenopathies and palpable purpura, Additionally, a moderate to high disease activity has been independently associated with subsequent lymphoma occurrence **(Simone Negrini, et al., 2022).**

4.2. Oral Manifestations

4.2.1. Dry Mouth and Saliva

Xerostomia refer to the subjective feeling of dry mouth and can present in people with normal saliva secretion. Hyposalivation can be objectively measured and typically is below 0.1 mL/min **(Bilal Talha,2023),** The condition can be either temporary or chronic and can be caused by a range of factors of which the most common is xerogenic medications. Other reasons may be radiation and chemotherapy for head and neck cancers, hormone disorders, infections, or systemic autoimmune diseases such as SS **(Bolstad, A.I, 2016).**

Saliva consists of two main components, serous and mucous, it contains minerals, electrolytes, enzymes, cytokines, growth factors, buffers, immunoglobulins (IgA), mucins, among other glycoproteins **(Bolstad, A.I, 2016).** Saliva plays a pivotal role in the homeostasis of the oral cavity; Because of its functional properties it helps to protect teeth and mucous membranes, phonation, dental remineralization, bolus swallowing and maintenance of pH. It also helps to maintain a good digestion, and to prevent oral colonization by pathogens through its enzymatic processes **(Rodríguez J, et al., 2015).**

Patients with xerostomia suffer not only from reduced quantity of saliva but also a reduced quality, the normal stimulated salivary flow rate is between 1.5 to 2.0 mL/min, while the unstimulated flow rate ranges from 0.3 to 0.4 mL/min. A diagnosis of hyposalivation is if stimulated salivary flow is less than 0.5 to 0.7 mL/min or unstimulated flow of under 0.1 mL/min **(Bilal Talha,2023)**. Hyposalivation is a condition that contributes to the development of opportunistic infections in the oral cavity; unlike xerostomia, which is the subjective sensation of dry mouth without a decrease in salivary flow **(Rodríguez J, Martínez G. et al., 2015).**

Because of the exocrinopathy in SS, hyposalivation contributes to the ideal environmental conditions for the colonization by opportunistic pathogens such as *Streptococcus mutans* and *Candida albicans* **(Rodríguez J, Sánchez R. et al, 2015).** The lack of self-cleansing processes and the absence of enzyme systems commonly found in saliva contribute to halitosis, oral candidiasis (a prevalence of chronic atrophic candidiasis of 37% in SS have been reported), Halitosis and recurrent infections, including parotitis, angular cheilitis, ulcerations, atrophic glossitis and grooves or fissuration of the tongue were the most reported lesions **(Anil S, et al., 2014).**

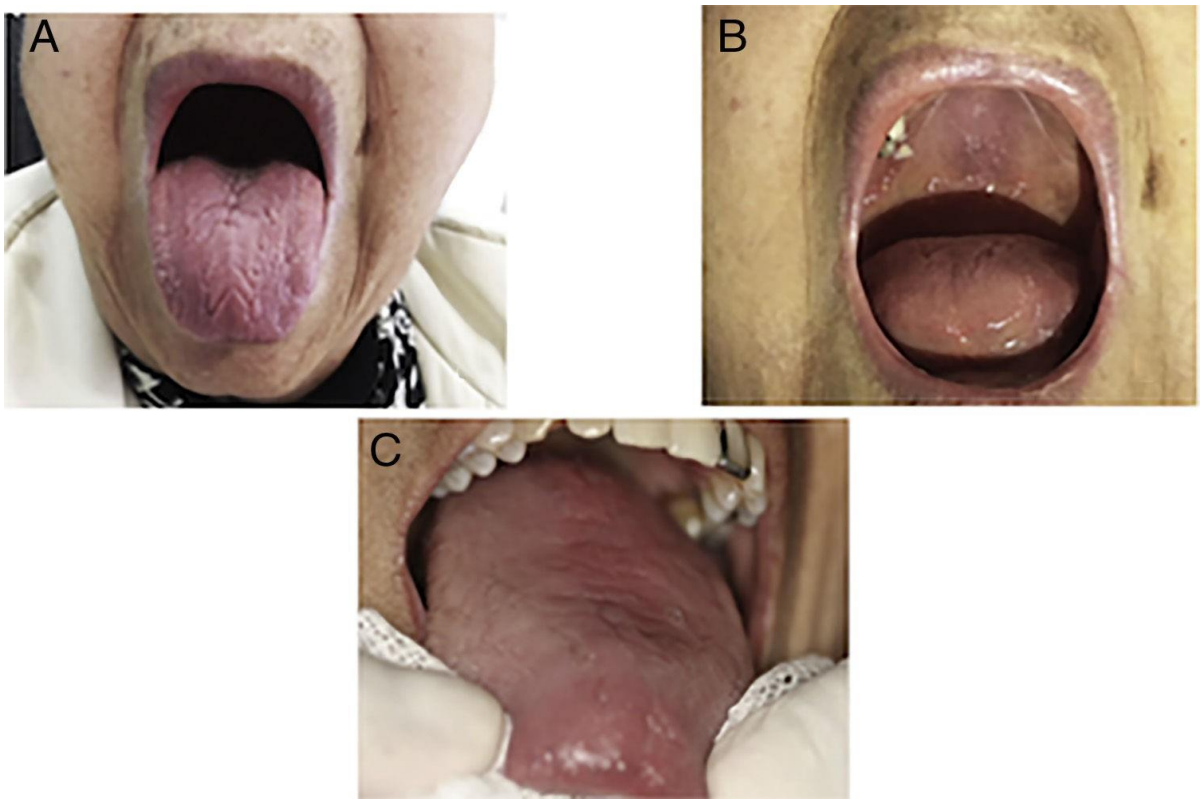

Fig.4. Oral symptoms in Sjögren's syndrome.

Panel A: dry mouth. Panel B: Candida in palate. Panel C: Candida on the tongue.

Prolonged dry mouth may result in **(Bilal Talha,2023) (Bolstad, A.I, 2016)*:***

- A sensation of oral dryness.
- Oral burning or soreness.
- Diminished or altered taste.
- The need to sip water when swallowing.
- Difficulty chewing & swallowing dry foods, e.g., crackers.
- A sensation of thickened saliva.
- Sensitivity to acidic or spicy foods.
- Difficulty in speaking.
- Difficulty wearing dental prosthesis.

4.2.2. Dental Caries

Reduced salivary flow and changes in saliva composition make patients at a greater risk for development of dental caries. The important buffer and remineralization capacities are reduced, as well as the protective effect against microorganisms **(Bolstad, A.I, 2016).**

A recent study found significant differences in the prevalence of incisal, cervical/ root, and total caries exist in the SS population, compared with non-SS population with salivary hypofunction caused by other factors. These differences in caries were observed despite a lack of statistically significant differences between the 2 groups in either parotid stimulated salivary flow or unstimulated salivary flow **(Berman N, et al., 2019).**

Studies of sialochemistry in patients with SS vs healthy controls have reported a number of significant differences, including changes in electrolytes, salivary immunoglobulins, antimicrobial proteins, lipids, glycosylated mucins, and other salivary constituents **(Nayab M.A., et al., 2016)**.

The most frequently reported sialochemical findings in SS include heterogeneous electrolyte levels in whole-mouth unstimulated salivary flow (i.e., increased Na, K, and immunoglobulin levels) vs stimulated parotid salivary flow (i.e., increased Cl, decreased phosphate, increased lactoferrin) **(Berman N, et al., 2019).**

This implies that host factors and qualitative differences, rather than quantitative changes in saliva flow may serve as important additional risk factors for caries development in the SS population.

4.2.3. Periodontal Diseases

Reports showed conflicted results regarding SS relation to periodontal disease. According to the published literature in the early years, no significant difference could be detected concerning the periodontal status of SS patients, compared with that of the patients with other immune diseases as well as with that of systemically healthy subjects. However, in recent years, putative links between periodontal diseases and SS have been reported in several studies **(Yang B, et al., 2023).**

A recent systematic review and meta-analysis showed that PI and GI in total SS patients were greater than the healthy controls **(Shih-Yun Wu, et al., 2021).** This might be due to the decrease of salivary glands functions, which are critically important for the maintenance of oral health. Xerostomia was shown to be associated with plaque accumulation and bleeding on probing. The change of salivary viscosity, the decline of self-cleaning ability, the reduction of lubricating ability, the loss of antimicrobial molecules could all contribute to plaque accumulation **(S. Mizutani, et al., 2015).**

it was also shown that patients with periodontitis could manifest a higher risk of subsequent SS development (50% higher than the general population), recommending that periodontists pay increased attention to the signs and symptoms of SS in patients with periodontal disease **(Lin C.-Y. et al., 2019)**.

The authors also suggest that this pathogenic link may be mediated by a modified immune inflammatory response, contributing to this association **(Lin C.-Y. et al., 2019).** Similar results were generated by the study of Lu et al. showing that three years prior to SS diagnosis, the utilization of ambulatory dental services for gingivitis and periodontitis was significantly higher in these patients. Hence, dental practitioners could play an essential role in the early detection and diagnosis of primary SS **(Gheorghe DN, et al., 2023).**

5. Diagnosis

Evaluation of a patient with suspected Sjogren syndrome should include an evaluation of oral and ocular dryness and function. In addition to the history, this may include the performance of a Schirmer test, slit-lamp exam with vital dye staining, salivary flow rate, and/or nuclear scintigraphic evaluation of the salivary glandular function. Assessment of autoantibodies (ANA, RF, SS-A, and SS-B) should also be performed. most specific single test is a minor salivary gland (lip) biopsy which will demonstrate FLS in positive specimens **(Carsons SE, 2023).**

5.1. Schirmer's test

Schirmer's test is a simple procedure used to assess the amount of lachrymal production. The test is performed by placing a strip of sterile paper in the lateral third of the lower eyelid of each eye and then measuring the length of the moistened portion of the strip. A Schirmer's test result ≤ 5 mm/5 min in at least one eye is considered positive **(Shiboski CH, et al., 2017).**

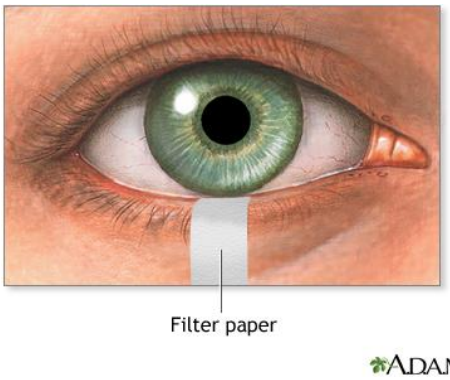

Fig.5. Schirmer's Test: MedlinePlus Medical Encyclopedia Image, (n.d.)

5.2. Ocular staining

Evaluation of the ocular surface is performed by an experienced ophthalmologist through the instillation of topical dyes to determine the integrity of the epithelium layers of the cornea and conjunctiva. Fluorescein is used to determine the integrity of the corneal epithelium, while lissamine green (or rose Bengal) is used for evaluating the integrity of the conjunctiva. According to the 2016 ACR/EULAR criteria, an Ocular Staining Score ≥ 5 in at least one eye **(Shiboski CH, et al., 2017) (Simone Negrini, et al., 2022).**

5.3. Sialometry

Unstimulated whole saliva production is evaluated by collecting the patient's saliva in a calibrated tube for 15 min following the protocol for saliva collection redacted by Navazesh and Kumar. An unstimulated whole saliva flow rate ≤ 0.1 mL/min is considered pathologic **(Aoun G, et al., 2016).**

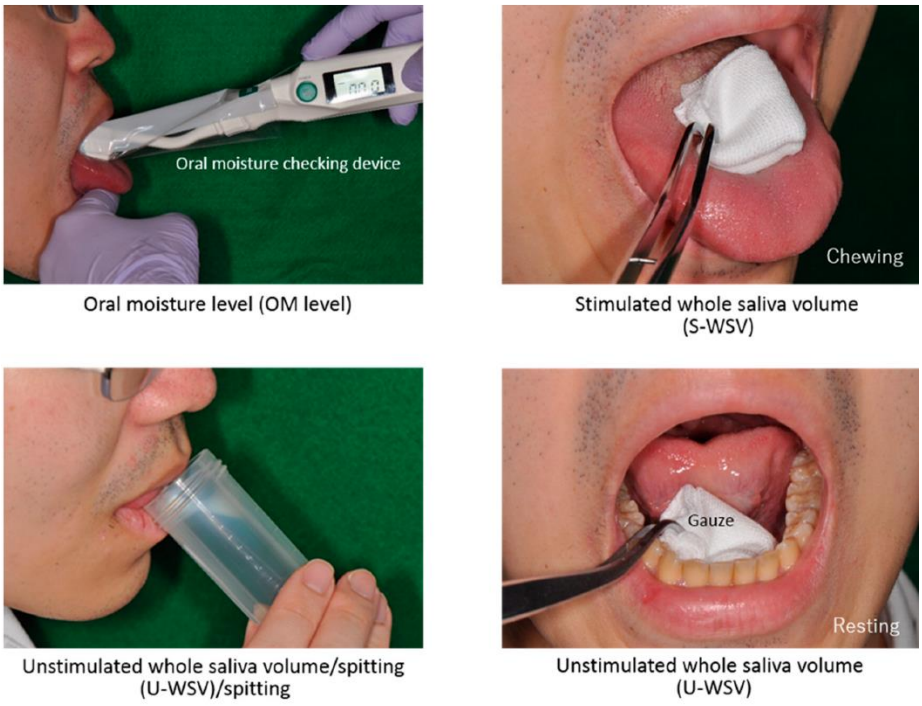

Fig.6.Outline of each sialometry measurement test (Goto T. 2020).

5.4. Autoantibodies

Antinuclear antibodies (ANAs), rheumatoid factor (RF), and Ro/SSA and La/SSB autoantibodies are typical serological findings in SS. ANA are present in the sera of up to 85% of patients, and also RF is commonly positive in SS; for this reason, they had been included as SS criteria in different previous classification sets, nevertheless, The new 2016 ACR/EULAR criteria have excluded isolated anti-SSB/La positivity among the items since anti-SSA/Ro antibodies are usually detected either solely or concomitantly with antiSSB/La, whereas anti-SSB/La positive-SSA/Ro negative patients are rare **(Shiboski CH, et al., 2017) (Franceschini F, et al., 2017).**

5.5. Salivary gland biopsy

Labial salivary gland biopsy is the key test to confirm SS diagnosis and it may be decisive in patients with sicca symptoms without anti-SSA/Ro antibodies. Also, it provides prognostic information since a high degree of lymphoid infiltration does increase the risk of lymphoma development **(Carubbi F, et al., 2015)**.

Minor salivary gland biopsy is a simple procedure that can be performed under local anesthesia and with a low rate of side effects. While Parotid gland biopsy is generally not necessary for the diagnosis of SS, but it may be indicated to investigate atypical parotid enlargement suggestive of neoplastic pathology **(Shiboski CH, et al., 2017) (Carubbi F, et al., 2015)**.

5.6. Disease severity and activity measures

Over the past two decades, significant efforts have been put into developing and validating effective outcome-measuring scores for pSS. Patient-reported outcomes (PROs); such as the visual analog scale (VAS) for symptoms, EULAR Sicca Score

(ESS), and patient's global assessment (PGA), have been widely used to evaluate the subjective symptoms of patients with pSS **(Ture, H. Y. et al., 2023).**

Both EULAR Sjogren's Syndrome Patient-Reported Index (ESSPRI), and EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) are EULAR-validated outcomes measuring scores. They measure the subjective and objective clinical disease activity of patients with pSS, respectively, and are demonstrated to be highly reproducible and to be able to detect change in disease activity **(de Wolff, et al., 2021).**

Recently, Clinical ESSDAI (ClinESSDAI), which does not include the biological domain, was developed for measuring a "true" clinical effect. By contrast, Clinical Trials ESSDAI (ClinTrialsESSDAI) consists of the frequently active clinical domains of the ESSDAI **(Ture, H. Y. et al., 2023).**

6. Treatment

Since a curative treatment of SS is currently unavailable, the goal is to alleviate symptoms of the exocrinopathy, as well as controlling the extra-glandular manifestations of the disease. Management of SS patients requires an integrated multidisciplinary approach, including different health care figures, such as family physicians, clinical immunologists or rheumatologists, ophthalmologists, otorhinolaryngologists and/or dentists. Depending on the systemic involvement, consultation with other specialists (e.g., pulmonologist, neurologist, gynecologist, etc.) may be indicated **(Simone Negrini, et al., 2022).**

In 2019 the EULAR study group released updated recommendations for the management of SS with topical and systemic therapies. Dryness should be managed with topical therapy as first step approach, sparing systemic therapies for active

disease, whereas systemic manifestations should be treated with a targeted-organ approach with subsequent therapeutic steps **(Ramos-Casals M, et al., 2020).**

Early diagnosis and treatment can help prevent complications and improve the quality of life for patients with Sjögren's syndrome **(Akpek E.K, et al., 2019).**

6.1. Ocular Dryness Management

The most common manifestation of SS is dry eyes, treated with artificial tears, lubricating ointments, and anti-inflammatory agents. **(Saraux, A., et al., 2016)**

- Artificial Tears and Lubricants: Over-the-counter (OTC) artificial tears are often the first-line treatment. More severe cases require preservative-free formulations.
- Cyclosporine (Restasis) and Lifitegrast (Xiidra): Cyclosporine A has been shown to increase tear production by modulating local immune response. While Lifitegrast blocks lymphocyte function-associated antigen 1 (LFA-1), reducing ocular inflammation **(Bowman, 2021).**
- Punctal Occlusion: This minor surgical procedure involves inserting plugs into the tear ducts to prevent tear drainage.

6.2. Treatment for Dry Mouth

Salivary gland dysfunction leads to difficulties in swallowing and increased dental caries. Treatments focus on stimulating saliva production. **(Elizabeth J.Price, 2021)**

- Pilocarpine (Salagen) and Cevimeline (Evoxac): These muscarinic agonists stimulate salivary secretion and improve oral dryness.
- Saliva Substitutes: OTC saliva substitutes provide temporary relief but do not improve glandular function.

- Dental Care: Regular fluoride treatment and antimicrobial mouth rinses help prevent complications such as cavities and oral infections.

6.3. Systemic Treatment Approaches

In patients with systemic involvement, immunosuppressive therapies are often required. **(Saraux, A., et al., 2016)**

a. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs such as ibuprofen are used to manage mild joint and muscle pain. However, they do not alter disease progression **(Luo et al., 2021).**

b. Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

For moderate to severe SS, DMARDs are used to suppress immune activity:

- Hydroxychloroquine (Plaquenil): Commonly used in rheumatic diseases, hydroxychloroquine reduces fatigue and joint pain in SS patients **(Wang X, et al., 2021).**
- Methotrexate and Azathioprine: These immunosuppressants are used in patients with systemic organ involvement.

6.4. Biologic Therapies

Biologic agents targeting B cells and inflammatory cytokines have shown promise in treating SS. **(Bowman, 2021)**.

- Rituximab (Anti-CD20 Therapy): Rituximab depletes B cells, reducing autoantibody production. Studies have demonstrated mixed results regarding its efficacy in SS
- Belimumab (Anti-BAFF Therapy): This monoclonal antibody reduces B-cell survival and is being explored as a treatment option for SS.

Table 1 | Treatments for the manifestations of primary Sjögren's Syndrome (Saraux, A., et al., 2016)

Manifestations of pSS	Treatment and/or course of action
Dryness	
Dry mouth	• Topical fluoride • Gustatory and masticatory stimulation • Pharmaceutical agents; chlorhexidine varnish, gel or rinse; electrostimulation • Secretagogues: pilocarpine and cevimeline • Education and environment modification; elimination of offending drugs
Dry eyes	• Education and environment modification; elimination of offending drugs; artificial tears; gels and/or ointments • Local ciclosporin • Pulsed glucocorticoids • Punctal plugs • Secretagogues: pilocarpine and cevimeline
Meiombian disease	• Artificial tears with lipid components; warm compress and massage; topical azithromycin; liposomal spray; oral doxycycline; excision of the meibomian glands; systemic anti-inflammatory medication; eyelid surgery
Parotid enlargement	
Acute bilateral severe parotid swelling	• Look for lymphoma • If lymphoma excluded, treat with glucocorticoids
Chronic bilateral parotid swelling	• Look for lymphoma • Surgery required in rare cases
Acute unilateral severe parotid swelling	• Look for infection (ultrasonography): if present, treat with appropriate antibiotics • Look for infection or calcification in the ducts • If infection and calcification excluded, treat with glucocortioids <20 mg per day for <1 month)
Extraglandular signs	
Non-life-threatening signs	• Exercise for fatigue • NSAIDs for arthralgia or arthritis • Hydroxychloroquine for arthralgia, arthritis, fatigue or cutaneous signs • Imunosuppressant drugs (e.g. leflunomide, sulfasalazine, azathioprine, ciclosporin, cyclophosphamide) and/or glucocorticoids should be considered according to disease activity
Life-threatening signs	Pulsed methylprednisolone and plasma exchange if cryoglobulinaemia
Co-occurrence of cryoglobulinaemia and vasculitis	Rituximab should be considered

Conclusion

This study has provided a comprehensive understanding of Sjögren's syndrome, highlighting its clinical features, impact on oral health, and its broader systemic implications. The evaluation of oral health in patients with primary Sjögren's syndrome has underscored the significant challenges posed by reduced salivary flow, increased risk of oral infections, and the subsequent decline in quality of life. The correlation between disease activity, oral health status, and overall patient well-being reinforces the need for multidisciplinary care and early intervention strategies.

Furthermore, this research emphasizes the importance of specialist referrals and targeted management approaches to mitigate the oral health complications associated with Sjögren's syndrome. Given the progressive nature of the disease and its potential systemic effects, an integrated treatment plan that includes both dental and medical care is crucial for improving patient outcomes. Continued research and clinical awareness are essential for refining treatment protocols and enhancing the quality of life for individuals affected by this condition.

References

A

1. Ahn, J.K., Hwang, J. and Seo, G.H. (2020) 'Risk of non-Hodgkin's lymphoma and thyroid cancer in primary Sjögren's syndrome measured using the Korean Health Insurance Claims Database', Clinical and Experimental Rheumatology, 38(126), pp. 40–46.
2. Akpek, E.K., Bunya, V.Y. and Saldanha, I.J. (2019) 'Sjögren's syndrome: More than just dry eye', Cornea, 38, pp. 658–661.
3. Akyol, L., Önem, S., Özgen, M. and Sayarlıoğlu, M. (2015) 'Sjögren's syndrome after silicone breast implantation', European Journal of Rheumatology.
4. Alani H, Henty JR, Thompson NL, Jury E, Ciurtin C. (2018). Systematic review and meta-analysis of the epidemiology of polyautoimmunity in Sjögren's syndrome (secondary Sjögren's syndrome) focusing on autoimmune rheumatic diseases. Scand J Rheumatol. Mar;47(2):141-154.
5. Anil, S., Vellappally, S., Hashem, M., Preethanath, R.S., Patil, S. and Samaranayake, L.P. (2014) 'Xerostomia in geriatric patients: a burgeoning global concern', Journal of Investigative and Clinical Dentistry, 5, pp. 1–8.
6. Aoun, G., Nasseh, I. and Berberi, A. (2016) 'Evaluation of the oral component of Sjögren's syndrome: An overview', Journal of International Society for Preventive and Community Dentistry, 6(4), pp. 278-284.
7. Azuma N., Katada Y., Yoshikawa T., Yokoyama Y., Nishioka A., Sekiguchi M., Kitano M., Kitano S., Sano H., Matsui K. (2021). Evaluation of changes in oral health-related quality of life over time in patients with Sjögren's syndrome. Mod. Rheumatol.; 31:669–677.

B

8. Berman, N., Vivino, F., Baker, J., Dunham, J. and Pinto, A. (2019) 'Risk factors for caries development in primary Sjogren syndrome', Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, 128(2), pp. 117-122.
9. Bernatsky, S., Smargiassi, A., Johnson, M., Kaplan, G.G., Barnabe, C. and Svenson, L., et al. (2015) 'Fine particulate air pollution, nitrogen dioxide, and systemic autoimmune rheumatic disease in Calgary, Alberta', Environmental Research, 140, pp. 474–478.
10. Bhuwan Khatri, Kandice L. Tessneer, Astrid Rasmussen, et al. (2022) 'Genome-wide association study identifies Sjögren's risk loci with functional implications in immune and glandular cells', Annals of Rheumatic Diseases, 13, pp. 4287:10-12.

11. Bilal, Talha. and Swarnkar, S.A. (2023) 'Xerostomia', in StatPearls [Internet], Treasure Island (FL): StatPearls Publishing, 2025 Jan.
12. Bjork, A., Mofors, J. and Wahren-Herlenius, M. (2020) 'Environmental factors in the pathogenesis of primary Sjögren's syndrome', Journal of Internal Medicine, 287, pp. 475–492.
13. Bombardieri, M., Argyropoulou, O.D., Ferro, F., et al. (2020) 'One year in review 2020: pathogenesis of primary Sjogren's syndrome', Clinical and Experimental Rheumatology, 126(4), pp. 3–9.
14. Bolstad, A.I. and Skarstein, K. (2016) 'Epidemiology of Sjögren's Syndrome—from an Oral Perspective', Current Oral Health Reports, 3, pp. 328–336.
15. Bowman, S.J. (2021) 'Current and future therapies for primary Sjögren syndrome', Nature Reviews Rheumatology, 17, pp. 475-486.
16. Brandt JE, Priori R, Valesini G, Fairweather D. (2015). Sex differences in Sjögren's syndrome: a comprehensive review of immune mechanisms. Biol Sex Differ.; 6:19.
17. Brito-Zerón, Nihan Acar-Denizli, Wan-Fai Ng, et al. (2020). Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjögren's syndrome. Rheumatology (Oxford).; 59(9): pp.2350-2359.
18. Brito-Zerón, P., Baldini, C., Bootsma, H., et al. (2016) 'Sjogren syndrome', Nature Reviews Disease Primers, 2, p. 16047.
19. Brito-Zerón, P., Theander, E., Baldini, C., et al. (2016) 'Early diagnosis of primary Sjogren's syndrome: EULAR-SS task force clinical recommendations', Expert Review of Clinical Immunology, 12(2), pp. 137–156.

C

20. Chaigne, B., Lasfargues, G., Marie, I., Huttenberger, B., Lavigne, C. and Marchand-Adam, S., et al. (2015) 'Primary Sjögren's syndrome and occupational risk factors: a case-control study', Journal of Autoimmunity, 60, pp. 80–85.
21. Carlos Andrés Reyes Jarabaa, Nehomar Eduardo Pájaro Galvisa, Oscar Vicente Vergara Serpaa, et al. (2023) 'Sjögren's syndrome: Epidemiology and clinical manifestations', Revista Colombiana de Reumatología, 29(4), pp. 313-321.
22. Carsons, S.E. and Patel, B.C. (2023) 'Sjogren Syndrome', in StatPearls [Internet], Treasure Island (FL): StatPearls Publishing, 2025 Jan.
23. Cartee DL, Maker S, Dalonges D, Manski MC. (2015). Sjogren's Syndrome: Oral Manifestations and Treatment, a Dental Perspective. J Dent Hyg 89(6):365-71.
24. Carubbi, F., Alunno, A., Cipriani, P., et al. (2015) 'A retrospective, multicenter study evaluating the prognostic value of minor salivary gland histology in a large cohort of patients with primary Sjogren's syndrome', Lupus, 24(3), pp. 315–320.

25. Chang AY, Skirbekk VF, Tyrovolas S, Kassebaum NJ, Dieleman JL. (2019). Measuring population ageing: an analysis of the Global Burden of Disease Study 2017. Lancet Public Health. 4(3): e159–e167.
26. Choi, B.Y., Oh, H.J., Lee, Y.J. and Song, Y.W. (2016) 'Prevalence and clinical impact of fibromyalgia in patients with primary Sjogren's syndrome', Clinical and Experimental Rheumatology, 2(96), pp. 9-13.
27. Conteduca, G., Indiveri, F., Filaci, G. and Negrini, S. (2018) 'Beyond APECED: An update on the role of the autoimmune regulator gene (AIRE) in physiology and disease', Autoimmunity Reviews, 17(4), pp. 325–330.

D

28. De Wolff, L., Arends, S., Pontarini, P., Bombardieri, M., Bowman, S.J. and Bootsma, H. (2021) 'Development and performance of the Clinical Trials ESSDAI (ClinTrialsESSDAI), consisting of frequently active clinical domains, in two randomised controlled trials in primary Sjogren's syndrome', Clinical and Experimental Rheumatology, 39(6), pp. S100-S106.

E

29. E.K. Kapsogeorgou, A.G. Tzioufas. (2020) 'Interaction of human salivary gland epithelial cells with B lymphocytes: implications in the pathogenesis of Sjögren's syndrome', Mediterranean Journal of Rheumatology, 31(4), pp. 424-426.
30. Eisenbarth, S.C., Colegio, O.R., O'Connor, W., Sutterwala, F. and Flavell, R.A. (2008) 'Crucial role for the NALP3 inflammasome in the immunostimulatory properties of aluminium adjuvants', Nature, 453, pp. 1122–1126.
31. Eleanor Thurtle, Alice Grosjean, Monia Steenackers, Katharina Strege, Giovanna Barcelos, Pushpendra Goswami. (2023). Epidemiology of Sjögren's: A Systematic Literature Review. Rheumatol Ther. Nov 10;11(1):1–17.
32. Elizabeth J Price, Alan N Baer, (2021). How to treat Sjögren's syndrome, Rheumatology, June 60 (6): 2574–2587.

F

33. Ferraro, S., Orona, N., Villalon, L., Saldiva, P.H., Tasat, D.R. and Berra, A. (2015) 'Air particulate matter exacerbates lung response on Sjögren's syndrome animals', Experimental Toxicology and Pathology, 67, pp. 125–131.
34. Franceschini, F., Cavazzana, I., Andreoli, L. and Tincani, A. (2017) 'The 2016 classification criteria for primary Sjogren's syndrome: what's new?', BMC Medicine, 15(1), p. 69.

35. Furer, V., Rondaan, C., Heijstek, M.W., et al. (2020) '2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases', Annals of the Rheumatic Diseases, 79, pp. 39–52.

36. F.B. Vivino, V.Y. Bunya, G. Massaro-Giordano, C.R. Johr, S.L. Giattino, A. Schorpion, et al. (2019) Sjogren's syndrome: an update on disease pathogenesis, clinical manifestations and treatment. Clin Immunol, 203: 81-121

G

37. G. Cafaro, C. Croia, O.D. Argyropoulou, M.C. Leone, M. Orlandi, F. Finamore, et al. (2019) 'One year in review 2019: Sjögren's syndrome', Clinical and Experimental Rheumatology, 37(118), pp. 3-15.

38. G.M. Verstappen, S. Pringle, H. Bootsma, et al. (2021) 'Epithelial-immune cell interplay in primary Sjögren syndrome salivary gland pathogenesis', Nature Reviews Rheumatology, 17(6), pp. 333-348.

39. Generali E, Costanzo A, Mainetti C, Selmi C. (2017). Cutaneous and Mucosal Manifestations of Sjogren's Syndrome. Clin Rev Allergy Immunol 53(3):357-70

40. Gheorghe, D.N., Popescu, D.M., Dinescu, S.C., Silaghi, M., Surlin, P. and Ciurea, P.L. (2023) 'Association between Sjögren's Syndrome and Periodontitis: Epidemiological, Fundamental and Clinical Data: A Systematic Review', Diagnostics (Basel), 13(8), p. 1401.

41. Goto, T., Kishimoto, T., Iwawaki, Y., Fujimoto, K., Ishida, Y., Watanabe, M., Nagao, K., & Ichikawa, T. (2020). Reliability of Screening Methods to Diagnose Oral Dryness and Evaluate Saliva Secretion. Dentistry Journal, 8(3), 102.

42. Gupta S, Gupta N. (2017). Sjögren syndrome and pregnancy: a literature review. Perm J. 21:16–047.

43. Gwathmey, K.G. and Satkowiak, K. (2021) 'Peripheral nervous system manifestations of rheumatological diseases', Journal of Neurological Sciences, 424, p. 117421.

H

44. Huybrechts KF, Bateman BT, Zhu Y, Straub L, Mogun H, Kim SC, et al. (2021). Hydroxychloroquine early in pregnancy and risk of birth defects. Am J Obstet Gynecol.224(3): 290.e1-e22.

45. Hsiao, Y.H., Chen, Y.T., Tseng, C.M., Wu, L.A., Lin, W.C. and Su, V.Y., et al. (2015) 'Sleep disorders and increased risk of autoimmune diseases in individuals without sleep apnea', Sleep, 38, pp. 581–586.

I

46. Igoe A, Scofield RH. (2013). Autoimmunity and infection in Sjogren's syndrome. Curr Opin Rheumatol, 25(4):480-7.

47. Imgenberg-Kreuz, A., Rasmussen, K. and Sivils, K., et al. (2021) 'Genetics and epigenetics in primary Sjögren's syndrome', Rheumatology, 60(5), pp. 2085-2098.

J

48. J. Li, M. Zhao, W. Luo, et al. (2023) 'B cell metabolism in autoimmune diseases: signaling pathways and interventions', Frontiers in Immunology, 14, p. 1232820.

49. J. Luo., Xu, S., Lv, Y., Huang, X., Zhang, H. and Zhu, X., et al. (2019) 'Clinical features and potential relevant factors of renal involvement in primary Sjögren's syndrome', International Rheumatology Diseases, 22, pp. 182-190.

K

50. Kiadaliri AA, Mohammad AJ, Englund M. (2018) Hospitalizations due to systemic connective tissue diseases: Secular trends and regional disparities in Sweden, 1998-2016. Int J Rheum Dis. Nov;21(11):1900-1906.

51. Kuklinski, E. and Asbell, P.A. (2017) 'Sjogren's syndrome from the perspective of ophthalmology', Clinical Immunology, 182, pp. 55–61.

52. Kuo, C.F., Grainge, M.J., Valdes, A.M., et al. (2015) 'Familial risk of Sjogren's syndrome and co-aggregation of autoimmune diseases in affected families: a nationwide population study', Arthritis & Rheumatology, 67(7), pp. 1904–1912.

L

53. Lendrem D, Mitchell S, McMeekin P, et al. (2014) Health-related utility values of patients with primary Sjogren's syndrome and its predictors. Ann Rheum Dis.;73(7):1362–8.

54. Leone, M.C., Alunno, A., Cafaro, G., et al. (2017) 'The clinical spectrum of primary Sjogren's syndrome: beyond exocrine glands', Reumatismo, 69(3), pp. 93–100.

55. Lessard, C.J., Li, H., Adrianto, I., et al. (2013) 'Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjogren's syndrome', Nature Genetics, 45(11), pp. 1284–1292.

56. Lin C.-Y., Tseng, C.-F., Liu, J.-M., Chuang, H.-C., Lei, W.-T., Liu, L., Yu, Y.-C. and Hsu, R.-J. (2019) 'Association between periodontal disease and subsequent Sjögren's syndrome: A nationwide population-based Cohort Study', International Journal of Environmental Research and Public Health, 16, p. 771.

57. Luo, Y., Zhang, Y., Kuai, L., et al. (2021) 'Efficacy and safety of Tripterygium glycosides in Sjögren's syndrome treatment: Evidence from 12 randomized controlled trials', Annals of Palliative Medicine, 10(7), pp. 8215-8231.

M

58. M. Akiyama, W. Alshehri, K. Yoshimoto, et al. (2023) 'T follicular helper cells and T peripheral helper cells in rheumatic and musculoskeletal diseases', Annals of the Rheumatic Diseases, 82(11), pp. 1371-1381

59. M Ghafoor. (2011) Sjögren's Before Sjögren: Did Henrik Sjögren (1899–1986) Really Discover Sjögren's Disease? J Maxillofac Oral Surg.11(3):373–374.

60. Maciel G, Crowson CS, Matteson EL, Cornec D. (2017). Incidence and mortality of physician-diagnosed primary Sjögren syndrome: time trends over a 40-year period in a population-based US cohort. Mayo Clin Proc.;92(5):734-43.

61. Mariette X, Criswell LA. Primary Sjogren's Syndrome. N Engl J Med (2018);378(10):931-39.

62. McCoy, S.S., Sampene, E. and Baer, A.N. (2020) 'Association of Sjögren's Syndrome with reduced lifetime sex hormone exposure: a case-control study', Arthritis Care & Research, 72, p. 9.

63. Mehrnaz Maleki-Fischbach, Liudmila Kastsianok, Matthew Koslow, Edward D. Chan. (2024) 'Manifestations and management of Sjögren's disease', Arthritis Research & Therapy, 26, p. 43.

64. Melko, K. (2017) July 1. The daily struggle with Sjogren's syndrome: Guiding dental patients to relief from pain. Registered Dental Hygienists. https://www.rdhmag.com/patient-care/article/16409782/the-daily-struggle-with-sjogrens-syndrome-guiding-dental-patients-to-relief-from-pain

65. Morthen, M.K., Tellefsen, S., Richards, S.M., Lieberman, S.M., Rahimi Darabad, R. and Kam, W.R., et al. (2019) 'Testosterone influence on gene expression in lacrimal glands of mouse models of Sjögren syndrome', Investigative Ophthalmology & Visual Science, 60, p. 6.

N

66. Nakajima, T., Nakamura, H., Owen, C.A., Yoshida, S., Tsuduki, K. and Chubachi, S., et al. (2016) 'Plasma cathepsin S and cathepsin S/cystatin C ratios are potential biomarkers for COPD', Disease Markers, 2016, p. 4093870.

67. Nayab M.A. Chaudhury, Proctor GB, Karlsson NG, Carpenter GH, Flowers SA. (2016) Reduced Mucin-7 (Muc7) Sialylation and Altered Saliva Rheology in Sjögren's Syndrome Associated Oral Dryness. Mol Cell Proteomics.;15(3):1048-59

68. Nezos, A. and Mavragani, C.P. (2015) 'Contribution of Genetic Factors to Sjögren's Syndrome and Sjögren's Syndrome Related Lymphomagenesis', Journal of Immunological Research, 2015, p. 754825.

P

69. Parisis D, Chivasso C, Perret J, Soyfoo MS, Delporte C. (2020). Current state of knowledge on primary sjögren's syndrome, an autoimmune exocrinopathy. J Clin Med 9(7):2299.

70. Patel, P., Singh, S., Zhang, P., Rishty, S. and Wang, S. (2025) 'Headaches in Sjogren's disease: A narrative review', Headache, 65, pp. 191-196.

71. Popov, Y. and Salomon-Escoto, K. (2018) 'Gastrointestinal and hepatic disease in Sjogren syndrome', Rheumatic Disease Clinics of North America, 44(1), pp. 143–151.

72. Porcelli, B., Pozza, A., Bizzaro, N., et al. (2016) 'Association between stressful life events and autoimmune diseases: A systematic review and meta-analysis of retrospective case-control studies', Autoimmunity Reviews, 15, pp. 325–334.

Q

73. Qianfan, Yang., Kennicott, K., Zhu, R., Kim, J., Wakefield, H., Studener, K. and Liang, Y. (2023) 'Sex hormone influence on female-biased autoimmune diseases hints at puberty as an important factor in pathogenesis', Frontiers in Immunology, 11, p. 1051624.

R

74. Ramirez Sepulveda JI, Kvarnstrom M, Brauner S, Baldini C, Wahren-Herlenius M. (2017) Difference in clinical presentation between women and men in incident primary Sjögren's syndrome. Biol Sex Differ. 8:16.

75. Ramos-Casals, M., De Vita, S. and Tzioufas, A.G. (2005) 'Hepatitis C virus, Sjögren's syndrome and B-cell lymphoma: linking infection, autoimmunity and cancer', Autoimmunity Reviews, 4, pp. 8–15.

76. Ramos-Casals, M., Brito-Zerón, P. and Bombardieri, S. (2020) 'EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies', Annals of the Rheumatic Diseases, 79, pp. 3-18.

77. Ramos-Casals, M., Brito-Zeron, P., Seror, R., et al. (2015) 'Characterization of systemic disease in primary Sjogren's syndrome: EULAR-SS Task Force recommendations for articular, cutaneous, pulmonary and renal involvements', Rheumatology, 54(12), pp. 2230–2238.

78. Rodrigues KC, Grosjean A, Hügle T, Dumusc A. (2021). POS1415 Socio-economic impact of Sjögren's syndrome in Western Switzerland: a cross-sectional study. Ann Rheum Dis. 80:991.
79. Rodríguez, J., Martínez, G., Rodríguez, N., Chapa, M. and Solís, J. (2015) 'Dental perspective on Sjögren's syndrome: literature review', Journal of Oral Research, 4(3), pp. 211-222.
80. Rodríguez, J., Sánchez, R., Garza, M., Nakagoshi, M., Solís, J., Arévalo, K. and Garza, E. (2015) 'Physicochemical and antimicrobial evaluation of chitosan and hydroxypropyl methylcellulose films for prolonged release of pilocarpine', Journal of Oral Research, 4(1), pp. 25–31.

S

81. S. Colafrancesco, C. Perricone, Y. Shoenfeld. (2016) 'Chapter 10 – Sjögren's Syndrome and Environmental Factors', in Sjögren's Syndrome, Academic Press, pp. 157–170.
82. S. Katsiougiannis, R. Tenta, F.N. Skopouli. (2015) 'Endoplasmic reticulum stress causes autophagy and apoptosis leading to cellular redistribution of the autoantigens Ro/Sjögren's syndrome-related antigen A (SSA) and La/SSB in salivary gland epithelial cells', Clinical and Experimental Immunology, 181(2), pp. 244-252.
83. S. Mizutani, D. Ekuni, T. Tomofuji., et al. (2015) 'Relationship between xerostomia and gingival condition in young adults', Journal of Periodontal Research, 50, pp. 74-79.
84. Saraux, A., Pers, J.-O. and Devauchelle-Pensec, V. (2016) 'Treatment of primary Sjögren syndrome', Nature Reviews Rheumatology, 12(8), pp. 456–471.
85. Schirmer's test: MedlinePlus Medical Encyclopedia Image. (n.d.). reviewed (2023) https://medlineplus.gov/ency/imagepages/9888.htm
86. Šijan Gobeljić M., Milić V., Pejnović N., Damjanov N. (2020). Chemosensory dysfunction, Oral disorders and Oral health-related quality of life in patients with primary Sjögren's syndrome: Comparative cross-sectional study. BMC Oral Health. 20:187.
87. Simone Negrini, Giacomo Emmi, Monica Greco, Matteo Borro, et al. (2022) 'Sjögren's syndrome: a systemic autoimmune disease', Clinical and Experimental Medicine, 22, pp. 9–25.
88. Shiboski CH, Shiboski SC, Seror R, et al. (2017). 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 76:9-16, 35-43.

89. Shih-Yun, Wu, Ching-Yi, W., Ming-Han, C., Hsin-Yi, H., Yu-hsuan, C., Yen-Po, T., Yu-Lin, L. and Shih-Yuan, L. (2021) 'Periodontal conditions in patients with Sjögren's syndrome: A meta-analysis', Journal of Dental Sciences, 16(4), pp. 1222-1232.
90. Sjögren's Foundation, Inc. (2024, July 22) 'Celebrating World Sjögren's Day', Sjögren's Foundation. Available at: https://sjogrens.org/news/2024/celebrating-world-sjogrens-day.
91. Smatti, M.K., Cyprian, F.S., Nasrallah, G.K., Al Thani, A.A., Almishal, R.O. and Yassine, H.M. (2019) 'Viruses and autoimmunity: A review on the potential interaction and molecular mechanisms', Viruses, 11(8), p. 762.
92. Sriya K Ranatunga, Mar 24, (2023). MD-MPH Southern Illinois University School of Medicine. Sjogren Syndrome.
93. Stojan, G., Baer, A.N. and Danoff, S.K. (2013) 'Pulmonary manifestations of Sjogren's syndrome', Current Allergy and Asthma Reports, 13(4), pp. 354–360.

T

94. Thompson AE, Anisimowicz Y, Miedema B, Hogg W, Wodchis WP, Aubrey-Bassler K. (2016). The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. BMC Fam Pract. 17:38.
95. Tian Y, Yang H, Liu N, Li Y, Chen J. (2021). Advances in pathogenesis of Sjögren's syndrome. J Immunol Res; 5928232:1.
96. Ting Zhao, Runrun Zhang, Zhaofu Li, Dongdong Qin and Xinchang Wang. (2024) 'A comprehensive review of Sjögren's syndrome: Classification criteria, risk factors, and signaling pathways', Autoimmune Reviews, 10(17), pp. 2-6.
97. Toussirot, E., Bossert, M., Herbein, G. and Saas, P. (2012) 'Comments on the article by Tabache F. et al. "Acute polyarthritis after influenza A H1N1 immunization", Joint Bone Spine, 2011: primary Sjögren's syndrome occurring after influenza A H1N1 vaccine administration', Joint Bone Spine, 79, p. 107.
98. Ture, H.Y., Kim, N.R. and Nam, E.J. (2023) 'EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) and Other Patient-Reported Outcomes in the Assessment of Glandular Dysfunction in Primary Sjögren's Syndrome', Life, 13(10), p. 1991.

U

99. Upala S, Yong WC, Sanguankeo A. (2016). Association between primary Sjögren's syndrome and pregnancy complications: a systematic review and meta-analysis. Clin Rheumatol. 35(8):1949–1955.

V

100. V.G. Blinova, V.I. Vasilyev, E.B. Rodionova, et al. (2023) 'The role of regulatory T cells in the onset and progression of primary Sjögren's syndrome cells', Journal of Immunological Research, 12(10), p. 1359.

101. Virginia F.M. Trevisani, Aysa César Pinheiro, Sonia Cristina de Magalhães Souza Fialho, et al.(2022) Recommendations for evaluation and diagnosis of extra-glandular manifestations of primary Sjögren syndrome: results of an epidemiologic systematic review/ meta-analysis and a consensus guideline from the Brazilian society of rheumatology (hepatic, gastrointestinal and pancreatic). 62:35:9-10.

W

102. W. Chen, F. Yang, G. Xu, et al. (2021) 'Follicular helper T cells and follicular regulatory T cells in the immunopathology of primary Sjögren's syndrome', Journal of Leukocyte Biology, 109(2), pp. 437-447.

103. Wang, X., Zhang, T., Guo, Z., Pu, J., Riaz, F., Feng, R., Fang, X., Song, J., Liang, Y., Wu, Z., et al. (2021) 'The Efficiency of Hydroxychloroquine for the Treatment of Primary Sjögren's Syndrome: A Systematic Review and Meta-Analysis', Frontiers in Pharmacology, 12, p. 693796.

104. Westerlund A, Kejs AMT, Beydogan H, Gairy K. (2021). Primary Sjögren's syndrome: a retrospective cohort study of burden of Illness in Sweden. Rheumatol Ther. 8:955–971.

105. Wigley, F.M. and Flavahan, N.A. (2016) 'Raynaud's phenomenon', New England Journal of Medicine, 375, pp. 556–565.

Y

106. Y. Cui, L. Xia, Q. Zhao, S. Chen, Gu ZJBp. (2018). Anxiety and depression in primary Sjögren's syndrome: a cross-sectional study. BMC Psychiatry, 18, pp. 131.

107. Y. Cui, L. Li, R. Yin, Q. Zhao, S. Chen, Q. Zhang, et al. (2018) Depression in primary Sjögren's syndrome: a systematic review and meta-analysis. Psychol Health Med, 23, pp. 198-209.

108. Y. Zong, Y. Yang, J. Zhao, et al. (2023) 'Characterisation of macrophage infiltration and polarisation based on integrated transcriptomic and histological analyses in Primary Sjögren's syndrome', Frontiers in Immunology, 14, p. 1292146.

109. Yang, B., Pang, X., Guan, J., Liu, X., Li, X., Wang, Y., Chen, Z. and Cheng, B. (2023) 'The association of periodontal diseases and Sjogren's syndrome: A systematic review and meta-analysis', Frontiers in Medicine, 9, p. 904638.