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## **A focus on Sjogren's Dry Eye Disease - pathogenesis, patient management, and new advancements in therapy**

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## **Abstract**

**Introduction:** Sjogren's syndrome (SS) is a systemic chronic inflammatory autoimmune disease of unknown etiology that primarily affects exocrine glands. Most commonly Sjogren's syndrome presents with dryness of the mouth and eyes, but it can also affect major organs and systems of the body and increase the risk of non-Hodgkin lymphoma. Due to non-specific symptoms that pose diagnostic challenges and a lack of standardized screening tools and classification criteria, the global incidence and prevalence of the disease are hard to evaluate. Studies estimate that Sjogren's syndrome affects between 400,000 to 3.1 million adults worldwide and most likely is a condition significantly underdiagnosed.

**Aim of the study:** Review of current knowledge about Sjogren's dry eye disease, underlying pathologies, diagnostic problems, and current treatment options with a focus on the most recent advancements in therapy.

**Methods and materials:** A review of chosen literature in the PubMed database, MDPI database, and GoogleScholar in the years 2000-2023 was conducted using the following keywords: "Sjogren's syndrome", "Sjogren's syndrome ophthalmology", "Sjogren's dry eye syndrome", "Sjogren's syndrome associated dry eye", "Lymphoma in Sjogren's syndrome", "Diagnosing Sjogren's syndrome dry eye", "Sjogren's syndrome epidemiology".

**Results:** Sjogren's syndrome is a far from rare autoimmune disease that affects many organs of the body and can significantly lower quality of life and increase mortality and morbidity. Due to its surreptitious symptom onset, Sjogren's syndrome is commonly underdiagnosed. New diagnostic and treatment modalities for Sjogren's syndrome dry eye are on the horizon.

**Conclusions:** Standardized, internationally recognized criteria and a high level of clinical suspiciousness are needed for a timely and accurate diagnosis of Sjogren's syndrome. Quick diagnosis is a significant facilitating factor for maintaining a high quality of life in Sjogren's syndrome dry eye.

**Keywords:** Sjogren's syndrome, Sjogren's syndrome dry eye disease, Sjogren's syndrome new therapies, non-Sjogren's syndrome dry eye, Sjogren's syndrome clinical trials.

## I. Introduction

Sjogren's syndrome (SS) is a chronic autoimmune disorder first described in a thesis by Swedish ophthalmologist Henrik Sjögren in 1933 characterized by lymphocyte infiltration of the exocrine glands. Due to a lack of standardization, incidence and prevalence rates of SS are hard to estimate [2]. Sources say the disease affects anywhere from 0.06% (Wu et al.) [4] to even 0.5% to 1% of the global population (Carsons et al.) [3], showing a strong female predilection with the female-to-male ratio being approximately 9:1, and with incidence estimated to be half of that of rheumatoid arthritis (RA) [3]. The primary and most common symptoms of Sjogren's Syndrome are xerostomia and xerophthalmia. Patients additionally often present with lingering fatigue, chronic joint and muscle pain, and skin lesions. In about one-half of affected patients, the disease also affects major body organs such as the lungs, kidneys, and connective tissue as well as the gastrointestinal, cardiovascular, and nervous systems [3]. A wide range of hematological manifestations such as anemia, hemocytopenia, gammopathy, and lymphoproliferative disorders are the leading cause of mortality in patients with Sjogren's syndrome. Studies have clearly shown that Sjogren's syndrome can increase the risk of non-Hodgkin lymphoma [1]. SS is associated with other autoimmune diseases, most commonly with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [3], which can signify common underlying pathologies.

Primary symptoms of Sjogren's syndrome are non-specific and pose diagnostic challenges. Additionally, patients can be asymptomatic or only present mild symptoms. Ophthalmologists' offices are often the first to come in touch with a Sjogren's syndrome-associated dry eye. Wu et al. estimate that about 10% of patients with dry eye disease (DED) suffer from SS [5]. However, Qin et al. argue that high prevalence of non-Sjogren's syndrome dry eye disease, and the lack of standardized screening tools that could help differentiate DED from Sjogren's syndrome dry eye (SSDE) in a clinical setting often result in a reported median diagnostic delay of 10 years [6]. In effect, undiagnosed patients have a lower quality of life and increased morbidity and mortality than patients diagnosed with Sjogren's syndrome early due to the lack of regular checkups, targeted prevention, and early detection and treatment of developing disease-related complications.

As of today, Sjogren's syndrome remains incurable. Eye symptoms stemming from the disease are primarily treated the same as non-Sjogren's syndrome dry eye

(NSSDE) with topical eye drops aimed at replacing moisture and diminishing inflammation, often in a trial-and-error manner. However, recent studies have arisen with promising results of innovative diagnostic and directed therapeutic options that raise hope for better disease management in the future.

**II. Aim:** Overview of current knowledge about Sjogren's syndrome-associated dry eye, diagnostic possibilities, and limitations with an outlook on diagnostic tools to come in the future and a summary of current treatment modalities with a focus on novelty treatment options.

**III. Materials and methods:** A review of chosen literature in the PubMed database, MDPI database, and GoogleScholar in the years 2000-2023 was conducted using the following keywords: "Sjogren's syndrome", "Sjogren's syndrome ophthalmology", "Sjogren's dry eye syndrome", "Sjogren's syndrome associated dry eye", "Lymphoma in Sjogren's syndrome", "Diagnosing Sjogren's syndrome dry eye", "Sjogren's syndrome epidemiology".

#### **IV. Pathophysiology**

The precise etiology of Sjogren's syndrome is unknown, although it is likely that a genetic predisposition [3] and environmental triggers such as Epstein-Barr virus infections [10][11], hormonal changes, surgeries, traumas, and other stress triggers play a role [5]. The underlying pathology in SS is thought to be focal lymphocytic sialadenitis (FLS) [3]. FLS is the presence of more than 50 lymphocytes around the blood vessels and ducts of the salivary glands, usually surrounded by unaffected gland tissue [7]. Lymphocyte aggregations (foci) mostly consist of T-lymphocytes but B-lymphocytes, plasma cells, humoral factors, and other inflammatory cells can also be present. The direct mechanism by which exocrine gland function is diminished is unknown. Inflammation of the skin, bronchus, lung, kidney, and vaginal exocrine glands can cause symptoms outside the head and neck. Immune complexes deposited in joints, muscles, and other organs can cause fatigue, chronic pain, and vasculitis [8]. Malignant transformation of B-lymphocytes can be the cause of non-Hodgkin lymphoma, although it is a rare complication.

#### **V. Diagnosis - the old and the new**

Ophthalmologic patients that should raise suspicion of SS will complain of dry and gritty eyes, foreign body sensation, reduced tear production, itching and burning sensations, excessive blinking, light sensitivity, blurred vision, and eyestrain. Prolonged periods of visual effort and weather extremes such as humid or cold air can

worsen symptoms. It is important to keep in mind that there is a group of patients who is asymptomatic despite signs of significant inflammation upon examination. Common SS symptoms largely overlap with those of dry eye disease, so it is necessary for clinicians to retain a high level of suspiciousness in the diagnostic process. It is crucial to ask whether the patient has other symptoms common in SS such as dry mouth, difficulties swallowing or speaking, skin rashes, neuropathies, fatigue, and chronic pain, or autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus, among others. A physical examination can reveal the absence of tears in the lacrimal sac, blepharitis, conjunctival hyperemia, meniscal height below 0.3 mm and tear break-up time below 10s [17]. Slit-lamp examination with vital dye staining often reveals keratoconjunctivitis sicca, which is the most characteristic eye lesion in Sjogren's syndrome, and Schirmer's test confirms dry eye. Biopsy of the minor salivary glands from the inner lip has been considered the single golden standard test for confirming Sjogren's syndrome, however salivary flow rate, parotid scintigraphy and antibody testing (SS-A, SS-B, ANA, RF) are also useful in establishing a diagnosis [3]. In 2002, a revised version of American-European Consensus Criteria for Sjögren's Syndrome was published [12] and was for a long time the primary tool in clinical trials, epidemiological surveys, and clinical settings to help with diagnosing Sjogren's syndrome, although it is now thought to predispose to overdiagnosing certain groups of patients while overlooking others [12]. In 2016, the American College of Rheumatology/European League Against Rheumatism criteria was released and it is now the most used diagnostic tool [5]. Novel diagnostic modalities focus on advanced imaging such as In Vivo Confocal Microscopy (IVCM) for assessment of changes in corneal epithelium, sub-basal nerves, stroma and endothelium [5] and serum testing, and tear and saliva proteomics in the hope of finding biomarkers. Agmon-Levi et al. in a study involving 74 female patients with primary SS recently found a link between serum vitamin D levels and primary Sjogren's syndrome [18]. Moreover, the European League Against Rheumatism (EULAR) has recently recognized the B-cell activating factor (BAFF), a modulator of B-cell hyperactivation, as a useful biomarker in SS. Human tears contain more than 1500 proteins, and research performed in the last few years revealed that some of them, gel-forming mucins MUC5AC for example, could be highly specific to SS. Quantitative and structural changes in proteins such as lactoferrin and group IIA phospholipase A2 (PLA2G2A) can suggest meibomian gland dysfunction, which is a

cause of NSSDE and can help in differential diagnosis. Studies show that patients with SSDE have higher tear matrix metalloproteinase-9 (MMP-9) levels and lower thrombospondin (TSP-1) levels than patients with non-SS DED [13]. The aforementioned are not Sjogren's syndrome-specific proteins, so using ratios instead of separate values seems a better tool for differentiating between Sjogren's syndrome-related dry eye and DED not related to Sjogren's syndrome. Versura et al. in conducted clinical trials have also shown that tear proteins such as LACTO, LYS-C, and LIPOC-1 are more specific to Sjogren's syndrome than the tools currently used in clinical practice [14]. Wu et al. concluded that epidermal fatty acid binding protein (E-FABP) could also be a helpful diagnostic biomarker of Sjogren's syndrome [5]. Lastly, scientific advances of the last few years have made it possible to study the role of exosomes and microRNAs as biomarkers in Sjogren's syndrome [5]. Such pathways are being investigated. Although current results are promising to bring earlier and more accurate diagnoses in the future, further research is necessary to bring these novelties from the bench to the bedside.

## **VI. Patient management and treatment modalities - the old and the new**

Sjogren's syndrome is a chronic, insidious, and incurable disease that can debilitate patients over time. Conventional treatment options for SSDE are limited to relieving symptoms and preventing or delaying new ones. Artificial tear substitutes in the form of preservative-free drops used during the day and preservative-free gels or ointments at night to replace moisture are the most wide-range therapy for SSDE due to low costs and high availability. Custom-made biologic tear substitutes in the form of autologous serum or platelet-rich plasma drops containing growth factors, fibronectin, and other anti-inflammatory molecules are treatment options that have been proven to be more effective than artificial tear drops. Unfortunately, costs and storage requirements limit wider accessibility of this therapy. Moreover, topical corticosteroid therapy implemented early on in the treatment process has proven to give good results and topical Cyclosporin A is recommended in mild dry eye symptoms. The latter therapy is effective but requires consistency in dosing and has a delayed onset of 4 to 12 weeks. Recently, the FDA has approved a nanomicellar formulation of the drug which allows for more effective penetration and dissolution of hydrophobic Cyclosporin A in ocular structures, significantly improving dry eye symptoms (Mandal et al.) [15].

A fairly new drug Lifitegrast is an integrin antagonist that, similarly to Cyclosporin A, is aimed at diminishing inflammation in SSDE. The onset time is only 2-4 weeks, but the medication more often causes side effects such as dysgeusia, irritation, and pain. Until recently, no comparative studies were available that would collate Cyclosporin A and Lifitegrast efficacy in the treatment of Sjogren's syndrome dry eye [4]. Locatelli et al. in a 2023 review of sixty-four individuals [21] concluded that more patients preferred Cyclosporin A over Lifitegrast. Other available treatment modalities also include interventional procedures such as punctal plug occlusion which are often performed to prevent tear drainage. Cauterization is recommended only after other occlusion methods have failed due to the risk of inducing excessive lacrimation. Neuromodulators using electric, such as iTear, chemical, such as Varenicline, or mechanical stimulation have also been accepted for treatment in SSDE. Drug-delivery systems like cul-de-sac ophthalmic inserts are also on the market and can be applied by the patient themselves in a home setting, which is relieving for many busy individuals struggling with dry eye. Ophthalmologists can also surgically implant a subcutaneous reservoir that ensures continuous lubrication, but this method is not preferred due to the risk of serious infections. There are however subconjunctival and episcleral implant drug-delivery systems undergoing trial that will be mentioned below. Severe cases of Sjogren's syndrome often require systemic multi-drug therapy with corticosteroids, muscarinic antagonists, and hydroxychloroquine. Although not specifically registered for treatment of Sjogren's syndrome, disease-modifying antirheumatic drugs such as methotrexate and azathioprine have been used as alternative treatment options in patients who display poor corticoid tolerance, and in some cases have proven to be successful substitutes. Novelty treatment options in SSDE are aimed at improving drug delivery and targeting immunomodulatory pathways leading to dry eye symptoms. In recent years, biological therapy with immunomodulators such as Rituximab has been employed in the treatment of severe, multidrug-resistant Sjogren's syndrome. Treatment results and the efficacy of Rituximab are unclear and the therapy remains controversial. Ianalumab, another biological medicine, is a B-cell activating factor inhibitor that has been recently under study and shown to reduce disease activity [16]. Iguratimod, a macrophage migration inhibitory factor, and Abatacept, a T-cell costimulation modulator are also under investigation but have shown promising results in the treatment of SSDE to date.

Anterior segment ocular drug-delivery systems are also in trial. TOP 163 is a non-systemic kinase inhibitor that targets kinases that are thought to be upregulated in DED. Clinical trials are ongoing, but preliminary results show a decrease in ocular dryness, discomfort, and grittiness compared to placebo with comparable safety and tolerability. A study comparing tears of SS patients and healthy controls showed that the former have significantly less lacritin, an endogenous glycoprotein that promotes corneal epithelium damage repair and lacrimation. Vijmasi et al. found that mice treated with lacritin proved a 46% increase in tear production by week 3 of the trial in comparison to mice treated with placebo [22]. Additionally, a decrease in lymphocyte infiltration was observed in eyes treated with lacritin. More clinical trials are needed, but studies to date are promising. RGN-259 is a synthetic replacement of thymosin  $\beta$ 4 which promotes damage repair in almost all cells of the body. Clinical trials ARISE II and ARISE III found significant improvement in relieving symptoms along with a high safety profile of the drug. ARISE IV is an additional clinical trial planned for 2024 [4]. Contact-lens drug delivery has also been under study due to long contact time and close proximity to the cornea that provides the best bioavailability of any non-invasive drug formulations. Drug delivery contact lens systems also have their limitations, mainly lens thickness, water content, and hydrophobic or hydrophilic properties of the drug itself. The addition of vitamin E, surfactants, and using molecular imprinting as a drug-loading technology seems to be helpful in combating these problems. Cyclosporine A in the form of FDA-approved drug Restasis, dexamethasone, and diclofenac have all been loaded into contact lenses with success. Acrylic and polysaccharide rewetting agents in contact lens systems are already available on the market for patients. Molecularly imprinted lenses carrying hydroxypropyl methylcellulose, a polysaccharide proven especially effective in relieving SSDE symptoms, showed the drug delivery rate to be 6x more effective in lenses than in conventional eye drops. Osmoprotectants in contact lenses need further clinical trials due to insufficient data. Subconjunctival and episcleral implants containing cyclosporine A are currently under investigation as other possible long-term drug delivery systems in the treatment of SSDE. Ocular iontophoresis, a drug delivery technique exploiting electrical charges to administer drugs into the anterior and posterior eye segments is under trial in the treatment of dry eye. Nanocarriers in the form of nanomicelles, nanoparticles, liposomes, dendrimers, microneedles, and



nanowafers are currently being tested as vehicles for targeted drug delivery in the treatment of SSDE.

Another research direction that is being extensively studied in autoimmune diseases is the use of mesenchymal stem cells (MSC). MSCs have proven immunomodulatory capabilities on T and B cells. In conducted trials, administering MSCs improved salivation, lowered lymphocyte infiltration, and reduced inflammatory response. The downside to MSC therapy is limited availability constricted by donor capability and long preparation times. However, there have been successful trials with MSC-derived exosomes that alleviate these problems.

## **VII. Conclusions**

Sjogren's syndrome is an insidious disease and although it is prevalent, diagnosis, treatment, and long-term management of patients remains a challenge for clinicians. Mild Sjogren's syndrome has a good prognosis, but delayed diagnosis lowers quality of life and contributes to increased morbidity and mortality. Better tools for patient referral and standardized Sjogren's syndrome classification criteria in the early stages of the disease are needed for a timely diagnosis. Novel diagnostic modalities such as proteomics and exosomes may benefit earlier and more accurate diagnosis. Technological advancements and a more in-depth understanding of underlying pathologies in Sjogren's syndrome give hope for revolutionary treatment options in the future. Novel drugs and drug-delivery systems still require clinical trials but give a promising perspective for better patient care in the future.

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2. Rafał Bogacz: analysis and interpretation of data (14%)
3. Magdalena Gaik: work integrity and coherence (14%)
4. Inga Magda: drafting of manuscript, data research, and analysis (14%)
5. Justyna Woźniak: intellectual content and data research (14%)
6. Karol Womperski: writing of the manuscript and first revision (14%)
7. Magdalena Osuch: concept and design (14%)

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