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Sjogren's Syndrome, An Update

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Abstract
Introduction: Sjogren's syndrome has been described as an inflammatory disease of the salivary and lacrimal glands characterized by typical dry mouth symptoms, dry eyes and lymphocytic infiltration of the glandular tissues.
Objective: To analyze the literature on the characteristics of Sjogren's syndrome regarding its prevalence, risk factors, symptoms, diagnosis and treatment.
Methodology: Current literature review was carried out using the following databases: Pubmed and SCOPUS. The keywords used were "Sjogren's syndrome, prevalence, risk factors, symptoms, diagnosis and treatment".
Results: The prevalence is between 1:100 and 2.2:1000, and affects women in more than 95% with 9:1 ratio. The most common morbidity is from non-Hodgkin's B-cell lymphomas. The main symptoms are keratoconjunctivitis sicca and xerostomia. Diagnosis is by evaluation of ocular and oral dryness, detection of anti-Ro and anti-La autoantibodies, and analysis of salivary gland biopsies. The most common treatments are systemic immunomodulatory and immunosuppressive agents, steroid and non-steroid therapies, and tacrolimus for steroid intolerant patients.
Conclusion: Sjogren's syndrome is one of the most frequent autoimmune rheumatic diseases with a predilection in women between 40 and 60 years of age. Morbidity is important in non-Hodgkin's B-cell lymphoma. Xerostomia is the most common symptom in dentistry. Diagnosis is made by histopathology and serology. Currently there is no cure, but treatments are to improve symptoms and prevent complications.

Keywords: Sjogren's Syndrome, autoimmune disease, immunotherapy, dry eye, dry mouth, lacrimal gland, salivary glands, inflammation

1. Introduction
Sjogren's syndrome (SS) is one of the most common autoimmune rheumatic diseases. It has a prevalence of 0.5-1% worldwide and 3% in the United States, occurring more in middle-aged women, with a ratio of 9:1. It affects the exocrine glands, including lacrimal and salivary glands. It can manifest as primary SS, which produces an isolated disease, or as secondary SS when it appears simultaneously with another autoimmune disease [1, 2]. This autoimmune rheumatic disease is 9-20 times more common in women between the fourth and sixth decade of life, and although it is most common between the ages of 30 and 60, it is also described in younger and older age groups [3, 4]. The lymphoid infiltrates produced by the disease cause keratoconjunctivitis sicca, xerostomia, and often dryness of other surfaces connected to the exocrine glands. It is associated with the production of autoantibodies due to B-cell activation. They are a constant immunoregulatory abnormality, along with systemic manifestations including fatigue, musculoskeletal complaints, features related to liver, pulmonary, renal and nervous system, as well as the development of lymphoma [5, 6]. It can range from dry symptoms to systemic disease characterized by periepithelial lymphocytic infiltration of affected tissue or immune complex deposition and lymphoma [7]. Extraglandular manifestations are common in pSS and include joint inflammation, skin, kidney, heart, lung, intestinal and neurological involvement [8, 9]. Dry eye and dry mouth symptoms are each reported by up to 30% of people

over 65 years of age, particularly in women [10]. Neurological involvement has been reported in up to 80% of adults with pSS and may precede diagnosis in up to 50-80% of cases. Psychiatric abnormalities including depression, anxiety and cognitive deficits have also been described [11]. Similar glandular features may also occur as a late complication in patients with other rheumatic disorders, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and scleroderma ("secondary" Sjogren's syndrome) [12]. It is of utmost importance to make this disease known, to be able to recognize its signs and symptoms and to be informed of the risk factors in order to be capable of providing an adequate and specific treatment plan depending on the type of affectation and degree of progression of the disease. So far it has not been possible to establish a unique and global treatment, but this study can guide the dentist to be able to address the syndrome when it is presented in the dental office. The aim of the study is to analyze the information in the literature on the characteristics of Sjogren's syndrome, particularly regarding its prevalence, risk factors, symptoms, diagnosis and treatment.

2. Materials and methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews. The search was performed using Boolean logical operators AND, OR and NOT. It was realized with the words "Sjogren's syndrome", "prevalence", "risk factors", "symptoms", "diagnosis" and "treatment". The keywords were used individually, as well as each of them related to each other.

3. Results & Discussion

3.1 Prevalence

Worldwide, the prevalence of SS is about 0.1 to 0.5% of the total population, and it is the second highest autoimmune disorder in the USA with a total population of up to 4 million people [13]. The prevalence of primary Sjogren's syndrome (pSS) is between 1:100 and 2.2:1000 and is therefore the most common connective tissue disease [14, 15]. Incidence of the syndrome ranges from 0.1 to 4.8% according to the American-European Consensus Criteria and 3 to 4% among the elderly. From 5% to 10% of patients may develop non-Hodgkin's lymphoma, the most serious complication of SS, within 10 to 15 years of follow-up [16, 17]. Patients with primary Sjogren's syndrome have a 10 to 44 times higher risk of lymphoma than healthy individuals, higher than that reported for systemic lupus erythematosus with an appearance of 9 to 33% and also in rheumatoid arthritis [4, 18]. The prevalence of SS among patients with rheumatoid arthritis was 8.7%, as diagnosed by rheumatologists [19]. The disease affects women in more than 95% of registered cases with a ratio of 9:1. The key clinical presentation of primary SjS is sicca syndrome, which occurs in more than 95% of cases at diagnosis, although patients may develop a wide variety of systemic manifestations [20, 21]. Available disease data estimate the prevalence of neurological symptoms at around 8.5-70% of patients diagnosed with pSS [22].

The worldwide prevalence of SS is about 0.1 to 0.5% of the total population. It is between 1:100 and 2.2:1000 and is therefore the most common connective tissue disease. It has a 10 to 44 times higher risk of lymphoma than healthy individuals, higher than that reported for systemic lupus erythematosus and rheumatoid arthritis. The disease affects more than 95% of women with a 9:1 ratio. There is also a prevalence of neurological symptoms in about 8.5-70% of patients diagnosed with pSS.

3.2 Risk Factors

Patients who demonstrate renal involvement are at risk for life-threatening complications. Renal involvement in SS is relatively rare and is seen in approximately 5-10%. Non-Hodgkin's lymphoma is another serious systemic manifestation of SS [23]. Morbidity arises not only from untreated xerostomia and dry keratoconjunctivitis, but also from extraglandular manifestations, including the development of non-Hodgkin's B-cell lymphomas. Between 5-10% of patients will have a B-cell lymphoma, mostly a low-grade lymphoma that develops from mucosa-associated lymphoid tissue [24, 25]. Severe clinical manifestations involving multiple organ systems with a high EULAR Sjogren syndrome disease activity index are present in 20-40%. The risk of non-Hodgkin's lymphoma and Non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue is generally estimated to be 10-15 times compared to the general population [26]. In the course of pSS, internal organs can be affected, and symptoms can affect any system. Neurological disorders are one of the extraglandular manifestations of the disease and are sometimes very painful [22]. There are several infectious agents that cause disease manifestations similar to Sjogren's syndrome, including hepatitis C virus, Epstein-Barr virus, cytomegalovirus and human T-lymphotropic virus-1 (HTLV-1) infections. It is found that by causing persistent infection in the salivary gland after the first infection, it will later lead to organ destruction, resulting in sicca syndrome in the oral cavity [13]. Speaking more specifically of risk factors in the dental practice, the use of dental implants is considered safe and generally have long-term success rates. It has been proposed that SS is a contraindication for dental implant placement. For example, due to lack of saliva and/or concomitant use of immunosuppressive therapies, or that the failure rate of implants will be higher than in healthy individuals [27]. Salivary dysfunction in the oral mucosa can lead to serious and costly oral health complications. In contrast, in certain cases salivary dysfunction is not extreme and patients who lose their complete dentition find themselves in need of dental implant placement as the only viable long-term alternative [28].

Morbidity arises not only from xerostomia, untreated dry keratoconjunctivitis or renal involvement, but also from extraglandular manifestations, including the development of non-Hodgkin's B-cell lymphomas. There are infectious agents similar to Sjogren's syndrome, including hepatitis C virus infections, Epstein-Barr virus, cytomegalovirus and HTLV-1. These eventually cause infection in the salivary gland and then organ destruction, leading to sicca syndrome in the oral cavity.

3.3 Signs and Symptoms

Sjogren's syndrome primarily affects the exocrine glands, resulting in keratoconjunctivitis sicca and xerostomia due to lymphocytic infiltration of the salivary and lacrimal glands along with arthritis, renal, hepatic and pulmonary involvement, chronic fatigue, musculoskeletal pain and vasculitis. Activated B lymphocytes are a hallmark of the disease, which is characterized by the presence of rheumatoid factor, hypergammaglobulinemia, anti-SSA/Ro and anti-

SSB/La antibodies [29, 30]. Classically, it has been postulated as a two-step process in which lymphocytic infiltration of the lacrimal and salivary glands is followed by destruction of epithelial cells, resulting in keratoconjunctivitis sicca and xerostomia [7, 31]. The main symptoms of the disease result in xerostomia/stomatitis and keratoconjunctivitis sicca that predominantly affects women in their perimenopausal and postmenopausal years [2, 10]. While xerostomia results in complications such as dental caries, chronic candidiasis and parotid gland inflammation, keratoconjunctivitis sicca can lead to corneal melting, uveitis, scleritis and optic neuritis [32]. The control of the symptoms and signs of xerostomia are not yet strong enough to recommend a particular treatment, pharmacologic or otherwise. Most of the treatments tested improve temporarily, but without control in the medium or long term, which makes the use of this type of therapeutic strategies difficult and unpredictable [33]. The presence of neurological symptoms is estimated in approximately 8.5 to 70% of patients diagnosed with pSS. The presence of multiple comorbidities related to SS, including anxiety, depression and fibromyalgia, can influence the severity of the patient's symptoms and further complicate the evaluation process [22, 28].

The main symptoms are keratoconjunctivitis sicca and xerostomia along with arthritis, renal, hepatic and pulmonary involvement, chronic fatigue, musculoskeletal pain and vasculitis. Xerostomia leads to dental caries, chronic candidiasis and inflammation of the parotid glands. Keratoconjunctivitis can lead to corneal melting, uveitis, scleritis and optic neuritis. Other uncommon symptoms include anxiety, depression and fibromyalgia.

3.4 Diagnosis

pSS is diagnosed using the American-European consensus group (AECG) classification criteria, that include subjective symptoms and objective tests such as histopathology and serology [9]. The main criteria for the diagnosis of pSS are based on assessing symptoms of ocular and oral dryness, evaluating the secretory capacity of the exocrine glands, detection of anti-Ro and anti-La autoantibodies, and evaluation of minor salivary gland biopsies for mononuclear cell infiltration by biopsy [7, 21]. The formation of lymphomononuclear cell infiltrates that organize as periductal infiltrates in the salivary glands of patients with primary Sjogren's syndrome is one of the hallmarks of the disease [34]. In addition, saliva and tear fluid represent attractive means for diagnosis by proteomic analysis, as the collection of these samples is noninvasive, their composition is not complex, and the analysis can be easily repeated to monitor the disease over time [21]. Proper diagnosis of SS requires objective evidence of dry eyes and/or objective evidence of dry mouth, as well as proof of autoimmunity [24]. Diagnosis may take several years once symptoms manifest, as symptoms are often nonspecific and many patients lack diagnostic markers. There are currently no treatments available that address the underlying disease etiology [14, 23]. Although traditional methods of diagnosis and treatment of SS are effective, in the era of personalized medicine, new biomarkers and novel approaches are required for the detection and treatment of SS. Exosomes represent an emerging field in biomarker discovery and management of SS [16].

The classification criteria for diagnosis are by the AECG that include subjective symptoms and objective tests such as histopathology and serology. They are based on evaluating the symptoms of ocular and oral dryness, evaluating the secretory capacity of the exocrine glands, detection of anti-Ro and anti-La autoantibodies, and evaluation of salivary gland biopsies as an autoimmunity test.

3.5 Treatment

It is known that there are some treatments that can improve symptoms and prevent complications of SS, but there is currently no cure. However, the recent development of new therapeutic options for the management of various autoimmune diseases is promising for patients with SS [35]. Symptomatic treatments of SS are the only treatments available so far, there is no therapeutic treatment available to cure the disease. This could be due to the heterogeneity of the disease pathology. The goals of treatment remain palliation of symptoms, prevention of complications and for rheumatologists, appropriate selection of patients for immunosuppressive therapy [2, 24].

3.5.1 Steroid and Non-Steroid Therapy

In addition to topical treatment of mucosal dryness, patients with Sjogren's syndrome may require treatment with immunomodulatory agents and systemic immunosuppressants to manage a variety of extraglandular manifestations along with ocular testing to diagnose and monitor the syndrome more accurately [10, 36].

The treatment of pSS warrants an organ-based approach, for which local treatment (tears, moistures) and systemic therapy; including non-steroidal anti-inflammatory drugs, glucocorticoids, disease-modifying antirheumatic drugs and biologics [9].

Currently, there is a growing trend towards non-steroidal therapy for the treatment of autoimmune diseases. In real-world practice, as patients have severe systemic complications or organ damage, they will have a poor prognosis even if treated with high-dose steroids and potent immunosuppressive drugs. Mycophenolate is an immunosuppressive drug with minor side effects. Hydroxychloroquine is the best studied drug for Sjogren's syndrome [30].

Patients presenting chronic dry mouth should be screened by Schirmer's test, labial gland biopsy, and salivary gland emission computed tomography for possible Sjogren's syndrome, even if serologic autoantibodies are negative, to facilitate early intervention. Tacrolimus is a possible treatment option in steroid-intolerant patients [37].

3.5.2 Pilocarpine and Malic Acid

Pilocarpine remains the best performing sialogogue drug for subjects with xerostomia due to radiation in head and neck cancer or diseases such as Sjogren's syndrome. For patients with dry mouth, the use of malic acid is given, along with other elements that counteract the deleterious effect on tooth enamel. In general, lubrication of the oral mucosa reduces the symptoms, although the effects are short-lived [33].

3.5.3 Rituximab

Randomized trials targeting B cells with rituximab remain elusive in this condition, unlike other autoimmune diseases. It is evident from most trials that rituximab has a positive impact on B-cell numbers and activity in both the peripheral blood and salivary glands, but clinical results vary between studies. New strategies to target B cells in primary Sjogren's syndrome, including ianalumab and belimumab, are underway and are expected to produce clear treatment effects [38, 39]. Although there did not appear to be an excess risk due to rituximab, the results of the TRACTISS trial do not support

the widespread use of rituximab in the treatment of primary SS, particularly in patients with recent disease onset and/or low disease activity [40].

There is currently no cure, but symptoms can be improved and complications prevented with new therapeutic options that are palliation of symptoms, prevention of complications and appropriate selection of patients for immunosuppressive therapy. Examples of options are with immunomodulatory and systemic immunosuppressive agents; steroid and non-steroid therapies, mycophenolate, hydroxychloroquine, tacrolimus in steroid intolerant patients, pilocarpine and malic acid and finally rituximab.

4. Conclusions

The prevalence is between 1:100 and 2.2:1000 and affects more than 95% of women with a ratio of 9:1. Morbidity arises from renal involvement and extraglandular manifestations, including the development of non-Hodgkin's B-cell lymphomas. The main symptoms are keratoconjunctivitis sicca and xerostomia, together with arthritis, renal, hepatic and pulmonary involvement, chronic fatigue, musculoskeletal pain, and vasculitis. Diagnosis is by evaluation of ocular and oral dryness, exocrine gland secretory capacity, detection of anti-Ro and anti-La autoantibodies, and assessment of salivary gland biopsies. Currently there is no cure, but the most common treatments are immunomodulatory and systemic immunosuppressive agents, steroid and non-steroid therapies and tacrolimus in steroid intolerant patients.

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