

SJÖGREN'S SYNDROME: TRENDS IN DIAGNOSTICS AND TREATMENT FROM A DENTISTRY PERSPECTIVE

Sjögrenov syndróm: trendy v diagnostike a liečbe z hľadiska zubného lekárstva

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Abstract

In clinical practice, xerostomia or oral dryness associated with Sjögren's syndrome is a chronic condition encountered by most dentists, often causing a negative impact on the oral health-related quality of the patient. Xerostomia is caused due to salivary gland dysfunction. It is related to reduced salivary secretion or the absence of saliva flow, more frequently, exhibits qualitative changes in saliva proteins and immunoglobulin concentrations. There are several options for treatment and symptom management: salivary stimulants, topical agents, saliva substitutes, nerve stimulation and new developing methods. This review explores the current status of diagnostic and therapeutic management of patients affected by xerostomia with Sjögren's syndrome (Fig. 7, Ref. 27). Text in PDF www.lekarsky.herba.sk.

KEY WORDS: Sjögren's syndrome, xerostomia, hyposalivation, artificial saliva, neurostimulation.
Lek Obz 2025, 74 (2): 59-64

Abstrakt

V klinickej praxi je xerostómia alebo suchosť v ústach spojená so Sjögrenovým syndrómom chronickým chorobným stavom, s ktorým sa stretáva väčšina zubných lekárov a často má negatívny vplyv na kvalitu ústneho zdravia pacienta. Xerostómia je spôsobená dysfunkciou slinných žliaz. Súvisí so zníženou sekreáciou slín alebo absenciou prietoku slín, častejšie sa prejavuje kvalitatívnymi zmenami v koncentráciách slinných proteínov a imunoglobulínov. Existuje niekoľko možností liečby a manažmentu symptómov: stimulanty slín, lokálne látky, náhrady slín, nervová stimulácia a nové vyvíjajúce sa metódy. Tento prehľad skúma súčasný stav diagnostického a terapeutického manažmentu pacientov postihnutých xerostómiou pri Sjögrenovom syndrome (obr. 7, lit. 24). Text v PDF www.lekarsky.herba.sk.

KLÚČOVÉ SLOVÁ: Sjögrenov syndróm, xerostómia, hyposalivácia, umelé sliny, neurostimulácia.
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Introduction

Sjögren's syndrome (abbr. SSy) is a chronic inflammatory autoimmune disease of unknown origin that affects the exocrine glands. Symptoms of dry eyes and xerostomia are the hallmarks of the disease which may also present with various organ manifestations. An increased risk of oral and dental diseases is a prominent consequence of SSy due to the lack of saliva. Saliva is a key component in maintaining a balanced oral microbiome and it exerts a large variety of functions that help to promote oral health such as protection of the oral and peri-oral tissues by lubrication, dilution of sugars after food and drink intake, antimicrobial and cleansing activity, degrading some bacterial cell walls and inhibiting growth, buffering (neutralising) acid production and controlling plaque pH with bicarbonate, remineralisation of enamel with calcium and phosphates, and tissue re-

pair. The importance of the complex interaction between host, saliva and the oral microbiota becomes evident when the salivary flow is reduced, and the composition is altered, increasing the risk of associated oral diseases such as dental caries, gingivitis and oral fungal infections. Salivary components provide an important nutritional source for several microorganisms, and the complex interaction of many salivary inorganic and organic components is essential for the maintenance of a balanced and beneficial microbiota and for symbiosis.

Due to the wide range of signs and symptoms, patients with SSy may consult various healthcare practitioners, including rheumatologists, otorhinolaryngologists, dentists and ophthalmologists. Therefore, it is very important for doctors to be always informed and properly updated about current aspects of clinical manifestations of the disease, the classification criteria, proper diagno-

sis and current treatment options. Historically, the SSy has been classified as “primary” and “secondary” disease (17). The primary SSy syndrome occurs in the absence of another underlying disease while the secondary SSy occurs as a part of other autoimmune diseases. The secondary SSy co-exists especially with systemic lupus erythematosus (15–36%), rheumatoid arthritis (20–32%) as well as limited and systemic sclerosis (11–24%), less frequently with multiple sclerosis and autoimmune hepatitis and thyreoiditis (2).

Epidemiology

The heterogeneity of the available prevalence and incidence data for Sjögren’s syndrome is explained by differences in study design and classification criteria. The global incidence rates range between 3 and 11 cases per 100,000 patients, while the prevalence is around 0.01–0.72%. These figures are likely underestimated, since many asymptomatic patients may never be diagnosed. Regarding gender, it is much more frequent in women, with a ratio close to 10:1 (female: male). However, there are differences in its manifestation in men and women: severe ocular involvement predominates in men, while the manifestations and systemic involvement are much greater in women (26). The disease can occur at any age. The mean age at the time of first diagnosis of primary SSy is 56 years, with another peak occurring between 20 and 40 years. However, first symptoms may occur years before diagnosis. In children, the condition is much rarer, with a higher prevalence in girls (16).

Diagnostic evaluation. In patients who have experienced symptoms of dryness in the eyes or mouth more than three months, there are objective function tests (Schirmer’s test), serological tests (Anti-Ro/SSA), and histological examinations (salivary gland biopsy) available.

Clinical picture. The most frequently observed clinical manifestations are xerostomia in 80%, xerophthalmia in 70% and parotidomegaly in 30% of patients (1). In the oral cavity, viscous saliva can be observed at the salivary gland duct orifices (Fig. 1).

Figure 1. Viscous saliva on papilla parotidea (Source – own clinical material).

Obrázok 1. Viskózne sliny na papile parotidea (zdroj – vlastný klinický materiál).



Objective tests

Sialometry. Normal saliva production is about 900 ml within 24 hours. In Škach’s sialometry method, the patient first spits his / her saliva for 5 minutes into a calibrated glass cylinder without stimulation („peace“ saliva). The amount of the collected saliva is measured. Then the patient bites pieces of sterile wax for the next 5 minutes (stimulated saliva). Normal saliva production is 1 – 2 ml per min., hyposialia less than 0.7 ml per min., asialia unstimulated whole saliva flow rate ≤ 0.1 ml per min. Recently, sialometry is considered an approximate examination because of many influences on the saliva production. If repeated, it can provide more helpful information (21).

Imaging techniques. As a non-invasive method, *ultrasonography* of the major salivary glands is an integral part of daily clinical practice (5). *Parotid sialography* with contrast filling is invasive, and considered for an obsolete method, rarely used nowadays. *Salivary gland scintigraphy* with radioactive technecium lacks sufficient specificity but is helpful for functional evaluation including accumulation and expulsion of the ^{99m}Tc . Imaging findings of salivary gland involvement by SS are best demonstrated on *magnetic resonance imaging* for all major salivary glands, i. e. sublingual, submandibular and parotid (25) (Fig. 2-5)

Figure 2. Coronal MRI scan of initial stage of SS (Source – own clinical material).

Obrázok 2. Koronálny MRI sken počiatocného štádia SS (zdroj – vlastný klinický materiál).

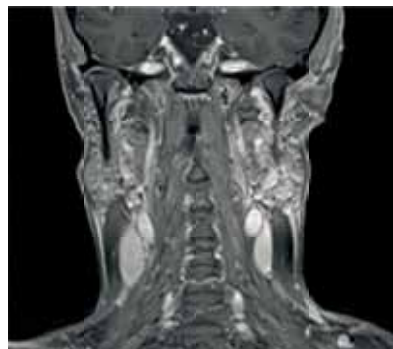


Figure 3. Coronal MRI scan of progressed stage of SS (Source – own clinical material).

Obrázok 3. Koronálny MRI sken progresívneho štádia SS (zdroj – vlastný klinický materiál).

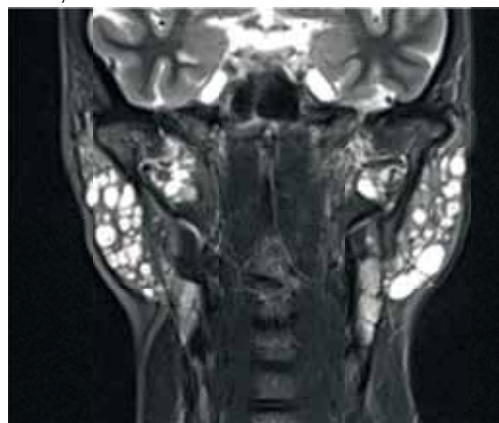


Figure 4. Axial MRI scan of initial stage of SS (Source – own clinical material).

Obrázok 4. Axiálny MRI sken počiatočného štádia SS (zdroj – vlastný klinický materiál).

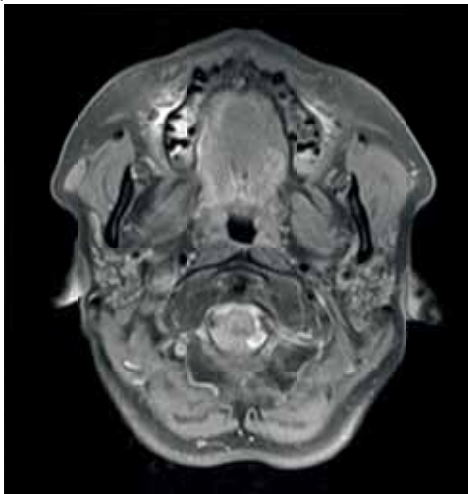
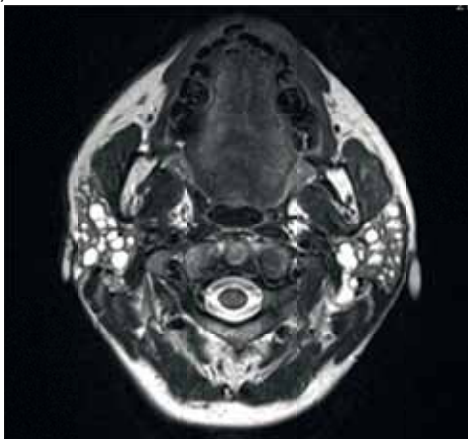


Figure 5. Axial MRI scan of progressed stage of SS (Source – own clinical material).

Obrázok 5. Axiálny MRI sken progresívneho štádia SS (zdroj – vlastný klinický materiál).



Histopathology. The histopathological features of salivary glands in the SS include parenchymal and ductal changes. A decrease or even disappearance of acini, lymphocyte infiltration and proliferation of the lining cells, and formation of myoepithelial cell islands can be observed. Lobular fibrosis, often ignored in the gland pathology, is also related to the severity of inflammation (6). Tissue specimens can be harvested intraorally from mucosa of the lower lip or from the parotid gland by transcutaneous approach (22). The classification criteria are fulfilled when a labial salivary gland exhibits focal lymphocytic sialadenitis with a focus score of ≥ 1 foci/4 mm² (12).

Laboratory testing. Immunofluorescence testing for antinuclear antibodies (ANA) is highly relevant for the diagnosis of connective tissue disorders. Up to 83% of patients with the primary SS test positive for ANA. In patients with positive ANA titers, a fine speckled fluorescence pattern is strongly indicative of anti-Ro/SSA and/or anti-La/SSB antibodies, which is revealed in ap-

proximately 40% to 75% and 23% to 52% of primary SS patients, respectively. Positive antibody titers correlate with early onset of the disease, more intense tissue infiltration, and higher prevalence of extraglandular manifestations. However, patients with other connective tissue disorders may also test positive for anti-Ro/SSA antibodies. Clinical image is crucial for differentiation of an overlapping disease. Other serological abnormalities include the presence of rheumatoid factors (60–75%) as well as polyclonal hypergammaglobulinemia as a sign of increased B cell activity (24).

SS as precancerosis

Conditions in SS are considered as precancerous due to oral mucosa and lymphoproliferative malignancies. Intraorally, missing the protective effect of saliva on hard and soft oral tissues can cause oral health problems such as dental caries (Fig. 6) and oral infections. Individuals with xerostomia often complain of problems with eating, speaking, swallowing and wearing dentures. Dry, hard food may be particularly difficult to chew and swallow. Denture wearers may have problems with denture retention, denture sores and the tongue sticking to the palate. Patients with xerostomia often complain of taste disorders (dysgeusia), a painful tongue (glossodynia) (Fig. 7) and an increased need to drink water, especially at night. Xerostomia can lead to significantly increased dental caries, parotid gland enlargement, inflammation and fissuring of the lips (cheilitis), inflammation or ulcers of the tongue and buccal mucosa, oral candidiasis, salivary gland infection (sialadenitis), halitosis and cracking and fissuring of the oral mucosa.

Patients with SS have a 20 to 40-fold risk of developing non-hodgkin lymphoma (abbr. NHL) compared to the general population. NHL has a prevalence of about 4% in SS patients and occurs classically following a median of 7.5 years after its initial diagnosis (7).

Figure 6. Root surface caries associated with xerostomia (Source nature.com).

Obrázok 6. Zubný kaz na povrchu koreňa spojený s xerostómiou (zdroj nature.com).



Treatment Trends in Dentistry Saliva Alternatives

One of the main symptoms of the SS is hyposalivation and xerostomia, caused by the targeting of the exocrine glands, including the salivary glands.

Figure 7. Dry tongue in patient with SSy (Source medicinetoday.com).

Obrázok 7. Suchý jazyk u pacienta so SSy (zdroj medicinetoday.com).



In the early stages of the disease, when salivary function is diminished but still present, salivary flow can be stimulated by the use of lozenges and chewing gums, systemic pharmacotherapy, or electrostimulation of the salivary glands. However, in case of an advanced disease process, when the salivary function is irreversibly impaired, saliva substitutes such as mouth sprays, gels, and mouthwashes can be used for the relief of the symptoms of xerostomia.

Saliva alternatives, otherwise called artificial saliva, basically function by moisturizing the weakened, dehydrated oral tissue. The biological and physical characteristics of artificial saliva must be similar to that of normal human saliva. The artificial saliva is usually a mix of buffering agents, cellulose derivatives, and flavouring agents. Saliva replacements are accessible in different forms such as liquids, sprays, gels, oils, mouthwash, chewing gums, and toothpaste. It provides a form of hydration that is important in securing oral tissues, speech functioning and the process of eating (8).

The stimulants for salivation are divided into topical and systemic agents. In the case of topical agents, the act of chewing alone enhances salivary production and could be supplemented with the use of xylitol, sorbitol (18). Chewing gums containing sorbitol after meal high in sugar is effective in normalizing pH. The foods or sweets enriched with citric acid may contribute to symptomatic comfort from xerostomia but the cariogenicity (or enamel erosions) have to be considered in dentate patients as citrate chelates calcium ions, potentially increasing caries activity (13).

Although not an ideal medical therapy, acupuncture has been found to be useful in enhancing salivary production. Clinical studies have shown the beneficial use of acupuncture in treating xerostomia and hyposalivation associated with SS (4, 20). Acupuncture can stimulate the parasympathetic and sympathetic nervous sys-

tems by neuronal activations. Additionally, acupuncture therapy produces the release of neuropeptides such as the vasodilator calcitonin gene-related peptide. These neuropeptides have anti-inflammatory properties and trophic effects on the salivary gland and increase the blood flow in the acini (27). Furthermore, it can directly affect the local blood flow in the proximity of the salivary gland, increasing the salivary secretion. Acupuncture may also activate neuronal circuit that activates the salivary nuclei in the pons, subsequently influencing salivary glands via the cranial nerves.

The use of systemic agents has been found effective in producing salivary production and flow, of which pilocarpine HCl has made promising clinical results. Pilocarpine is a cholinomimetic drug with mild β -adrenergic actions. Clinical trials have showed that Pilocarpine in doses of 5–10 mg 3–4 times daily could minimize the signs of xerostomia and produce more saliva. However, there have been reports of certain adverse effects such as diaphoresis, flushing, and polyuria. It is contraindicated in patients with uncontrolled asthma, narrow-angle glaucoma, or acute iritis. Precautionary measures need to be followed in patients with blood disorders and cardiovascular diseases (15). Another cholinomimetic drugs, such as cevimeline HCl, have been tested and proven clinically effective, and daily intake of 30 mg of cevimeline has shown remarkable clinical results in improving the salivary flow and production in patients with the SS. Cevimeline has a more selective affinity for M3 subtype muscarinic receptors, and this drug has been widely used in patients experiencing post radiation xerostomia (3). Anetholetrithione, originally used to increase the bile output, is another agent that improves salivation in patients experiencing minor salivary dysfunction, (9). Lastly, interferon (genetically modified protein), either in injectable form at high doses or natural interferon in the form of lozanges, has also been proven successful in the increase of salivary production and flow rate, while modifying the immunomodulatory action in the SS patients.

Electrical Nerve Stimulation

Electrical nerve stimulation (abbr. ENS) is a non-invasive peripheral stimulation technique used to relieve pain and stimulate saliva production. This method employs transcutaneous or intraoral devices. **During the transcutaneous ENS**, pulsed electrical currents are delivered across the intact surface of the skin to activate underlying nerves. Maximum efficacy effect occurs when ENS generates a strong but non-painful electrical paraesthesia beneath the electrodes. The effect is generally rapid in onset and offset, so patients are encouraged to administer ENS as needed throughout the day. The transcutaneous ENS is divided into three techniques: conventional (low-intensity, high-frequency), acupuncture-like (high-intensity, low-frequency) and intense (high-intensity, high-frequency).

The application of electric current through the oral mucosa to the afferent neuronal pathway causes neuro-

electrical stimulation of the salivary glands, which has been reported to increase the production of saliva and reduce symptoms of xerostomia. In this method, electrodes are placed over the parotid gland, enhancing parotid flow and volume of saliva, stimulating directly the auriculotemporal nerve (efferent pathway) that supplies the secretomotor drive to the parotid gland (10). The ENS works directly on parotid gland, stimulating salivary secretion arc. This neuronal mechanism has three basic components: afferent receptors and nerves which carry impulses generated by masticatory and gustatory actions, a central connecting and processing center (salivatory nucleus), and an efferent neuronal pathway consisting of parasympathetic and sympathetic nerve bundles that separately but in a coordinated manner innervate the blood vessels and acini of their target glands leading to regulation of salivary secretion. The afferent nerves carry impulses from the periphery to the salivary nuclei (salivation center) in the medulla oblongata, which in turn directs signals to the efferent part of the reflex arch, leading to initiation of salivation. The greatest advantage of this technique over other sialogogues is the almost complete absence of any lasting local or systemic side effects. Its main disadvantage is the placement of the extraoral device, which is often impractical and unsuitable for patients (11). ENS, as a treatment technique, is a non-invasive technique with fewer side effects when compared with conventional drug therapy, with the most common complaints being an allergic-type of skin reaction. Digital ENS machines are becoming more widely available, featuring automated frequency sweeps and more complex stimulation patterns. Although still in its developing stage, this method could prove critical in the moderation of symptoms of hyposalivation and xerostomia experienced by patients with SS.

Another treatment approach is the use of **intraoral electro-stimulators**, which produce salivation by applying reduced electronic flow levels to the oral mucosa. Continuous use increases the efficiency of neural stimulations and salivary flow. They can either be a replaceable mouthguard-like device or fixed to a dental implant. Salivary pacemakers have been recently tried to improve salivation and indirectly minimize the long-term effects of oral dryness. Devices such as the Salitron system (Biosonics Inc, USA), GenNarino, SaliPen, and Saliwell Crown (implant-supported device) have shown effectiveness in increasing salivation in xerostomia patients. A modern technique, known as intensity-modulated radiotherapy, has been found to be beneficial in minimizing oral dryness in postradiation xerostomia.

Neuroelectrostimulation to increase salivary secretion led to the development of a device that was marketed in the USA. The first-generation neuroelectrostimulation device consisted of a hand-held probe tipped with stainless steel electrodes and a console that housed a battery and the electronic signal-generating power source, which was similar in size and shape to a video or CD player. The probe was applied to the intra-oral

mucosal surfaces by the user (between the dorsum of the tongue and palate) for a few minutes each day, delivering a stimulating signal to sensitive neurons in the mouth to induce salivation. The second-generation salivary neuroelectrostimulator is a removable intraoral appliance produced for individual patients by using their teeth pattern molds. It is similar to a mouthguard used to treat temporomandibular joint disorders and bruxism. It has a horseshoe-like shape and fits on the lower dentition. It is designed for easy insertion and removal by the patient (23). The electronic components are embedded within the appliance to allow safe and contamination-free intraoral application. A remote control permits the patient to communicate with the device and modify its functions (11).

Third-generation implant-supported neuroelectrostimulating device can be permanently applied in the oral cavity as it can be screwed onto an osteo-integrated dental implant inserted in the third molar area. It is intended for patients requiring frequent or constant stimulation. Use of this dental implant-based neuroelectrostimulator avoids the inconvenience associated with the repeated application and removal of a splint-based stimulator. The components of the second-generation device have been miniaturized and reconfigured into a unit that has the dimensions and shape of a molar tooth. This device can be mounted onto a commercially available osseointegrated implant (19). A wetness sensor has been embedded into the device to detect changes in oral wetness/dryness. The osseointegrated implant is positioned in the region of the lower third molar (wisdom tooth) to ensure close proximity to the lingual nerve that carries both afferent and efferent salivary impulses, and to avoid interference with normal oral function.

Surgical Treatment of SS

Two surgical options are available. *Ligation of Stensen's duct*, performed under local anaesthesia, aims to prevent the ascendant infection into the parotid gland. In the recurrent parotitis, refractory to medical management or in case of suspicion for salivary gland malignancy, *conservative parotidectomy* under general anaesthesia is indicated (14).

Conclusions

Saliva is extremely important in the functioning and health of the oral cavity. Alterations in its quantity or quality are associated with complications that increase suffering and lead to many diseases. Dentists play a crucial role in helping diminish xerostomia symptoms and improving the quality of life for patients affected by it. Artificial salivary agents or saliva-stimulating agents have been found to be beneficial in reducing the subjective symptoms associated with xerostomia. Another approach, transcutaneous electrical stimulation, provides a safer, nonpharmacological therapeutic option for treating patients with xerostomia in cases where systemic drug therapy is contraindicated, or found to be associated with severe side effects. New developments

and trends are becoming available as the scientific approach becomes more methodical and more studies are conducted. The management of a patient with SS is complicated and demanding. The alleviation of symptoms and improvement of quality of life requires the cooperation of different medical specialists, making it more demanding.*

* The authors declare that the study was conducted in accordance with the ethical standards of the 1975 Helsinki Declaration, revised in 2000.

Conflict of interest: the authors declare that they have no conflict of interest.

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Accepted for publication: 16. 12. 2024.

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