People's Democratic Republic of Algeria
وزارة التعليم العالي والبحث العلمي
Ministry of higher Education and Scientific Research
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Thesis

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In partial fulfillment of the requirement for the

Master's degree

Food Sciences

Option

Nutrition & Pathology

BOUABDELLAH Rayane

Diploma of MASTER

Food Sciences

Option Nutrition & Pathology

Theme

INFLUENCE OF DIETARY BEHAVIOUR, ANTHROPOMETRIC PARAMETERS AND PHYSICAL ACTIVITY ON GOUGEROT-SJÖGREN'S SYNDROME: A CASE-CONTROL STUDY

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Academic year 2024 - 2025

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Introduction

Autoimmune diseases represent an increasing challenge for modern medicine. Among them, Sjögren's Syndrome (SS), also known as "dry syndrome," stands out due to its underestimated prevalence and the multiple repercussions it has on patients' daily lives. Although rarely highlighted in the media, this autoimmune condition profoundly affects the physical and psychological well-being of those who suffer from it (Jones, 2018). This syndrome, characterised by excessive dryness of mucous membranes, particularly of the eyes and mouth, may occur in isolation or as part of complex autoimmune pathologies (Kumar et al., 2019).

Beyond daily discomfort, SS can lead to severe complications, including vision impairment, swallowing difficulties, oral and dental issues, and in advanced forms, the involvement of internal organs (Perez et al., 2017). While immune and genetic mechanisms are largely implicated in its pathophysiology, many recent studies have highlighted the influence of environmental and behavioural factors in its onset and worsening (Taylor et al., 2016; Davis et al., 2021). Thus, modern dietary habits—rich in additives, nanoparticles, and ultra-processed foods—are suspected of exacerbating symptoms. Conversely, diets rich in antioxidants, omega-3, and polyphenols may offer a protective effect (Nguyen et al., 2020). Recent studies also suggest that the quality of drinking water may play a role in the genesis of this condition (Liu et al., 2020).

Furthermore, exposure to certain chemical pollutants, notably present in cosmetics, toothpastes, perfumes, or some occupational environments, is also considered an aggravating factor (Chen et al., 2018). It should also be noted that lifestyle plays a crucial role; indeed, physical inactivity, associated with chronic inflammation, may worsen the symptoms, while regular physical activity is beneficial by promoting blood circulation and immune homeostasis (Wang et al., 2020). Chronic stress and sleep quality are also identified as factors that negatively influence the progression of SS (Robinson et al., 2019).

The aim of this study is to carry out a case-control investigation involving a population of patients with SS compared to healthy controls, targeting the following objectives:

- ✓ Epidemiological characterisation of the study population
- ✓ Evaluation of dietary frequency
- ✓ Investigation of risk factors associated with SS
- ✓ Exploration of blood markers (biochemical, immunological, and haematological)

1. Overview of autoimmune diseases

Autoimmune diseases represent a group of chronic conditions characterised by dysfunction of the immune system.

The immune system, which is normally responsible for defending the body against pathogens, becomes unable to distinguish between "self" and "non-self," and thus attacks the individual's own cells and tissues (Rose & Bona, 1993).

Two main categories are generally distinguished:

- ✓ Organ-specific autoimmune diseases, which target a single organ or tissue (e.g., type 1 diabetes, Hashimoto's thyroiditis).
- ✓ Systemic autoimmune diseases, which affect multiple organs and systems, such as systemic lupus erythematosus or Sjögren's Syndrome (SS).

These conditions are multifactorial in origin. Their development results from a complex interaction between:

- ✓ Genetic factors (HLA gene polymorphisms, immune regulation mutations);
- ✓ Environmental factors (viral infections, toxins, oxidative stress);
- ✓ Hormonal factors, which partly explain their higher prevalence among women (Fairweather & Rose, 2004).

The prevalence of autoimmune diseases is steadily increasing worldwide, affecting approximately 5 to 8% of the population, with significant repercussions on quality of life, mental health, and patients' functional abilities.

Among these diseases, Sjögren's Syndrome (SS) stands out due to the predominance of exocrine manifestations, particularly ocular and oral dryness, but it may also present with systemic complications and associated autoimmune conditions (Table 1)

1. Le syndrome de Gougerot-Sjögren (SGS)

Sjögren's Syndrome (SGS) is a chronic systemic autoimmune disease characterised by lymphocytic infiltration of exocrine glands, primarily the salivary and lacrimal glands, leading to xerostomia (dry mouth) and xerophthalmia (dry eyes) (Fox et al., 2005).

Two forms of SS exist:

• Primary SS, occurring in isolation

• Secondary SS, associated with other autoimmune diseases such as rheumatoid arthritis, lupus, or scleroderma.

The syndrome predominantly affects women (in nearly 90% of cases), particularly between the ages of 40 and 60. Its origin is multifactorial, involving genetic, hormonal, environmental

Table 1: Comparative table of autoimmune diseases (Theofilopoulos, et al., 2017).

Organ-Specific Autoimmune Diseases	Non-Organ-Specific Autoimmune Diseases (Systemic)
Endocrin glands - Thyroiditis: Hashimoto's disease, Graves' disease - Addison's disease - Type 1 diabetes - Other autoimmune endocrinopathies	**Connective tissue diseases** - Rheumatoid arthritis - Systemic lupus erythematosus - Systemic sclerosis (scleroderma) - Sjögren's Syndrome - Inflammatory myopathies - Mixed connective tissue disease
Liver and digestive tract - Autoimmune hepatitis - Primary biliary cirrhosis - Pernicious anaemia - Coeliac disease	Primary vasculitides - Giant cell arteritis - Takayasu arteritis - Kawasaki disease - Polyarteritis nodosa - Granulomatosis with polyangiitis (Wegener's) - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) - Microscopic polyangiitis - IgA vasculitis - Anti-GBM disease (Goodpasture's syndrome) - Behçet's disease
Nervous system - Myasthenia gravis - Lambert-Eaton myasthenic syndrome - Guillain-Barré syndrome - Multiple sclerosis	- Relapsing polychondritis - Antiphospholipid syndrome

factors (viral infections, exposure to certain toxins), and immune system imbalances leading to auto-reactivity (Mariette & Criswell, 2008).

2. **Immunological Findings:**

• Hypergammaglobulinaemia

• Presence of specific autoantibodies: anti-SSA/Ro and anti-SSB/La

• Sometimes positive rheumatoid factor and antinuclear antibodies (ANA)

Although the diagnosis of SS relies on a combination of clinical, biological, and histological criteria (ACR/EULAR criteria), its progression can be insidious with highly variable manifestations among patients.

3. **Beyond dryness symptoms, SS may lead to:**

• Joint pain

• Severe chronic fatigue

• Pulmonary, renal, or neurological involvement

• Increased risk of lymphoma

Thus, dry syndrome represents a clinical challenge, not only because of its multiple manifestations but also due to the absence of a specific curative treatment. Management is multidisciplinary, aiming to alleviate symptoms, prevent complications, and improve patients' quality of life.

4. **Clinical Manifestations**

SGS presents a wide range of clinical signs, which may be glandular (exocrine) or extraglandular (systemic). The most characteristic symptoms are related to mucosal dryness, but other systems may also be affected.

5. **Ocular Dryness (Xerophthalmia)**

Ocular dryness is one of the most common symptoms. It manifests as a sensation of grit in the eyes, burning, tingling, or even blurred vision. It can lead to dry keratoconjunctivitis with a risk of corneal ulceration or infection if untreated (Fox, 2005).

6. **1.1.2. Oral Dryness (Xerostomia)**

Xerostomia presents as persistent dry mouth, difficulties in chewing, swallowing, or speaking, and altered taste. It increases the risk of dental caries, gingivitis, oral thrush, and can impair patients' nutritional status.

7. **Histological Aspects of Salivary Glands:**

Observation of healthy salivary glands shows well-organised acini, clearly defined intercalated ducts, intact glandular architecture, and absence of infiltrates.

Salivary glands affected by SS show structured lymphocytic infiltrates (focus score), acinar atrophy, fibrosis, and ductal dilatation, corresponding to histopathological diagnostic criteria. These lesions explain xerostomia and glandular dysfunction in patients (Figure 2) (Van Ginkel et al., 2023; Erkılınç et al., 2021; Li et al., 2021; Gutierrez et al., 2018).

8. Other Forms of Dryness:

SS may also cause dryness in:

• Nasal passages (crusting, bleeding)

• Pharyngeal and laryngeal areas (hoarseness, dry cough)

• Skin (dryness, itching)

• Vaginal area in women (leading to dyspareunia)

• Digestive tract (digestive disorders and constipation)

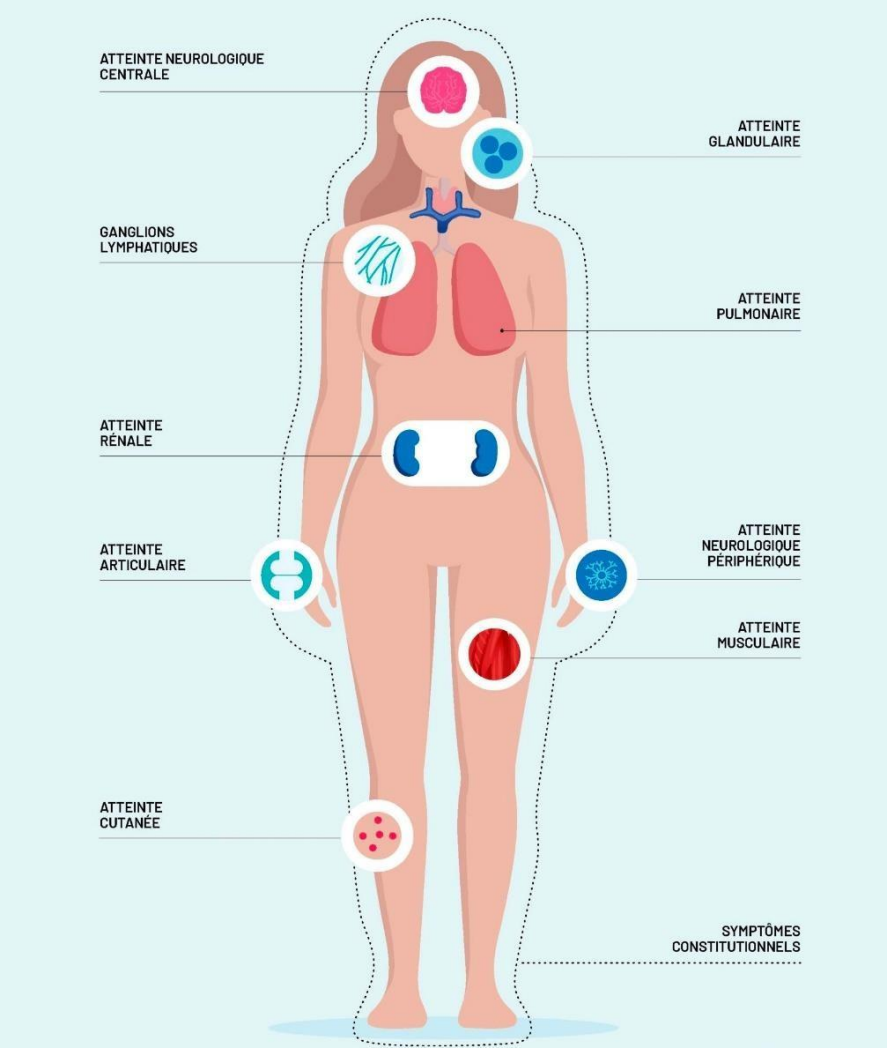
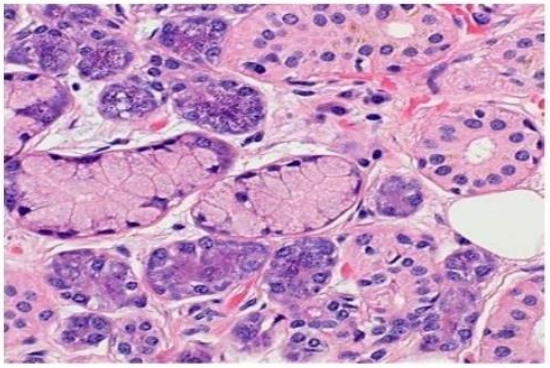
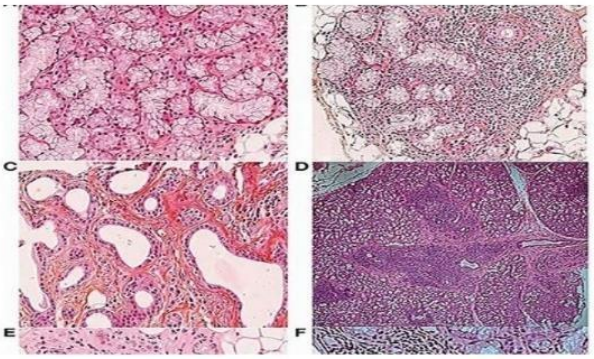


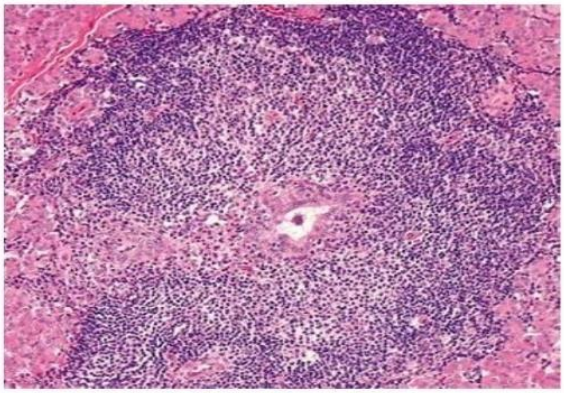
Figure 1. The symptoms of GSS The different locations of GSS in humans (Lodba et al., 2024

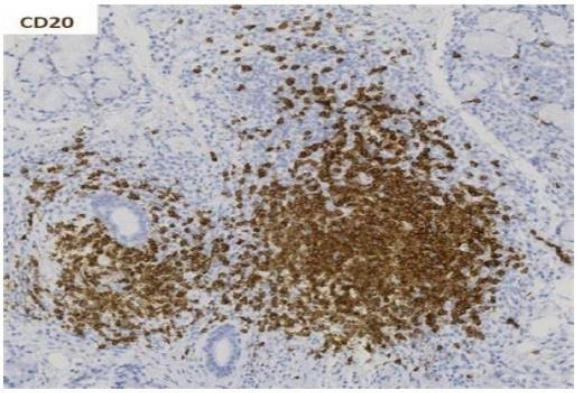


Glande salivaire saine : acini bien organisés, canaux intercalaires clairement définis, architecture glandulaire intacte et bien préservée, absence d'infiltrat.

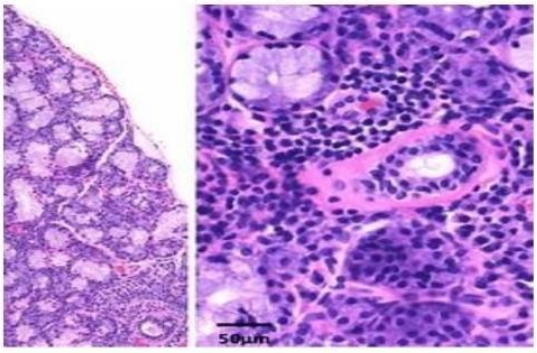


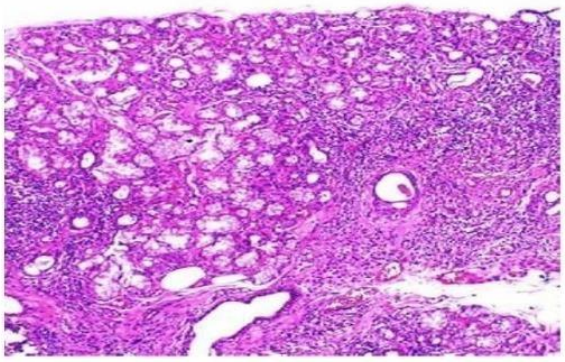
Atteinte modérée (focus score 1) : présence d'un infiltrat lymphocytaire discret autour des acini, début de destruction glandulaire. Infiltration lymphocytaire, fibrose, atrophie acinaire





Infiltration lymphocytaire focale prononcée : accumulation dense de lymphocytes parfois en follicules près des canaux, caractéristique du SGS.
Immuno-coloration CD20 montrant l'accumulation de lymphocytes B dans les foyers





Infiltration péri-canalaire importante : focus lymphocytaires autour des conduits, avec au moins 50 lymphocytes par 4 mm², critère diagnostique du SGS.
Infiltrat lymphoplasmocytaire diffus avec formation de foyers (focus score élevé).

Figure 2 : Aspect histologiques des glandes salivaires saines à celles atteintes de SGS (Van Ginkel et al., 2023 ; Erkılınç et al., 2021; Li et al., 2021 ; Gutierrez et al., 2018)

9. Diagnosis and Classification Criteria (ACR/EULAR)

The diagnosis of SS is based on a combination of clinical, biological, ophthalmological, and histopathological criteria. In 2016, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) proposed standardised classification criteria to improve diagnostic reliability, especially in clinical studies.

The system is based on a weighted score from five key elements. A diagnosis of SS can be made when a total score of ≥ 4 is reached.

Criteria and Their Weighting: • Labial salivary gland biopsy with focal lymphocytic infiltration ≥ 1 focus/4 mm²: 3 points • Presence of anti-SSA/Ro antibodies: 3 points • Schirmer's test ≤ 5 mm/5 min (indicating lacrimal hyposecretion): 1 point • Positive corneal staining with fluorescein or lissamine green: 1 point • Unstimulated salivary flow ≤ 0.1 ml/min: 1 point

Other clinical signs (xerostomia, xerophthalmia) are not scored but should prompt further investigations (Table 2).

Table 2: ACR/EULAR 2016 Classification Criteria for SS (Shiboski et al., 2017)

Criteria	Score
Labial salivary gland biopsy with focus score ≥ 1	3
Presence of anti-SSA/Ro antibodies	3
Schirmer's test ≤ 5 mm/5 min	1
Positive corneal staining (fluorescein or lissamine green)	1
Unstimulated salivary flow ≤ 0.1 ml/min	1

Common Additional Examinations: • Autoantibody testing (anti-SSA/Ro, anti-SSB/La, ANA, rheumatoid factor) • Labial salivary gland biopsy (lower lip) • Ophthalmological tests (Schirmer, Break-up Time, conjunctival staining) • Imaging (sialography, salivary gland ultrasound)

10. Complications

Although initially localised to the exocrine glands, SS can progress to systemic forms and lead to multiple complications. These vary depending on the duration of the disease, symptom severity, and individual immune response.

Mild Complications: • Recurrent dental caries due to xerostomia • Oral infections such as thrush • Eye irritation, mild keratoconjunctivitis • Chronic fatigue, often disabling but without organ involvement

Moderate Complications: • Articular involvement: non-erosive inflammatory joint pain • Cutaneous involvement: purpura, chronic urticaria • Mild pulmonary involvement: dry cough, chronic bronchitis • Mild peripheral neuropathies

Severe Complications: • Diffuse pulmonary involvement: interstitial pneumonia, fibrosis • Renal involvement: chronic interstitial nephritis, tubular acidosis • Central neuropathies: myelitis, central nervous system involvement • Systemic vasculitis: inflammation of small vessels • Risk of non-Hodgkin lymphoma, especially MALT lymphoma, with a 15 to 20-fold increased risk compared to the general population

11. Associated Conditions

SS is not limited to isolated involvement of exocrine glands. It can coexist with other autoimmune diseases, complicating diagnosis and management. In its so-called "secondary" form, the syndrome appears alongside another well-identified autoimmune disease.

The most frequently associated diseases are:

- ✓ Rheumatoid arthritis
- ✓ Systemic lupus erythematosus
- ✓ Systemic sclerosis
- ✓ Hashimoto’s thyroiditis
- ✓ Primary biliary cirrhosis
- ✓ Coeliac disease

These associations can worsen clinical manifestations and lead to additional complications, such as more pronounced joint involvement, skin disorders, or multivisceral involvement. The presence of these associated pathologies justifies enhanced monitoring and a multidisciplinary therapeutic approach.

12. Therapeutic Approaches

The treatment of SS is essentially symptomatic, as there is currently no specific curative treatment. The therapeutic approach must be tailored to each patient, considering symptom severity, complications, and associated conditions. It combines classical medical treatments

with complementary strategies aimed at improving quality of life (Mariette & Criswell, 2018) (Table 3).

Table 1 : The Medical Treatment of Sjögren's Syndrome (Ramos-Casals et al., 2020)

Medical Treatment	International Practice	In Algeria
Lacrimal Substitutes	Artificial tears (e.g., Restasis, Xiidra) widely available in many countries to treat ocular dryness.	Artificial tears are available, but some branded medications may not always be accessible; preference for generics.
Oral Hydration	Use of saliva substitutes (e.g., Salivaire, Xero-Lube).	Similar products available but often more limited, with preference for more accessible local solutions.
Systemic Anti-inflammatories	NSAIDs like ibuprofen and corticosteroids are used to reduce inflammation. Immunosuppressants like cyclophosphamide and methotrexate are used for severe cases.	Similar use of NSAIDs, but access to immunosuppressants and specific treatments may be limited due to cost or availability.
Immunosuppressors (e.g., methotrexate, cyclophosphamide)	Used in severe or refractory cases. Rituximab, a monoclonal antibody, is sometimes used in resistant forms.	Methotrexate and other immunosuppressants are available but less frequently used due to less developed protocols and limited availability of specialised drugs (such as rituximab).

Analgesics and Pain Relievers	Medications like paracetamol and opioids are used to manage pain. Topical analgesics such as gels are common.	Common use of basic analgesics like paracetamol. Access to opioids and stronger painkillers is regulated and limited.
Hormonal Treatments	Oestrogens or other hormonal therapies are sometimes used, especially in menopausal women to alleviate dryness.	Hormonal treatment is available but less commonly used due to reluctance in some local medical practices.
Biological Therapies	Rituximab (a monoclonal antibody) is used to treat severe and refractory forms of the syndrome.	The use of biological therapies is still limited in Algeria, mainly due to costs and restricted availability of treatments like rituximab.

13. Complementary Approach: Nutritional Therapy

Nutritional therapy is not a specific treatment for SS, but it can represent a useful complementary strategy. An anti-inflammatory diet, such as the Mediterranean diet, rich in omega-3s, antioxidants, polyphenols, vitamins, and minerals, may help modulate inflammation and improve certain symptoms, particularly chronic fatigue.

Regular consumption of oily fish, vegetable oils, green vegetables, berries, and seeds is recommended. Several studies highlight that this type of diet may have a positive impact on autoimmune diseases by reducing oxidative stress and promoting immune balance (Duarte et al., 2021).

14. Risk Factors and Etiopathogenesis

SS is a multifactorial disease resulting from the interaction of various factors: genetic, environmental, nutritional, behavioural, and hormonal. These elements influence not only the onset of the disease but also its progression and the severity of clinical manifestations (Lessard et al., 2013).

15. Dietary Patterns

Diet plays an important role in modulating the immune response. Diets high in refined sugars, trans fats, and ultra-processed foods promote a state of chronic inflammation. In contrast, a diet rich in antioxidants, omega-3s, fibre, polyphenols, and vitamins, such as the Mediterranean diet, appears to have beneficial effects in autoimmune diseases by reducing oxidative stress and rebalancing the immune response (Duarte et al., 2021).

16. Salt Intake

Excessive salt consumption may activate Th17 lymphocytes, thereby promoting the production of pro-inflammatory cytokines such as IL-17, which are known to be involved in several autoimmune diseases. This mechanism may contribute to the worsening of inflammation in dry syndrome (Wu et al., 2013).

17. Other Factors

Certain food additives, nanoparticles, artificial sweeteners, or preservatives can disrupt the intestinal barrier and microbiota. These alterations may induce dysbiosis, leading to inappropriate immune activation that could favour the development of autoimmune conditions (Lerner et al., 2017).

18. Lifestyle: Sedentariness and Physical Activity

Sedentariness is associated with low-grade inflammation, reduced lymphatic circulation, and worsening of symptoms. Conversely, regular physical activity helps improve quality of life, regulate stress, stimulate natural defences, and reduce inflammatory markers (Wang et al., 2020).

19. Smoking

Active or passive smoking is recognised as an aggravating factor of dry syndrome. It contributes to mucosal dryness, alters the structure of salivary glands, and exacerbates local inflammation, which can worsen ocular and oral symptoms (Vitali et al., 2012).

20. Exposure to Pesticides and Others

Long-term exposure to pesticides, industrial solvents, or chemicals found in certain cosmetics or household products may induce an abnormal autoimmune response. These substances act via epigenetic or immunotoxic mechanisms that disrupt immune balance (Yoshida et al., 2022).

21. Polypharmacy and Iatrogenic Effects

Certain commonly used medications, such as tricyclic antidepressants, antihistamines, beta-blockers, or diuretics, may cause dry mouth or eyes. These side effects can mimic or worsen the symptoms of dry syndrome, making diagnosis more complex (Navazesh & Kumar, 2009).

22. Hormonal Treatments

Hormonal changes, notably the decrease in oestrogens after menopause, seem to play an important role in the onset or worsening of SS. Oestrogens influence the immune response, and their decline may favour autoimmunity. Hormone replacement therapy can alleviate certain symptoms, although its use remains controversial (Bianchi et al., 2021).

polyphenols, and fibres warrant evaluation through rigorous clinical trials to confirm their benefits in SS.

Adapted physical activity: The impact of tailored physical activity on immune modulation and fatigue in SS remains underexplored and justifies larger-scale intervention studies.

Psychological dimensions: Taking into account psychological aspects such as anxiety, depression, and sleep quality could enrich patient-centred therapeutic approaches, fostering overall well-being.

Biotherapies and personalised medicine: Emerging immunomodulatory biotherapies and the integration of artificial intelligence in healthcare could, in the medium term, revolutionise SS management by offering more precise and predictive therapeutic strategies.

In summary, the results of our study emphasise the need for a holistic, multidimensional approach to SS management, placing the patient at the heart of care pathways while integrating ongoing scientific and technological advances. These perspectives herald significant progress in the understanding, diagnosis, and management of Sjögren's syndrome in the coming years.

الملخص

مرضاً مناعياً ذاتياً مزمناً يصيب الغدد خارجية الإفراز، وخاصة الغدد اللعابية والدمعية، مما (SGS) يُعدّ متلازمة جوغرن شوغرن يؤدي إلى جفاف الفم والعينين. بالإضافة إلى الأعراض الغددية، قد تترافق هذه المتلازمة مع مظاهر جهازية متنوعة تشمل إصابة المفاصل والرئتين والجهاز الدموي، فضلًا عن زيادة خطر الإصابة باللمفومة. يهدف هذا العمل إلى تقييم تأثير السلوكيات الغذائية .والمعايير الأنثروبومترية والنشاط البدني على متلازمة جوغرن شوغرن من خلال دراسة حالة-شاهد

(متوسط العمر: 58.73 ± 5.64 سنة) و40 شخصاً سليماً (متوسط SGS شملت الدراسة 154 مشاركاً، منهم 114 مريضاً مصاباً بـ وحدة 6.67 ± 10.35) يمارسون نشاطاً بدنياً أقل بشكل ملحوظ SGS العمر: 54.58 ± 11.97 سنة). أظهرت النتائج أن مرضى من الناحية الغذائية، كان استهلاك .(p<0.001) (الأسبوع/MET وحدة 4.36 ± 41.60) مقارنة بالشواهد (الأسبوع/MET المرضى للفواكه والخضروات أقل (5.82 ± 2.00 مرات/الأسبوع) بينما كان استهلاكهم للمنتجات السكرية والمصنعة أعلى (3.45 كان متوسط :SGS ± 2.78 مرات/الأسبوع). كما أظهرت المؤشرات البيولوجية زيادة ملحوظة في مؤشرات الالتهاب لدى مرضى ، وبلغت سرعة ترسيب (p<0.01) ملغ/لتر مقابل 2.4 ± 0.0 ملغ/لتر لدى الشواهد 11.20 ± 12.17 (CRP) التفاعلي C بروتين .(p<0.001) كريات الدم الحمراء 54.00 ± 20.93 مم/ساعة مقارنة بـ 11.0 ± 1.41 مم/ساعة

يرتبط بنمط حياة خامل وعادات غذائية مؤيدة للالتهاب واستجابة مناعية التهابية مفرطة. يمكن أن تساهم SGS تؤكد هذه النتائج أن مقاربة شاملة تجمع بين التغذية المضادة للالتهاب والنشاط البدني المناسب والمتابعة الطبية الدقيقة في تحسين جودة حياة المرضى .والحد من المضاعفات الجهازية

، لكلمات المفتاحية : (CRP) التفاعلي C متلازمة جوغرن شوغرن، الالتهاب، التغذية، النشاط البدني، دراسة حالة-شاهد، بروتين ا VS) سرعة ترسيب كريات الدم

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Résumé

Le syndrome de Gougerot-Sjögren est une maladie auto-immune systémique chronique, caractérisée principalement par une atteinte des glandes exocrines, provoquant une sécheresse des muqueuses oculaires, buccales et génitales. Cette pathologie, majoritairement féminine, peut évoluer vers des formes systémiques sévères avec des complications multiviscérales.

Ce travail vise à explorer l'impact de certains facteurs comportementaux et environnementaux — notamment le régime alimentaire, l'activité physique, la sédentarité, le tabagisme et l'exposition aux substances toxiques — sur l'apparition, l'évolution et la sévérité du syndrome sec.

Une étude cas-témoins a été menée à l'aide de questionnaires structurés permettant de recueillir des données cliniques, alimentaires et comportementales auprès de patient(e)s atteints du syndrome de Gougerot-Sjögren et d'un groupe témoin. L'analyse statistique a permis d'identifier certains profils de risque et de suggérer des pistes de prévention.

Les résultats mettent en évidence une association entre certains comportements nutritionnels, une faible activité physique et une intensité accrue des symptômes. Ils soulignent également l'intérêt d'une prise en charge globale intégrant les dimensions médicales, nutritionnelles et hygiéno-diététiques.

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Abstract

Sjögren's syndrome is a chronic systemic autoimmune disease primarily characterized by dysfunction of the exocrine glands, leading to dryness of the eyes, mouth, and other mucous membranes. Predominantly affecting women, it may progress to systemic complications involving multiple organs.

This study aims to explore the influence of lifestyle and environmental factors—specifically diet, physical activity, sedentary behavior, tobacco use, and exposure to chemical substances—on the onset, progression, and severity of the disease.

A case-control study was conducted using structured questionnaires to collect clinical, nutritional, and behavioral data from patients diagnosed with Sjögren's syndrome and a matched control group. Statistical analyses were used to identify potential risk profiles and propose preventive strategies.

The results reveal a correlation between certain dietary patterns, low levels of physical activity, and the severity of symptoms. These findings highlight the importance of a comprehensive approach to care, incorporating medical, nutritional, and lifestyle components to improve patient outcomes.

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BIBLIOGRAPHIC REFERENCES

- Ansari, N., & Salesi, M. (2024). The association between primary Sjögren's syndrome and non-Hodgkin's lymphoma: A systematic review and meta-analysis of cohort studies. Clinical Rheumatology, 43(7), 2177–2186. https://doi.org/10.1007/s10067-024-06993-6
- Baer, A. N., Walitt, B., Pettinger, M., McGowan, J., & Parks, C. G. (2018). Anemia and its association with interstitial lung disease and other clinical features in primary Sjögren's syndrome. Clinical Rheumatology, 37(7), 1925–1931. https://doi.org/10.1007/s10067-018-4114-4
- Baer, A. N., et al. (2023). Update on Sjögren's syndrome and emerging therapeutic targets. Nature Reviews Rheumatology, 19, 243–259.
- Baldini, C., Chatzis, L. G., & Fulvio, G. (2024). Pathogenesis of Sjögren's disease: One year in review 2024. Clinical and Experimental Rheumatology.
- Bianchi, V. E., Herrera, P. F., & Laura, R. (2021). Effect of estrogen replacement on autoimmune diseases in postmenopausal women. Frontiers in Endocrinology, 12, 653889.
- Brito-Zerón, P., Acar-Denizli, N., Retamozo, S., & Ramos-Casals, M. (2020). The burden of comorbidity and complexity in primary Sjögren's syndrome: Clinical and immunological aspects. Rheumatology (Oxford), 59(7), 1234–1244. https://doi.org/10.1093/rheumatology/kez508
- Brito-Zerón, P., Retamozo, S., & Ramos-Casals, M. (2018). Phenotyping Sjögren's syndrome: Towards a personalised management of the disease. Clinical and Experimental Rheumatology, 36(Suppl 112), 55–63. PMID: 29584477
- Brito-Zerón, P., Baldini, C., & Bootsma, H. (2016). Sjögren syndrome: Clinical and immunological features. Clinical and Experimental Rheumatology, 34(1 Suppl 98), 9–17.
- Cafaro, G., Gerli, R., & Perricone, C. (2021). Women, autoimmunity and Sjögren's syndrome: Impact of gender in the disease. Current Pharmaceutical Design, 27(18), 2142–2152. https://doi.org/10.2174/1381612827666210217112411
- Calder, P. C. (2017). Omega-3 fatty acids and inflammatory processes: From molecules to man. Biochemical Society Transactions, 45(5), 1105–1115.
- Carsons, S. E., Vivino, F. B., Parke, A., Carteron, N., Sankar, V., Brasington, R. D., & Massarotti, E. M. (2014). The management of Sjögren's syndrome: Current practice guidelines and future directions. Clinical Advances in Hematology & Oncology, 12(11), 740–747. PMID: 25686954
- Castrillon, J., et al. (2020). Gastrointestinal symptoms and food intolerance in Sjögren's syndrome. Clinical and Experimental Rheumatology, 38(Suppl. 126), 115–121. de Souza, H. F., et al. (2024). Plant-based diet induces remission in autoimmune disease: Case reports in Sjögren's syndrome and lupus. Frontiers in Nutrition, 11, 1198.
- Chen, J., Gao, Q., & Du, L. (2018). Cosmetic exposure and risk of autoimmunity. Autoimmunity Reviews, 17(7), 689–696.

- Davis, K. J., Walker, M. A., & Yu, G. (2021). Environmental triggers of autoimmunity: A systemic review. Environmental Health Perspectives, 129(3), 3601.

- Duarte, J. H., Silva, A. R., & Martins, F. O. (2021). Mediterranean diet and autoimmune disorders. Frontiers in Immunology, 12, 627509.
- Fairweather, D., & Rose, N. R. (2004). Sex differences in autoimmune disease. Journal of Autoimmunity, 23(1), 49–55.

- Erkılınç, G., Doğru, A., Arslan, Y., & Çiriş, M. (2021). Evaluation of histopathological results of minor salivary gland biopsies in patients with the diagnosis of Sjögren's syndrome. Rheumatology International, 41, 2035–2045.

- Fox, R. I. (2005). Sjögren's syndrome. Lancet, 366(9482), 321–331.
- Jones, R. (2018). Living with dry syndrome: Impact on daily life and treatment strategies. Autoimmunity Reviews, 17(5), 512–517.

- Ferrer, M., et al. (2025). Effects of physical exercise in primary Sjögren's syndrome: A systematic review. Journal of Autoimmunity Research, 12(3), 150–162. Gonzalez-Martin, J. J., et al. (2022). Cardiovascular risk in Sjögren's Syndrome. Rheumatology (Oxford), 61(1), 72–81. https://doi.org/10.1093/rheumatology/keab317

- Gutierrez, J. O., Zurita, M. F., & Zurita, L. A. (2018). Sjögren's syndrome associated with Fanconi's syndrome and osteomalacia – Case report. Case Reports in Medicine. Hernández-Molina, G., et al. (2021). Association of body mass index and systemic damage in primary Sjögren's syndrome: A cross-sectional study. Clinical Rheumatology, 40(9), 3463–3470.https://doi.org/10.1007/s10067-021-05697-w

- Jeon, C. H., et al. (2025). Renal involvement in primary Sjögren's syndrome: New perspectives. Autoimmunity Reviews, 24(2), 103456.

- Jeon, H., Park, Y., Lee, J. J., Suh, Y.-S., Kwok, S.-K., Park, S.-H., Kim, W.-U., & Koh, J. H. (2025). The prevalence, clinical features, and long term outcome of patients with primary.

- Kumar, N., Patel, R., & Mehta, V. (2019). Autoimmune mechanisms in Sjögren's syndrome. Current Rheumatology Reports, 21(3), 18.

- Li, Z., Chen, M., & Qiu, Y. (2021). Recent advances of salivary gland biopsy in Sjögren's syndrome. Frontiers in Medicine, Article 792593.

- Liu, Y., Zhao, M., & Wang, Y. (2020). Drinking water contaminants and autoimmune response. Environmental Research, 184, 109–140.

- Lodba, A., et al. (2024). Environmental exposures and autoimmune diseases: The case of primary Sjögren's syndrome. Environmental Health Perspectives, 132(1).

- Lodba, A., Ancuta, C., Tatarciuc, D., Ghiorghe, A., Lodba, L.-O., & Iordache, C. (2024). Comparative analysis of glandular and extraglandular manifestations in primary and secondary Sjögren's syndrome: A study in two academic centers in North-East Romania. Diagnostics, 14(21), 2367. https://doi.org/10.3390/diagnostics14212367

- Manzo, C., et al. (2021). Autoimmunity and gastrointestinal symptoms: Links to surgical history. Journal of Clinical Medicine, 10(6), 1175. https://doi.org/10.3390/jcm10061175

- Mariette, X., & Criswell, L. A. (2018). Primary Sjögren's Syndrome. New England Journal of Medicine, 378(10), 931–939. https://doi.org/10.1056/NEJMra1703502

- Mariette, X., & Seror, R. (2021). Management of primary Sjögren's syndrome: Treatment of systemic manifestations. UpToDate.

- Mariette, X., et al. (2025). Advances in biological therapy for primary Sjögren's syndrome: Current trends and future directions. Best Practice & Research Clinical Rheumatology.

- Mauro, D., Lin, X., Pontarini, E., Wehr, P., Guggino, G., Tang, Y., … Bombardieri, M. (2024). $CD8^+$ tissue-resident memory T cells are expanded in primary Sjögren's disease and can be therapeutically targeted by CD103 blockade. Annals of the Rheumatic Diseases, 83(10), 1345–1357. https://doi.org/10.1136/ard-2023-225069

- Mavragani, C. P., & Moutsopoulos, H. M. (2019). Sjögren's syndrome. Annual Review of Pathology, 14, 535–557.

- Mavragani, C. P., & Moutsopoulos, H. M. (2020). Sjögren's syndrome. Annual Review of Pathology, 15, 407–434.
-

- Monteiro, C. A., et al. (2023). Ultra-processed foods, inflammation, and autoimmune diseases. Nutrients, 15(2), 345. https://doi.org/10.3390/nu15020345

- Navazesh, M., & Kumar, S. K. S. (2009). Dry mouth: Clinical approach in diagnosis and management. Compendium of Continuing Education in Dentistry, 30(6), 326–333.

- Ng, W. F., & Bowman, S. J. (2010). Primary Sjögren's syndrome: Too dry and too tired. Rheumatology (Oxford), 49(5), 844–853. https://doi.org/10.1093/rheumatology/kep477 Nocturne, G., & Mariette, X. (2021). Advances in understanding the pathogenesis of primary Sjögren's syndrome. Nature Reviews Rheumatology, 17(9), 549–561. https://doi.org/10.1038/s41584-021-00623-1

- Ng, W. F., & Bowman, S. J. (2021). Primary Sjögren's syndrome: Too dry and too tired. Rheumatology (Oxford), 60(5), 2158–2170.

- Nguyen, A. D., Lebrun, D., & Martin, C. (2020). Antioxidants and omega-3 fatty acids in autoimmune diseases. Nutrients, 12(2), 543.

- Nocturne, G., & Mariette, X. (2013). Advances in understanding the pathogenesis of primary Sjögren's syndrome. Nature Reviews Rheumatology, 9(9), 544–556. https://doi.org/10.1038/nrrheum.110

- Pedersen, A. M. L., Bender, D. V., & Blom, M. (2001). Oral manifestations of primary Sjögren's syndrome: Implications for diagnosis and therapy. Acta Odontologica Scandinavica, 59(3), 116–120. https://doi.org/10.1080/000163501750266383

- Perdan-Pirkmajer, K., et al. (2022). Oxidative stress in autoimmune diseases. Free Radical Biology and Medicine, 182, 51–63. https://doi.org/10.1016/j.freeradbiomed.2021.01.012

- Perez, P., Martinez, C., & Rubio, F. (2017). Ocular and oral complications of autoimmune exocrinopathies. Clinical Ophthalmology, 11, 2239–2245.

- Perricone, C., De Carolis, C., & Perricone, R. (2019). Co-morbidities in primary Sjögren's syndrome: Current perspectives. Frontiers in Immunology, 10, Article 1409. https://doi.org/10.3389/fimmu.2019.01409

- Ramos-Casals, M., et al. (2020). Clinical and therapeutic update of primary Sjögren's syndrome. Expert Review of Clinical Immunology, 16(5), 365–378. https://doi.org/10.1080/1744666X.2020.1754779

- Ramos-Casals, M., Brito-Zerón, P., & Bombardieri, S. (2012). EULAR recommendations for the management of Sjögren's syndrome. Annals of the Rheumatic Diseases, 71(1), 3–10.

- Rischmueller, M., Tieu, J., & Lester, S. (2016). Primary Sjögren's syndrome. Best Practice & Research Clinical Rheumatology, 30(1), 189–220.

- Robinson, R., King, M., & Patel, H. (2019). Sleep, stress and autoimmune activity: Clinical correlation. Sleep Medicine Reviews, 47, 101–109.

- Rose, N. R., & Bona, C. (1993). Defining criteria for autoimmune diseases. Clinical Immunology and Immunopathology, 68(1), 134–139.

- Schiødt, M., Reibel, J., & Praetorius, F. (2001). Dental caries in primary Sjögren's syndrome: A review. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 92(2), 181–186. https://doi.org/10.1067/moe.114760

- Segal, B., et al. (2023). Fibromyalgia overlap in Sjögren's syndrome: Prevalence and impact. Clinical and Experimental Rheumatology, 41(2), 456–464.

- Seror, R., et al. (2010). ESSDAI: A disease activity index for primary Sjögren's syndrome. Annals of the Rheumatic Diseases, 69(6), 1103–1109.

- Seror, R., et al. (2015). EULAR Sjögren's syndrome disease activity index (ESSDAI): A user guide. RMD Open, 1(1), e000022. https://doi.org/10.1136/rmdopen-2014-000022

- Shiboski, C. H., et al. (2017). 2016 ACR/EULAR classification criteria for primary Sjögren's syndrome. Annals of the Rheumatic Diseases, 76(1), 9–16. https://doi.org/10.1136/annrheumdis-2016-210571

- Shiboski, C. H., et al. (2017). 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A data driven, expert consensus methodology involving three international patient cohorts. Arthritis & Rheumatology, 69(1), 35–45. https://doi.org/10.1002/art.39859

- Sieiro Santos, C., Rego Salgueiro, R., Moriano Morales, C., Álvarez Castro, C., & Díez Álvarez, E. (2023). Risk factors for cardiovascular disease in primary Sjögren's syndrome: A 20 year

follow up multicenter cohort study. Clinical Rheumatology, 42(11), 3021–3031. https://doi.org/10.1007/s10067-023-06686-6

- Smith, M., Lee, Y., & Tanaka, H. (2020). Chronic diseases and global health systems: A rising challenge. International Journal of Public Health, 65(1), 13–21.

- Taylor, K. E., Wong, Q., & Levin, L. (2016). Genetic risk factors in Sjögren's syndrome. Nature Reviews Rheumatology, 12(5), 277–288.

- Tilg, H., Zmora, N., & Adolph, T. E. (2020). The intestinal microbiota fuelling metabolic inflammation. Nature Reviews Immunology, 20(1), 40–54.

- Tzioufas, A. G., et al. (2020). Update on Sjögren's Syndrome and associated autoimmunity. Journal of Autoimmunity, 114, 102432. https://doi.org/10.1016/j.jaut.2020.102432

- Van Ginkel, M. S., et al. (2023). Increased diagnostic accuracy of the labial gland biopsy in primary Sjögren syndrome when multiple histopathological features are included. Arthritis & Rheumatology, 75(3), 412–420.

- Vitali, C., Bombardieri, S., & Jonsson, R. (2002). Classification criteria for Sjögren's syndrome: A revised version of the European criteria. Annals of the Rheumatic Diseases, 61(6), 554–558.

- Vivino, F. B. (2018). Dry mouth and Sjögren's syndrome. New England Journal of Medicine, 378(10), 931–939.

- Wang, X., Li, Y., & Chen, J. (2020). Exercise improves immune regulation in chronic autoimmune disease. Journal of Autoimmunity, 110, 102–112.

- Wu, C., Yosef, N., & Thalhamer, T. (2013). Induction of pathogenic TH17 cells by high salt intake. Nature, 496(7446), 518–522.

- Wu, H., et al. (2021). Omega-3 fatty acids and Sjögren's syndrome. Rheumatology (Oxford), 60(9), 4156–4164. https://doi.org/10.1093/rheumatology/keab187

- Yoshida, K., Tashiro, S., & Kondo, N. (2022). Pesticides and autoimmunity: Evidence and perspectives. Clinical Reviews in Allergy & Immunology, 62(2), 174–183.