KORALEWICZ, Mateusz, SZATKOWSKA, Olga, CHOINKA, Martyna, TSCHUSCHKE, Max, WDOWIAK, Natalia and ADAMSKA, Kinga. The Role of Gut Microbiome Alterations in the Pathogenesis and Management of Sjögren's Syndrome. Quality in Sport. 2024;22:54743. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.22.54743
https://apcz.umk.pl/QS/article/view/54743

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 29.08.2024. Revised: 19.09.2024. Accepted: 20.09.2024. Published: 23.09.2024.

The Role of Gut Microbiome Alterations in the Pathogenesis and Management of Sjögren's Syndrome

Koralewicz Mateusz, Szatkowska Olga, Choinka Martyna, Tschuschke Max, Wdowiak Natalia, Adamska Kinga

Abstract:

Sjögren's syndrome (SS) is a systemic autoimmune disorder characterized by inflammation and damage to the exocrine glands, leading to symptoms such as ocular and oral dryness, and a range of extraglandular manifestations including polyneuropathies, lung and kidney dysfunction, and systemic vasculitis. Although the exact etiology of SS remains unclear, recent research has highlighted the significant role of gut microbiota in its pathogenesis. Alterations in the gut microbiome, known as dysbiosis, have been implicated in the onset and progression of autoimmune diseases, including SS. This review synthesizes current research on the impact of microbiota on SS, focusing on microbial dysbiosis, its impact on disease severity, and potential therapeutic interventions. Evidence indicates that specific microbial changes, such as reductions in beneficial bacteria and alterations in short-chain fatty acid (SCFA) production, correlate with increased disease activity and systemic inflammation. Microbiome-targeted therapies, including probiotics, prebiotics, and fecal microbiota transplantation, have shown promise in improving SS symptoms and modulating immune responses. Notably, butyrate and specific probiotic strains have demonstrated potential in reducing inflammation and enhancing salivary flow in preclinical studies. However, further research is needed to validate these findings and assess long-term efficacy.

This review underscores the importance of gut microbiota in SS and suggests that microbiome-focused treatments could offer new avenues for managing this condition, improving patient outcomes, and potentially preventing disease onset.

Keywords:
Sjögren's syndrome, gut microbiota, dysbiosis; fecal microbiota transplantation, autoimmune disease

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disorder that primarily affects the exocrine glands. Inflammation and subsequent damage to the lacrimal and salivary glands result in significant ocular and oral dryness. In addition to these glandular manifestations, over 50% of individuals with pSS experience extra-glandular symptoms, including polyneuropathies, lung and kidney dysfunction, arthralgia and fatigue. Immune complex deposition in the skin, joints, and other organs can also lead to systemic vasculitis. In rare cases, malignant transformation of B lymphocytes can occur, resulting in non-Hodgkin lymphoma (Zehrfeld et al. 2024).

Sjögren's syndrome (SS) is named after the Swedish ophthalmologist Henrik Samuel Conrad Sjögren (1899–1986), who first associated the triad of keratoconjunctivitis sicca, xerostomia, and polyarthritis in 1933 (Sjögren 1933). The disease often coexists with other autoimmune disorders such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and is then referred to as secondary Sjögren's or Sjögren's overlap syndrome.

SS is a relatively common condition, with the pooled incidence rate in a recent meta-analysis estimated at 6.92 cases per 100,000 people per year, while the prevalence rate was found to be 60.82 cases per 100,000 inhabitants (0.06%) (Qin et al. 2014). Specifically for Europe, three significant epidemiological studies have been reviewed and a combined prevalence was estimated at approximately 39 per 100,000 (0.04%) (Cornec and Chiche 2014). While SS can occur at any age, symptoms typically manifest around the fifth decade of life, with a strong predilection for women, as evidenced by a female-to-male ratio of about 9:1 (Qin et al. 2014).

As with many other autoimmune diseases, the exact cause of SS remains unknown (Bombardieri 2020). Exposure to specific environmental factors in genetically susceptible individuals is thought to play a crucial role, leading to immune system dysregulation and disease onset. In particular, the disruption of innate immune barriers is pivotal in SS pathogenesis, especially during the early stages of the disease, through mechanisms involving the interferon (IFN) pathway (Brito-Zerón et al. 2016, Shimizu et al. 2021). Additionally, the adaptive immune system plays a central role in SS development, with persistent B-cell activation and the proliferation of Th1 and Th17 cells contributing to disease progression (Chivasso et al. 2021). Recent research has also highlighted the significant role of epithelial cell function in the pathogenesis of this disease (Goules et al. 2017).

An increasing body of research underscores the significant role of gut microbiota in the onset and progression of autoimmune diseases. The microbiota within the gastrointestinal tract offers crucial health benefits to its host, particularly by maintaining immune system homeostasis.

Dysbiosis of the gut microbiota has been linked to various autoimmune diseases such as RA and SLE, suggesting that alterations in the gut's microbial environment may also play a key role in the pathogenesis of SS (Zhong et al. 2018). These microbial changes are thought to contribute to the onset and exacerbation of SS by affecting mucosal immune responses and systemic inflammation. Modifying the gut microbiota through dietary interventions, probiotics, prebiotics, and other microbiome-focused therapies may offer promising opportunities for alleviating symptoms and improving the quality of life for patients with SS. Investigating the interaction between gut microbiota and the host immune system in SS could lead to the development of innovative treatments and improve patient outcomes.

This paper seeks to provide a thorough review of the current research on gut microbiota in SS, exploring its potential involvement in disease development and progression. By synthesizing recent findings, this review aims to highlight the potential for microbiota-targeted therapies in managing SS and to identify areas where further research is needed.

Role of Microbiota in Sjögren's Syndrome Pathogenesis

The gut microbiota plays a crucial role in regulating the balance between proinflammatory and anti-inflammatory immune responses in the body. Disruption of this balance has been identified as a critical factor in the onset and progression of rheumatic diseases (Mao et al. 2018). The pathogenesis of SS appears to be closely linked to alterations in the composition of gut microbiota. A recent study has provided compelling evidence supporting this connection. An association between specific microbial families and genera and risks of developing SS was found. It was reduced with the presence of the family Porphyromonadaceae, genus Subdoligranulum, genus Butyricicoccus and genus Lachnospiraceae. Genus Fusicatenibacter and genus Ruminiclostridium were found to increase the risk of disease development (Cao et al. 2023). The development of SS may be influenced by multiple pathways involving the microbiome, including metabolite changes, molecular mimicry, and the breakdown of epithelial tolerance.

Alterations in gut microbial metabolites, particularly short-chain fatty acids (SCFAs) like butyrate, play a significant role in SS pathogenesis. Studies have shown a reduction in butyrate-producing bacteria such as *Faecalibacterium prausnitzii*, *Blautia*, *Roseburia*, *Ruminococcus*, *Lachnospira*, *Bacteroides fragilis*, and *Bifidobacterium* in SS patients (Cano-Ortiz et al. 2020, Moon et al. 2020, Lee et al. 2020). Butyrate is crucial for maintaining gut barrier integrity by providing energy to colonic epithelial cells. The decline in these bacteria correlates with increased levels of proinflammatory cytokines, including IL-6, IL-12, IL-17, and TNF-alpha, alongside a decrease in anti-inflammatory markers such as IL-10 and FOXP3 mRNA, essential for the development and function of regulatory T cells (Tregs). Moreover, functional analyses reveal a decrease in gene expression related to critical metabolic pathways, such as glutathione and butanoate metabolism, while showing an increase in genes involved in lipoic acid and retinol metabolism, as well as lipopolysaccharide production and glycosaminoglycan degradation (Cano-Ortiz et al. 2020). These changes suggest a metabolic dysregulation contributing to bacterial pathogenesis and chronic inflammation in SS.

Molecular mimicry, where infectious agents trigger autoimmune responses, could be another essential mechanism in SS development.

For instance, cross-reactivity between the Coxsackie virus 2B protein and Ro60 autoantibodies has been associated with the emergence and persistence of these antibodies, which are crucial to SS pathogenesis (Stathopoulou et al. 2005). Research has shown that serum from patients with anti-Ro60 antibodies reacts with *Bacteroides thetaiotaomicron* lysates (Greiling et al. 2018), while the OmpA antigen from *E. coli* can induce antibodies targeting SS-A/Ro and SS-B/La, leading to inflammation of the glands (Yanagisawa et al. 2018). Furthermore, a peptide from *Capnocytophaga ochracea*, called vWFA, has been shown to stimulate Ro60-reactive T cells, resulting in increased IL-2 production (Szymula et al. 2014). Proteins from *E. coli* and *Staphylococcus aureus* may also induce cross-reactive antibodies through molecular mimicry, which could play a role in symptoms such as fatigue (Zhang et al. 2018). While these findings underscore the role of molecular mimicry in SS, further studies are needed to identify the specific microbial proteins involved.

The breakdown of epithelial tolerance is another significant factor in SS, although the underlying mechanisms are not yet fully understood. Salivary gland epithelial cells (SGECs) in SS may express immune checkpoint molecules that influence immune responses (Verstappen et al. 2021). Patients with SS have been observed to have a reduced presence of beneficial bacteria such as *Haemophilus parainfluenzae*, which could potentially lead to weakening of immune tolerance by lowering PD-L1 expression on SGECs and thus diminishing their regulation of CD4+ T cell proliferation (Tseng et al. 2021). Furthermore, *Prevotella melaninogenica*, a bacterium associated with SS, has the ability to increase the expression of MHC molecules and CD80 in gland cells, which may lead to the activation of IFN-related inflammatory pathways (Alam et al. 2020, Moon et al. 2020). The increased presence of Prevotella in families with enzymes that degrade mucin indicates its potential involvement in compromising the protective mucus layer of the colon (Wright et al. 2000). In SS, the microbiota may contribute to the breakdown of epithelial tolerance by depleting energy for epithelial cells, impairing their immunomodulatory functions, and disrupting the protective mucus barrier.

Disease activity

An early study on a mouse model of SS revealed significant differences in the oral and stool microbiomes of SS subjects compared to controls, marked by reduced microbial richness and distinct genera changes in these mucosal sites. Notably, the most severe cases of keratoconjunctivitis sicca and combined systemic and ocular disease correlated with the lowest stool microbiota diversity. Treatment with antibiotics, which reduced stool microbiome diversity, was found to worsen ocular inflammation. However, no significant differences were found in the conjunctival microbiome. (de Paiva et al. 2016)

A study on 42 pSS patients and 35 healthy control subjects found that severe intestinal dysbiosis is significantly more common in patients with pSS compared to controls (21% vs. 3%). Patients with severe dysbiosis exhibited higher disease activity, as reflected by elevated ESSDAI and ClinESSDAI scores, lower levels of complement component 4, and increased levels of fecal calprotectin, indicating greater systemic and gastrointestinal inflammation. However, dysbiosis was not linked to disease duration, ESSPRI scores, or IBS-like symptoms. (Mandl et al. 2017)

An observational study on 10 SS patients, 14 subjects with dry eye syndrome (DES) and 12 healthy controls found an association between increased disease activity and gut dysbiosis in SS, especially with respect to the severity of ocular symptoms like dry eye.

Specifically, changes in gut microbiota composition - such as lower levels of beneficial bacteria like Bifidobacterium and alterations in the Firmicutes/Bacteroidetes ratio - were associated with more severe dry eye symptoms, including decreased tear secretion, shorter tear break-up time, and higher corneal staining scores. SS was characterized by significant gut dysbiosis compared to both environmental dry eye syndrome and healthy controls, while dry eye patients displayed microbiome changes that fell between these two groups, with gut dysbiosis partially correlating with the severity of dry eye symptoms (Moon et al. 2020). Moreover, other studies also found similar dysbiosis patterns in non-pSS individuals with symptoms like sicca, suggesting that microbial changes might precede full disease development (Wang et al. 2022).

A recent study found that 30.4% of pSS patients involved had an anxiety disorder, which could potentially both result from and exacerbate dry eye discomfort. A bidirectional relationship exists between anxiety and gut dysbiosis in pSS-mediated dry eye. Specific gut microbiota alterations, such as increased Prevotella, were linked to dry eye severity, while Bacteroidetes and Odoribacter were associated with pSS activity. The findings suggest that changes in the gut microbiota contribute to both anxiety and the severity of pSS-related symptoms (Zhang et al. 2023).

These findings suggest that the severity of SS, particularly regarding eye-related symptoms, could be affected by imbalances in gut microbiota. This underscores the potential impact of gut dysbiosis in increasing the activity of the disease and highlights the need to comprehend these microbial changes in order to develop targeted therapies, such as probiotics, which could help to lower the symptoms and control disease progression in patients with SS.

Microbiome-Related Interventions in Sjögren's Syndrome

Recent advancements in understanding the gut and oral microbiome's role in autoimmune diseases have sparked interest in microbiome-targeted therapies for SS. Various interventions, ranging from probiotics and prebiotics to more complex treatments like fecal microbiota transplantation (FMT) and microbial metabolite supplementation, have been explored in both preclinical and clinical studies.

A preclinical study using NOD mice as an animal model of SS investigated the effects of sodium butyrate on SS. Sodium butyrate, a SCFA produced by gut microbiota, was administered to mice to evaluate its therapeutic potential. The intervention led to an increase in salivary flow rates and a reduction in inflammation in the salivary glands of the mice, indicating that butyrate alleviated symptoms of SS. Furthermore, butyrate treatment decreased the infiltration of IL-17 and IL-21 producing cells into the salivary glands and shifted the balance of B cells by increasing IL-10-producing B cells and decreasing IL-17-producing B cells. The study concluded that butyrate regulates the immune response in SS through modulation of circadian-clock-related genes and suggests its potential as a therapeutic agent for managing SS (Kim et al. 2021).

Another preclinical study examined the potential of using probiotics, specifically *Lactobacillus acidophilus*, and SCFAs, particularly propionate, as treatments for SS in the same mouse model. The probiotic improved the gut microbiota composition, particularly by restoring the Bacteroides ratio and increasing beneficial bacteria like *Ruminococcaceae*.

Administering *L. acidophilus* improved saliva flow and reduced inflammation by decreasing inflammatory cytokine-producing cells and modulating immune responses through the SIGNR3 pathway and the STIM1-STING axis. It also altered the gut microbiome by enhancing propionate-producing bacteria. Similarly, propionate improved saliva flow, reduced tissue inflammation, and balanced T17 cells, while also inhibiting the STIM1-STING pathway and type I IFN production (Woo et al. 2023). These findings suggest that both *L. acidophilus* and propionate have potential as therapeutic agents for SS by improving gut microbiome health and modulating immune responses.

A recent study explored the tolerance and effectiveness of two adhesive biofilms in patients with pSS who suffer from dry mouth (xerostomia). The two biofilms tested were a prebiotic biofilm (containing milk proteins, soy derivatives, and glycerin) and a sodium alginate biofilm. 10 patients with pSS participated in the study, applying the biofilms daily for two 1-month periods, separated by a 1-month washout period. The primary outcomes were the tolerance of these biofilms, assessed through visual analog scales (VAS) by both patients and practitioners, and their effectiveness in improving mouth dryness and related symptoms. The study also explored changes in oral microbiota composition as a secondary outcome. The results indicated that both biofilms were well tolerated, with the sodium alginate biofilm slightly more effective in improving mouth dryness. The prebiotic biofilm, however, appeared to have a protective effect against the emergence of certain bacteria, like *Treponema*, which were promoted by the sodium alginate biofilm (Orliaguet et al. 2023). These results suggest that while both biofilms can be used to manage dry mouth in pSS patients, the choice of biofilm may influence the oral microbiota in different ways. The prebiotic biofilm, in particular, could offer protective benefits against harmful bacteria, highlighting the potential for targeted microbial modulation in the management of SS-related symptoms.

A randomized clinical trial aimed to assess the short-term efficacy of probiotics in reducing oral Candida growth in 32 patients with SS divided into two groups: one receiving probiotic capsules and the other receiving placebo capsules for 5 weeks. The probiotic group showed a statistically significant reduction in oral candidal load over the course of the study, whereas the placebo group did not. This suggests that the probiotic intervention effectively reduced the fungal colonization in SS patients. However, no significant difference in pain reduction was observed (Kamal et al. 2020). These results suggest that probiotics containing specific strains like *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*, and *Bifidobacterium bifidum* may offer a novel and effective approach to reducing oral candidal colonization in SS patients. Given the side effects and resistance issues associated with conventional antifungal treatments, probiotics could be a safer alternative, although more research is needed to confirm these findings over a longer duration and in larger populations. However, the lack of impact on pain and discomfort suggests that probiotics should be used alongside other treatments to manage SS symptoms comprehensively.

A 3-month study on 16 pSS patients aimed to investigate the changes in intestinal microecology in patients with pSS and the effects of the traditional Chinese medicine formula, Yangyin Yiqi Huoxue Recipe (YYHR) on these changes. pSS patients exhibited lower abundance and diversity of intestinal bacteria compared to healthy controls. Post-treatment, there was a significant reduction in ESSDAI scores, erythrocyte sedimentation rate (ESR), and IgG levels, indicating improvement in disease activity.

Treatment with YYHR led to significant changes in the proportions of various bacterial phyla, families, and genera. For instance, the proportions of *Actinobacteria*, *Firmicutes*, *Fusobacteria*, and *Proteobacteria* decreased, while *Bacteroidetes*, *Tenericutes*, and *Candidate-division TM7* increased. Similarly, at the genus level, there was a decrease in *Bifidobacterium*, *Bacteroides*, *Escherichia-Shigella*, *Faecalibacterium*, and *Prevotella*, with an increase in *Clostridia* (Wu et al. 2019).

A study involving 229 participants investigated the effects of hydroxychloroquine (HCQ) on microbial dysbiosis in pSS across the gut, oral cavity, and vagina. The study revealed significant microbial imbalances in pSS patients, which may contribute to disease development, and similar patterns were observed in non-pSS individuals with related symptoms, suggesting that microbial changes might precede full disease development. HCQ treatment for 3-6 months improved microbiota richness and aligned with clinical remission, though some patients experienced a decline after 6-12 months due to reduced treatment adherence (Wang et al. 2022). The findings highlight HCQ's role in alleviating microbial dysbiosis and suggest that ongoing treatment is essential for sustained benefits, underscoring the potential of microbial modulation in pSS management and prevention.

A study on 10 individuals with DE symptoms and signs meeting criteria for SS or positive early SS markers explored the safety and potential efficacy of Fecal Microbial Transplant (FMT) as a treatment for immune-mediated dry eye (DE). Participants received two FMTs via enema, administered one week apart, with the donor being a healthy 33-year-old female. The study found that the gut microbiome profiles of participants began to shift toward resembling the donor's microbiome after the FMT, indicating a successful transplant. Clinically, half of the participants reported improvements in their DE symptoms three months following the FMT, suggesting a potential therapeutic benefit of FMT for managing immune-mediated DE. The procedure was safe, with no adverse events reported among the ten participants. However, the study noted that these results were preliminary, and further research is needed to validate these findings and explore the full therapeutic potential of FMT for this condition (Watane et al. 2021).

These studies collectively underscore the therapeutic potential of microbiome-related interventions in SS, ranging from probiotics and microbial metabolites to more complex interventions like FMT. While these findings are promising, the variability in patient responses and the complexity of microbiome-host interactions indicate that personalized treatment approaches may be necessary to optimize outcomes. Continued research is essential to fully assess the long-term efficacy and safety of these interventions in clinical practice.

Tab. 1: Summary of interventional studies on gut microbiome.

Authors	Year	Title	Study Cohort	Intervention	Result
Kim et al.	2021	Short-chain fatty acid butyrate induces IL-10-producing B cells by regulating circadian-clock-related genes to ameliorate Sjogren's syndrome	NOD mice	Butyrate	Increased salivary flow rate and decreased infiltration of inflammatory cells into the salivary glands. Butyrate increased salisphere formation in SGSCs. treatment with butyrate prevented cell death, which is induced by IFNγ and TNFα.
Woo et al.	2023	Lactobacillus acidophilus and propionate attenuate Sjögren's syndrome by modulating the STIM1-STING signaling pathway	NOD mice	Probiotic (L. acidophilus)	Decreaed infltration of infammatory cells into the salivary gland, improved T17:Treg balance, increased expression of SIGNR3, change in Bacteroides:Firmicutes ratio aND species richness and diversity.
Watane et al.	2021	Fecal Microbial Transplant in Individuals with Immune-mediated Dry Eye	Patients with dry eye (n = 10)	Fecal Microbial Transplant (FMT)	5 individuals reported improved symptoms (gastrointestinal and dry eye) 3 months after FMT and 5 individuals noted no differences. However, no significant trends were noted between baseline and 3 months when examining T cell profiles and DE metrics over time No adverse reactions

					to the FMT were reported.
Orliaguet et al.	2023	Tolerance to intraoral biofilms and their effectiveness in improving mouth dryness and modifying oral microbiota in patients with primary Sjögren's syndrome: "Predelfi study"	pSS patients (n = 10)	Sodium alginate biofilm, prebiotic biofilm	Improvement in the VAS for mouth dryness for the sodium alginate biofilm versus prebiotic biofilm, while no difference in the VAS scores was observed for other parameters.
Wu et al.	2019	Changes of Intestinal Microecology in Patients with Primary Sjogren's Syndrome after Therapy of Yangyin Yiqi Huoxue Recipe	pSS patients (n = 16)	Yangyin Yiqi Huoxue Recipe (YYHR)	YYHR decreased disease activity, increased the diversity of intestinal flora, significantly changed the composition and abundance of intestinal flora, and regulated the imbalance of intestinal microecology.
Wang et al.	2022	Microbiota dysbiosis in primary Sjo¨ gren's syndrome and the ameliorative effect of hydroxychloroquine	pSS (n = 133), non-pSS sicca patients (n = 56), healthy controls (n = 40)	Hydroxychloroquine (HCQ)	3-6 month treatment with HCQ improved microbiota richness and aligned with clinical remission; some patients experienced a decline after 6-12 months due to reduced treatment adherence.
Kamal et al.	2020	Probiotics as a prophylaxis to prevent oral	SS patients (n = 32)	Probiotic (Lactobacillus bulgaricus, S.	Significantly reduced candidal load in highly susceptible SS

		candidiasis in patients with Sjogren's syndrome: a double-blinded, placebo-controlled, randomized trial		thermophilus, L. acidophilus, Bifdobacterium bifdum)	patients; no significant effect on oral pain.

Discussion

Our findings highlight the pivotal role of gut microbiota dysbiosis in the pathogenesis and progression of SS. The study confirms that alterations in gut microbiome composition, particularly reduced diversity and imbalances in microbial families, correlate with increased disease severity and systemic inflammation in SS patients. The observed changes in the gut microbiota, including reductions in beneficial bacteria and alterations in microbial metabolites like SCFA, support the hypothesis that dysbiosis contributes to the onset and exacerbation of SS.

The therapeutic potential of microbiome-targeted interventions, such as probiotics and microbial metabolites, emerges as a promising avenue for managing SS. *Lactobacillus acidophilus* and propionate administration demonstrated significant improvements in salivary flow, reduced inflammation, and modulation of immune responses through pathways such as SIGNR3 and STIM1-STING. These findings suggest that enhancing gut microbiome health could alleviate SS symptoms and mitigate disease progression. Additionally, the efficacy of butyrate and the potential benefits of prebiotic and probiotic treatments underscore the value of microbiome modulation in pSS management.

The results from studies on FMT and traditional Chinese medicine formulations, like YYHR, further support the therapeutic potential of microbiome-related interventions. However, while promising, these treatments require further validation through larger-scale studies and long-term follow-ups to confirm their safety and efficacy. Future research should focus on validating probiotics and FMT in SS through randomized controlled trials that explore the efficacy, safety, and long-term impact of specific strains, multi-strain formulations, and FMT protocols. Additionally, studies should examine the potential of combining microbiome-targeted therapies with standard treatments, assess their effects in early-stage SS, and evaluate their impact on quality of life to optimize disease management.

Conclusions

In conclusion, this review underscores the critical role of gut microbiota dysbiosis in the pathogenesis and progression of pSS. The observed alterations in microbial diversity and metabolite production correlate with increased disease severity, highlighting the potential of microbiome-targeted therapies to manage SS symptoms and slow disease progression. Interventions such as probiotics, prebiotics, and FMT show promising results in modulating immune responses and improving clinical outcomes.

However, further research is essential to validate these findings through larger, randomized controlled trials, explore the combination of these therapies with conventional treatments, and assess their long-term safety and effectiveness in diverse patient populations.

Disclosure

Author's contribution

Conceptualization: MK, OS; Investigation: MK, OS, MT; Writing - rough preparation: MK, OS, MC; Writing - review and editing: MT, KA, NW; Visualization: MK, MC
All authors have read and agreed with the published version of the manuscript.

Funding Statement

None.

Acknowledgments

None.

Conflict of Interest Statement

None.

References:

1. Zehrfeld N, Witte T, Ernst D. Update Sjögren-Syndrom : Diagnostik, Therapie und Fallstricke [Update on Sjögren's syndrome : Diagnostics, treatment, and challenges]. Z Rheumatol. 2024 Apr;83(3):217-228. German. https://doi.org/10.1007/s00393-024-01493-z Epub 2024 Mar 18. PMID: 38498147.
2. Henrik S. Zur Kenntnis der keratoconjunctivitis sicca. Keratitis filiformis bei Hypofunktion der Tränendrüsen [On knowledge of keratoconjunctivitis sicca. Keratitis filiformis due to lacrimal gland hypofunction] Acta Ophthalmol. 1933;2:1–151.
3. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, Zhong R. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis. 2015 Nov;74(11):1983-9. https://doi.org/10.1136/annrheumdis-2014-205375 Epub 2014 Jun 17. PMID: 24938285.
4. Cornec D, Chiche L. Is primary Sjögren's syndrome an orphan disease? A critical appraisal of prevalence studies in Europe. Ann Rheum Dis. 2015 Mar;74(3):e25. https://doi.org/10.1136/annrheumdis-2014-206860 Epub 2014 Nov 7. PMID: 25381229.
5. Bombardieri M, Argyropoulou OD, Ferro F, Coleby R, Pontarini E, Governato G, Lucchesi D, Fulvio G, Tzioufas AG, Baldini C. One year in review 2020: pathogenesis of primary Sjögren's syndrome. Clin Exp Rheumatol. 2020 Jul-Aug;38 Suppl 126(4):3-9. Epub 2020 Sep 29. PMID: 33025887.
6. Brito-Zerón P, Baldini C, Bootsma H, Bowman SJ, Jonsson R, Mariette X, Sivils K, Theander E, Tzioufas A, Ramos-Casals M. Sjögren syndrome. Nat Rev Dis Primers. 2016 Jul 7;2:16047. https://doi.org/10.1038/nrdp.2016.47 PMID: 27383445.

7. Shimizu T, Nakamura H, Kawakami A. Role of the Innate Immunity Signaling Pathway in the Pathogenesis of Sjögren's Syndrome. Int J Mol Sci. 2021 Mar 17;22(6):3090. https://doi.org/10.3390/ijms22063090 PMID: 33803026; PMCID: PMC8002742.
8. Chivasso C, Sarrand J, Perret J, Delporte C, Soyfoo MS. The Involvement of Innate and Adaptive Immunity in the Initiation and Perpetuation of Sjögren's Syndrome. Int J Mol Sci. 2021 Jan 11;22(2):658. https://doi.org/10.3390/ijms22020658 PMID: 33440862; PMCID: PMC7826728.
9. Goules AV, Kapsogeorgou EK, Tzioufas AG. Insight into pathogenesis of Sjögren's syndrome: Dissection on autoimmune infiltrates and epithelial cells. Clin Immunol. 2017 Sep;182:30-40. https://doi.org/10.1016/j.clim.2017.03.007 Epub 2017 Mar 19. PMID: 28330683.
10. Zhong D, Wu C, Zeng X, Wang Q. The role of gut microbiota in the pathogenesis of rheumatic diseases. Clin Rheumatol (2018) 37(1):25–34. https://doi.org/10.1007/s10067-017-3821-4
11. Mao K, Baptista AP, Tamoutounour S, Zhuang L, Bouladoux N, Martins AJ, et al. Innate and adaptive lymphocytes sequentially shape the gut microbiota and lipid metabolism. Nature (2018) 554(7691):255–9. https://doi.org/10.1038/nature25437
12. Cao Y, Lu H, Xu W, Zhong M. Gut microbiota and Sjögren's syndrome: a two-sample Mendelian randomization study. Front Immunol. 2023 Jun 13;14:1187906. https://doi.org/10.3389/fimmu.2023.1187906 PMID: 37383227; PMCID: PMC10299808.
13. Cano-Ortiz A, Laborda-Illanes A, Plaza-Andrades I, Membrillo Del Pozo A, Villarrubia Cuadrado A, Rodríguez Calvo de Mora M, Leiva-Gea I, Sanchez-Alcoholado L, Queipo-Ortuño MI. Connection between the Gut Microbiome, Systemic Inflammation, Gut Permeability and FOXP3 Expression in Patients with Primary Sjögren's Syndrome. Int J Mol Sci. 2020 Nov 19;21(22):8733. https://doi.org/10.3390/ijms21228733 PMID: 33228011; PMCID: PMC7699261.
14. Moon J, Choi SH, Yoon CH, Kim MK. Gut dysbiosis is prevailing in sjögren's syndrome and is related to dry eye severity. PloS One (2020) 15(2):e0229029. https://doi.org/10.1371/journal.pone.0229029
15. Lee J, Alam J, Choi E, Ko YK, Lee A, Choi Y. Association of a dysbiotic oral microbiota with the development of focal lymphocytic sialadenitis in IkB-z-deficient mice. NPJ Biofilms Microbiomes (2020) 6(1):49. https://doi.org/10.1038/s41522-020-00158-4
16. Stathopoulou EA, Routsias JG, Stea EA, Moutsopoulos HM, Tzioufas AG. Cross-Reaction Between Antibodies to the Major Epitope of Ro60 kD Autoantigen and a Homologous Peptide of Coxsackie Virus 2B Protein. Clin Exp Immunol (2005) 141(1):148–54. https://doi.org/10.1111/j.1365-2249.2005.02812.x
17. Greiling TM, Dehner C, Chen X, Hughes K, Iñiguez AJ, Boccitto M, et al.. Commensal Orthologs of the Human Autoantigen Ro60 as Triggers of Autoimmunity in Lupus. Sci Transl Med (2018) 10(434):eaan2306. https://doi.org/10.1126/scitranslmed.aan2306

18. Yanagisawa N, Ueshiba H, Abe Y, Kato H, Higuchi T, Yagi J. Outer Membrane Protein of Gut Commensal Microorganism Induces Autoantibody Production and Extra-Intestinal Gland Inflammation in Mice. Int J Mol Sci (2018) 19(10):3241. https://doi.org/10.3390/ijms19103241
19. Szymula A, Rosenthal J, Szczerba BM, Bagavant H, Fu SM, Deshmukh US. T Cell Epitope Mimicry Between Sjögren's Syndrome Antigen A (SSA)/Ro60 and Oral, Gut, Skin and Vaginal Bacteria. Clin Immunol (2014) 152(1-2):1–9. https://doi.org/10.1016/j.clim.2014.02.004
20. Zhang P, Minardi LM, Kuenstner JT, Zekan SM, Kruzelock R. Anti-Microbial Antibodies, Host Immunity, and Autoimmune Disease. Front Med (Lausanne) (2018) 5:153. https://doi.org/10.3389/fmed.2018.00153
21. Verstappen GM, Pringle S, Bootsma H, Kroese FGM. Epithelial-Immune Cell Interplay in Primary Sjögren Syndrome Salivary Gland Pathogenesis. Nat Rev Rheumatol (2021) 17(6):333–48. https://doi.org/10.1038/s41584-021-00605-2
22. Tseng YC, Yang HY, Lin WT, Chang CB, Chien HC, Wang HP, et al.. Salivary Dysbiosis in Sjögren's Syndrome and a Commensal-Mediated Immunomodulatory Effect of Salivary Gland Epithelial Cells. NPJ Biofilms Microbiomes (2021) 7(1):21. https://doi.org/10.1038/s41522-021-00192-w
23. Alam J, Lee A, Lee J, Kwon DI, Park HK, Park JH, et al.. Dysbiotic Oral Microbiota and Infected Salivary Glands in Sjögren's Syndrome. PloS One (2020) 15(3):e0230667. https://doi.org/10.1371/journal.pone.0230667
24. Moon J, Choi SH, Yoon CH, Kim MK. Gut Dysbiosis is Prevailing in Sjögren's Syndrome and is Related to Dry Eye Severity. PloS One (2020) 15(2):e0229029. https://doi.org/10.1371/journal.pone.0229029
25. Wright DP, Rosendale DI, Robertson AM. Prevotella Enzymes Involved in Mucin Oligosaccharide Degradation and Evidence for a Small Operon of Genes Expressed During Growth on Mucin. FEMS Microbiol Lett (2000) 190(1):73–9. https://doi.org/10.1111/j.1574-6968.2000.tb09265.x
26. de Paiva CS, Jones DB, Stern ME, Bian F, Moore QL, Corbiere S, Streckfus CF, Hutchinson DS, Ajami NJ, Petrosino JF, Pflugfelder SC. Altered Mucosal Microbiome Diversity and Disease Severity in Sjögren Syndrome. Sci Rep. 2016 Apr 18;6:23561. https://doi.org/10.1038/srep23561 PMID: 27087247; PMCID: PMC4834578.
27. Mandl T, Marsal J, Olsson P, Ohlsson B, Andréasson K. Severe intestinal dysbiosis is prevalent in primary Sjögren's syndrome and is associated with systemic disease activity. Arthritis Res Ther. 2017 Oct 24;19(1):237. https://doi.org/10.1186/s13075-017-1446-2 PMID: 29065905; PMCID: PMC5655865.
28. Moon J, Choi SH, Yoon CH, Kim MK. Gut dysbiosis is prevailing in Sjögren's syndrome and is related to dry eye severity. PLoS One. 2020 Feb 14;15(2):e0229029. https://doi.org/10.1371/journal.pone.0229029 PMID: 32059038; PMCID: PMC7021297.
29. Wang X, Pang K, Wang J, Zhang B, Liu Z, Lu S, Xu X, Zhu L, Zhou Z, Niu M, Gao J, Li J, Zhao F, Wu J. Microbiota dysbiosis in primary Sjögren's syndrome and the ameliorative effect of hydroxychloroquine. Cell Rep. 2022 Sep 13;40(11):111352. https://doi.org/10.1016/j.celrep.2022.111352 PMID: 36103827.

30. Zhang Y, Gan M, He Y, Liu T, Xu M. Anxiety Disorders and Gut Dysbiosis in Primary Sjögren's Syndrome-Mediated Dry Eye Patients. Int J Gen Med. 2023 May 9;16:1735-1746. https://doi.org/10.2147/IJGM.S405225 PMID: 37193253; PMCID: PMC10182797.
31. Kim DS, Woo JS, Min HK, Choi JW, Moon JH, Park MJ, Kwok SK, Park SH, Cho ML. Short-chain fatty acid butyrate induces IL-10-producing B cells by regulating circadian-clock-related genes to ameliorate Sjögren's syndrome. J Autoimmun. 2021 May;119:102611. https://doi.org/10.1016/j.jaut.2021.102611 Epub 2021 Feb 22. PMID: 33631650.
32. Woo JS, Hwang SH, Yang S, Lee KH, Lee YS, Choi JW, Park JS, Jhun J, Park SH, Cho ML. Lactobacillus acidophilus and propionate attenuate Sjögren's syndrome by modulating the STIM1-STING signaling pathway. Cell Commun Signal. 2023 Jun 14;21(1):135. https://doi.org/10.1186/s12964-023-01141-0 PMID: 37316856; PMCID: PMC10265917.
33. Orliaguet M, Fong SB, Le Pottier L, Meuric V, Boisramé S, Bonnaure-Mallet M, Pers JO. Tolerance to intraoral biofilms and their effectiveness in improving mouth dryness and modifying oral microbiota in patients with primary Sjögren's syndrome: "Predelfi study". Front Microbiol. 2023 Feb 8;14:1071683. https://doi.org/10.3389/fmicb.2023.1071683 PMID: 37293235; PMCID: PMC10245914.
34. Kamal Y, Kandil M, Eissa M, Yousef R, Elsaadany B. Probiotics as a prophylaxis to prevent oral candidiasis in patients with Sjogren's syndrome: a double-blinded, placebo-controlled, randomized trial. Rheumatol Int. 2020 Jun;40(6):873-879. https://doi.org/10.1007/s00296-020-04558-9 Epub 2020 Mar 26. PMID: 32219478.
35. Wu GL, Lu HF, Chen YL, Wang Q, Cao H, Li TY. Changes of Intestinal Microecology in Patients with Primary Sjogren's Syndrome after Therapy of Yangyin Yiqi Huoxue Recipe (). Chin J Integr Med. 2019 Sep;25(9):654-662. https://doi.org/10.1007/s11655-019-2939-4 Epub 2019 Jun 4. PMID: 31161440.
36. Watane A, Cavuoto KM, Rojas M, Dermer H, Day JO, Banerjee S, Galor A. Fecal Microbial Transplant in Individuals With Immune-Mediated Dry Eye. Am J Ophthalmol. 2022 Jan;233:90-100. https://doi.org/10.1016/j.ajo.2021.06.022 Epub 2021 Jun 30. PMID: 34214453; PMCID: PMC8678170.