






## Experimental Eye Research

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Review

# The relationship between dry eye disease and human microbiota: A review of the science

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## Highlights

- The human microbiota is multi-faceted and may influence the risk for dry eye disease.
- Sjogren's Syndrome and microbial dysbiosis have been associated with dry eye disease.
- Dysregulated balance of pro & anti-inflammatory organisms linked to dry eye disease.
- Topical hypotensives have been associated with both dysbiosis and dry eye disease.
- Larger controlled studies are needed to identify microbiota mechanisms and signals.

## Abstract

A complex relationship exists between human microbiota and the risk for ophthalmic disease. While the homeostatic composition of human microbiota is still being established, including what defines dysbiosis (i.e. changes in diversity and abundance), pilot research has begun to identify the potential influence of demographics, geography, and co-morbidities on the microbiota and describe their impact on ocular health. This review specifically focuses on the scientific relationships of the human oral and gut microbiota to dry eye disease (DED), a set of conditions impacting the tear film and ocular surface. Although data are sparse and often conflict across studies, the literature generally supports associations between microbial imbalance (dysbiosis) and DED and alterations in microbial diversity and abundance to specific aspects of DED. This review examines the relevant science and mechanistic relationships linking gut and oral dysbiosis and DED. Various physiochemical factors and therapeutic approaches that alter microbiota, including medications and fecal transplants are examined in relation to DED.

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## Introduction

DED encompasses a set of chronic debilitating conditions affecting the vision and quality of life of millions of persons globally (Stapleton et al., 2017). DED is common, with rising prevalence ranging from 5 to 50% in various populations (Stapleton et al., 2017). DED symptoms can create significant economic burden with a high societal impact as the disease often limits the ability to carry out activities of daily living, reduces work productivity, and detrimentally impacts psychological health (Guo and Akpek, 2020). As defined by the by the Tear Film and Ocular Surface Society (TFOS), DED is “a *multifactorial disease* of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles” (Craig et al., 2017). DED symptoms include pain complaints, oftentimes characterized as “dryness”, “aching”, “tenderness”, to name a few descriptors, and visual complaints (Kalangara et al., 2017).

Human microbiota encompass the microbial species residing in and on the human body and have long been implicated in disease and health (De Luca and Shoenfeld, 2019). Made up of trillions of symbiotic microbial cells, human microbiota are primarily constructed of bacteria in the gut, but also includes entities such as fungi, viruses, and protozoa residing in other places like the skin, oral, and ocular surfaces (Ursell et al., 2012). Systemically, alterations in human gut and oral microbiota have been linked to, amongst many others, inflammatory skin disease, metabolic disease, and even cancers (Ohtani, 2015; Sanz et al., 2015; Zeeuwen et al., 2013). Microbial imbalance has also been

linked to various inflammatory ocular disease states such as uveitis, keratitis, and age-related macular degeneration (Shivaji, 2021). Subsequently, ocular inflammation induced by various human microbiota has also been implicated in DED, however these relationships are less well understood and further studies investigating this topic are warranted. Therefore, as the gut contains the largest concentration of microbiota in the human body, it is important to consider how these organisms and their potential inflammatory down-stream effects impact manifestations of DED. Furthermore, as various DED syndromes such as Sjögren's are known to have oral manifestations, it is also worth considering if oral microbiota affect ocular symptoms. As such, this review will focus on how both the gut and oral microbiota are related to DED.

Advances in sequencing abilities and reduction in costs have allowed for an ever more detailed view of the bacterial microbiome, which consists of the genes found within the bacterial microbiota. 16S ribosomal ribonucleic acid (rRNA) microbiome analysis has become a main technique used to assess bacterial profiles of various samples. Many of the studies mentioned here utilize 16S rRNA analysis so, to spare redundancy, unless otherwise specified this method of analysis will constitute the data provided in this review. However, while 16s rRNA analysis has become a cost-effective way to characterize bacteria, it does have limitations to consider such as its inability to identify viruses, fungi, or microorganisms other than bacteria. Additionally, because 16S rRNA analysis depends on the database used to match genes, the ability of 16S rRNA analysis to identify differences in strains of bacterial species is limited. However, other methods of characterizing microbiota exist including metabolite analysis given that metabolites associated with certain microbes have also been strongly linked to inflammatory and autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis (Yoon et al., 2021).

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## Section snippets

### Study inclusion criteria

This review includes all relevant available published articles examining DED and the human microbiome. However, to spare redundancy, if 3 or more articles reported similar results only the most recent 3 were explicitly reported in the manuscript. We included

data and theories from all randomized trials, systematic reviews, study protocols, diagnostic studies, case reports, proof of concept articles, clinical practice guidelines, qualitative research, animal studies, quality improvement studies, ...

## Results

Our literature review yielded four main themes of available research: 1) the relationship between gut microbiota and DED; 2) the relationship between oral microbiota and DED; 3) the relationship between various modulating factors, DED, and microbiota; 4) scientific methods to alter microbiota. Scientific mechanisms related to DED within the screened microbiota literature pointed to several main paradigms: a) gut microbiota diversity; b) gut microbiota composition; c) gut metabolome; d) oral ...

### Gut microbiota diversity

Gut dysbiosis has been linked to DED, with particular focus on variances in bacterial diversity in the setting of Sjögren's syndrome (SS). One such measure of diversity, namely  $\alpha$ -diversity, is widely utilized and is a description of the number and relative abundances of taxa found within a single sample (Walters and Martiny, 2020). Specifically, a study in the Netherlands compared the gut microbiomes of 39 individuals with primary SS (pSS) to 965 controls and found decreased values of ...

### Oral microbiota diversity

Studies of human oral microbiota have found similar  $\alpha$ -diversity in individuals with various DED subtypes and controls. A study in India of saliva samples from 35 individuals with pSS and 35 controls found similar bacterial  $\alpha$ -diversity between groups (Sharma et al., 2020). Similar results were found in other geographical locations. A Chinese study compared the buccal bacterial  $\alpha$ -diversity of 10 individuals with pSS and 10 controls and found no significant difference between groups (Li et al., ...

### Topical glaucoma therapies

Topical glaucoma therapy has been implicated in the ocular dysbiosis related to DED, as defined by clinical and symptom assessment (5 Item Dry Eye Questionnaire, DEQ-5) (Chang et al., 2022). A US study examined both eyes of individuals with unilateral glaucoma (n=10) (only one eye treated with eye drops) and compared findings between the treated and untreated eye as well as to healthy controls (n=7) (Chang et al., 2022). In individuals with glaucoma,  $\alpha$ -diversity was increased in both eyes ...

## Limitations to the review

Our review has some limitations to acknowledge, including that current studies utilized small samples sizes in comparative cohorts. In addition, many available studies utilized limited cross-sectional designs and have limited diversity in participants. The limited data in human subjects warrants caution in drawing conclusions from associations, especially when applying findings across different racial populations and when considering the impact of time. Larger, longitudinal studies with ...

## Declaration of interest

Professor Alon Harris would like to disclose that he received remuneration from AdOM, Qlaris, and Cipla for serving as a consultant, and he serves on the board of AdOM, Qlaris and SlitLed. Professor Alon Harris holds an ownership interest in AdOM, Oxymap, Qlaris, and SlitLed. If you have questions regarding paid relationships that your physician/researcher may have with industry, you are encouraged to talk with your physician/researcher, or check for industry relationships posted on individual ...

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## CRedit authorship contribution statement

**Gal Antman:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Lukas Ritzer:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Anat Galor:** Writing – review & editing, Supervision. **Alice Verticchio Vercellin:** Writing – review & editing. **Brent A. Siesky:** Writing – review & editing. **Denise Alabi:** Writing – review & editing. **Jason Vayner:** Writing – review & editing. **Fani Segev:** Writing – review & ...

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