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Features of the human eye microbiota in normal and pathological conditions

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Microorganisms isolated from the ocular surface and conjunctiva have been primarily associated with ocular surface diseases such as blepharitis, trachoma, and dry eye syndrome, and have also suggested a role for the ocular and nonocular microbiome in retinal diseases including age-related macular degeneration, glaucoma, uveitis, and diabetic retinopathy. However, relatively little attention is paid to understanding that microorganisms are an integral part of the structure of the eye. Colonizer pioneers interacting with the receptors of eye cells form local immunity, activating pro-inflammatory cytokines. During human ontogenesis, the qualitative and quantitative composition of the ocular microbiome changes depending on the environment.
In 2008, when the "human microbiome" project was launched, the eye was excluded from this study due to the low biomass of the environment.
The purpose of this review is to summarize current data on the microbiota of the human eye in normal conditions and its changes in ophthalmological diseases. We summarized research results from around the world and found that this contradicts conventional wisdom. So, at first glance, the area for settlement is quite small, however, the ability of microorganisms to form structurally specific colonies, using various adhesive factors, creates not just a surface biofilm, but a unique individual landscape of the eye. However, not all of these microorganisms can be isolated using culture methods, so perhaps this is what influenced the formation of the theory about the low biomass of the eye microbiome.
Conclusion: The healthy ocular surface is characterized by a relatively stable microbiome with a relatively low diversity of microorganisms of a certain species. Biofilm landscapes are an integral anatomical unit of the eye, as this structure plays a role in maintaining its homeostasis by activating or inhibiting local cytokines.

Key words:
eye microbiome, ocular surface, ophthalmic diseases, ocular dysbiosis

Introduction. Today, there is a significant increase in eye diseases among both adults and children, associated with obesity, insulin resistance, type 2 diabetes, hypertension, ischemic heart disease, hyperlipidemia, and stroke. Glaucoma is also a leading cause of irreversible vision loss worldwide [1]. Moreover, conjunctival tumors, which account for about 9% of all eye tumors, are more common in middle-aged men (46 ± 18 years). These tumors are mainly localized within the palpebral fissure and are malignant in about 20% of cases [2, 3]. So, what causes these disorders, and how are eye diseases connected to the ocular microbiome?

The first studies documenting the presence of microbes on the surface of the eye date back to 1930, when only conventional culture methods were used to identify microorganisms. Over time, improved and more sensitive research methods have provided more accurate data. High-tech gene sequencing has become the gold standard for studying the ocular surface microbiome. The most reliable diagnostic methods include 16S rRNA and 16SrRNA gene-based sequencing and whole metagenome sequencing.

The study of the ocular surface microbiome is a new research field aiming to understand how the microbial community may help maintain homeostasis or potentially contribute to diseases that arise due to shifts in microbial populations. Typically, the normal ocular microbiota represents both bacterial colonization and temporary and/or recurrent bacterial contamination. The normal resident ocular microbiota consists of relatively constant bacterial species that colonize specific eye biotopes during birth and human ontogenesis, and it has the capacity for rapid recovery if disrupted. The autochthonous eye microflora is currently divided into obligate microflora, which according to modern concepts of the microbiome, constantly inhabits the oral cavity, urogenital system, gastrointestinal tract (GIT), and skin. Whether it is present in ocular biotopes remains unclear. Facultative microbiota, which is accidental and/or temporary, consists of microorganisms originating from the environment and depends on the host's immune

system status. Transient microbiota, composed of conditionally pathogenic microorganisms that colonize ocular biotopes for a limited period without causing disease or inducing temporary (fleeting) symptoms. However, in cases of resident microflora disruption or death, transient organisms may occupy the freed niche, potentially leading to pathology. Allochthonous microbiota includes microbes that are not typical for a specific biotope.

Normal colonization of ocular biotopes involves a stable presence of biofilm-forming microorganisms balanced by host defense mechanisms. Resident microorganisms present on the healthy ocular surface are constant or represent recurrent contamination, provided there are no systemic or autoimmune diseases. In contrast, colonization by allochthonous microorganisms is more commonly found on the eyelid margins. The microbiota of the eye's internal contents forms from both the wall-associated microbiota and those constantly entering the biotope from the external environment or other organs. It includes microorganisms from both resident and transient microbiota.

Sequencing of 16S rRNA and 16SrRNA genes from conjunctival swabs can achieve almost 100% success, while the positivity rate of bacterial culture for establishing the ocular surface microbiome is only 60% and fungal culture ranges from 3% to 65%. The ocular surface is constantly exposed to environmental bacteria, and traditional culture-based microbiological studies yield low diversity of microorganisms from this area and are therefore uninformative, which is a major challenge in ophthalmology.

Aim. The purpose of this review is to summarize current data on the microbiota of the human eye in normal conditions and its changes in ophthalmological diseases.

Material and methods

3 independent authors systematically reviewed the studies published in English using the PubMed, MEDLINE database or Google Scholar through September 2024. The following search terms were used: "eye microbiome", "ocular surface", "ophthalmic diseases", "ocular dysbiosis". We included case-control studies, cohort studies, meta-analyses, review articles, and our own data. Additionally, published articles cited in the studies identified using the above criteria were selected.

Results

The stable presence of commensal bacteria on the eye surface has long been a subject of debate. In the 1960s and 70s, it was believed that in 30–50% of the population, conjunctival microbiota was either entirely absent or represented by a minimal number of microorganisms due to various eye diseases [4,5] and the presence of protective proteins in the tear fluid. However, clinical studies over the past 10 years have shown that, like any mucosal or skin surface, the eye harbors numerous Gram-positive and Gram-negative microorganisms. In 2009, researchers at the Bascom Palmer Eye Institute launched the Eye Microbiome Project. This effort provided new data on ocular microbiota, revealing significant diversity in the composition of commensal microorganisms on the eye surface and conjunctiva, averaging 221 bacterial species, primarily from the phyla Proteobacteria (64%), Actinobacteria (19.6%), and Firmicutes (3.9%) [6]. However, studies by Huang et al. identified 526 species, and Zhou et al. identified about 610 microbial species from the eye surface.

At birth, the microbiota of the eye surface and conjunctiva in newborns closely resembles the cervical microbiota of the mother [7], and includes primarily: Treponema spp., Haemophilus vaginalis, Streptococcus viridans, Staphylococcus epidermidis, Micrococcus spp., Bacillus spp., Bacteroides spp., Propionibacterium acnes, Peptococcus spp., Peptostreptococcus spp., Gardnerella spp., Lactobacillus spp., Bifidobacteria spp., Escherichia coli, Neisseria spp., Staphylococcus aureus, and Candida spp. In the days following birth, the eye microbiome gradually changes, and the pioneer microbes of the developing biofilm are most often representatives of the genera Staphylococcus spp., Escherichia coli, Streptococcus spp., Micrococcus spp., Corynebacterium spp., and Propionibacterium spp. [8,9], which may remain the foundation of the eye's biofilm throughout life. The origin of microorganisms entering the ocular biotope ecosystem is diverse, but skin and gastrointestinal tract (GIT) microbiota dominate. The formed biofilm remains relatively stable throughout life, but antibiotic use, surgery, contact lens wear, frequent use of cosmetics, seasonal allergies, and other factors affect the quantitative and qualitative dynamics of the eye microbiome [10,11]. Under these conditions, the biofilm base may include genera such as Haemophilus spp., Pseudomonas spp., Neisseria spp., and Chlamydia spp., which are less common in a healthy eye microbiome. The number of transient surface microbes increases, including Rothia spp., Herbaspirillum spp., Leptotrichia spp., and Rhizobium spp. In 5% of cases, Peptococcus spp., Clostridium spp., Peptostreptococcus spp., Cephalosporium spp., and Fusarium spp. are isolated from the ocular surface using bacteriological methods.

In addition to bacteria, the eye microbiome also includes fungi, with 65 genera identified to date. The fungal core of the resident ocular microflora consists mainly of Malassezia spp., Rhodotorula spp., Davidiella spp., Aspergillus spp., Alternaria spp., Setosphaeria spp., and Haematonectria spp., accounting for over 80% of the fungal microbiome [12,13].

Some fungi, such as Penicillium spp., Malassezia spp., Aspergillus spp., Phialophora spp., and Trichoderma spp., can be detected using conventional bacteriological methods. However, genera such as Rhodotorula spp., Davidiella spp., and Alternaria spp. have been identified via high-throughput sequencing methods.

Since fungi are known to be causative agents of eye diseases like keratitis, endophthalmitis, blepharitis, conjunctivitis, and keratomycosis, it is crucial to evaluate the role and the quantitative and qualitative changes of the fungal microbiome on the ocular surface.

Characteristics of the Ocular Surface Microbiome

The ocular surface includes the cornea, conjunctiva, upper and lower eyelids, and eyelashes. It is in constant contact with the environment and is continuously influenced by it. Dynamic fluctuations in the ocular surface microbiome play an important role in maintaining local homeostasis and preventing the proliferation of pathogenic species. Commensal microorganisms present on the eye surface suppress the growth of pathogenic bacteria, fungi, and viruses through competitive mechanisms. Modification of these populations on the surface of the eye, particularly an increase in Corynebacterium spp., Propionibacterium spp., Streptococcus spp., and Staphylococcus spp., is linked to both physiological and pathological transformations. It is also worth noting that the eye surface is a low-biomass niche, containing about 0.06 bacteria per conjunctival cell, compared to 10 bacteria per epithelial cell in the intestines.

According to literature, alterations in normal ocular microflora are primarily associated with infectious diseases of the eyelids, such as blepharitis, chalazion, or even bruising under the eye. Diseases of the conjunctiva — including conjunctivitis and pinguecula — as well as of the cornea — such as keratitis and corneal ulcers — are also significant factors influencing the microbiome's quantitative and qualitative changes.

The most common route for acute infectious conjunctivitis and keratitis is contact with contaminated fingers. However, bacteria may also reach the conjunctiva from the eyelid margins and surrounding skin, the nasopharynx via the nasolacrimal duct, infected eye drops, or contact lenses. Factors contributing to infection include obstruction of the nasolacrimal duct, abnormal tear fluid, and epithelial damage due to trauma, dry eye syndrome, or conditions such as Bell's palsy in adults and preseptal/orbital cellulitis in children. Wearing contact lenses is also a major risk factor for microbial keratitis [14, 15].

In a study conducted by Zhang H. et al., the ocular surface microbiome of contact lens users was compared with that of non-users using 16S rRNA gene sequencing. Among non-users, there was an increased abundance of Haemophilus spp., Neisseria spp., Streptococcus spp., Corynebacterium spp., Lactobacillus spp., Staphylococcus spp., and Rothia spp. [16], and a lower abundance of Pseudomonas spp., Acinetobacter spp., and Methylobacterium spp. compared to lens wearers. These results suggest that prolonged use of contact lenses alters the eye microbiome, making it more similar to that of the skin. There are also differences in microbial abundance between users of soft contact lenses and orthokeratology lenses [17]. For example, in orthokeratology lens users, there is a decrease in Bacillus spp., Tatumella spp., and Lactobacillus plethora, while the abundance of Delftia spp. decreases and Elizabethkingia spp. increases in users of soft lenses.

It is also hypothesized that various forms of dry eye syndrome are linked to changes in the ocular surface microbiome [18,19]. Dry eye can be associated with meibomian gland dysfunction, which leads to a deficiency in the lipid layer that normally slows down tear evaporation. In other cases, dry eye syndrome is associated with insufficient tear secretion in primary and secondary Sjögren's syndrome, which affects the secretory function of the conjunctiva. Sjögren's syndrome is an autoimmune condition that causes lymphocytic infiltration and destruction of lacrimal glands, which produce the aqueous layer of the tear film—leading to dry eye. In such cases, microorganisms play a critical role. For instance, clinical studies of conjunctival swabs from patients with dry eye syndrome showed a decrease in microbial diversity and an increase in the abundance of Brevibacterium spp., Corynebacterium macginleyi, Propionibacterium spp., Corynebacterium spp., Streptophyta spp., Enhydrobacter spp., and Staphylococcus spp. [20]. These bacteria produce lipolytic exoenzymes that can hydrolyze cholesterol esters and damage the lipid components of the tear film.

The core fungal microbiome of the ocular surface consists of: Alternaria spp., Fusarium spp., Aspergillus niger, Aspergillus flavus, Curvularia spp., Penicillium spp., Helminthosporium spp., Candida albicans, C. guilliermondii, C. parapsilosis, Saccharomyces cerevisiae, Hormodendrum spp., Rhodotorula rubra. These are the most frequently isolated fungi from the ocular surface. However, the fungal microbiome is influenced by factors such as age, lifestyle, diet, and climate, resulting in changes over time. Under such influences, transient fungal species can appear, including: Retroconis spp., Diaporthe spp., Rhizoctonia spp., Myrothecium spp., Gibberella spp., Cephaliophora spp., Macrophomina spp., Lasiodiplodia spp., Botryosphaeria spp., Bipolaris spp., Pleurostomophora spp., Cochliobolus spp. and Neocosmospora spp..

The stable ocular surface microbiome includes genera such as: Amycolatopsis spp., Snodgrasslela spp., Cutibacterium spp., Sphingomonas spp., Ochrobactrum spp., Bacillus spp., Cupriavidus spp., Lactococcus spp., Pseudomonas spp., Acinetobacter spp., Bacillus spp., Chryseobacterium spp., Neisseria spp., Methylobacterium spp., Acinetobacter spp., Haemophilus spp., Streptococcus spp., Corynebacterium spp., Lactobacillus spp., Staphylococcus spp., Rothia spp.. Changes in the microbiome under normal physiological conditions can vary slightly in both quantity and quality from person to person. For instance, an increased abundance of Amycolatopsis spp., which produces many types of antibiotics such as epoxyquinomycin (from Amycolatopsis sulphurea) and vancomycin (from Amycolatopsis orientalis), may occur. These bacteria are capable of enzymatically hydrolyzing ester bonds in polylactic acid biofilms and have anticancer activity in vitro, potentially counteracting leukemia and lung cancer.

Tear film microbiome

The lacrimal glands, located above each eyeball, continuously secrete tear fluid, which is distributed across the eye surface each time the eyelids blink. Excess fluid drains through the lacrimal ducts into the nose, thereby also in-

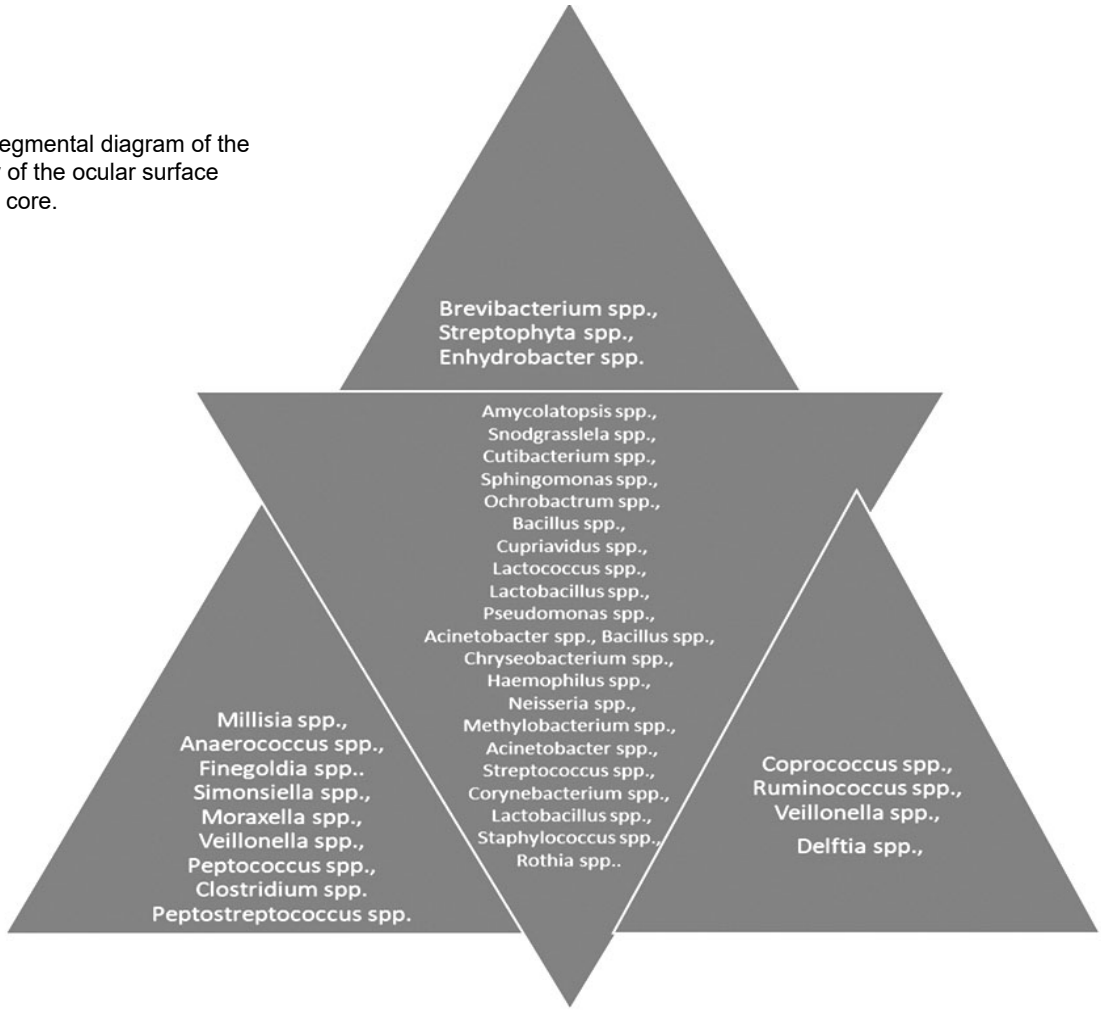

Figure 1. Segmental diagram of the connectivity of the ocular surface microbiome core.

fluencing the microbiome of the nasal passages and oropharynx.

The tear film consists of three layers: an outer lipid layer, middle aqueous layer and an inner mucin layer. Each layer plays an important role in maintaining tear film homeostasis, covering the cornea and conjunctiva, and performing several vital functions. The tear film provides lubrication,prevents desiccation of the ocular epithelium,ensures a smooth optical surface for light refraction, supplies oxygen, serves as a key component of the innate immune system, protecting against potential pathogens. The lipid component of the tear film is primarily produced by the meibomian (tarsal) glands of the eyelid, while enzymes and proteins are mostly synthesized in the main lacrimal glands. Some proteins also come from epithelial cells of the cornea and conjunctiva, serum exudates and neutrophils, which are especially present in tears after waking up.

The lipid layer contains cholesterol esters, wax esters, triglycerides, and phospholipids. Cholesterol is essential for maintaining the integrity of cell membranes, is a precursor of vitamin D and steroid hormones, and plays a critical role in the development of the central nervous system. In tears, cholesterol is one of the main non-polar lipids produced by the meibomian glands. Its concentration in tears is about 560 mg/L (1.45 mM), while in meibum it ranges from 0.02% to 0.5%. Tear samples often show higher cholesterol levels than those found directly in the meibomian glands. Triglycerides, along with other non-polar lipids (wax esters, cholesterol esters, cholesterol, hydrocarbons), form the bulk of the lipid layer in the tear film, comprising about 4% of the gland's secretions. The most common triglyceride is triolein (containing only oleic acid), which accounts for up to 20% of all triglycerides. Lipids help reduce surface tension and slow down tear evaporation. Ocular surface microorganisms influence the lipid layer. For example Staphylococcus epidermidis, Propionibacterium acnes, and Propionibacterium granulosum secrete cholesterol esterase and wax ester esterase [22], Staphylococcus aureus can produce phospholipases, lipases, and enzymes that modify fatty acids. Corynebacterium macginleyi and Corynebacterium accolens are lipophilic bacteria capable of hydrolyzing triolein, releasing oleic acid [23]. This is of enormous importance for clinical medicine, particularly for individuals who wear contact lenses or suffer from "dry eye syndrome". The accumulation of tear film components—such as lipids, proteins, and mucins—can begin within just a few minutes of wearing lenses, disrupting tear film structure. Any pathological changes in the microbiome of contact lens wearers can lead to irreversible eye

conditions. It is thus hypothesized that resident microflora helps maintain lipid balance in the tear film. For instance, in dry eye syndrome, the ratio of cholesterol esters to wax esters in the meibomian glands significantly decreases, though the functional and structural consequences remain speculative. Cholesterol regulation through esters in the eye lens may be critical, as lens cholesterol levels are extremely high and are linked to lifespan and cataract formation. Cholesterol has been extensively studied since it was found that its levels can rise to 50% with age in the human aortic intima and may contribute to atherosclerotic plaque formation. In dry eye, ophthalmologists often encounter altered cholesterol-to-cholesterol ester ratios, which are significantly reduced in the meibomian glands [24, 25].

The mucin layer of the tear film consists of mucins secreted by goblet cells, which help lower surface tension and evenly spread the tear film across the eye. Microorganisms influence mucin production—for instance, Corynebacterium spp. helps stimulate mucin circulation and maintain the tear film's antimicrobial properties. On the other hand, excessive proliferation of mucin-degrading bacteria or mucinase-producing microbes can destroy the tear film's composition.

Taken together, resident and transient eye microorganisms affect tear composition by using tear components and secreting enzymes and metabolites as substrates for their growth and reproduction. In some cases, these organisms may also originate from neighboring biotopes of the human body.

Conjunctival Microbiome

In addition, the microbiomes of the conjunctiva and cornea have very similar microbial taxonomic profiles, differing mainly in proportions. According to the literature, the number of genera constituting the core resident conjunctival microbiota ranges from 12 to 24. Based on this, we identified a typical core of the conjunctival microbiota, which includes: Pseudomonas spp., Bradyrhizobium spp., Corynebacterium spp. (C. xerosis, C. pseudodiphtheriticum), Acinetobacter spp., Brevundimonas spp., Aquabacterium spp., Sphingomonas spp., Streptophyta spp., Methylobacterium spp., Bacillus spp., Ralstonia spp., Staphylococcus spp., Streptococcus spp. (S. pneumoniae, S. viridans), Millisia spp., Anaerococcus spp., Finegoldia spp., Simonsiella spp., Moraxella catarrhalis and Veillonella spp., Peptococcus spp., Clostridium spp., Peptostreptococcus spp., Cephalosporium spp., Cutibacterium spp., Rhodococcus spp., Klebsiella spp., Erwinia spp. These microorganisms are commonly found in healthy individuals. However, both the qualitative and quantitative composition of the conjunctival microbiome may vary significantly depending on numerous factors, such as age, lifestyle, immunity, environmental exposure, and underlying systemic diseases.

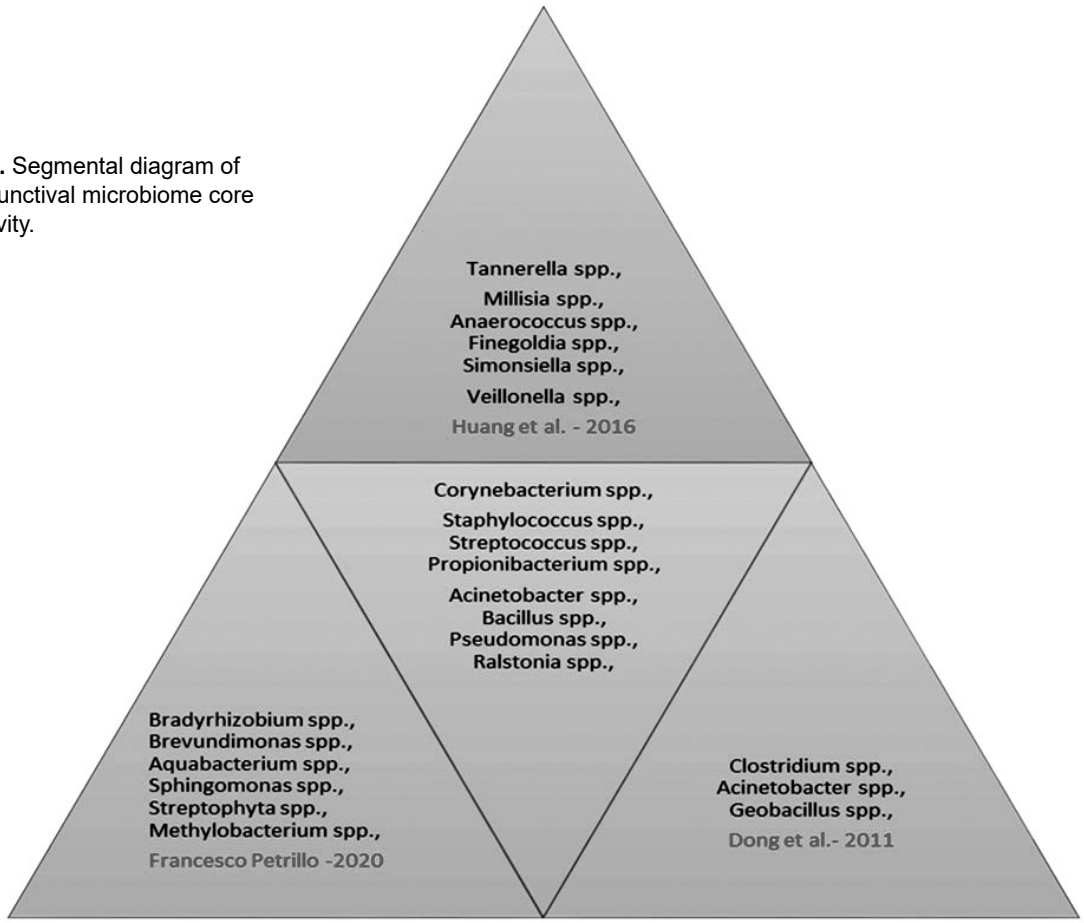

Figure 2. Segmental diagram of the conjunctival microbiome core connectivity.

Vitreous Body Microbiome

The vitreous body is transparent and composed mainly of water and proteins, and until recently, it was considered a sterile biotope. However, microorganisms potentially responsible for acute or chronic eye diseases have now been found on the inner parts of the eye. Diagnosis of such infections is challenging, especially due to the inability to culture many microorganisms using standard methods, while PCR-based techniques often yield inconsistent results. A promising approach to overcome this limitation is the use of deep metagenomic sequencing. Indeed, metagenomic studies have demonstrated that the vitreous body of patients with endophthalmitis contains a wide variety of microorganisms that would otherwise be undetectable by routine diagnostic methods.

Research involving microbiomes related to systemic scleroderma and ocular conditions such as keratitis, uveitis, and dry eye disease in patients with Sjögren's syndrome (particularly those with comorbidities) consistently points to a decrease in microbial diversity, but an increase in the abundance of: Acinetobacter spp., Bacillus spp., Enterobacter spp., Stenotrophomonas spp., Escherichia spp., Klebsiella spp., Neisseria spp., Paenibacillus spp., Pseudomonas spp., Staphylococcus spp., Streptococcus spp. These genera were identified in vitreous samples of patients with endophthalmitis [26–29]. Additionally, Propionibacterium spp. has been linked to conditions such as uveitis and endophthalmitis. Sporomusa spp. is typically present in individuals who have pets (especially cats and dogs). Tannerella forsythia is often detected in patients with atherosclerosis, as it can induce foam cell formation and accelerate the development of atherosclerotic lesions. It's also found in women with bacterial vaginosis.

The core microbiome of the vitreous body in healthy individuals [30] includes: Acetonema spp., Anaerotruncus spp., Arthrobacter spp., Bacillus spp., Bdellovibrio spp., Geobacillus spp., Janthinobacterium spp., Mesorhizobium spp., Paenibacillus spp., Pelosinus spp., Pimelobacter spp., Propionibacterium spp., Sediminibacterium spp., Shigella spp., Shimwellia spp., Sporomusa spp., Tannerella spp., Thermosinus spp. However, a decrease in the abundance of these species is often observed in patients with retinitis. Among the fungi isolated in the samples in cases of endophthalmitis, the following were identified: Cryptococcus neoformans, Sporothrix schenckii, Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, in addition to Aspergillus spp., Fusarium spp. [31]. Fungal retinitis is rare but has been associated with: Torulopsis glabrata, Pseudomyxoma peritonei [32], Candida albicans [33].

Causes and clinical manifestations of ocular dysbiosis

Microbial communities of the human eye are specific and changes in their structure may contribute to the pathogenesis of diseases. A healthy microbiome is characterized by a diverse environment, while an abnormal microbiome (dysbiosis) can alter ocular homeostasis, triggering a cascade of infectious and inflammatory processes [34, 35]. In the last two decades, there has been a trend in changing the species composition of the eye microbiome towards an increase in the percentage of conditionally pathogenic microflora. Among the reasons for the shift in the microbiological landscape, the following are distinguished: hormonal disorders (use of hormonal drugs); inflammatory processes of adjacent areas (barley, phlegmon); eyelid swelling; stagnant phenomena; use of medications; unfavorable environment (too dry climate, dust); work in hazardous production, including frequent contact with a large number of chemicals; neoplasms located in the bulbar region; contact with cosmetics and detergents, as well as foreign microobjects; chalazion (barley); complications when using contact lenses; ectropion (a condition in which the eyelid turns outward); entropion (a condition in which the eyelid turns inward); side effects when using eye drops or complications; droopy eyelid syndrome, which occurs when the eyelid can easily roll down; hay fever (also known as allergic rhinitis); trauma, such as blunt trauma or burns; orbital cellulitis; prolonged computer use; prolonged use of antihistamines; use of antidepressants and hypertension medications; TORCH infections and taking medications that can affect fetal development during pregnancy; acne; use of birth control pills; Parkinson's disease; autoimmune and systemic diseases, including Sjögren's syndrome, rheumatoid arthritis, lupus, scleroderma, graft-versus-host disease, sarcoidosis, thyroid disease; vitamin A deficiency.

The presence of a healthy ocular microbiome strengthens the innate local immune barrier, significantly increasing the concentration of immune factors in the tear film, including IgA, complement proteins, and acute phase proteins. Changes in the quantitative and qualitative indicators of a healthy microbiome influence the occurrence of specific syndromes, in particular, red eye syndrome, dry eye syndrome, and conjunctival chemosis [36, 37].

Dysbiotic disorders are clinically manifested by: a feeling of stinging, burning, or irritation in the eyes. Patients complain of a sticky mucus in or around the eyes; increased sensitivity to light; redness of the eyes; a feeling as if something has gotten into the eyes; difficulty wearing contact lenses; difficulty driving at night; tearing, which is the body's reaction to the irritation of dry eyes; tingling, burning, or pressure in the eyes; a feeling of sand or a foreign body. Epiphora is a controversial symptom associated with dry eye irritation and the resulting intermittent painful tearing. Pain is sharp, dull, and may be described as a localized pain behind the eye or even around the orbit. Redness is a common complaint that is often exacerbated by the outflow effect of vasoconstrictors, which are found in many over-the-counter eye drops designed to reduce redness. Vasoconstrictors can reduce redness in the short term by constricting the episcleral vessels, but can have a draining effect and increase redness after the drops are stopped for a short period of time. Blurred vision, especially intermittent blurring, is a common complaint and can also be described as seeing glare or halos around lights at night. Fluctuating vision and difficulty reading; feeling

heavy eyelids or difficulty opening the eyes; excessive blinking; decreased blink rate; altered color perception; eyelid twitching; dryness is a common problem for contact lens wearers, and irritation can make contact lenses uncomfortable or even impossible to wear; tired eyes (closing the eyes may provide relief for some people with dry eye syndrome); inability to cry.

Classification of Ocular Dysbiosis

Normal ocular microflora is an open biocenosis and a highly sensitive indicator system that responds to environmental influences with quantitative and qualitative changes and/or dynamic fluctuations. According to modern ideas, the ocular microbiome creates a mucopolysaccharide biofilm, which is a joint product with the macroorganism. An imbalance of ocular microorganisms that are part of the biofilm can lead to excessive growth of certain species that can cause inflammation, both local and systemic. Or systemic diseases of the macroorganism can affect the qualitative and quantitative indicators of the ocular microbiome. Having collected literature data, we tried to form dysbiotic disorders and diseases that most often correlate with changes in the quantitative and qualitative indicators of ocular microbiome microorganisms.

Thus, the following forms of ocular dysbiosis can be distinguished. Primary ocular dysbiosis, which is associated with changes in the qualitative and quantitative indicators of microorganisms caused by seasonal changes in climate and dietary habits. Secondary dysbiosis is a change mainly associated with systemic or autoimmune diseases. Mixed dysbiosis, which includes a complex of causes that affect the quantitative and qualitative indicators of the ocular microbiome.

The clinical classification of ocular dysbiosis includes acute and chronic dysbiosis. Acute ocular dysbiosis occurs suddenly against the background of trauma, burn, use of drugs, etc. Acute dysbiosis includes three degrees of violation of qualitative and quantitative indicators of the ocular microbiome. Chronic ocular dysbiosis is characterized by changes in microbial indicators of the microbiome core over a long period of time and pronounced clinical symptoms.

The first degree of ocular dysbiosis is associated with dynamic fluctuations of opportunistic microflora, which is the core of the ocular surface and includes the cornea, conjunctiva, eyelid and eyelashes. Often manifests as contact blepharoconjunctivitis. A classic allergic reaction of the eye to direct contact with an allergen, especially cosmetics or hygiene products. Develops in a delayed type, may appear a few days after contact.

The physical barrier of the ocular surface consists of intact and densely packed epithelial cells that are tightly connected to each other. The chemical barrier includes antibacterial substances such as lysozyme and secretory immunoglobulin A and mucins, which are mainly secreted by goblet cells. These proteins can inhibit microbial growth and neutralize toxins. However, with an increase in the quantitative indicators of microorganisms that make up the ocular microbiome, the expression of immunocompetent cells is observed, which will subsequently lead to infiltration of ocular tissues by immune cells, including Th1 and Th17 cells that secrete pro-inflammatory cytokines, represented by IFN-γ and IL-17. [38]. These cytokines cause damage to the physicochemical barriers, including epithelial squamous metaplasia, destruction of the epithelial tight junction, dysfunction and loss of goblet cells, as well as depletion of antibacterial components in tears. The destruction of the physicochemical barrier initiates an immune response, intensifying the inflammatory process.

The second degree of dysbiosis is characterized by symptoms indicating changes in the qualitative parameters of the ocular microbiome, which under physiological conditions can be compensated by an increase in other types of microorganisms. For example, neuropathy, in which there is a decrease in the frequency of blinking and a decrease in gland secretion, which ultimately causes tear film instability.

Microorganisms that are part of the ocular microbiome can interact with the nervous system by directly stimulating neurons or by secreting neurotransmitters. They can also, as previously described, produce lipids to maintain tear film stability. In addition, factors that cause inflammation can regulate the activity of the nervous system. IL-2 can bind directly to the delta-opioid receptor in peripheral nerve cells. IL-1β can inhibit nerve-mediated secretion of the lacrimal glands. Androgen plays an anti-inflammatory role by inducing the synthesis of TGF-β and reducing the levels of TNF-α and IL-1β. [39]. It also promotes the secretion of the lacrimal and meibomian glands. At this stage, patients often complain of a painless but rapid decrease in visual acuity, impaired color perception.

Allergic simple or seasonal conjunctivitis is characterized by eyelid edema, narrowing of the palpebral fissure, and lacrimation. Frequent dynamic fluctuations in the quantitative and qualitative parameters of the ocular microbiome require a substrate and this affects the composition of the tear, depleting and changing the tear film. As a result, tear film homeostasis is disrupted, and ultimately dry eye symptoms occur. If normally the main microbiota of the ocular surface consists of 21 genera in healthy people, then this quantitative indicator is 2 times lower than in patients with dry eye syndrome.

The qualitative and quantitative composition of microorganisms also depends on systemic and autoimmune diseases. For example, in diabetes mellitus and autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma and idiopathic Sjögren's syndrome, Graves' disease, patients complain of pain in the eyeballs, heartburn, tearing, decreased visual acuity, a feeling of sand, and photophobia. Changes in the microbiome of ocular biotopes primarily correlate with the severity of the underlying disease.

The third degree of dysbiosis is partly associated with allergic reactions, leading to allergic conjunctivitis, allergic rhinoconjunctivitis, and atopic keratoconjunctivitis.

Changes in the microbiome include a decrease in the qualitative parameters of the ocular surface and conjunctiva core and an increase in the quantitative parameters among Staphylococcus spp., Streptococcus spp., Coprococcus spp., Ruminococcus spp., Veillonella spp., Delftia spp., Pseudomonas spp., Moraxella spp. [40]. The altered microbial profile leads to increased levels of pro-inflammatory metabolites caused by the activation of pathogenicity factors of these microorganisms, which contributes to oxidative stress and T-cell dysregulation. [41,42].

The third degree of dysbacteriosis is clinically associated with infectious processes such as keratitis, iridocyclitis, retinopathy, retinitis, angiopathy, and uveitis. Damaged blood vessels can leak fluid and cause edema. Aberrant angiogenesis leads to bleeding into the middle part of the eye and scarring or causes dangerously high pressure inside the eye.

Analysis of the microbial composition in patients with uveitis revealed a decrease in the quantitative index among the genera Ruminococcus spp., Oscillospora spp., Faecalibacterium spp., Ruminococcus spp., Dialister spp., Dorea spp., Blautia spp., Clostridium spp., Coprococcus spp., Bifidobacterium spp., Odoribacter spp., Veillonella spp., Faecalibacterium prausnitzii, Akkermansia spp., Mitsuokella spp., Magasphaera spp., Roseburia spp., Bacteroides spp., Clostridium spp., Lachnospira spp., but an increase in the number of microorganisms among representatives of the genus Prevotella spp. [43].

To date, the etiological factors of chronic conjunctivitis are Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis, Moraxella lacunata, Chlamydia trachomatis, Streptococcus pyogenes, Streptococcus viridans, Streptococcus faecalis, P. aeruginosa, Corynebacterium spp., Micrococcus spp., Bacillus spp., Propionibacterium spp., Proteus, spp., Klebsiella, spp., Eschericha, and less commonly L. monocytogenes. [44].

Trauma or surgery on the eye, congenital anomalies such as strabismus, hyperopia, myopia, existing corneal abnormalities and wearing contact lenses, keratomycoses are the main causes of keratitis. Among the pathogens of bacterial keratitis (in more than 80% of cases), there are: Pseudomonas spp., Corynebacterium spp., Staphylococcus spp., Peptoniphilus spp., Sphingomonas spp., Paracoccus spp., Bosea spp., Pneumococcus spp., Escherichia coli, Neisseria spp., Proteus vulgaris, Moraxella spp., Sarcina spp., and Streptococcus spp., (Streptococcus pneumoniae, Streptococcus feacalis, Streptococcus viridans). In rare cases, keratitis caused by Nocardia spp. and Acanthameba spp. is diagnosed. In 3% of cases, it is a mixed infection: viral-bacterial and viral-bacterial-fungal. [45].

Patients with blepharitis have an increase in the relative abundance of the genera Staphylococcus spp., Streptophyta spp., Corynebacterium spp. and Enhydrobacter spp., together with a decrease in the quantitative index of Propionibacterium spp. [46].

Chronic ocular dysbiosis is associated with chronic and recurrent inflammatory processes accompanied by immune cell infiltration, which can lead to uveal damage and complications. Common complications of uveitis are mainly cystic macular edema, glaucoma, and cataracts.

In patients with glaucoma, there is an increase in qualitative and quantitative indicators among the genera Paenibacillus spp., and Dermacoccus spp., but a decrease in Morganella spp., and Lactococcus spp. [47]. Corynebacterium spp., Cutibacterium spp., Blautia spp., Akkermansia spp., Faecalibacterium spp., Ruminococcus spp., Dorea spp., Roseburia spp., Lachnospira spp., and Komagataeibacter spp. are the dominant genera in patients with glaucoma, but a decrease in the quantitative indicator of Staphylococcus warneri is observed [48].

Keratomycoses are often combined with keratitis and other corneal pathologies. Mycotic keratitis is one of the main causes of infectious keratitis, with a worldwide prevalence of 17-36%. Symptoms of keratomycosis vary depending on the etiological factor, however, all are characterized by acute eye pain, redness of the conjunctiva and eyelids, decreased vision, corneal ulceration, and stromal infiltrates. Superficial keratomycosis leads to thinning of the epithelium. Small grayish-white formations appear on the surface of the cornea. In the case of untimely diagnosis or lack of treatment, they grow deep and die, forming a fistula. Fistulas most often occur in patients with systemic diseases such as diabetes and anemia. As a rule, such patients have non-healing fistulas on other areas of the skin, usually the nasolabial triangle. Fungal ulcers are most often located in the center of the cornea. They resemble a disk, 2 to 8 mm in diameter, with a gray center and raised edges [49]. More than 70 species of fungi, of which Fusarium spp. (Fusarium solani), Alternaria spp., Cladosporium spp., Pseudallescheria spp., Geotrichum spp., Curvularia spp., Acremonium spp., Scedosporium spp., Penicillium spp., Cylindrocarpon spp., Scytalidium spp., Trichophyton spp.(Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton schoenleinii, Trichophyton erinaceия), Aspergillus spp.(Aspergillus flavus and Aspergillus fumigatus), Phaeoisaria clematidis, Pleurothecium recurvatum, Candida spp. (C. albicans, C. guilliermondii and C. parapsilosis), account for 95% of all cases. The geographical distribution of fungi is primarily due to the close anatomical connection between the paranasal sinuses and the orbit. Fungal sinusitis often invades the orbit, leading to ocular keratosis. Often this process can be quite acute for 48 hours, during which symptoms such as bilateral ophthalmoplegia, chemosis, and proptosis of both eyes may occur. Another option is orbital cellulitis caused by Candida spp. and Aspergillus spp. Candida spp. are more common in people with chronic ocular surface disease, and Fusarium spp. and Aspergillus spp. are more common in patients who wear contact lenses [50]. Increased Fusarium solani counts are associated with rapid complications, including corneal perforation, while Curvularia spp. fungi

tend to cause persistent infection, manifesting as lightly pigmented lesions.

Keratomycosis is difficult to treat, the use of topical corticosteroids can enhance fungal replication and reduce the resistance of corneal tissue to fungal invasion, leading to increased penetration through the cornea. Fungal replication and dead fungal hyphae cause a severe allergic and inflammatory reaction, and the release of fungal proteases destroys the stroma.

Conclusions

Microbial dysbiosis of the ocular surface, conjunctiva, and vitreous is a new area of research. Interpretation of ocular surface microbiome results can be challenging due to the many variables associated with the characteristics of this unusual environment. As a result of such variability, there is still no consensus on what constitutes the ocular microbial core and what influences its stability. In this review, we have highlighted the composition of microbiomes in various ocular surface, conjunctiva, and vitreous diseases, formed a possible core microbiome, taking into account the results of many years of research by specialists around the world, and attempted to classify changes in ocular dysbiosis taking into account changes in quantitative and qualitative indicators of microorganisms, since dysbiosis is an important mechanism in the development of ocular diseases and a future therapeutic target. We hope that our current review has illustrated the variability in obtaining accurate data on the ocular microbiome and the difficulties in interpreting the results, and has highlighted the need for standardization throughout the process.

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