

Gut microbiota disorders and ophthalmic diseases

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ABSTRACT

Introduction: The intestinal microbiota is one of the key elements in maintaining human homeostasis. Disruption of its balance, known as dysbiosis, is now increasingly implicated as a contributing factor for many diseases, including ophthalmic conditions.

Materials and methods: This review synthesizes a current literature review 2020–2025 addressing the relationship between the interplay between gut microbiota dysbiosis and major ophthalmic disorders, notably age-related macular degeneration (AMD), retinopathy of prematurity (ROP), glaucoma, diabetic retinopathy (DR), and autoimmune uveitis.

Results: Potential pathogenic mechanisms are discussed, including compromised intestinal barrier integrity, aberrant immune activation, the presence of bacterial endotoxins (e.g., LPS), and the influence of microbially derived metabolites on the gut–retina

axis. Particular emphasis is placed on the roles of Th17 and Treg cells, inflammatory cytokines, and the importance of short-chain fatty acids (SCFAs), among other bioactive molecules. The significance of the neonatal microbiome and its influence on the development of ophthalmic diseases in premature infants is also highlighted.

Conclusions: Gut microbiota dysregulation may represent a key contributor in the development and progression of several ophthalmic conditions. The microbiota–gut–retina axis represents an emerging and promising therapeutic target for future research and therapies. Integrating microbiota-targeted interventions may significantly improve treatment outcomes and quality of life for ophthalmic patients.

Keywords: gut microbiota disorders; gut–retina axis; microbiota–gut–retina axis; ophthalmic diseases.

INTRODUCTION

The human intestinal microbiota is one of the most important components of the body that enables proper physiological function. It is defined as a community of bacteria, archaea, and eukaryotes colonizing the gastrointestinal tract, which has co-evolved with the host over thousands of years, forming a complex and mutually beneficial relationship [1].

The significance of this system is evidenced, among other things, by the mathematical ratio of human cells (10^{13}) to commensal microbiota cells (10^{14}). Studies have shown that the human intestine can harbor up to ten trillion different symbionts (comprising about 50 bacterial phyla and approx. 100–1,000 bacterial species) [2]. The human microbiome is primarily composed of 2 dominant bacterial phyla: *Bacteroidetes* and *Firmicutes*, with lesser representation from *Actinobacteria*, *Cyanobacteria*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia* [3]. Any disruption in the balance between the host and the intestinal microbiota – due to aging, dietary changes, or antibiotic use – can trigger the development of various diseases, even those unrelated to the gastrointestinal system [4].

In recent years, there has been growing interest in the role of gut microbiota disturbances and their potential links to systemic diseases. Several new concepts have emerged describing such correlations, including the microbiota–gut–brain axis and the microbiota–gut–retina axis. Reports on microbiome involvement

in neurological and psychiatric disorders mainly focus on diseases such as migraine, stress, depression, Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke, autism spectrum disorder, and attention deficit hyperactivity disorder [5, 6]. It is suggested that the gut–nervous system connection regulates immune responses, the endocrine system, and bacterial metabolites. Moreover, the intestinal microbiota may influence neurotransmission and vascular barriers, leading to neuropsychological changes and cerebrovascular function disorders [5].

The literature regarding the gut–retina connection is relatively recent and based on fewer studies. To date, correlations have been described between microbiota disturbances and retinal diseases (age-related macular degeneration – AMD, diabetic retinopathy – DR, retinopathy of prematurity – ROP, hereditary retinal dystrophies), uveitis, glaucoma, dry eye syndrome, bacterial and fungal keratitis, and ocular mucosal disease [6, 7, 8].

This article provides the most recent literature review from the past 5 years (search period: 2020–2025), focusing on the correlation between gut microbiota disorders and the development of ophthalmic diseases. The aim of this paper is to explore the role of intestinal dysbiosis as a potential risk factor and analyze its involvement in the pathogenesis of ophthalmic disorders. This topic represents a potentially vast area for future research. It is not excluded that treating this issue may become a crucial element in holistic ophthalmic patient care.

DISRUPTION OF INTESTINAL HOMEOSTASIS

Published reports indicate that the most dominant types of bacteria, accounting for up to 90% of the total microbial population in humans, are *Bacteroidetes* and *Firmicutes*, followed by *Proteobacteria*, *Fusobacteria*, *Tenericutes*, *Actinobacteria*, and *Verrucomicrobia* [4]. In both health and disease, the intestine contains microorganisms with both immunoprotective and pro-inflammatory functions. Therefore, any disruption of intestinal homeostasis leads to the development of inflammation. This state is referred to as dysbiosis, in which the quantitative ratio of bacteria in the gut changes in favor of pathogenic microbes. Its structure is influenced by host-related factors such as age, sex, genetics, and intrinsic intestinal factors (such as pH, bile acids, transit time, and mucus), as well as environmental factors (e.g., nutrients and medications) and microbiological factors (e.g., adhesion capacity, bacterial enzymes, metabolic strategies, bacteriophages) [8].

Under homeostatic conditions, an immunological response occurs between the microbiome and the host. Metabolites secreted by microbes act as signaling molecules and influence the regulation of the host's neuroimmuno-inflammatory axis. Moreover, they enhance the intestinal barrier while preventing pathogens from entering the body [9]. Reported anti-inflammatory factors affecting homeostasis include, among others, short-chain fatty acids (SCFAs), among other bioactive molecules, bacteriocins, secondary bile acids, indoles, and polyamines [10].

MECHANISM OF ACTION ON THE RETINA

Dysbiosis initiates the formation of the inflammatory form of lipopolysaccharide (LPS) (lipid A [endotoxin] + O antigen), which passes through the intestines (either by direct diffusion due to increased intestinal permeability or through absorption by enterocytes) into the bloodstream, causing LPS-related toxicity, i.e., endotoxemia. As a result of the inflammatory process developing within the retina, along with increased levels of oxidative stress factors, pathological changes in the eye occur [9]. Other mechanisms involved in the development of retinal disorders include an imbalance between effector and regulatory T cell populations, or reduced production of anti-inflammatory metabolites by bacteria (i.e., SCFAs). Important mechanisms also include abnormal sensitization of T cells to self-antigens in response to cross-reactivity with microbial antigens, as well as increased intestinal permeability (which may lead to excessive immune system activation by allowing microbial antigens to enter systemic circulation) [11].

GUT MICROBIOTA AND AGE

The importance of the gut microbiota is evident already at the early stages of life. The human microbiome develops after birth and contributes to the maturation of the immune system in newborns [12]. It should be remembered that the composition

of the microbiome is dynamic and changes significantly over time, especially in the group of premature infants. Changes in the composition and dominance of organisms are primarily due to environmental factors and the mode of colonization, which can occur in 2 distinct ways. In children born via vaginal delivery, increased presence of *Bacteroides*, *Lactobacillus*, and *Prevotella* in the gut microbiota is described, while in newborns delivered via cesarean section, the microbiota is dominated by skin-residing microbes such as *Staphylococcus*, *Streptococcus*, and *Propionibacterium* [2, 13].

Additionally, the composition of the gut microbiota is influenced by gestational age, type of feeding (maternal or formula), antibiotic use, and the presence of other environmental factors (length of hospitalization, birth weight, sex, genetic factors, race/ethnicity, mother's education, and maternal diseases) [2].

Microbial colonization of the infant gastrointestinal tract enables the production of essential amino acids (including glutamic acid, lysine, threonine, methionine, and tryptophan – depending on the bacterial species) and vitamins (such as K2, A, and B-group vitamins: B1, B5, B6, B7, B9, B12), beginning around the fourth month of life [12, 14]. The gut microbiome gradually acquires a configuration similar to that of an adult between the ages of 3 and 6 years and remains stable throughout adulthood [12]. It is reported that a healthy gut microbiota mainly consists of *Firmicutes* and *Bacteroidetes*, followed by *Actinobacteria* and *Verrucomicrobia*. For example, studies comparing healthy, well-nourished individuals and obese individuals revealed a higher presence of beneficial bacteria (e.g., *Anaerotruncus colihominis*, *Butyrivibrio crossotus*, *Akkermansia* spp., and *Faecalibacterium* spp.) producing the anti-inflammatory compound butyrate, demonstrating a greater tendency toward hydrogen production, development of a methanogenic/acetate ecosystem, and reduced production of harmful hydrogen sulfide. In contrast, in diseased individuals, a higher proportion of pro-inflammatory bacteria was observed, including *Bacteroides*, *Ruminococcus gnavus*, *Parabacteroides*, *Campylobacter*, *Dialister*, *Porphyromonas*, *Staphylococcus*, and *Anaerostipes*. Most of these species inhibit the degradation of harmful metabolites (β -glucuronide, aromatic amino acids, and nitrite reduction), thereby prolonging their presence in the patient's body and influencing the development of various diseases [15].

AGE-RELATED MACULAR DEGENERATION

Many risk factors may be involved in the development of AMD. Smoking is considered the most significant modifiable risk factor for AMD, leading to oxidative stress, ischemia, hypoxia, and ultimately the development of choroidal neovascularization (CNV). Other environmental factors include sunlight exposure and obesity.

To date, the only factor shown to have a protective effect is a healthy diet rich in omega-3 fatty acids, lutein, zeaxanthin, and antioxidants, as recommended by the Age-Related Eye Disease Study 2 (AREDS2). For this reason, attention toward the microbiota may prove to be a promising direction in this disease [16].

One of the proposed mechanisms underlying the correlation between microbiota disorders and AMD development may be the immune response – both cellular and humoral – associated with intestinal dysbiosis. Increased leukocyte migration, especially of T lymphocytes, leads to enhanced inflammatory response and the production of cytokines such as tumor necrosis factor α (TNF- α), interleukin (IL) 1 β , IL-6, IL-17, and IL-18. This cascade of events results in the activation of retina-specific T lymphocytes, increased microglial recruitment, and mast cell activation within the retina, immune activation of the retinal pigment epithelium, and subsequent disease progression [11, 17].

These assumptions were partially confirmed in a study by Andriessen et al., conducted on mice with diet-induced intestinal dysbiosis. It was demonstrated that the localization of microglia and macrophages within CNV lesions was twice as high compared to mice fed a normal diet [11, 18].

In the gut microbiota of individuals with AMD, an abnormal *Firmicutes/Bacteroidetes* ratio was observed. In a study by Lin et al., an increased abundance of *Prevotella*, *Holdemanella*, and *Desulfovibrio* was found, along with a reduction in *Dorea*, *Blautia*, and *Oscillospira* [11]. In another study, a distinct microbial profile was described in patients with neovascular AMD (nAMD) compared to healthy controls, enriched with *Anaerotruncus*, *Oscillibacter*, *Ruminococcus torques*, and *Eubacterium ventriosum*. Additionally, a decrease in *Bacteroides eggerthii* and increase in *Firmicutes/Bacteroidetes* ratio was observed in patients with nAMD [10, 17].

In a recent study by Parekh et al., a higher prevalence of *Desulfovibrionales* and *Terrisporobacter species* was observed in patients with advanced AMD compared to those with intermediate AMD. The study also highlighted alterations in specific SCFAs, reporting a significant reduction in the levels of 12 SCFAs, most notably acetate ($p = 0.002$), butyrate ($p = 0.04$), and propionate ($p = 0.01$). Furthermore, decreased concentrations of 12 bile acids were noted, including taurocholic acid ($p = 0.02$) and tauroursodeoxycholic acid ($p = 0.04$) [19].

Treatment in this disease primarily focuses on restoring intestinal homeostasis and counteracting dysbiosis. One method described in the literature is supplementation with the probiotic strain *L. paracasei* KW3110. This is a lactic acid-producing bacterium that may activate macrophages (but paradoxically suppresses inflammation) and, by altering the *Firmicutes/Bacteroidetes* ratio, contributes to reducing AMD development in individuals at risk [11].

RETINOPATHY OF PREMATURITY

Recent reports suggest that disturbances in the microbiota identified in preterm infants may also play a role in the development of ROP. The first study addressing this topic was conducted by Skondra et al., in which a particular correlation was found between bacteria from the *Enterobacteriaceae* family and the development of Type 1 ROP. Gut microbiota in preterm infants was tested weekly from birth, and a significant correlation between the aforementioned bacterial family and

ROP was observed in 28 weeks gestational age (Hbd) preterm infants. Additionally, it was initially hypothesized that some species of *Enterobacteriaceae* may influence vascular endothelial growth factor (VEGF) production both directly and indirectly by reducing the production of IGF-1. The consequence of these changes leads to the development of Phase I ROP, characterized by VEGF-dependent angiogenesis in the retina [20]. In another publication, it was shown that pro-inflammatory strains of *Escherichia coli* further increase VEGF expression, which is also associated with Phase II ROP, involving neovascularization and potential retinal detachment [21].

The main factors promoting dysbiosis in preterm infants include immunological immaturity, low birth weight, and the presence of inflammatory conditions associated with prematurity, such as bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC) [21]. It was shown that microbiota disturbances are similar in ROP, BPD, and NEC, which may contribute to their correlation, coexistence, and the progression of ROP severity. In both ROP and NEC, an increase in *Proteobacteria* and a decrease in *Firmicutes* and *Bacteroidetes* were described. Additionally, in ROP, an increased number of *Enterobacteriaceae* was found, while in BPD – an increase in *Escherichia* and *Shigella* species (also belonging to the aforementioned family) was observed [22].

In ROP, an increased presence of *Staphylococcus* spp. has also been reported, which was confirmed in a study by Westaway et al., where a higher proportion of this genus was observed in the microbiota of preterm infants with severe ROP [13, 21, 22].

Support for these observations is provided by the study by Modrzejewska et al., in which a macroscopic role of both *Enterobacteriaceae* and *Staphylococcus* spp. in the development of ROP was demonstrated – based on positive cultures from natural body orifices (primarily rectal and throat swabs) [23].

Current treatment of ROP for many years has relied on laser photocoagulation and intravitreal injections of anti-VEGF agents. The treatment method is adjusted individually, depending on the retinal findings and the infant's general clinical condition. These procedures may be used separately, concurrently, or sequentially at different treatment stages [24]. Increasing data suggest that early intervention and appropriate therapeutic strategies are key to the effective management of severe ROP. In a study by Modrzejewska and Nazwalska, it was shown that in cases of aggressive ROP (A-ROP) and ROP stage 3(+), combined therapy, including simultaneous administration of ranibizumab (IVR) and laser treatment, yielded favorable outcomes. It was suggested that a lower dose of ranibizumab (0.12 mg) may be effective in both monotherapy and combination therapy, without increasing the risk of recurrence or complications during a 2-year follow-up. Furthermore, initiating treatment with IVR may reduce the risk of high myopia development. In cases of coexisting multi-organ infections, it is recommended to adjust the treatment order – e.g., IVR followed by laser in A-ROP(+), or the reverse in ROP 3(+). Although low-dose ranibizumab is characterized by a favorable safety profile, the authors emphasize the need for further evaluation of potential vascular and neurological complications [25].

One of the new, additionally described treatment methods, based on current knowledge about microbiota disturbances in preterm infants with ROP, is early-stage supplementation with probiotic strains. In the study by Westaway et al., it was shown that probiotic use in preterm infants led to a clear change in gut microbiota composition – with increased levels of beneficial *Bifidobacterium* species and reduced levels of potentially pathogenic strains. Such microbiota modulation may help reduce systemic inflammatory response, which – as suggested by other studies – plays a significant role in the pathogenesis of ROP. Although the mechanism of probiotic influence on retinal development requires further research, their use appears to be a promising direction in the prevention and therapy of this disease in preterm newborns [13].

GLAUCOMA

For gut microbiota disturbances to be relevant in glaucoma, the initial condition for the pathogenesis must be an increase in intraocular pressure (IOP), leading to a breakdown of the blood–retinal barrier (BRB). According to Chen et al., in an *in vivo* study, glaucoma develops when CD4+ T lymphocytes, activated in response to gut bacteria, cross the BRB and interact with retinal microglia (GCC) expressing heat shock proteins (HSPs), thereby inducing neurodegeneration. The migration of CD4+ T cells to the GCC correlates with elevated IOP prior to the degeneration of retinal ganglion cells (RGCs) and their axons. A higher prevalence of T cells specific for HSP27 and HSP60 was observed. Moreover, it was found that elevated IOP promotes the influx of CD4+ T cells into the retina, potentially contributing to the prolonged neurodegenerative phase observed in glaucoma [26].

Another explanation, proposed by Wang and Wei in Rowan et al. study, is the “2-hit” hypothesis: during the first hit, gut dysbiosis and microbiota disturbances occur. The weakening of the gut barrier leads to inflammation induced by pathogenic bacteria. During the second hit, autoreactive T lymphocytes enter the systemic circulation and cross the blood–retinal barrier, triggering increased HSP expression, microglial activation, neuroinflammation, and ultimately neurodegeneration [27].

Zhang et al. demonstrated that a significantly higher *Firmicutes/Bacteroidetes* ratio and increased presence of *Verrucomicrobia* correlate with a higher prevalence of glaucoma [28]. Gong et al. observed increased abundance of the *Prevotellaceae*, *Enterobacteriaceae* families, and *Escherichia coli*, with decreased levels of the *Megamonas* genus and *Bacteroides plebeius* species in patients with glaucoma compared to control groups [29]. On the other hand, Chen et al. found that the *Dysgonamondaceae* family occurred more frequently in patients with primary open-angle glaucoma (POAG), whereas *Barnesiellaceae* was more common in healthy individuals, suggesting a shift in specific gut bacterial species or microbiome patterns that may contribute to neuroinflammation and, consequently, the pathogenesis of glaucoma. Furthermore, in this study, a microbiome rich in *Dysgonamonadaceae* and poor in *Barnesiellaceae*

was found to result in increased production of SCFAs, which intensify microglial activation, the overproduction of pro-inflammatory cytokines, and ultimately the loss of RGC [30]. This is a different concept from that observed in other ophthalmic diseases, where SCFA supplementation is typically recommended for protective purposes.

In another study regarding glaucoma treatment, SCFA supplementation was advised due to their direct neuromodulatory effects, immune modulation, anti-inflammatory properties in the gut, and intestinal barrier strengthening. Moreover, probiotics and prebiotics were also reported as beneficial in glaucoma treatment, acting similarly to SCFAs, although without neuromodulatory functions. Aside from these methods, a more radical treatment is also being explored: fecal microbiota transplantation (FMT), which may completely restore gut homeostasis and reduce both systemic and localized inflammation within the eye [31].

DIABETIC RETINOPATHY

The pathomechanism of DR begins with an elevation of blood glucose levels. This leads to a systemic inflammatory response and the development of intestinal dysbiosis. This condition is characterized by the translocation of bacterial antigens (mainly from Gram– bacteria), such as LPS, into the circulation, initiating a cascade of events both at the macroscopic level and within cellular pathways (microscopically). Within the human body, there is an increase in pro-inflammatory cytokines (TNF- α , IL-6) in response to bacterial components, activation of multiple metabolic pathways (NF- κ B, NLRP3 inflammasomes), an increase in free radicals, and a decrease in antioxidants, such as SCFAs.

Short-chain fatty acids, which are produced by the gut microbiota, function not only as antioxidants but also regulate inflammation and the secretion of GLP-1 (glucagon-like peptide-1). Therefore, a decrease in SCFAs leads to reduced levels of this incretin hormone, which correlates with an increase in VEGF levels and retinal neovascularization.

This entire cascade results in the disruption of the BRB, damage to the retinal endothelial cells, neuronal apoptosis, and occlusion of microvascular retinal vessels [32].

In a study by Campagnoli et al., an increase in pro-inflammatory bacteria such as *Bacteroidetes*, *Proteobacteria*, and *Burkholderiaceae* was described, along with a reduction in SCFA-producing bacteria such as *Faecalibacterium*, *Bifidobacterium*, and *Lactobacillus* [10]. Moreover, a dominance of *Bacteroidetes* and a decrease in *Firmicutes* were noted in individuals with diagnosed DR. A particularly interesting finding came from Huang et al., where among patients with DR, an increase in the *Bifidobacterium* genus was observed (which is considered a beneficial commensal), along with a decrease in highly pathogenic bacteria such as *Escherichia-Shigella*, *Faecalibacterium*, and *Clostridium* [33].

The study by Hou et al. aimed to investigate the influence of gut microbiota on retinal microglia, neurons, and

blood vessels in adult diabetic rats, as well as to explore novel therapeutic approaches for DR. Extended monitoring over a 6-month period identified gut dysbiosis marked by an elevated mean number of microbial taxa. It was found that oral administration of broad-spectrum antibiotics (ABX) via gavage effectively reduced the diversity of both gut microbiota and retinal microglia in adult male rats, irrespective of the presence of type 2 diabetes. Notably, in adult male rats with long-standing type 2 diabetes, a progressive loss of retinal RGCs was observed without concurrent significant alterations in retinal microglial activity or vascular structure. Interestingly, ABX treatment mitigated microglial activation and lessened RGC degeneration in these diabetic subjects [34].

The treatment of DR focuses on managing the underlying disease, primarily by controlling blood glucose levels using antidiabetic medications. In the study by Huang et al., sodium butyrate was found to be beneficial – not only did it stabilize blood sugar levels, but it also alleviated retinal thinning and improved visual function, as evidenced in electroretinography results. Additionally, butyrate effectively increased the expression of tight junction proteins such as ZO-1 and occluding in the small intestine, thereby strengthening the gut barrier and preventing microbial antigens from entering systemic circulation [35].

UVEITIS

The pathogenesis of uveitis in the context of gut microbiota is similar to the mechanisms described in other ophthalmic conditions [11]; however, special emphasis is placed on the autoimmune component. Uveitis is frequently associated with autoimmune diseases and may be triggered by the activation of retina-specific T lymphocytes, which become stimulated in response to intestinal antigens – particularly in conditions of dysbiosis [36, 37].

A key factor is the disruption of the balance between Th17 and Treg cells, which leads to a predominance of pro-inflammatory responses and the development of autoimmune reactions against host tissues such as epithelial, endothelial, glial, and retinal cells. In animal models, it has been demonstrated that dysbiosis intensifies Th17-mediated responses, while the presence of commensal bacteria that promote Treg populations (e.g., *Bacteroides fragilis*) has a protective effect [38]. In studies on transgenic HLA-B27 rats, significant alterations in the microbiota composition were found, including a decrease in *Bacteroides* and an increase in *Prevotella*, which may contribute to uveitis development [39].

An interesting observation was made in a study by Mi et al., which investigated the correlation between gut microbiota dysbiosis and the development of acute anterior uveitis (AAU). The study demonstrated a higher abundance of species such as *Bifidobacterium catenulatum*, *Bacteroides coprocola*, unclassified *Parabacteroides*, and *Prevotella* in individuals at increased risk of AAU. Conversely, a gut microbiota enriched in *Lachnospiraceae* (unclassified), *Alistipes finegoldii*, *Erysipelotrichaceae*,

Erysipelotrichia, *Erysipelotrichales*, and *Bacteroides ovatus* was associated with a lower risk of AAU [40].

One promising direction is microbiota-targeted interventions. Experimental studies have shown that oral antibiotics and probiotics can modulate immune responses and reduce uveitis severity. For instance, *Lactobacillus rhamnosus* GG has been shown to stimulate Treg populations and suppress the expression of pro-inflammatory cytokines in the eye [41]. These effects were confirmed in a study by Nakamura et al., in which a reduction in bacteria such as *Dorea*, *Lactobacillus*, *Clostridium*, and *Coprococcus* correlated with protection against uveitis in a mouse model of autoimmune disease [38, 41].

Thus, uveitis may represent one of the most well-documented examples of the microbiota–gut–eye axis, in which a local ophthalmic pathology can be directly induced by disturbances in the gut microbiota.

CONCLUSIONS

Disorders of the gut microbiota are playing an increasingly important role in the pathogenesis of many ophthalmic diseases, as confirmed by the latest scientific evidence. The literature review indicates a complex network of interactions within the gut–retina axis, associated with the development of conditions such as AMD, glaucoma, DR, ROP, and uveitis.

The mechanisms underlying these correlations include enhanced immune system activity, intestinal barrier dysfunction, endotoxin translocation, and the effects of bacterial metabolites, SCFAs, among other bioactive molecules. Special emphasis is placed on the interaction between Th17 and Treg lymphocytes, microglial activation, and the increased concentration of pro-inflammatory cytokines in the retina.

The collected data suggest that gut microbiota is emerging as a potential therapeutic target in ophthalmology. Despite promising research findings, further well-designed clinical and translational studies are needed to achieve a comprehensive understanding of this axis and to develop effective treatment and prevention strategies. A holistic approach to ophthalmic patients, which includes evaluation and modulation of the microbiota, may significantly improve treatment outcomes and quality of life in the future.

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