Clinical Ophthalmology

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REVIEW

The Link Between Gastrointestinal Microbiome and Ocular Disorders

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Abstract: The gut-eye axis has been hypothesized to be a factor in many eye pathologies. This review examines papers from PubMed about this topic. Bacterial commensals could either be protective by regulating the immune system or prove to be damaging to the gut mucosal wall and incite an inflammatory process. The balance between the two appears to be crucial in maintaining eye health. Imbalances have been implicated in ophthalmologic conditions. The use of probiotics, dietary modifications, antibiotics, and faecal microbiota transplant in mice with pathologies such as those encountered in our practice appears to reverse disease course or at least prevent its progression. Clinical trials are currently underway to investigate their clinical significance in diseased patients.

Keywords: ophthalmology, gastrointestinal microbiome, gut-eye axis, inflammation, faecal microbiota transplant

Introduction

The field of ophthalmology is among the fastest developing areas in medicine. Numerous pathologies are investigated for possible inciting factors with well-established diseases to tailor appropriate management protocols. One of the potential triggers is the gut microbiota. Changes in gut microbiota composition, as evidenced from stool samples of patients with eye pathologies, are correlated with ocular inflammation.[1] In this article, we explore different mechanisms believed to be responsible for this, possible treatment modalities, and how a holistic approach to various ophthalmic conditions could potentially alter patient health outcomes.

Methods

A search on PubMed was carried out using the terms "ophthalmology", "gastrointestinal", and "microbiome". Papers deemed relevant for this paper were thoroughly examined and selected for this article. These papers were mainly concerning uveitis, retina, and glaucoma. The literature chosen presents confirmed associations between gut microbial compositions and eye disorders through analysed stool samples. The chosen articles also illustrate the studied mechanisms by which inflammation could be driven by gut microbiota in animal models. In addition, they include proposed and proven therapies based on animal models.

Review

Gastrointestinal Microbiome

The gastrointestinal tract is one of the most significant interfaces between the environment and the human host. It houses 70% of the immune system with a diversity of micro-organisms.[2] The gut microbiome refers to the pooled genome of symbiotic and pathogenic microorganisms inhabiting the gut. These include bacteria, viruses, fungi, and archaea. Interestingly, bacteria housed in the gut contain more genomes than all cells in the body combined.[3] Microbes are variably distributed in the gut, with the colon harbouring the highest diversity and abundance of microorganisms.[3] As you move further along the gastrointestinal tract, anaerobes become the predominant commensals. The *Firmicutes* and *Bacteroidetes* phyla make up 80–90% of the entire gut microbiome. The *Clostridium* genus represents 95% of *Firmicutes*. The *Bacteroidetes* phylum mainly consists of *Bacteroides*

Received: 2 April 2023
Accepted: 18 July 2023
Published: 25 July 2023

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and *Prevotella*.[4,5] Their role has been poorly understood and implicated primarily in pathologies localised to the gastrointestinal system. It has come to light recently that this ecosystem is linked to both innate and adaptive immunity, with a potential impact on eye health.[6]

Gut-Eye Axis

A great deal of emerging evidence suggests a possible link between gut microbiota and other bodily systems, namely, the brain and the eyes. The notion of the gut-eye axis has been recently proposed, whereby changes in gut microbiota have demonstrated an effect on ocular health and possibly an inciting factor to various pathologies.[7] Though not fully understood, several theories explain this idea. These include the T-cell threshold, leaky gut, and molecular mimicry models. In addition, the complement system and genetic defects, namely, HLA-B27, have been proposed to influence the inflammatory process.[8] It is essential to bear in mind that while the correlation between gut dysbiosis and eye pathologies exists, these models do not always provide definitive answers regarding their pathogenesis.

The T-cell threshold model puts forward a practical viewpoint in which certain bacteria can kick-start inflammation. If the dominant bacteria were pro-inflammatory, following the imbalance between gut commensals, T-helper cells can be activated and thus be key in driving the pathogenesis of uveitis. Several studies have linked *Bacteroidetes* to ocular inflammatory disorders, namely, Behçet's disease and Sjögren's syndrome.[1,9,10]

The leaky gut model suggests that microbial constituents can migrate into the bloodstream, possibly through a damaged mucosal barrier. Laboratory analysis of aqueous humour confirmed the presence of intraocular gut microbiota, which now opens many avenues for us to explore the implications of such findings.[11]

Ocular Immune Privilege

It has come to our understanding that the eye is unique because it holds features that, in theory, prevent an immunological response. These include a blood-retinal barrier (BRB) and a lack of direct lymphatic drainage.[12] How does the gut microbiota travel to the eye? One possible explanation is molecular mimicry. The immune system recognises antigens by T-cell receptors and antibodies. While this process is specific, it is not confined to a single antigen. Hence, gut microbiota may exhibit similarities to self-antigens found in other bodily systems, potentially triggering an autoimmune cascade.[13]

Anterior chamber-associated immune deviation (ACAID) is a component of ocular immune privilege. It is an immunological response to antigens entering the anterior chamber. This leads to systemic suppression of potentially damaging cell-mediated and humoral responses that might damage sensitive ocular tissue. For this to happen, transforming growth factor-beta (TGF-B) in aqueous humour induces the development of F4/80+ monocytes, which phagocytose the antigen. This antigen-presenting cell (APC) travels through the trabecular meshwork and into the venous system, reaching the spleen. Here, it induces the development of regulatory T-cells (Tregs) that inhibit T-helper cells. Therefore, an intact spleen is required for ACAID to function.[14,15] However, adequate immune stimulation can overcome this immunoregulatory environment.[16]

Uveitis

The uvea is comprised of the iris, ciliary body, and choroid. Uveitis is an ocular inflammatory disease that can arise from autoimmunity or when the immune system fends off infection. However, the immune system can also attack healthy eye tissue. These are possibly seen because of the leaky gut and molecular mimicry models. Both models share a common factor: the involvement of a specific subset of T-helper cells, Th17, as evident by animal models.[17]

Behcet's disease (BD) is an immune-related disease of undetermined cause. It is characterized by recurrent oro-genital ulcers, mucocutaneous lesions, and severe organ involvement. It has been previously linked to stress and environmental factors.[18] Genetic predisposition to HLA-B51 has been investigated, but the link remains unknown.[19] The gut microbiome of patients afflicted with this disease displayed considerable changes when stool samples were analysed. Stool samples were enriched with *Parabacteroides*, sulphate-reducing bacteria *Bilophila* and *Desulfovibrionaceae* species. In addition, it was also noted that butyrate-producing bacteria *Clostridium* and methanogens were reduced.[20] Butyrate is a short-chain fatty acid (SCFA) and is thought to play a role in maintaining the integrity of the intestinal barrier by assembling tight junctions.[21] Transplantation of BD faeces in mice illustrated remarkable results in which gut integrity was breached due to decreased expression of tight junctions, with the subsequent effects of experimental uveitis.[22]

HLA-B27 spondyloarthropathies (SpA) are a spectrum of disorders that overlap. These include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, acute anterior uveitis, and undifferentiated SpA.[23] They are one of the more classic examples of how gut dysbiosis affects the eye due to the number of extensive studies being carried out. From recent studies, segmented filamentous bacteria (SFB) have been illustrated to be a common culprit in initiating an arthritogenic reaction. The Th17 response, induced in the mesenteric lymph nodes by dendritic cells, in such patients specifically targets SFB, resulting in a breach in the mucosal barrier.[24] This is not the first time that microorganisms have been linked to autoimmunity. *Salmonella*, a pathogenic gram-negative bacterium, has been well studied and is an excellent example of how a microbe strongly correlates to reactive arthritis and, subsequently, uveitis.[25] This is thought to result from cross-reactivity between HLA-B27 and pathogenic surface antigens.[26] Other enteric gram-negative pathogens, which mimic HLA-B27, associated with SpA and uveitis include *Shigella, Chlamydia* and *Yersinia*.[27]

HLA-B27 SpA and BD have shown the most significant correlation between gut dysbiosis and uveitis. Another example with a positive correlation is Vogt-Koyanagi-Harada syndrome (VKH). In this uveitis syndrome, a study demonstrated heightened levels of gram-negative bacteria, eg, *Bacteroides* and *Paraprevotella*, in patients' stools with a decrease in butyrate-producing bacteria. This alteration also has the potential to be reversed with immunosuppressive therapy which coincided with the dampening of intraocular inflammation. The composition of gut microbiome could depend on host genotype and the pathogenesis of VKH as a result of the interaction between the two.[28]

Another disease linked to gut dysbiosis is Birdshot Chorioretinopathy.[29] However, it is not as extensively explored. This favours a potentially strong relationship between uveitis and gut dysbiosis and paves the way for future research opportunities.

Dry Eye Syndrome

Dry eye syndrome (DES) is one of the most common diagnoses made in the eye clinic. While the name might suggest, a decrease in tear production, it can also be due to a decrease in the quality of tears. It is classically associated with Sjogren's syndrome (SS), but most commonly with advancing age.

SS is an autoimmune disorder targeting lacrimal, salivary glands, and other bodily systems. It classically leads to DES that sometimes can be refractory to conventional treatment. They have been linked to autoreactive antibodies, particularly anti-SSA/Ro and anti-SSB/LA. Several clinical studies have correlated gut dysbiosis to SS and DES. The common finding was an increase in *Bacteroidetes*, an opportunistic commensal, and a decrease in *Firmicutes* and *Faecalibacterium*. The latter two gut commensals have been observed to produce SCFAs, such as butyrate, which modulates microglial maturation or Treg cells.[30] The gut microbiota has a role in regulating the balance between Th17 and Treg cells. This was evident when germ-free mice were colonized with SS bacteria, resulting in decreased Treg cells.[31] One study concluded that the degree of dysbiosis was partly correlated with the severity of ocular surface disease.[32]

Age-related DES is thought to be driven by an inflammatory process. Many mechanisms have been implicated in this condition with gut dysbiosis being the newly studied contributor. In terms of dysbiosis, it shares a similar pattern to that of SS having an abundance of *Bacteroidetes*.[32] Interestingly, besides altering the body's immune system, gut microbiota can have an effect on neuronal activity. Reduced SCFA has been found to alter the circadian rhythm, which in turn reduces lacrimal gland secretions.[33,34]

In contrary to the above, there are studies that suggest a high *Firmicutes* to *Bacteroides* (F/B) ratio is linked to DES as evident by mice faecal and human conjunctival samples.[35,36] One theory hypothesised that any disruption to F/B ratio can trigger an immunological and inflammatory pathway.[37] This can further support the idea that gut dysbiosis in either direction can lead to DES.

Retina

The retina houses neurosensory photoreceptors crucial for converting light energy into signals carried to the brain to form an image. Gut dysbiosis has been attributed to various retinal pathologies, with proposed mechanisms discussed previously.

Type 2 diabetes mellitus (T2DM) is a chronic, multisystem metabolic disorder with an increasing prevalence worldwide. It is of great interest to practising ophthalmologists, as it leads to diabetic retinopathy (DR), a significant cause of blindness.[38] Adipose tissue, from increased body habitus, drives the process of chronic inflammation, which is the leading cause of insulin resistance.[39] However, gut dysbiosis may play a role in disease pathogenesis. It has been found that *Bacteroidetes* can break the gut mucosal barrier and enter the bloodstream, with low SCFA levels contributing to inflammation. In addition, it was also noted that *Bacteroidetes* produce lipopolysaccharides (LPS), which are interestingly offensive to the gut mucosal barrier and play a role in retina inflammation by increasing interleukin-6 (IL-6).[40–42]

Age-related macular degeneration (ARMD) is another leading cause of blindness in Western countries, mainly affecting the elderly. ARMD is thought to occur from defects in the complement system, most notably attributed to the complement factor H (CFH) gene.[43] Again, gut dysbiosis has been linked to ARMD and can lead to inappropriate complement activation, a potential influencer of the gut-eye axis, as stated before.[44] Furthermore, one of the landmark studies in ARMD, the age-related eye disease study (AREDS), has demonstrated that antioxidant and mineral supplementation, including zinc, has been shown to reduce disease progression. Zinc absorption may be affected by gut microbiota composition.[45]

The more advanced form of ARMD, which is not responsive to the AREDS formula, is characterised by the formation of choroidal neovascularization (CNV). A study on mice models found that high-fat diets disrupt gut microbiome, by increasing the F/B ratio and weakening gut barrier. Dysbiosis increases translocation of LPS and pathogen-associated molecular patterns (PAMP), a cause of metabolic endotoxemia. PAMP is recognised by pattern recognition receptors (PRR) on innate immune cells. This initiates the creation of cytokines and angiogenic factors. These include IL-6, IL-1, tumour necrosis factor-a (TNF-a), and vascular endothelial growth factor-A (VEGF-A).[46,47]

Glaucoma

Glaucoma is an optic neuropathy characterized by progressive visual field loss due to the death of retinal ganglion cells (RGCs). It is a leading cause of irreversible blindness worldwide. Raised intraocular pressure is the most important modifiable risk factor. Hence, most management focuses on bringing it down to an acceptable range. Unfortunately, this approach is not sufficient in a lot of cases. This is mainly due to other risk factors being in play that we cannot control, such as age, race, family history and eye morphology. While we were able to identify some risk factors, others remain to be uncovered.[48]

The gut microbiome plays a crucial role in building and maintaining the BRB. While specific good commensals regulate this, other opportunistic microflora can prove to be damaging to it. Heat shock proteins (HSPs) are found in eukaryotic and prokaryotic cells. They are produced in response to stress by bacteria in the gut. HSP27 and HSP60 trigger inflammation that activates T-cells, which are presensitized by the microflora, leading to microglial damage. Since microglia are known for their neuroprotective function, RGCs are exposed to neurodegeneration. Since specific HSPs have been identified, further research to develop a future targeted therapy could be on the way.[49–51]

Thyroid Eye Disease

Graves' disease (GD) is an immune disorder where autoantibodies stimulate the thyroid gland to overproduce thyroid hormone, resulting in a state of hyperthyroidism. These autoantibodies activate thyroid receptors of orbital fibroblasts. This leads to the release of T-cell chemo-attractants that allow fibroblasts to differentiate into myofibroblasts and lipofibroblasts. This is known as Graves' orbitopathy (GO).[52]

Three studies highlighted that mice with GO have an increased *Firmicutes* and a decreased *Bacteroides* populations, thus increasing the F/B ratio. The increased number of Firmicutes appears to increase orbital adipogenesis. Along this, an increase in CD4 T-cells and CD25 in the orbit was noted. CD25 is a Treg and is found to increase IL-2 which promotes expansion and proliferation of CD4, along with other cytokines. These cytokines are thought to drive inflammation and have direct effect on thyroid hormone production. The administration of vancomycin targets gram-positive *Firmicutes*, allowing *Bacteroides* to increase in numbers. Restoring the F/B balance correlates to reduced adipogenesis and lesser disease activity.[53–57]

An abundance of *Lactobacillus* has been noted in GD patients with a positive correlation with antibody levels and adipogenesis.[53] They are known to be beneficial probiotics, as discussed in the next section. However, certain groups have been found to secrete IL-6 and TNF-a.[58] The administration of antithyroid medications (methimazole and propylthiouracil) and immunosuppressants (azathioprine and mycophenolate mofetil) appears to decrease *Lactobacillus* levels.[54]

Future Therapies

Probiotics allow some bacterial gut commensals with anti-inflammatory properties to thrive in the gut environment. Sometimes probiotics compete against pathogens and allow immune system modification by dampening autoimmunity in the eye.[59,60] The IRT-5 regimen, including *Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus reuteri, Bifidobacterium bifidum*, and *Streptococcus thermophilus*, has demonstrated such an effect.[61] This is clinically significant in the cases of autoimmune dry eye, as evident by a study on mice that illustrated improvement in tear secretion after treatment with the IRT-5 regimen. This was due to the downregulation of APCs in the immune network.[62] In addition, *Bifidobacterium* promotes the isolation and utilization of SCFAs, therefore regulating gut mucosal immunity.[63] This is highly promising, as it creates a new approach to treating inflammatory eye pathologies. However, these formulations are currently challenging to implement in our management due to high variations in the strains they contain.[64]

Dietary modifications with SCFA administration attenuated uveitis severity through Treg induction in intestinal lamina propria.[65] SCFAs also reduce intraocular inflammation induced by LPS.[66] Dietary modifications appear to impact retinal disorders potentially associated with gut dysbiosis. It has now come to light that mice fed a high glycemic diet develop a disease similar to that of dry ARMD. When reverted to a low glycemic diet, this arrested the progression of the disease and, in some instances, reversed it. A cluster of *Clostridiales* was associated with a high glycemic index, while *Bacteroidales* was associated with a low glycemic index, further supporting the gut-retinal axis hypothesis.[3,67]

Moreover, a high-fat diet has been implicated in DR and ARMD. This results from bioactive lipids upregulating pathologic retinal angiogenesis, altering the inflammatory response, and affecting both the complement and coagulation cascades.[68] A combination of oral antibiotics consisting of ampicillin, neomycin, metronidazole, and vancomycin can significantly reduce gut *Firmicutes* and *Bacteroidetes abundance*. Furthermore, they increase the number of lymphoid tissue and retina Treg cells. Therefore, modulating the gut microbiome can potentially reduce the disease severity of autoimmune uveitis.[69] Vancomycin decreases the Th17 population in the small intestines of mice, whereas the combination of antibiotics decreases Th17 frequency in mesenteric lymph nodes.[70–72] Oral minocycline is a broad-spectrum antibiotic that provides anti-inflammatory, anti-apoptotic, immunomodulatory, and neuroprotective benefits.[73,74] Oral minocycline has also been shown to increase the number of good bacterial commensals in the gut and potentially reduce the severity of autoimmune uveitis.[17,75]

In faecal microbiota transplant (FMT), a diseased person gets their gastrointestinal tract transplanted with a healthy person's stool via colonoscopy. Along with probiotics, they repopulate target gut microbiota and reduce the severity of uveitis.[76] FMT can reverse disruptions to the gut barrier and inflammation affecting the retina, potentially improving the outcome of ARMD.[77] Interestingly, there is a report of a patient who underwent FMT for *Clostridium difficile* infection, which occurred as well to have SpA and psoriatic arthritis and witnessed an improvement in her arthritis.[78] Trials are currently underway to investigate the potential benefits of FMT on SpA, psoriatic arthritis, and rheumatoid arthritis (RA), which are all known to be associated with uveitis.[79–81] Regarding SS, a study observed that mice with a similar disease exhibited improved ocular surface homeostasis post-FMT transplantation. The reversal of dry eye in these mice was attributed to reduced T helper cells in the lacrimal gland.[82]

Conclusion

Gastrointestinal microbiome composition appears to be correlated with eye health. There seems to be an interplay between leaky gut, molecular mimicry, and T-cell threshold theories in driving the pathogenesis of ocular diseases through an inflammatory process. Various ophthalmic conditions, across its subspecialties, have been implicated. Gut dysbiosis patterns differ from one disease to the other owing to the vast variety of micro-organisms inhabiting the

gastrointestinal tract. Certain bacteria can be protective from some diseases but inciting in others proving harmful. Further research is warranted and is needed to expand our knowledge of the field. A database of micro-organisms and diseases associated with them is needed in order to start recognising pathologic patterns. Emerging therapies for dietary modification, probiotics, antibiotics, and FMT are being investigated with promising results that could alter the treatment process of many eye patients.

Ethical Approval

Ethical approval was not required from ethical committees and internal review boards. Informed consent is not applicable.

Funding

This research received no external funding.

Disclosure

There are no competing interests for the author to declare.

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