Immune-Mediated Uveitis and Lifestyle Factors: A Review

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Keywords

Immune-mediated uveitis · Smoking · Gut microbiome · Diet · Physical activity

Abstract

Uveitis is a leading cause of sight-threatening disease worldwide and is characterized by inflammation of the uvea, retina, and optic nerve. Among the forms of uveitis, immune-mediated uveitis represents the majority of cases in developed countries, while infectious uveitis is more common in developing countries. A Western lifestyle is thought to be one of the factors contributing to the difference and is responsible for the increasing incidence of immune-mediated uveitis. A vast range of studies have reported the importance of lifestyle factors, including smoking, gut microbiome, diet, and physical activity on immune-mediated uveitis patients and animal models of uveitis; however, there is a lack of an expert-led consensus initiative for the management of immune-mediated uveitis patients in the area of lifestyle. Herein, we summarize the advancements in the role of lifestyle factors in immune-mediated uveitis based on clinical and experimental evidence and make suggestions for patients to ameliorate inflammation and improve the prognosis, including quitting smoking, engaging in regular physical activity, consuming a personalized anti-inflammatory diet, and optimizing the gut microbiome.

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Introduction

Uveitis is a group of intraocular inflammatory diseases characterized by inflammation of the uvea and other tissues in the eye, including retina, retinal blood vessels, vitreous, and optic nerve. Uveitis is a leading cause of blindness worldwide and accounts for 10–15% of vision loss worldwide [1–3]. It is estimated that more than 2 million people worldwide suffer from uveitis and the number is increasing [1, 3]. Uveitis can be etiologically divided into infectious uveitis and immune-mediated uveitis. The former is generally more common in developing countries [4, 5], while the latter is dominant in developed countries [6–8].

Immune-mediated uveitis is primarily related to autoimmunity and autoinflammation. In principle, autoimmune diseases require the identification of self-antigens, while autoinflammatory diseases are independent of autoantibodies [9]. Autoinflammatory uveitis is a relatively recent concept without a clear mechanism compared with autoimmune uveitis. Generally, autoinflammatory uveitis derives from interactions between environmental microorganisms and mutations in genes controlling innate immune pathways [9]. Mutations in genes controlling innate immune pathways make the individual more sensitive to the immune response caused by foreign organisms and the subsequent development of inflammation. Behcet's disease, tubulointerstitial ne-

phritis/uveitis syndrome, and juvenile idiopathic arthritis-associated anterior uveitis are suspected to develop in this way [9].

Because great effort has been made to treat experimental autoimmune uveitis (EAU), the immunological mechanisms of autoimmune uveitis are relatively specific. Autoimmune uveitis is believed to be mediated by the differentiation of naïve CD4⁺ T-cells to Th1 lymphocytes and Th17 lymphocytes resulting from interactions between genetic and environmental factors [10–12]. Considering the specificity of the eye as a privileged site of immunity and the fact that retina-specific antigens are hidden away from inflammatory cells by the blood-retina barrier, it is now widely believed that 2 conditions are necessary for the development of autoimmune uveitis. The first condition is the activation of CD4⁺ T-cells specific for retinal antigens, such as retinal soluble antigen (S-Ag) and interphotoreceptor retinoid-binding protein (IRBP), in the periphery, in which individuals with mutations controlling the innate immune system tend to be more likely to develop autoimmune uveitis. The second is the breach of the blood-retina barrier so that the activated T-cell act on the retina antigens. Regarding the existence of blood-retina barrier, it is more complicated to study the interaction between industrialized factors and autoimmune uveitis compared with autoimmune diseases located in other organs. The available evidence suggests that lifestyle factors can promote the progression of autoimmune uveitis through 2 conditions mentioned above.

Compared with the extent of genetic research, studies of environmental risk factors have received limited attention in immune-mediated uveitis. Industrialization has brought great benefits to humans, including better medical conditions and improved health measures, significantly decreasing the incidence of infectious and prolonging life expectancy [13, 14]. Industrialization also caused radical shifts in lifestyle, which is found to be related to the pathogenesis of many autoimmune diseases over the past decade [13, 15, 16]. Currently, the lifestyle, sanitation, and physical environment of developed and developing countries are quite different. One explanation for the differential proportion of uveitis has been the lifestyle hypothesis. On the one hand, the incidence of infectious uveitis is reduced by excellent sanitation, and on the other hand, changes in lifestyle greatly improve the occurrence of immune-mediated uveitis. Thus, it is not surprising that the proportion of immune-mediated uveitis in developed and developing countries is vastly different. For this review, we focused on how lifestyle factors con-

tribute to immune-mediated uveitis (Fig. 1), and therapeutic strategies target the factors for immune-mediated uveitis.

Tobacco Smoking and Immune-Mediated Uveitis

Industrialization has resulted in a huge increase in tobacco production, which is accompanied by major public concern. Studies have revealed the relationship between smoking and many autoimmune diseases, including rheumatoid arthritis [17], multiple sclerosis [18], systemic lupus erythematosus [19], Graves' disease [20], and Hashimoto's thyroiditis [16].

Several studies have concluded that tobacco smoking is a significant risk factor for uveitis [21–23]. According to Lin et al. [21], smoking is a risk factor for both infectious and noninfectious uveitis, while another study found smoking is only relevant with noninfectious uveitis [22]. In a cross-sectional study on noninfectious uveitis, Roesel et al. [24] found that smoking is associated with an increased risk of uveitis activity, combined with an increased need for steroid eye drops and a higher risk for cataract and macular edema. Interestingly, smoking seems to be irrelevant with Behcet's disease [25], even nicotine was used to treat the ulcers of Behcet's patients without any ocular complications [26]. Considering available evidence is based on retrospective clinical studies, more effort remains to be done to understand which component of smoking affects this condition and how it contributes to the development of uveitis.

Tobacco smoking contains many different ingredients, including nicotine, polycyclic aromatic hydrocarbons, and the 4,000 known active compounds. Although nicotine has a protective effect in Behcet's disease and other autoimmune disease, other ingredients have pro-inflammatory influences through several pathways in autoimmune uveitis. Cigarette smoke extract can advance

Fig. 1. Role of lifestyle factors in autoimmune uveitis. (a) Smoking: smoking can increase the release of TNF- α , IL-1, IL-6, and IL-8 to enhance the function of inflammatory cells to contribute to the development of uveitis. (b) Gut microbiome: the gut microbiome activates T-cell specific for retina antigen in the gut or change the homeostasis of intestinal immune to act on the course of uveitis. (c) Diet: food antigens mimicking retina-specific autoantigens may participate in the occurrence of uveitis. (d) Physical activity: physical activity reduces the level of reactive oxygen species to ameliorate the symptom of uveitis. What's more, the lower burden of the white adipose tissue will reduce the level of IL-6 and TNF- α to improve the prognosis of uveitis patients.

(For figure see next page.)

the function of inflammatory systems through NF- κ B, GATA, PAX5, and Smad3/4 activation, resulting in the increased release of TNF- α , IL-1, IL-6, and IL-8 [27]. This activation may increase the number of inflammatory cells circulating in the blood, increasing the risks of vascular inflammation and abnormal microvascular structures, contributing to the breach of the blood-retina barrier [28]. Clinical evidence also has been found for an association between cigarette smoking and an increased risk of inflammatory macular edema, indicating that smoking causes damage to the blood-retinal barrier [24, 29, 30]. In addition to vascular inflammation, smoking or second-hand smoking exposure causes choroidal thinning in adults and children, as identified by optical coherence tomography [31–33]. Moreover, a dose-dependent effect on choroid thinning in children with exposure to second-hand smoking was reported by Yuan et al. [33]. The choroid is located between retina and sclera, and it is usually as a primary site in some types of immune-mediated uveitis, such as Vogt-Koyanagi-Harada (VKH) disease and sympathetic ophthalmitis. Changes in choroid structure may increase the risk of autoimmune uveitis located in choroid itself. Of note, the choroid mainly consists of blood vessels outside the retina and is responsible for sending oxygen and nutrients to the retina. The thinning of choroid indicates that the blood supply to the retina is abnormal and the structure around the blood-retina is more frail.

The association between smoking and immune-mediated uveitis has not been adequately examined due to a lack of experimental evidence. Exposure to cigarette smoking is a chronic process, whereas *B10.RIII* mice and classical animal models of EAU develop a relatively short course of disease and are immunized at an early age. Horai et al. [34] generated *R161H* mice on the uveitis-susceptible *B10.RIII* background, a spontaneous autoimmune uveitis model without uses of complete Freund's adjuvant and IRBP. *R161H* mice may be a more appropriate model to study it because the strain develops chronic-progressive ocular inflammation lasting >2 months. However, one study pointed out that exposure to smoking is similar to chronic disorders and the retina would not be affected before 5 years [31]. In addition to the duration of exposure, the complex ingredients in tobacco smoking make it more complicated. Although the mechanism by which smoking contributes to immune-mediated uveitis is obscure, quitting smoking is encouraged to reduce the recurrence and complications.

Gut Microbiome and Immune-Mediated Uveitis

The gut microbiome is composed of complex communities, intricately connected with host physiology. Our gut microbiome has accompanied us throughout the long period of human evolution, likely shaping our immune system and metabolic system [35]. Recently it has been confirmed that colonization by the gut microbiota shapes the marked B cell pool and individualized immunoglobulin repertoires, indicating the great importance of the gut microbiome to the immune system [36]. Another representative example is segmented filamentous bacteria, which can induce the differentiation of Th17 cells through the adherence to intestinal epithelial cells [37]. The gut microbiome is remodeled by changes in diet patterns and the application of antibiotics by forces of modernization. Alterations in the gut microbiome have been proven to participate in autoimmune diseases in both the intestine and extra intestine, including inflammatory bowel disease [38], multiple sclerosis [39], ankylosing spondylitis [40], rheumatoid arthritis [41], and psoriatic arthritis [42].

Information from animal models of EAU related to the gut microbiome has accumulated over the past 5 years. Two mechanisms of how the gut microbiome is involved in the development autoimmune uveitis were revealed [1]: the gut microbiome act as a trigger for activating T-cell specific for retina antigen in the gut, and [2] the gut microbiome modulate the balance of effector immune cell types (Th1 and Th17) and immunoregulatory cell types (Tregs).

Using the *R161H* mice model, Horai et al. [43] found that an enhanced frequency of retina-specific T cells received an activation signal in the gut before the onset of ocular inflammation, which was independent of the endogenous source of the cognate antigen. Moreover, this activation can be stimulated by bacteria-rich intestinal contents in vitro and trigger disease in naive wild-type recipients by transfer of T cells cultured with extracts of intestinal contents, implying that the gut microbiome likely mimics retina antigens that are identified by the IRBP-specific TCR [43]. In addition to antigen mimics, the gut microbiome also serves as an adjuvant because oral broad-spectrum and germ-free conditions decrease the severity of disease [43]. Therefore, one or more of a particular kind of microbe plays roles in activation, while certain other kinds of microbes create pro-inflammatory surroundings for this activation. Two groups reported the modulation effect of the gut microbiome on EAU model immunized with emulsion containing complete Freund's adjuvant and IRBP peptide [44, 45]. Nakumura et al. [44]

reported that oral broad-spectrum antibiotics administered in the short time but not intraperitoneal reduced the severity of clinical scores of *B10.RIII* mice through expansion of Tregs in eye-draining lymph nodes and gut-draining lymph nodes. Oral of broad-spectrum antibiotics reduced the major bacterial phyla, *Firmicutes*, and *Bacteroidetes*, as well as the bacterial class, *Alphaproteobacteria* [44]. Of note, the composition of the gut microbiome was significantly different between immunized and nonimmunized animals, and the diversity of gut microbiome was segregational between high clinical score animals and low score clinical animals, implying that there may exist certain types of gut microbiome that protect against or help to the course of uveitis [44]. Similar to *B10.RIII* mice, Heissigerova et al. [45] reported that germ-free conditions lower the gut bacterial load of *C57BL/6J* mice to induce fewer T-cell infiltration in the retina and also fewer Th1 and Th17 numbers in the eye-draining lymph node. Both spontaneous and induced model of autoimmune uveitis all confirmed great importance of the gut microbiome in the pathogenesis of disease, whether trigger disease or modulate disease.

The exact number of gut microbes is under debate. It was generally believed over the last decade that microbes residing in the human body outnumber human cells by at least 10-fold, while a current study find that the ratio is more close to 1:1 [46]. It still represents a large community, including bacteria, protozoa, parasitic, fungal, and viral components, residing within our body, even though the latter is more accurate. In such a large population of microbes, it remains a formidable challenge to distinguish whether activation of retina-specific T cells rely on 1 particular sequence of microbial component or the metabolite produced by multiple microbial interactions. Based on 16S rRNA gene and metagenomic analysis, the gut microbiome of patients with several types of uveitis was described, including acute anterior uveitis (AAU) [47], idiopathic uveitis [48], Behcet's disease [49, 50], and VKH [51]. In the clinical study of AAU, Huang et al. [47] reported a significant difference in gut microbiome beta diversity between AAU patients and controls but they did not find a significant difference in gut microbiome composition. In the study of idiopathic uveitis, several pathogenic fungi were enriched in the patients, including *Malassezia restricta*, *Candida albicans*, *Candida glabrata*, and *Aspergillus gracilis* [48]. In other studies, the unique gut microbiome characteristics of Behcet's disease and VKH patients were successfully described compared with healthy controls. Of note, a decrease in butyrate-producing bacteria was revealed in both Behcet's disease and

VKH patients [49–51]. Butyrate is a kind of short-chain fatty acids (SCFAs) that is a metabolite of the gut microbiome and plays a protective role in maintaining host immune homeostasis. The protective effect of SCFAs on EAU was confirmed through exogenous oral SCFA administration to *C57BL/6J* EAU mice [52]. The role of other identified microbiome remains to be elucidated in the future.

The available clinical studies have many limitations. Current studies have focused on “census taking” to distinguish the species and abundance of the microbiome. However, the host-microbe interaction is 2-way, which means that the alternation of the gut microbiome is a contributor as well as a result of autoimmune uveitis. Considering that the available evidence is speculative, it is important to clarify which microbes contribute to the development of autoimmune uveitis and which microbes protect against disease when it occurs. Moreover, the number of human gut microbiome studies in uveitis patients is small, and many subtypes of autoimmune uveitis have not been studied. To clarify the relationship between different subtypes of uveitis and the gut microbiome, more studies of higher quality, larger size, and broader scope are needed in the future. There is great significance in identifying the microbiome marker profile of gut microbiome-related uveitis and creating a beneficial gut environment by the use of fecal microbial transplantation or oral probiotics.

Diet and Immune-Mediated Uveitis

The gut is an important immunological organ that plays a unique role in the immunological responses. It is estimated that 70% of all lymphocytes are distributed in the mucosal system, a large proportion of which is the intestinal mucosal immune system [53]. As a crucial source of human nutrient intake, diet has been revealed by emerging evidence to be inextricably linked with the immune system. The close link between a Western diet and an increasing incidence of inflammatory diseases has also been widely discussed [54]. In addition to the effect on the gut microbiome mentioned above, food antigens and the pharmacological action of diet are 2 dominant mechanisms that could be responsible for the connection.

The eye, a typical immune privilege site, is traditionally thought to be separated from the immune system. However, with the further understanding of the pathogenesis of several ocular diseases, we know that the eye is not alone. The existence of gut-eye axis has been confirmed in age-related macular degeneration (AMD) [55], dry eye [56], glaucoma [57], and autoimmune uveitis

[34]. In addition, aberrant amplitudes of ERG a-, b-wave, and oscillatory potentials were recorded in an animal model of experimental colitis, reflecting abnormal retinal function caused by gut inflammation [58]. This study elucidates the mechanism of uveitis as one of the common extraintestinal symptoms of patient with inflammatory bowel disease. Thus, both ocular disease and gut inflammation highlight the significance of the gut-eye axis.

Based on the gut-eye axis, the role of diet on ocular disease has been widely described in recent years. A cross-sectional study reported that the advanced AMD was associated with a Western diet characterized by processed and red meats, French fries, high-fat dairy products, energy drinks, while an oriental diet composed of low glycemic index and whole-grain products contributed to a reduced risk of AMD [59]. This conclusion is also supported by experimental evidence that a high-glycemic diet, similar to a Western diet, caused symptoms of dry AMD in wild-type *C57BL/6J* mice, such as accumulation of phagosomes and lipofuscin, retinal pigment epithelium atrophy, photoreceptor cell loss, and the formation of large basal deposits [60]. Encouragingly, 2 multicenter phase III randomized clinical trials reported that a higher intake of antioxidant carotenoids, minerals, omega-3 long-chain polyunsaturated fatty acids (LCPUFAs), and B vitamins and a lower intake of saturated and monounsaturated fats decreased the risk of late AMD [61]. In addition to AMD, the role of diet on glaucoma was also reported. Data from 3 prospective cohorts showed that a low-carbohydrate diet is associated with a lower risk of initial paracentral VF loss in primary open-angle glaucoma [62]. Considering the complexity of dietary components and the primary stage of the gut-eye axis, the current research is still just the tip of the iceberg.

For EAU, 2 groups reported that diet plays protective and aggravating roles in a mouse model of EAU [63–65]. Dietary intake of ω 3 LCPUFAs has been shown to inhibit inflammation in a *C57BL/6* mice model of EAU [63, 64]. Interestingly, ω -3 LCPUFAs not only inhibit the production of the pro-inflammatory cytokines IL-1 and IL-17 mediated by dendritic cells but also reduce the amount of anti-inflammatory cytokines IL-10, but overall, the anti-inflammatory effect dominates. Another group found that a high-fat diet aggravated the severity of EAU and that melanocortin 5 receptor-deficient mice were not affected and developed EAU with a similar temporal pattern whether fed a high-fat diet or a normal-fat diet [65]. The pharmacological effects of diet are regulated by genetic factors, making the situation more complicated. The high-fat diet pattern is more similar to the Western

diet pattern, and the intake of ω -3 LCPUFAs usually depends on green leafy vegetables and wild fishes, which represent Mediterranean diet pattern. Experimental evidence reveals the potential hazards of the Western diet pattern and the protective effect of the Mediterranean diet pattern. Frustratingly, clinical studies on the pharmacological effects of diet on autoimmune uveitis patients are still lacking. Furthermore, TNF- α inhibitors have been widely used as a newly developing weapon for autoimmune disease, while a large number of patients are not sensitive to the biologics. Lifestyle is suspected to be associated with this insensitivity. As expected, a prospective cohort study is investigating whether a low intake of red and processed meat and a high-fiber diet improve the outcome of immune-mediated uveitis patients with TNF- α inhibitor treatment [66]. Increasing numbers of clinical studies are encouraged to fill the gap between the effects of dietary medicine and autoimmune uveitis.

Moreover, food antigens mimicking retina-specific autoantigens are a particular mechanism of autoimmune uveitis. Two environmental peptides mimicking the uveitogenic epitope from retinal S-Ag were described: “Cas” from as2casein, a common component of bovine milk, and “Rota” from surface protein vp4 from rotavirus, a common gastrointestinal pathogen [67]. Notably, oral administration of “Cas” with native cholera toxin successfully induced uveitis in rats, while S-Ag and “Rota” fail to induce the disease, although none of them could be digested. This finding supports the notion that extra-immune regulation protects the body from inflammation. In addition, the enhanced immune responses from uveitis patients to the 3 antigens compared with healthy controls indicate the pathogenic potential of food antigens. Similarly, a data-driven approach found that pigs shared unique epitopes with 40 immune-mediated diseases, including Behcet’s disease [68]. The study revealed that food is a vast library of self-antigens, and taking advantage of bioinformatics approaches to find more dietary autoimmune epitopes is vital for eliminating self-antigens from diet of uveitis patients. Moreover, one special case is uveitis in celiac disease. In a case report, a gluten-free diet helped to relieve gastrointestinal symptoms and uveitis [69]. The gluten component is not relevant to retina-specific antigens, autoinflammatory response, or autoimmune response caused by antigens from other dietary sources or microbial sources stimulate T-cell migration by gastrointestinal inflammation may lead to the ocular inflammation. Effective intervention with a gluten-free diet supports those healthy gastrointestinal conditions are necessary to avoid the immune response.

For immune-mediated uveitis tending to relapse and a prolonged duration of suffering, designing a plan including an anti-inflammatory custom diet is vital to avoid recurrence. However, current research advances cannot provide an exact answer to the question of what constitutes an anti-inflammatory diet, and further exploration will be an important direction in the future.

Physical Activity and Immune-Mediated Uveitis

It is generally believed that physical activity plays an important role in health. However, industrialization, while providing great convenience, has resulted in increased physical inactivity, which increases the prevalence of noncommunicable diseases. It is estimated that 31% of adults are physically inactive, and the ratio is even higher in developed countries [70]. Attaching increasing importance to physical activity, a recent study found an association between physical inactivity and the incidence of autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel diseases [71].

Regular physical activity helps to reduce the level of reactive oxygen species, which are induced by pro-inflammatory cytokines to damage the uvea [72]. Finally, physical inactivity groups are more likely to be obese. In particular, the white adipose tissue acts as an essential endocrine organ secreting adipokines, including the classical cytokines IL-6 and TNF- α [73]. As mentioned above, obesity can aggravate the severity of EAU though induced by high-fat diet [65]. Thus, it is not surprising that obese individuals tend to maintain a low-grade inflammatory state, and lower levels of the white adipose tissue contribute to improve the prognosis of obese patients with autoimmune uveitis. Although there is no consensus in this area, long-term regular physical activity has been shown repeatedly to improve the prognosis of patients with autoimmune diseases. In contrast, a study profiling blood components revealed that the secretion of IL-6 and TNF- α increased after acute physical activity [74]. Interestingly, this surge of IL-6 released by skeletal muscle is not the same as that in inflammation [75]. Nonetheless, it was considered prudent for patients experiencing inflammation activity to avoid physical activity. What's more, patients maintained on systemic corticosteroids need special attention because hip fracture is one of the common side effects of long-term glucocorticoid administration. Foster et al. [3] encouraged patients to perform regular, weight-bearing exercise to reduce the risk, while the initiative lacks support in the form of clinical evidence, and there is a view that weight on the hip joint should be

avoided. Although there is some debate about whether patients on systemic corticosteroids should perform weight-bearing exercise, in general, physical activity is encouraged to improve the quality of life of patients in remission of inflammation and reduce the risk of recurrence of inflammation.

Conclusion

A growing body of literature highlights the influence of lifestyle factors on immune-mediated uveitis. Currently, there is a lack of expert consensus of how uveitis patients should manage their daily lives. We viewed recent advances in lifestyle factors and developed therapeutic strategies for uveitis patients to enhance their quality of life, including quitting smoking, engaging in regular physical activity, consuming a personalized anti-inflammatory diet, and optimizing the gut microbiome. Additionally, more effort will be needed to figure out the composition of an anti-inflammatory diet and the characteristic of protective gut microbiome in the future.

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Author Contributions

Y.X. made the outline of the manuscript. X.G., Z.C., and Y.X. wrote and finalized the manuscript.

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