Intermittent Fasting to the Eye: A New Dimension Involved in Physiological and Pathological Changes

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Intermittent fasting (IF) is gaining popularity as a therapeutic dietary strategy that regulates metabolism and can alter the development of metabolic disorders. An increasing amount of research has connected ocular diseases to IF and discovered that it has a direct and indirect effect on the eye's physiological structure and pathological alterations. This article summarizes the progress of research on IF in regulating the physiological structures of the ocular vasculature, the anterior segment of the eye, the retina, and the choroid. We explored the therapeutic potential of IF for various common ocular diseases. In the future, a comprehensive study into the fundamental processes of IF will provide a direct and rigorous approach to eye disease prevention and therapy.

Keywords: intermittent fasting, energy metabolism, eye, inflammatory response, eye diseases

INTRODUCTION

Intermittent fasting (IF), also known as intermittent energy restriction (IER), is a new type of fasting therapy that alternates casual eating with restrictive eating for a set time, aiming to affect organism metabolism through dietary interventions. This easy-to-follow food restriction diet has been demonstrated to have numerous health benefits, including disease prevention and the slowing of aging. Dating back to 1997, Weindruch and Sohal showed that calorie restriction strategies might prolong lifespan by reducing body weight and oxidative stress (1). Subsequent studies have extended its beneficial effects to other aspects, such as diabetes, cardiovascular disease, cancer, and neurodegenerative diseases (2).

Currently, major IF diets include alternate-day fasting, periodic fasting, time-restricted fasting, and religion-related fasting. Alternate-day fasting is a form of fasting in which a day of normal eating alternates with a day of fasting, during which adequate water intake is ensured. It is currently

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Abbreviations: IF, intermittent fasting; IER, intermittent energy restriction; FGF21, fibroblast growth factor 21; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1 α; NAD, nicotinamide adenine dinucleotide; PARP1, polyadenosine diphosphate ribose polymerase 1; CD38, ADP-ribose cyclase; LEPR, leptin receptor; PRDM1, PR/SET structural domain 1; IGFBP-1, insulin-like growth factor binding protein-1; BDNF, brain-derived neurotrophic factor; HNF4α, hepatocyte nuclear factor 4α; ND, no data; CH, corneal hysteresis; CRF, corneal resistance factor; CT, choroidal thickness; CCT, central corneal thickness; ACD, anterior chamber depth; ACV, anterior chamber volume; CD, corneal density; LD, lens density; IOP, intraocular pressure; IOP-GAT, IOP with Goldmann applanation tonometer; IOPg, goldman-correlated IOP; CFT, central foveal thickness; SFCT, subfoveal choroidal thickness; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Apo, apolipoprotein; DR, diabetic retinopathy; RECs, retinal endothelial cells; TUDCA, taurodeoxycholate; GPBAR1, G protein-coupled bile acid receptor 1; MMPs, matrix metalloproteinases; EAU, experimental autoimmune uveoretinitis; AMD, age-related macular degeneration (AMD).

the most common form of IF. Periodic fasting is a diet that involves fasting for 1 or 2 days per week and regularly eating the rest of the time. The 5:2 light fasting method is the most typical form of periodic fasting, where only 2 days of a week restrict dietary intake. During the time-limited fasting, participants fasted only at specific times of the day. Religion-related fasting is a prevalent form of IF based on religious beliefs. Ramadan fasting entails abstaining from all food and water from dawn to sunset for over a month, and abstaining from drugs, smoking, and sexual activity (3). Most eye-related population studies have been conducted around Ramadan fasting (4–7).

The eye is a vital sensory organ that receives most information from the external environment. With lifestyle changes, eye diseases and ocular complications of metabolic disorders, such as diabetes and hypertension, are consistently increasing. Chronic ocular diseases affect patients' quality of life and impose a heavy economic burden on families and society. Dietary interventions have shown potential for prevention and adjunctive treatment in ocular pathologies due to its ease of acceptance and implementation. Nevertheless, there is a lack of evidence about IF and ocular disease. IF can alter a variety of ocular biological parameters and significantly impact some ocular surface diseases, retinopathies, etc. It is essential to understand the effects of IF on physical parameters and pathological changes in the eye. This review summarizes the benefits of IF on the eye and the prevention of ocular diseases by describing the effects of IF on various biological parameters of the eye and discusses possible physiological mechanisms of the effects of IF on the eye.

INTERMITTENT FASTING AND OCULAR BIOLOGICAL PARAMETERS

As a new dietary pattern, IF has an important role in the body's metabolism. At the same time, IF can also alter the sympathetic and parasympathetic tone and insulin sensitivity, improve blood circulation and flow patency, and thus alter ocular blood circulation, choroidal and retinal thickness, intraocular pressure (IOP), and the anterior segment of the eye. It has an important effect on the local metabolism and structure of the eye. This case is depicted in **Figure 1** and **Table 1**.

Intermittent Fasting and Ocular Blood Distribution

Intermittent Fasting Lowers Blood Pressure and Improves the Ocular Blood Supply

Hypertension plays a vital role in ocular blood perfusion and vascular distribution. The retina and other peripheral organs such as the brain and kidneys have similar vascular structures and physiological properties (8). When blood pressure rises, extensive retinal small artery stenosis and localized arteriovenous stenosis also occur, resulting in reduced retinal perfusion (9). If blood pressure remains high for an extended time, the blood-retinal barrier will be destroyed, leading to an exudative phase. Retinal hemorrhages and cotton wool spots appear during this period, leading to optic disc edema and macular edema (10). In addition, Hua et al. reported a significant decrease in vascular density in

patients with a 5–10-year history of hypertension, a change which is likely related to the chronic effects of hypertension (11).

During early IF, systolic and diastolic blood pressure may be reduced without weight loss in obese men with prediabetes. This improvement in blood pressure is likely related to reducing insulin levels during fasting (12). It has been shown that both systolic and diastolic blood pressure decrease in hypertensive patients during prolonged IF (13, 14). Under the same conditions, there was no significant change in overall blood pressure between the fasting and non-fasting healthy groups. Still, peak systolic velocity in the ophthalmic artery, central retinal artery, and temporal short posterior ciliary artery were decreased by approximately 19.18, 43.60, and 13.92%, respectively (15). This decrease in blood pressure improves ocular vascular structure and density and maintains normal ocular perfusion (15).

In addition, during IF, the sympathetic tone of the organism decreases, while the parasympathetic tone increases (16). Patients with hypertension have a problem with their autonomic function, which means their parasympathetic tone drops, and sympathetic nerves take over (17). This is because sympathetic nerves make immune cells produce proinflammatory factors, which send a signal to the brain that causes more sympathetic excitatory output (18, 19). On the other hand, sympathetic nerves can control how many hypertension-specific memory effector cells build up in the body (20). Under these effects, the blood vessels in the body are further constricted, and the blood pressure is further increased. In contrast, IF stimulates the vagus nerve, which innervates the heart and produces the opposite of sympathetic excitation, slowing cardiac conduction velocity, decreasing myocardial contractility, slowing heart rate, slowing heartbeat volume, and dilation of peripheral blood vessels, lowering blood pressure (17). Thus, IF can affect blood pressure by affecting sympathetic and parasympathetic tone affecting ocular blood flow. This case is depicted in **Figure 2**.

Intermittent Fasting Lowers Blood Glucose and Improves the Ocular Blood Supply

Chronic metabolic diseases such as diabetes can also affect blood flow to the eye. Normally, the avascular zone in the center of the foveal center is round or oval. This area is not bordered by gaps or breakdowns in the superficial or deep capillary plexus. In diabetic patients, both superficial and deep capillary plexuses show an increase in the size of the avascular zone in the central retinal notch (21). Multiple transcription factors are active in the early stages of diabetes. Increased pro-inflammatory chemicals in the retina trigger a low-grade inflammatory response that kills endothelial and pericytes, increases vascular permeability, disrupts the blood-retinal barrier, causes retinal edema, and worsens retinal ischemia over time (22). Chronic hyperglycemia can aggravate the condition by causing oxidative stress in the body and causing further damage to the microvascular endothelium (22).

Intermittent fasting can reduce insulin levels and increase the body's sensitivity to insulin in healthy individuals (12). In the case of prediabetic and type 2 diabetic patients, IF can effectively reduce the glycated hemoglobin ratio, insulin levels, and insulin resistance (12). Through IF, it is possible to reduce blood glucose
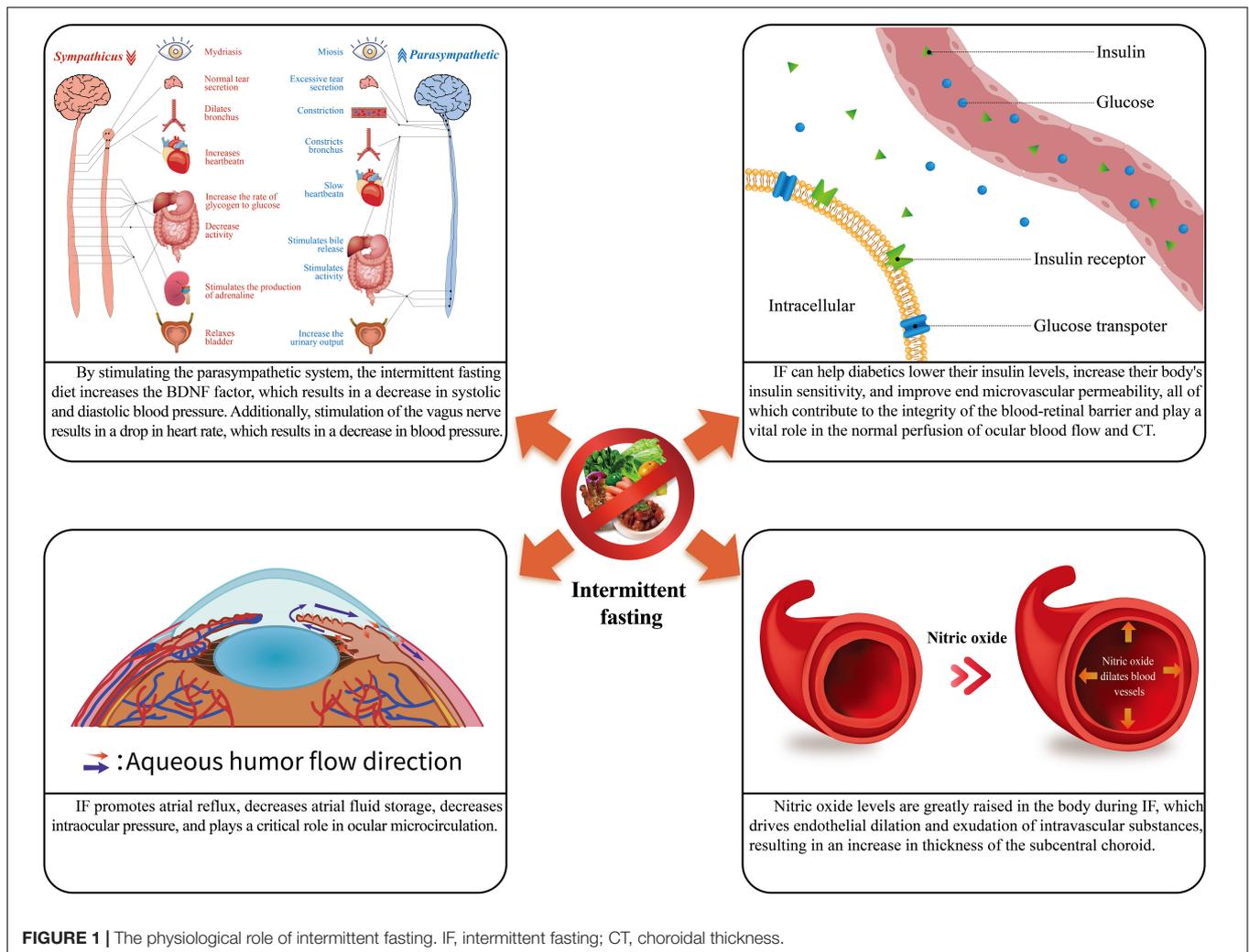
FIGURE 1 | The physiological role of intermittent fasting. IF, intermittent fasting; CT, choroidal thickness.

levels and improve end microvascular permeability in diabetic individuals, thus ensuring the integrity of the blood-retinal barrier and playing an essential role in the normal perfusion of ocular blood flow (23).

Intermittent Fasting and Retinal and Choroidal Thickness

The retina is short for the optic part of the retina, a visual sensory organ that lies immediately within the inner layer of the choroid. The choroid is a highly vascularized tissue found between the retina and the sclera that gives appropriate oxygen and nutrients to the retina and is engaged in a range of retina-related functions (24).

An investigation has found no substantial changes in retinal thickness during IF (25), which might be due to a stringent self-regulatory system in the retina when perfusion pressures fluctuate dramatically (26, 27). Previously, animal studies found that retinal blood flow self-regulates in a similar manner (28). A similar phenomenon is observed in the human body (29). Unlike the retina, IF can cause choroid thickening (30).

The choroid's self-regulation may cause a significant negative relationship between choroidal thickness and systolic blood pressure in the sub choroid (31, 32), and IF may thicken the choroid by lowering systolic blood pressure. In addition, there is a connection between neuromodulation and sub choroidal thickness. During IF, blood pressure drops, cardiac blood flow drops (33), and choroidal thickness under fovea increases when sympathetic tone drops and parasympathetic tone rises (16, 25). The choroidal thickness under the fovea increased by nearly 3% during the fasting period compared to the non-fasting period (25). Insulin sensitivity may influence the thickness of the choroidal layer at IF (34). There is a substantial thinning of choroidal thickness in diabetic patients and diabetic retinopathy (DR) patients (35). The nearly 37% reduction in choroidal thickness in the subcentral retinal recess compared to healthy subjects suggests that choroidal thickness is a great early predictor of DR. As a result, increased insulin sensitivity is expected to have a role in choroidal thickness change. Furthermore, nitric oxide levels in the body are greatly elevated during Ramadan (36). This stimulation of endothelial dilatation and intravascular material leakage may

TABLE 1 | Effects of intermittent fasting on ocular biologic parameters.

Study title	Duration	Subjects	Projection	Results
Eye microcirculation and blood pressure				
Gokmen and Ozgur (25)	At least 10 days	Healthy male and female volunteers over the age of 18 with no known systemic disease, and who fasted regularly during Ramadan	Ramadan fasting. Healthy subjects were measured at the same time each day (1:30 P.M.–2:00 P.M.)	There was no significant difference in superficial and deep vascular density index between fasting and non-fasting period
Inan et al (15)	1 month	28 eyes of 28 normal subjects without ocular disease	Ramadan fasting after 14 h. The first measurements were performed in the fasting conditions and blood pressure, heart rate, and intraocular pressure were measured by color Doppler presentation after 1 month.	Non-fasting people had higher peak systolic velocity in the ophthalmic artery, central retinal artery, and temporal short posterior ciliary artery than fasting-healthy volunteers. The central retinal artery's peak diastolic velocity was similarly higher in non-fasting people. Non-fasting individuals had a higher ophthalmic artery resistive index.
Retinal and choroidal thickness				
Uyar et al. (114)	1 month	A single eye of 87 healthy individuals	Ramadan fasting. Eyes were evaluated twice a day around 8.00 a.m. and 4.00 p.m. during Ramadan. Evaluations were repeated at the same time of the day, 1 month following Ramadan on the same subjects.	During fasting, temporal CT at 8 a.m. and foveal, temporal, and nasal CTs at 4 p.m. were significantly reduced. During fasting, the diurnal fluctuations in foveal and temporal CTs were significantly higher than the controls. In all segments measured at 4.00 p.m., retinal thicknesses were considerably decreased after fasting compared to controls.
Gokmen and Ozgur (25)	At least 10 days	Healthy male and female volunteers over the age of 18 with no known systemic disease, and who fasted regularly during Ramadan	Ramadan fasting. Healthy subjects were measured at the same time each day (1:30 P.M.–2:00 P.M.)	The choroidal thickness under the fovea center was found to be higher in the fasting period than in the non-fasting period. The mean total choroidal thickness was found to be reduced in the non-fasting period, although not to a statistically significant degree.
Ersan et al (30)	At least 20 days	42 healthy subjects with no ophthalmic or systemic disease	Ramadan fasting. Measured within 12 h after 21 consecutive days of fasting	CFT values were similar for fasting period and non-fasting period. The SFCT was significantly higher after consecutive fasting days toward the end of Ramadan, compared to the SFCT after 1 month of no fasting (1 month after Ramadan ended).
Intraocular pressure				
Kerimoglu et al. (42)	1 month	31 healthy subjects	Ramadan fasting. Measurements were taken at 0800 and 1600 h during Ramadan fasting and at 1 month during non-fasting periods.	Comparison of measurements between fasting and non-fasting periods at 0800 h revealed significantly higher values for IOP. Conversely at 1600 h, IOP was significantly lower during fasting.
Beyoğlu et al. (34)	ND	50 healthy fasting individuals in Ramadan (study group) and 50 healthy non-fasting subjects (control group)	Ramadan fasting. All measurement procedures are done between 16:00 and 17:00	There was a significant difference between Ramadan morning and control month morning. There was a significant difference between morning and afternoon of Ramadan. There was no significant difference between afternoon and dusk (after breaking one's fast) in Ramadan.
Oltulu et al. (43)	ND	Seventy-two eyes of 72 fasting subjects (study group), and 62 eyes of 62 non-fasting subjects (control group)	Ramadan fasting. The participants of the control group were asked to consume daily meals of breakfast and lunch with adequate liquid on the day of ocular response analyzer (ORA) measurements. Measurements were taken between 17:00 and 18:00, approximately 14 h after the end of the fast	While fasting did not lead to any change in LD and CCT, it caused a small decrease in ACD and ACV, and a significant decrease in CD values.
Uysal et al. (44)	1 month	36 healthy fasting male subjects	Ramadan fasting. All measurements were recorded at 8:00 am and 4:00 p.m. during Ramadan and during a 1-month follow-up after Ramadan was over.	There was statistically significant difference within the two groups in IOPg and IOPcc.

(Continued)

TABLE 1 | (Continued)

Study title	Duration	Subjects	Projection	Results
Preoptic biological parameters				
Beyoğlu et al (34)	ND	50 healthy fasting individuals in Ramadan (study group) and 50 healthy non-fasting subjects (control group)	Ramadan fasting. All measurement procedures are done between 16:00 and 17:00	The difference of IOP between the two groups was statistically significant, and the IOP value decreased significantly
Oltulu et al. (43)	ND	Seventy-two eyes of 72 fasting subjects (study group), and 62 eyes of 62 non-fasting subjects (control group)	Ramadan fasting. The participants of the control group were asked to consume daily meals of breakfast and lunch with adequate liquid on the day of ocular response analyzer (ORA) measurements. Measurements were taken between 17:00 and 18:00, approximately 14 h after the end of the fast	CH and CRF significantly decreased in fasting periods compared with non-fasting periods.
Uysal et al. (44)	1 month	36 healthy fasting male subjects	Ramadan fasting. All measurements were recorded at 8:00 am and 4:00 p.m. during Ramadan and during a 1-month follow-up after Ramadan was over.	No difference in the ORA measurements including CH and CRF; CCT and CV values between fasting and non-fasting periods or within a single day (diurnal changes).

ND, no data; CH, corneal hysteresis; CRF, corneal resistance factor; CT, choroidal thickness; CCT, central corneal thickness; ACD, anterior chamber depth; ACV, anterior chamber volume; CD, corneal density; LD, lens density; IOP-GAT, IOP with Goldmann applanation tonometer; IOPg, Goldman-correlated IOP; CFT, central foveal thickness; SFCT, subfoveal choroidal thickness; Ramadan fasting: after sunrise, no food and no water until sunset.

contribute to the increased choroidal thickness under the eye fossa (30).

Intermittent Fasting and Intraocular Pressure

The pressure created by the interplay of the eye's contents on the eye's wall and the contents of the eye is known as IOP. The intraocular contents include the lens, vitreous humor, and aqueous humor, of which the aqueous humor is the most critical factor affecting IOP. A balance between aqueous intake and outflow is required to maintain normal IOP. Any factor that interferes with the proper functioning of the aqueous humor circulation pathway may obstruct aqueous humor return and increase IOP. This case is depicted in **Figure 3**.

Previous studies have reached different conclusions. Some studies comparing the difference between IOP during fasting and non-fasting periods did not significantly change (11, 37). However, IF decreases insulin secretion and increases glucagon levels and sympathetic tone, which increases free fatty acid formation and thus increases local blood flow (38). Norepinephrine and cortisol produced during sympathetic excitation are elevated, and resistance to atrial outflow increases, causing IOP to rise. However, most studies have shown a significant decrease in IOP values during IF (34, 39–44). Kerimoglu et al. (42) found that in the Ramadan fasting population, IOP tended to be higher in the morning (fasting vs. non-fasting: 14.19 ± 3.53 mmHg vs. 12.03 ± 2.99 mmHg) and lower in the afternoon (fasting vs. non-fasting: 11.74 ± 2.39 mmHg vs. 13.13 ± 2.39 mmHg). This phenomenon may be related to dietary habits during Ramadan fasting (42). Fasting people intentionally consume more food and water before sunrise to tolerate hunger and thirst during the day (40), and in the morning, they drink more water, have an abundance of body fluids, and average aqueous humor production; in the afternoon, they become dehydrated

because they have not drunk water for a long time, their plasma osmolality rises relatively, and the amount of aqueous humor obtained by ultrafiltration decreases relatively, with a disadvantage. Another study evaluated IOP during fasting in patients with open-angle glaucoma, and these patients showed an IOP decrease of approximately 26–32% at various times compared to the non-fasted state (45).

It has been shown that during IF, low-density lipoprotein (LDL) and apolipoprotein (Apo) B levels decrease, and low-density lipoprotein (HDL) and Apo A-1 levels increase significantly (46). The depletion of lipid stores during this period may reduce prostaglandin secretion, which leads to a decrease in IOP (45). In addition, IOP reduction may also be associated with increased body dehydration, neuro-endocrine system function, and inflammatory mediators in the uveoscleral channels (34).

Studies in recent years have favored IF to reduce IOP, and most of the periods measured were distributed across the period of IF with high reliability. However, further studies with more samples need to be selected to confirm the relationship between IOP and IF.

## Intermittent Fasting and Preoptic Biological Parameters

The anterior segment of the eye includes the anterior chamber, posterior chamber, lens suspensory ligament, atrial angle, conjunctiva, tear film, and other structures in front of the lens. Some parameters commonly used in clinical practice include anterior chamber depth, anterior chamber volume, central corneal thickness (CCT), corneal curvature, etc. These parameters play an essential role in the screening and diagnosis of ophthalmic diseases in clinical practice.

Intermittent fasting alters anterior chamber depth and volume, which is mostly due to dehydration This difference may be noticed in both fasting and non-fasting groups, and at

FIGURE 2 | Normal blood circulation, eye structure, and retinal structure.
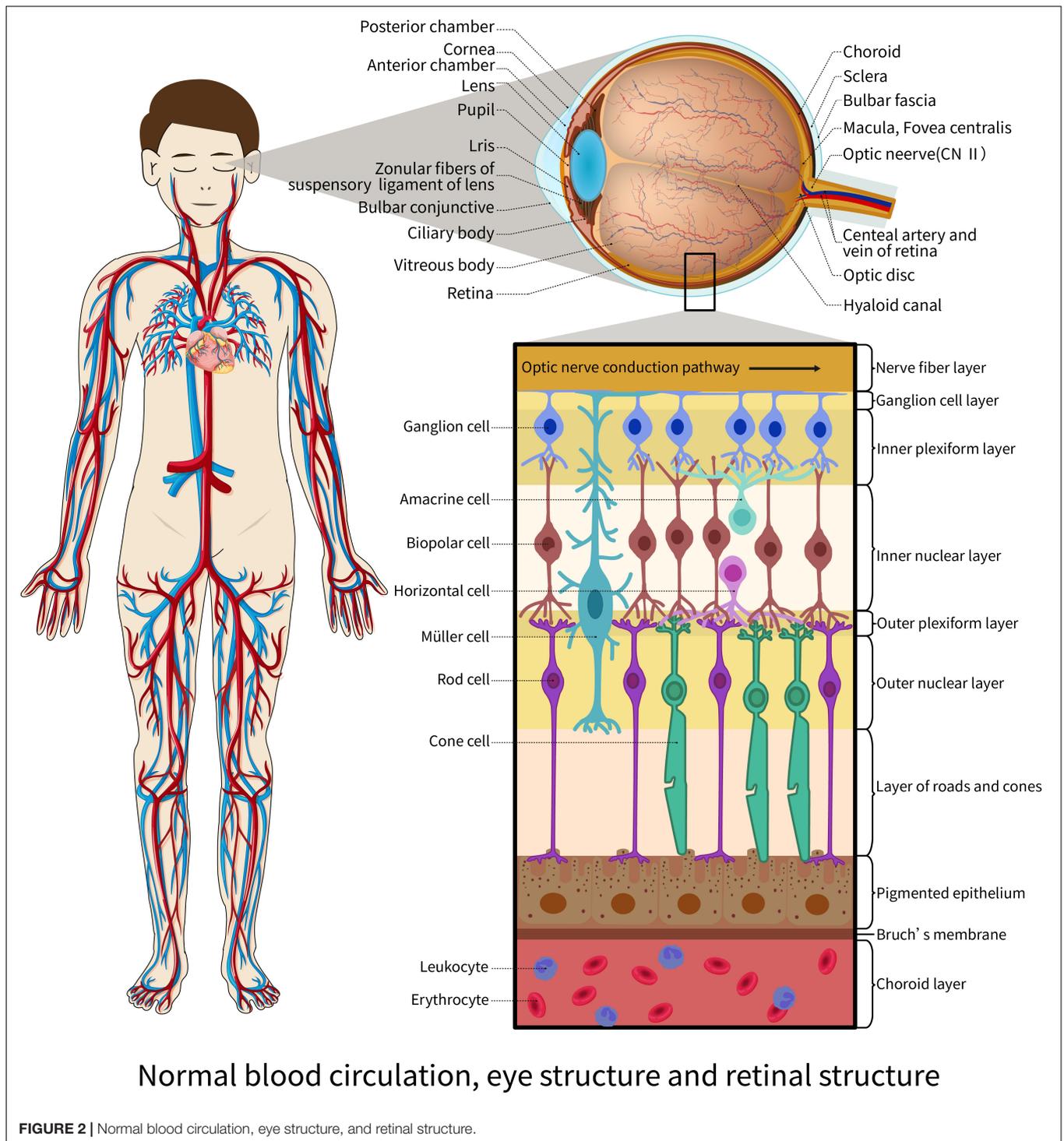
various moments during the fasting period. Compared to the non-fasting group, anterior chamber depth and axial length were dramatically reduced in the fasted group (34, 47). Furthermore, during IF, the depth and volume of the anterior chamber were variable at different times of the day. According to Nowroozzadeh et al. (48), anterior chamber depth increased substantially during Ramadan, with nearly 26% compared to

non-fasting periods. The anterior chamber depth values were greater in the morning than in the evening ($P = 0.01$), but the axial length of the eyes did not show such a significant change (48). Other studies with similar results have also been conducted (40). Furthermore, because there is a link between anterior chamber depth and IOP, with lower IOP being linked to deeper anterior chamber depth (48, 49), it is hypothesized

FIGURE 3 | Aqueous humor circulation pathway.
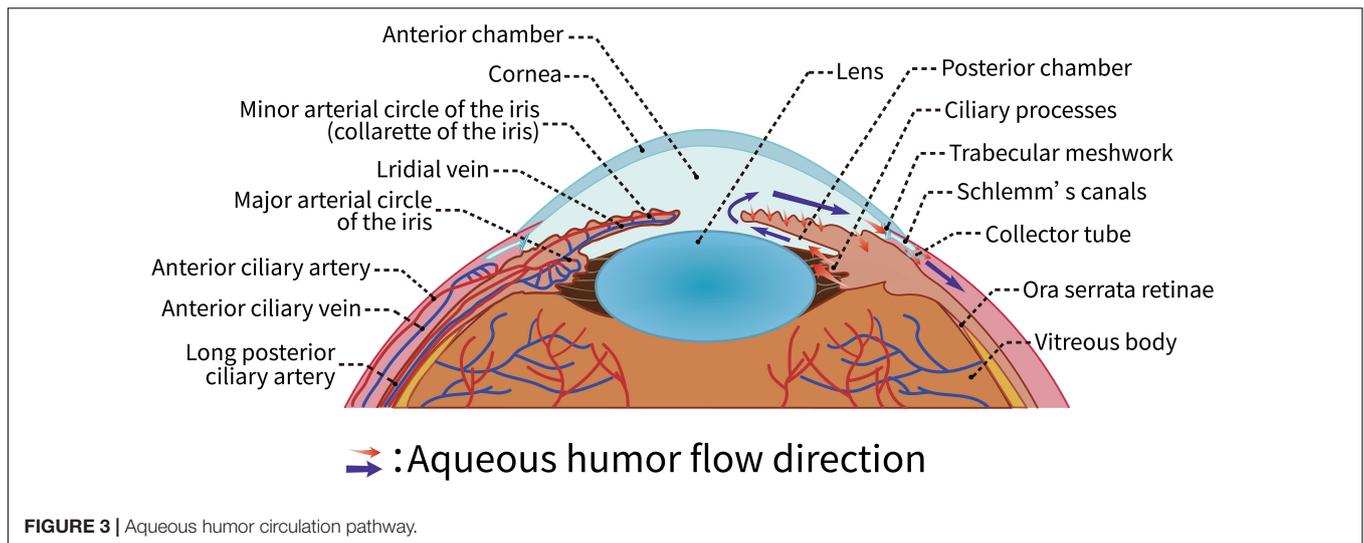
that IF might change the magnitude of anterior chamber depth by affecting IOP.

In addition, Beyoğlu et al. (34) evaluated corneal density and lens density changes in IF During IF, subjects were found to have a decrease in corneal density (fasting vs. non-fasting: right/left eye: $12.81 \pm 0.76/12.73 \pm 0.73$ vs. $13.28 \pm 1.01/13.07 \pm 0.77$) (34), an expression likely due to changes in corneal inflammatory mediators and increased osmolarity as a result of dehydration (50, 51). However, lens density did not differ significantly between the fasting and non-fasting groups (34), probably because of lens microcirculatory water channels (52), which maintain a more stable density even during longer periods of dehydration.

The tear film is a crucial medium for maintaining lubrication between the cornea and the conjunctiva and keeping harmful substances such as bacteria from entering the eye. An aqueous layer, a lipid layer, and a mucin layer make up the typical tear film. Tear secretion levels were substantially lower during IF (42). The assessment of tear break-up time (TBUT) did not change significantly between fasting and non-fasting periods (50). In addition, the activity of several enzymes, such as lysozyme, lactoferrin, and alpha-amylase, was reduced throughout the fasting period in the fasted population (53).

INTERMITTENT FASTING AND EYE DISEASE

Intermittent Fasting and Diabetic Retinopathy

Diabetic retinopathy (DR) is a major cause of low vision and blindness in adults today (54, 55) and is one of the microvascular complications caused by diabetes. The primary pathogenic alterations are retinal ischemia, aberrant neovascularization, retinal inflammation, increased vascular permeability, and neuronal and glial abnormalities (56). The current treatment of DR is mainly retinal laser photocoagulation, vitreous cavity injection, and vitrectomy. Ho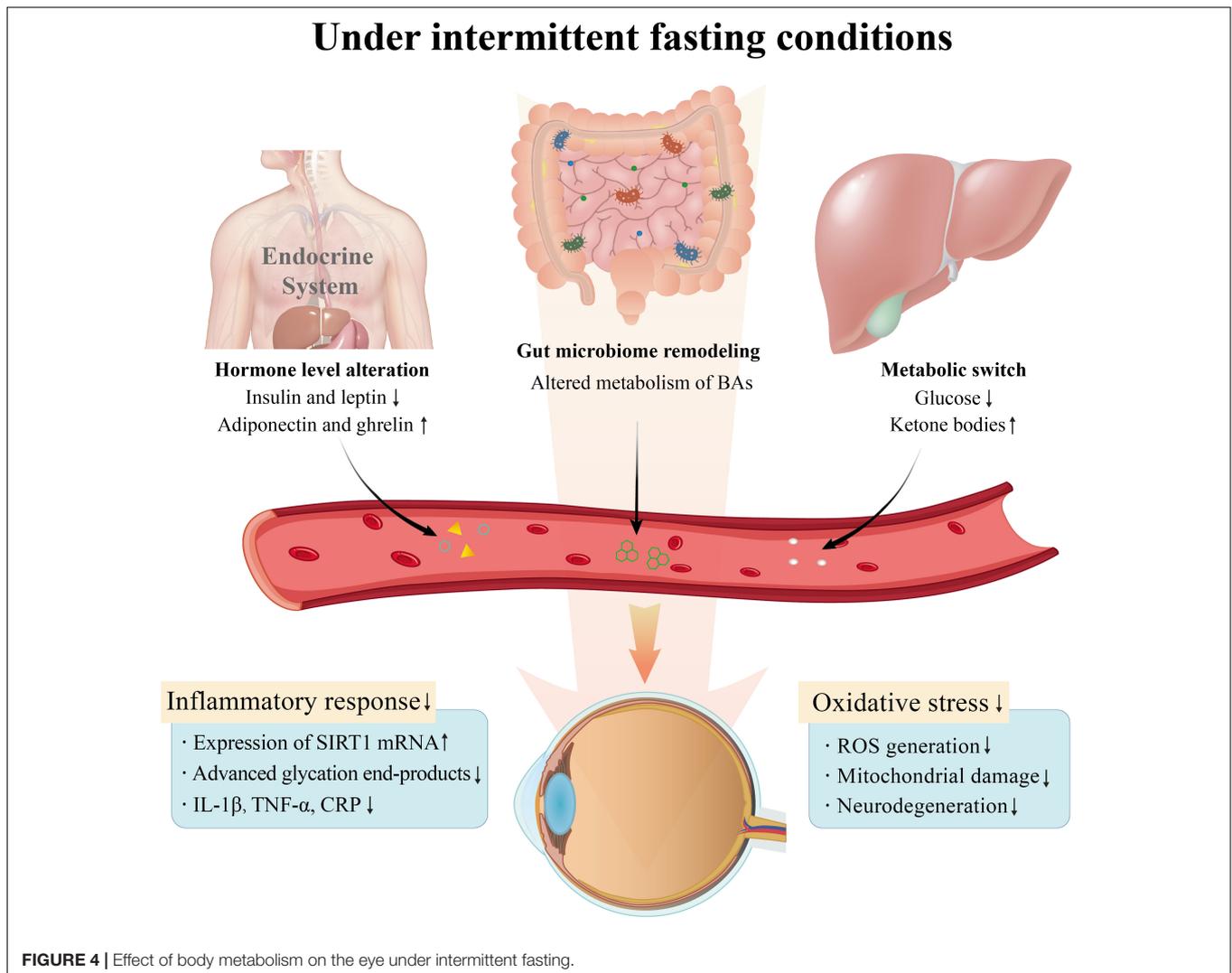wever, it is still unable to manage the condition of DR (57), and this therapy is mostly used on patients with advanced DR, with early prevention focusing on food and lifestyle modifications to prevent the disease from progressing further.

Intermittent Fasting Suppresses the Diabetic Retinopathy Inflammatory Response

The inflammatory response is a crucial pathophysiology of DR. Inflammatory variables such as intraretinal IL-1β, TNF-α, and C-reactive protein are considerably enhanced in DR in previous studies (58). Further research discovered that exposing retinal endothelial cells (RECs) to the inflammatory cytokines IL-1β and TNF-α increased glucose consumption while also causing oxidative damage to the cells. High glucose levels promote the mobility of leukocytes and the activation of proinflammatory molecules, which increases the synthesis of VEGF and TGF-1 in RECs (59) and can cause direct damage to RECs (60). Furthermore, lipid dysregulation is involved in the inflammatory response in DR. REC dysregulation is an early indication of DR. Lowering cholesterol and ceramide levels in the endothelium can decrease the progression of DR (61).

By lowering blood glucose and cholesterol levels, decreasing the generation of late glycosylation final products and inflammatory cytokines, boosting the release of heat shock proteins and adiponectin, and speeding up cellular self-phagocytosis, IF can reduce the inflammatory response in DR (62, 63).

Sirtuin 1 (SIRT1) is a nutrient-sensing deacetylase that becomes activated in low-nutrient states. SIRT1 activation boosts insulin secretion, reduces insulin resistance and weight loss, and controls inflammation (64, 65). SIRT1 activation inhibits NF-κB, [ADP-ribose] polymerase (PARP-1), and matrix-metallopeptidase 9 (MMP-9) activation (66–68). It decreases histone acetylation of the DNA (cytosine-5)-methyltransferase 1 (DNMT1) promoter, preventing inflammation and mitochondrial damage. In contrast, in the diabetic retina, increased DNA methylation of the SIRT1

Under intermittent fasting conditions

Endocrine System

Hormone level alteration
Insulin and leptin ↓
Adiponectin and ghrelin ↑

Gut microbiome remodeling
Altered metabolism of BAs

Metabolic switch
Glucose ↓
Ketone bodies ↑

Inflammatory response↓
· Expression of SIRT1 mRNA↑
· Advanced glycation end-products↓
· IL-1β, TNF-α, CRP↓

Oxidative stress ↓
· ROS generation↓
· Mitochondrial damage↓
· Neurodegeneration↓

FIGURE 4 | Effect of body metabolism on the eye under intermittent fasting.

promoter leads to transcriptional repression (69). SIRT1 expression and activity are both reduced, leading to reduced LXR signaling and dysregulation of retinal cholesterol metabolism, as well as increased production of proinflammatory cytokines (69). IF increased Sirt1 mRNA expression in the liver and retina and significantly increased SIRT1 activity in the retina of mice compared to non-fasted animals. The increased deacetylase activity led to increased LXRα activity, and LXRα activation inhibited NF-κB-dependent proinflammatory gene upregulation in retinal cells (69). Thus, IF activates SIRT1/LXR signaling and provides vigorous support for the treatment of DR.

Intermittent Fasting Inhibits Abnormal Capillary Neogenesis in Diabetic Retinopathy

The destruction or decrease of pericytes, abnormal callogenesis, and disruption of the blood-retinal barrier are all important symptoms of early DR (70). Pericytes share a stromal sheath with the endothelial cells of retinal capillaries. Hypertension, hyperglycemia, the production of late glycation end products, and hypoxia may disrupt the barrier function between pericytes and

endothelial cells, causing pericytes to apoptose and endothelial cells to generate additional capillaries owing to a lack of proliferative control (71). In DR, a reduction in the ratio of pericytes to capillary endothelial cells might lead to capillary degeneration and hence worsen hypoxia (72). Furthermore, the NF-κB pathway is activated, resulting in elevated levels of the intercellular adhesion factor ICAM-1 and vascular VCAM-1, which contribute to aberrant angiogenesis (73, 74). By reducing blood glucose and limiting the generation of proinflammatory molecules, IF can minimize retinal neovascularization and enhance retinal microcirculation (22, 56, 60). Based on the above, IF can be utilized as an additive force in treating DR that is anti-inflammatory and anti-vascularization in the near future.

Intermittent Fasting Improves Diabetic Retinopathy Glial Abnormalities

Müller cells, as the main glial cells of the retina, have a nutritional and supportive role in the retina (75). High glucose and hypoxic environments can lead to Müller cell inflammation and edema (70). Tu et al. (76) also showed an increase in oxidative stress

and inflammatory responses in Müller cells in a diabetic model and decreased their protective paracrine factor secretion, which promotes retinal inflammation. Due to the lack of therapy options other than glycemic management, the prognosis of patients with DR is typically dismal before the onset of the proliferative phase (77). By enhancing insulin sensitivity and reducing blood glucose, IF can prevent aberrant alterations in Müller cells, implying that we may utilize it as an adjuvant treatment to prevent the beginning of DR, and postpone its development, give patients a favorable prognosis.

No specific treatment has been developed in the early stages of DR because there is no treatment other than glycemic control until the proliferative phase develops, therefore, patient prognosis is generally poor (77). IF prevents abnormal changes in Müller cells by improving insulin sensitivity and lowering blood glucose, which suggests that we can gain insight into the function of Müller cells and their role in the pathogenesis of DR and that using IF as an adjuvant therapy may prevent the onset of DR, delay the progression of DR, and provide a possibility for a good prognosis for patients.

Intermittent Fasting and Dry Eye Syndrome and Ocular Surface Inflammation

The frequency and length of eye use have increased dramatically in modern society, as has the incidence of ocular surface illnesses. Dry eye is a multifactorial ocular surface disease defined by a tear film homeostasis problem, mainly associated with increased tear film instability, increased tear osmolarity and ocular surface inflammation development (78).

Diabetes is a systemic risk factor for dry eye, with more than half of type 2 diabetes patients experiencing dry eye symptoms (79). A sustained hyperglycemic condition damages the corneal epithelium directly, resulting in corneal ulcers and chronic corneal epithelial abnormalities (80). Hyperglycemia causes a decrease in conjunctival goblet cell density, a decrease in mucin density, and a decrease in tear film stability, in addition to direct epithelial damage; at the same time, hyperglycemia causes an increase in tear osmolarity, which causes mucin denaturation, a decrease in tear film stability, and yet another increase in osmolarity, creating a vicious cycle. A hyperglycemic environment can damage corneal neurons and impair neurotrophic function, which leads to the breakdown of corneal barrier integrity, decreased corneal sensitivity, decreased ocular surface gland production and blink frequency, and increased the advancement of dry eye (78, 81).

In diabetic patients, IF can effectively control blood glucose levels (82), resist the stress response, reduce autophagy, downregulate inflammatory expression (63), and reduce the damage caused by diabetes to the lacrimal vascular system and corneal autonomic nerves (80), resulting in corneal protection. On the other hand, a reduction in CD4 T cells has been observed to treat dry eyes in Sjogren's syndrome, an autoimmune condition (83, 84). CD3, CD4 T cells, and CD19 B cells are all reduced by IF (85). This might potentially how IF helps with dry eye

problems. In conclusion, IF may help diabetic individuals with dry eye symptoms and other ocular surface diseases.

However, IF might induce or worsen dry eye problems. Dehydration and decreased tear production can occur while fasting, resulting in dry eye symptoms. There are also substantial changes in tear composition, such as changes in tear film proteins and increased osmolarity (42, 50, 53), which can trigger the production of ocular surface proinflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs) (8, 9, 30), thereby aggravating dry eye. As a result, the effects of IF on dry eye need to be investigated further, and its therapeutic benefits must be considered holistically.

Intermittent Fasting and Glaucoma

Glaucoma, a progressive optic neuropathy defined by the loss of retinal ganglion cells, is the most prevalent neurodegenerative disease globally and results in permanent blindness (86). IOP that is pathologically raised is a significant risk factor for glaucoma. Glaucoma is caused by a disturbance of the aqueous circulation's dynamic balance: a few cases are caused by excessive aqueous humor production, while the majority are caused by restricted aqueous outflows, such as constriction or even closure of the anterior chamber angle and trabecular sclerosis. Elevated IOP damages the visual nerve in two ways: mechanical compression and ischemia of the optic nerve. The greater the length of IOP increase, the more serious the visual function degradation (87). Current glaucoma therapy is still centered on reducing IOP. However, effectiveness is insufficient, and the condition might worsen even after the goal IOP is attained, which may be associated with progressive neuropathy.

By modifying the body's metabolism, IF has been demonstrated to prevent aging and neurodegeneration (88, 89). Additionally, it can successfully reduce IOP and is critical in preventing the development of glaucoma. Although IF has been demonstrated to be advantageous in pathological neuropathy (90), there are minimal clinical data addressing retinal neurodegeneration, notably in glaucoma. Fasting for 48 h dramatically decreased acute IOP elevation-induced retinal ganglion cell loss, according to a recent study (86). The most plausible explanation for this phenomenon is that fasting regimens promote neuroprotection by inhibiting mTOR activity and activating cellular autophagy (91). Autophagy is the process of cytoplasmic breakdown and recycling *via* the autophagosomal-lysosomal pathway, which allows neurons to adapt to stressful environments and survive and is vital for neuronal homeostasis (91). Autophagic activity is inversely correlated with the activation state of the mammalian target of rapamycin (mTOR) and mTOR complex 1 (mTORC1) formation (92, 93). Activated mTOR inhibits the Unc51-like kinase 1 (ULK1) complex through phosphorylation, which inhibits autophagy (92, 93). In contrast, serine/threonine AMP-activated kinase (AMPK) is activated under low energy conditions and promotes autophagy by inhibiting mTORC1 and activating ULK1 (92, 94, 95). The study found a substantial drop in p-ULK1 in the fasting group of mice, indicating that IF can reduce the neurological damage caused by pathologically increased IOP

in glaucoma by activating AMPK and thereby blocking mTOR signaling to promote autophagy.

At the same time, in EAAC1-deficient mice (a normal-tension glaucoma animal model), IF administered every other day for 7 weeks increased neurotrophic factor expression. It lowered oxidative stress levels, preventing retinal ganglion cell degeneration and improving visual impairment (91). Along with promoting neuronal cell survival, IF stimulates retinal glial cells and protects against damage induced by pro-inflammatory factor release. A calorie-restricted feeding regimen reduced ischemia-induced retinal damage and suppressed reactive gliosis in elderly rats (96).

The biochemical mechanisms underpinning the effects of IF on retinal nerve cells and glaucoma remain unknown. There are no conclusive clinical trials establishing a definite link between IF and glaucoma. Further research on the physiological effects of IF on the retina and genetic variables is critical for glaucoma and other ocular illness therapies.

Intermittent Fasting and Other Eye Diseases

Other visual illnesses, such as autoimmune uveitis, age-related macular degeneration (AMD), and refractive error, may also be affected by IF. However, whether IF may definitively alter the onset and course of certain ocular illnesses is unknown.

Animals with provoked autoimmune uveitis had altered intestinal flora structure (97). As uveitis disease progressed, the experimental group of mice developed an increasingly distinct intestinal flora from controls, as well as an increase in the number of Treg cells in the retina, a decrease in cytokine levels, and the number of effector T cells in peripheral lymphoid tissues, and a decrease in the severity of uveitis following oral antibiotics. Further research (98) confirmed lymphocyte movement between the gut and the eye in uveitis, emphasizing the critical role of the intestinal flora composition in ocular illness. The above phenomenon may be explained by the concept of the intestinal-ocular axis, whereby the eye as a target organ is regulated by inflammatory factors and metabolites produced by flora in the intestine, such as TNF-α, bile acids, and SCFAs. Janowitz et al. (99) discovered that experimental autoimmune uveitis (EAU) mice exhibited lower intestinal α diversity than unimmunized animals before the beginning of ocular inflammation at the most severe stage of uveitis. The intestinal flora of EAU mice comprised Prevotella, Lactobacillus, Anaerobes, Parabacteroides, Firmicutes, and Clostridium, and an increase in the ileum. Intestinal microecology is a new aspect of the metabolic regulatory role of IF, and several studies have shown the potential of IF to alter flora composition. Pinto et al. (100) recently published a systematic review on the role of IF in remodeling the gut microbiota in humans and rats/mice. In this study, the authors found that both alternate-day fasting and time-restricted fasting regimens altered the ratio of intestinal flora, mainly the Firmicutes/Bacteroidetes ratio and Lactobacillus spp abundance. All these findings indicate that intestinal flora plays a role in the development and progression of autoimmune uveitis and that IF may

impact disease progression by altering the makeup of the intestinal flora.

Age-related macular degeneration (AMD) is the leading cause of blindness in adults over 50 in developed countries (101) and ranks highly among ocular illnesses. Admas et al. investigated the impact of high and low glycemic index meals on the progression of AMD (102). Aged rats fed a high glycemic index diet developed retinal lesions like those associated with AMD, including hyperpigmentation, atrophy, lipofuscin deposition in the retinal pigment epithelium, and photoreceptor degeneration, whereas mice fed a low glycemic index diet did not. The AMD phenotype was reduced and even reversed in mice fed a high glycemic index diet. A low glycemic diet developed through IF may have the same impact on AMD prevention and therapy.

Refractive errors (RE), which encompasses myopia, hyperopia, astigmatism, refractive error, and presbyopia, is one of the most prevalent ocular illnesses affecting individuals of all ages (103). External parallel light traveling through the eye's refractive system (the cornea, atrium, lens, and vitreous fluid) at rest does not concentrate on the central depression to generate a clear image. Previous research on IF and refractive error is limited, and the results are inconsistent. Some studies show (38) that Ramadan has no discernible effect on human vision or refractive error. However, several studies (38) discovered a modest difference in the CCT of fasting participants before and after Ramadan. In comparison, Gonen et al. (47) discovered that when fasting, the eye's axial length was slightly shorter, the corneal thickness was thinner at night, indicating diurnal fluctuation, and the anterior chamber depth decreased throughout the night. Blurred vision during hyperglycemia has been the consequence of temporary refractive alterations produced by lens modifications (104), although it might also be caused by retinal abnormalities. The degree of retinal thickness is connected with visual acuity (105, 106), and can also cause changes in the length of the eye axis, which can result in refractive errors (104). As a result, we may speculate about the role of IF in altering changes in certain ocular biological parameters or reducing refractive errors in diabetic and hyperglycemic conditions through blood glucose control.

CONCLUSION

Intermittent fasting improves the body's metabolism and the local microenvironment of the eyes, hence preventing the development of some eye illnesses. IF affects the availability of nutrients. Limited nutrient intake drives the glucose-ketogenic metabolic switch in the body. Large amounts of endogenous ketone bodies replace glucose as an important energy source for the brain, muscles, eyes, and other organs (107). On the one hand, IF mitigates retinal neurovascular damage from sustained high glucose. On the other hand, ketone bodies serve as a better fuel to reduce ocular inflammation and oxidative stress (108, 109). Multiple metabolism-related hormone levels are upregulated in response to altered nutritional status, including increased ghrelin and adiponectin and decreased insulin and leptin (110). The secretion of these intestinal hormones regulates satiety, adapts to energy deficiency, and

suppresses inflammation. Furthermore, this shift in eating patterns altered the body's lipid metabolism, resulting in weight loss and decreased total cholesterol, triglycerides, and LDL cholesterol concentrations. On the other hand, IF increased cellular sensitivity to insulin, increased glucose uptake by cells in diabetic patients, decreased inflammatory factor production, inhibited neutrophil and other cell adhesion, and decreased platelet aggregation. In addition to its direct effect on nutrient intake, moderate hunger also influences the systemic and local stress state and inflammation levels. Fasting-mimicking therapy stimulated SIRT1/LXR signaling in retinal arteries and neurons in mice, resulting in lower expression of various inflammatory markers than controls (69). In summary, IF attenuates oxidative damage and the inflammatory response in the eye in multiple ways, which is common in primary and secondary eye damage. This case is depicted in **Figure 4**.

The favorable benefits of IF have also been demonstrated in the prevention of hypertension, where IF increased BDNF factors, activated the parasympathetic nervous system, decreased heart rate, and acted as a vasodilator on blood vessels, resulting in a drop in systolic and diastolic blood pressure. During IF, the body's nitric oxide level increases dramatically, driving endothelial dilatation and intravascular material leakage, reducing blood pressure and alterations in choroidal thickness.

Intermittent fasting is used in various fields, including endocrine, cardiovascular, and tumor treatments, and it also has several beneficial effects on the body. However, this diet is not appropriate for everyone, particularly those who are underweight, pregnant, or nursing. Notably, the most immediate risk of IF is hypoglycemia in patients taking hypoglycemic medications, particularly insulin (both postprandial and basal) and sulfonylureas (including short-acting metronidazole), and caution should be exercised when administering IF to this group of patients (111). Intriguingly, IF regimens of different durations may have distinct or even opposite effects. Cerqueira et al. showed that a long-term calorie restriction strategy (32 weeks) induced glucose intolerance (112). Therefore, the selection of the period of IF protocol is a topic worthy of study.

Numerous investigations on the impact of IF on different ocular biological parameters have been conducted. However, research on ocular-related diseases such as glaucoma, retinopathy, and ocular surface diseases is still limited. Further

research is needed to determine whether IF can enhance the local ocular environment and treat ocular diseases. The intestinal-ocular axis has a vital function in the eye, not only for gut bacteria but also for the makeup of ocular microorganisms, which play a critical role in ocular metabolism and illness. However, the existence of ocular surface microbiota remains a concern, and the effect of IF on ocular microorganisms is unknown. This may provide a new direction for IF study. Meanwhile, due to the lack of evidence for the advantages of IF alone and the low compliance of IF participants, most fasting therapies now employed in clinical practice are confined to diseases with established effectiveness, such as diabetes. If used for other ocular disorders, IF also searches for medications or chemicals that may be used in place of IF to lower calorie intakes, such as metformin, resveratrol, or rapamycin (113), or that can be used to complement in-hospital therapy with IF regimens. Thus, in addition to investigating changes in fundus parameters and IF for ophthalmology, we should also investigate changes in the body's inflammatory response, metabolism, and gut flora and look for more effective therapies by integrating several therapeutic techniques.

AUTHOR CONTRIBUTIONS

JF and SZ contributed to the investigation and wrote the original draft of the manuscript. WL contributed significantly to the revision of this manuscript and the creation of the figures. TB and YL contributed significantly to the retrieval and screening of this manuscript. XC contributed to the methodology and conceptualization. All authors read and approved the final manuscript.

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