Evidence of vascular involvement in myopia: a review

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The benign public perception of myopia (nearsightedness) as a visual inconvenience masks the severity of its sight-threatening consequences. Myopia is a significant risk factor for posterior pole conditions such as maculopathy, choroidal neovascularization and glaucoma, all of which have a vascular component. These associations strongly suggest that myopic eyes might experience vascular alterations prior to the development of complications. Myopic eyes are out of focus because they are larger in size, which in turn affects their overall structure and function, including those of the vascular beds. By reviewing the vascular changes that characterize myopia, this review aims to provide an understanding of the gross, cellular and molecular alterations identified at the structural and functional levels with the goal to provide an understanding of the latest evidence in the field of experimental and clinical myopia vascular research. From the evidence presented, we hypothesize that the interaction between excessive myopic eye growth and vascular alterations are tipping-points for the development of sight-threatening changes.

KEYWORDS

myopia, vascular, structure, function, evidence

1. Introduction

The blinding consequences of myopia are often overlooked (1–7). Myopic eyes are larger in size, which alters not only their focusing ability, but also their anatomy and physiology (8). All myopes, regardless of degree, are at increased risk of visual impairment (3, 9, 10). This has significant implications due to the predicted global increase in myopia prevalence and the potential public health crisis it represents (8, 11). As we learn about the role that peripheral refraction (12, 13), light intensity (14, 15), time spent outdoors (16, 17), or the on/off pathways play in the development of myopia (18, 19), the controversy is no longer whether myopia is genetic or environmental, but whether we can identify the variables that interact in this multifactorial condition. Currently, there are no preventive markers for myopic degeneration, which is predicted to threaten the eyesight of five billion people by 2050. Myopic eyes have thinner choroids and scleras and, if they progress into high myopia, they can have secondary macular defects in Bruch's membrane along with a complete loss of retinal pigment epithelium, choriocapillaris, and retinal photoreceptors, which confirms the effect of myopia on the ocular vasculature.

The eye's vascular network comprises a complex grid of supply and drainage structures. The retina has a high metabolic rate and oxygen consumption per unit weight in the body (20). In humans, the retina is supplied by the central retinal artery (CRA) - directly in charge of the inner two thirds by diffusion to rods, cones and outer layers - and the choroid, supplying the outer third. The retina is particularly vulnerable to ischemia because of its high oxygen demand and low vascularity of the inner layers (21, 22). The choroid has a high flow rate, low oxygen exchange

and a fenestrated capillary bed. While the choroidal circulation is mainly controlled by sympathetic innervation and thought not to be autoregulated (23), the retinal circulation is ruled by locally controlled autoregulatory mechanisms, including mediators released by endothelial cells (23). A web-like capillary network spreads throughout the retina to provide additional supply (24), connects arteries and veins, and allows direct transport of oxygen, water and lipids to the tissues by diffusion. Capillaries are most abundant in the macula but absent from the fovea (capillary-free zone), which obtains its nutrients from the choriocapillaris (25). The superficial optic nerve head zone is supplied by the central retinal artery, while the short posterior ciliary arteries supply the lamina cribrosa (24, 26).

Until recently, the perfusion features of the human myopic eye had only been studied in human pathological myopia (27, 28) and experimental models of myopia (29–33). This review aims to summarize the latest evidence and controversies in the field of experimental and clinical myopia vascular research by addressing the structural and functional gross, cellular and molecular vascular alterations identified in myopic eyes.

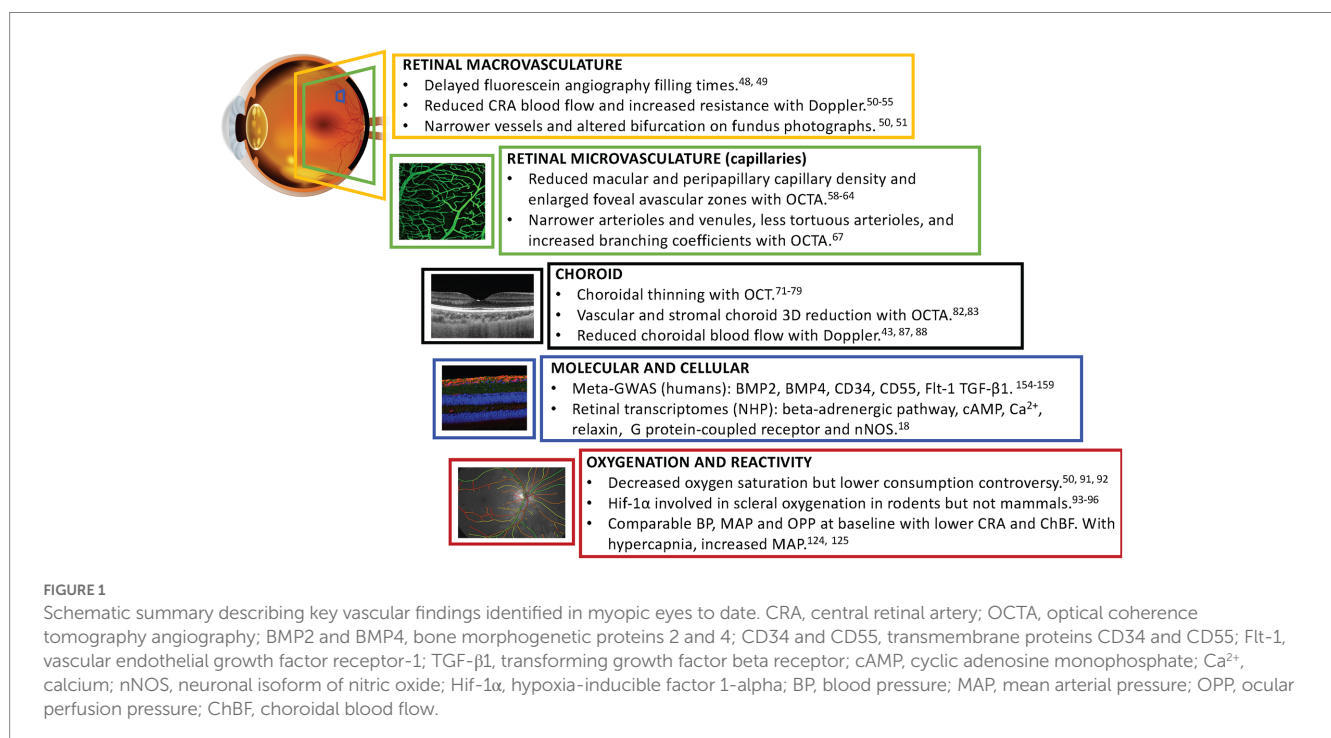## 2. Vascular features of the human myopic eye

Most of the techniques used to assess ocular hemodynamics *in vivo* are non-invasive imaging systems that assess retinal blood-flow velocity directly or indirectly (laser doppler velocimetry, LDV) (34), oxygen saturation (oximetry) (35), capillary perfusion (optical coherence tomography angiography, OCTA) (36), microvascular health (adaptive optics scanning light ophthalmoscope fluorescein angiography, AOSLO FA) (37), blood flow (laser speckle contrast imaging LSCI) (38), choroidal pulsatile ocular blood flow (POBF) (39), retrobulbar blood velocity (color doppler imaging, CDI) and retinal blood velocity (laser doppler velocimetry, LDV) (34), amongst others. Until recently, the only method providing a measure of absolute retinal blood flow was the combination of LDV blood velocity with retinal vessel diameter measures from fundus photographs (40, 41). This technique is time-consuming and impractical in the clinic. The recent development of doppler optical coherence tomography (DOCT) provides full quantitative volumetric information of blood flow and vascular/structural anatomy (42). Due to the variety of techniques available, it is imperative to consider the unique technical, anatomical and clinical characteristics of each instrument when interpreting outcomes.

It is hypothesized that the compromised hemodynamics observed in young healthy myopes is an early feature of the decreased ocular blood flow reported in pathological myopia. Such vascular features would increase the susceptibility of the myopic eye for vascular and age-related eye diseases. For instance, impaired retinal blood flow might increase the risk to develop chorioretinal atrophy in high myopia. These changes possibly interact with the known effect of aging on the retinal and choroidal vasculature, including decreased tissue perfusion, deep capillary plexus vessel density, venous, capillary and choroidal blood flow and loss of endothelial cells amongst others (43–50). Below we review experimental and clinical evidence suggesting the existence of vascular alterations in physiological and degenerative myopia (Figure 1).

3. The effect of myopia on the retinal vasculature

The retinal vasculature provides metabolic support to neural and glial cells while minimally interfering with light-sensing mechanisms (51). One of the first pieces of evidence describing an altered retinal circulation in myopic eyes was the discovery of delayed filling times in the arterial, arterial–venous and venous phases of high myopic eyes using fluorescein angiography in the 1970s (52, 53). Subsequently, myopic eyes have been found to exhibit narrower vessel diameters

FIGURE 1

Schematic summary describing key vascular findings identified in myopic eyes to date. CRA, central retinal artery; OCTA, optical coherence tomography angiography; BMP2 and BMP4, bone morphogenetic proteins 2 and 4; CD34 and CD55, transmembrane proteins CD34 and CD55; Flt-1, vascular endothelial growth factor receptor-1; TGF-β1, transforming growth factor beta receptor; cAMP, cyclic adenosine monophosphate; Ca²⁺, calcium; nNOS, neuronal isoform of nitric oxide; Hif-1α, hypoxia-inducible factor 1-alpha; BP, blood pressure; MAP, mean arterial pressure; OPP, ocular perfusion pressure; ChBF, choroidal blood flow.

(54), altered bifurcation (55) and reduced central retinal artery (CRA) diameter and blood flow (56–59). This effect appears localized to the CRA once it branches out of the ophthalmic artery (OA), and therefore affects the inner retina but not structures supplied by the OA such as eyelids, lacrimal gland, conjunctiva, posterior uveal tract or extraocular muscles. In degenerative myopia, both choroidal and retinal blood flow appear reduced, which has been hypothesized to be partly due to increased vascular resistance or adaptive changes the myopic eye experiences to cope with its enlargement (27, 28, 60).

At the retinal microvascular level, healthy myopic eyes show reduced macular superficial, deep and radial peripapillary capillary vessel density, along with increased density inside the disc and enlarged foveal avascular zones (61–67). There is controversy, however, to whether these reductions in capillary densities actually result in altered capillary blood flow (63, 64), since there is evidence that reductions in capillary density are not necessarily associated with choroidal thickness (66) or retinal nerve fiber layer function (68). In terms of anatomy, myopic eyes with greater axial lengths exhibit narrower and less tortuous arterioles and venules, and greater branching coefficients (69). The lower capillary density observed in myopic eyes has been proposed to be a protective mechanism for decreased risk of diabetic retinopathy, but the protective effect has not been confirmed in later studies (70).

The alterations observed in healthy myopic eyes may be precursors of changes seen in pathological myopia and possibly involved in the pathophysiology of myopic degeneration: decreased density of the deep radial capillary plexus and a reduction in OA blood flow that relates to the severity of the retinal degeneration (27).

4. The effect of myopia on the choroidal vasculature

Choroidal thickness is a marker of myopia development first identified in experimental myopia in avian eyes (32, 71). In fact, gross anatomical changes in choroidal appearance from myopic chick eyes led to a series of publications confirming bidirectional choroidal thickness changes in response to defocus (72). These changes have been observed in mammal, non-human and human primate eyes (72–80). In addition, during childhood the choroid thickens with normal eye development, but to a lesser extent in children developing myopia, which confirms the role the choroid may play during myopia development (81, 82). There is also evidence of a three-dimensional reduction in choroidal vascular and stromal components in myopic eyes, mainly in the nasal and subfoveal region (83), although this vascular thinning remains controversial (84). The ocular pulsatile blood flow, thought to be mainly choroidal (85), also appears reduced in myopic eyes (39). This reduction, however, might be an artefact of enlarged eye volume (56, 86), since ocular pulsatile calculations depend on intraocular volume (87). In experimental models of myopia, choroidal flow reductions relate to thickness changes, suggesting an altered choroidal supply and thickness changes that might be responsible for choroidal flow changes or vice versa (88). However, this relationship has not been confirmed in humans - choroidal blood flow might remain constant in eyes with non-pathological myopia (89). There is also evidence that moderate, but not high myopes, exhibit greater ocular perfusion pressure as the choroid thins (90), and choriocapillaris flow deficits are greater in high myopes with no pathology (91). This suggests that early vascular anatomical and functional differences between moderate and high myopes need to be evaluated longitudinally and might represent clinically applicable biomarkers of early pathologic myopia.

A major cause of visual impairment in pathological myopia is loss of photoreceptors, which are nourished by the choroid. Therefore, any choroidal dysfunction can have detrimental consequences in myopic eyes. In fact, eyes with degenerative myopia exhibit lower posterior ciliary artery blood flow, which supply the choroid (27). Choroidal structure measures such as thickness, luminal and stromal area, and choroidal vascularity index are also significantly reduced in pathological myopia. In addition, thickness and vascularity index appear associated with degeneration severity and visual acuity, highlighting the role the choroid represents for degenerative myopia (92, 93).

5. Retinal oxygen saturation in myopia

The retina is characterized by its high metabolic rate and considered one of the tissues with the largest oxygen consumption per unit weight in the body (20). Retinal oximetry performed using commercially available systems like the Oxymap has identified a lower arterio/venous oxygen saturation ratio in myopic eyes that points towards a possibly lower retinal oxygen consumption (94). However, a significantly larger cross-sectional study with 1,461 participants found that when age, gender, body mass index (BMI), intraocular pressure (IOP) and axial length (AL) were corrected for, longer and more myopic eyes did not exhibited a lower, but a greater oxygen and arterio-venous ratio saturation (95). These findings suggest that as eyes grow larger, they might be able to maintain an adequate oxygenation profile for its growing size, until they reach a degenerative state and the oxygenation profile is affected (96). There is also work suggesting that myopic choroidal thinning and reduced choroidal blood flow might affect scleral oxygenation (97). If this is correct, manipulating hypoxia signaling pathways might be a myopia control alternative in the future (98). Recent evidence suggests that, in fact, anti-hypoxia drugs reducing Hif-1α levels can slow axial elongation (99), which points towards a possible relationship between myopia, hypoxia and Hif-1α. This relationship has also been described in genetic analyses revealing a moderate involvement of the Hif-1α signaling pathway in myopia (98, 100), However, tree shrews induced with myopia do not exhibit changes in scleral Hif-1α mRNA expression (101, 102), and guinea pigs with induced myopia show reduced scleral Hif-1α mRNA, highlighting the need for additional work in this field (102).

6. Vascular reactivity in myopia

The presence of structural and hemodynamic changes in the retinal vasculature in myopia suggests that myopic eyes might be suffering from an abnormal vascular function before degenerative changes occur (1, 54, 103–108). However, assessing ocular blood flow under normal conditions is not sufficient to detect vascular dysfunction. Retinal vascular function is assessed using provocation tests, indispensable to evaluate retinal reactivity and autoregulation (109–115). Autoregulation is the inherent local mechanism that ensures sufficient and stable blood flow under changing conditions to preserve adequate function of the surrounding tissues (116). Vascular regulation or vasoreactivity can be assessed by quantifying blood flow or vessel diameter changes that occur in response to flicker light (metabolic autoregulation), variations in the concentration of

breathing oxygen (metabolic), or changes in systemic and intraocular pressure (shear-dependent and myogenic) (113, 117–120). Both the ocular and cerebral circulation exhibit an autoregulatory capacity (110, 117, 121–124). Three studies have evaluated the vascular reactivity profile of myopic eyes to date, and they used hypercapnia (increased pCO_2) and hyperoxia (increased pO_2) as provocation tests to assess the response from the retinal vasculature under stress conditions (125–127). Under room-air conditions prior to the provocation test, myopic and non-myopic eyes exhibited comparable systemic and ocular perfusion pressures –myopes exhibiting lower central retinal artery and choroidal blood flow. After inducing hypercapnia, myopic but not emmetropic eyes showed an increase in mean arterial pressure, along with a greater choroidal blood flow response, suggesting that myopes had a significantly lower resting choroidal flow that was highly responsive to CO_2 (125, 126). These results insinuate an altered autoregulation ability in myopic eyes that, due to the increase mean arterial pressure observed, may lie in an autonomic dysregulation. Interestingly, there is evidence that eyes with pathological myopia eyes have comparable retinal vascular reactivity, suggesting that the retinal oxygen consumption, but not the choroidal, is altered in high-myopic eyes (128).

7. Molecular and cellular evidence of vascular changes in myopia

In order to understand the nature of the architectural and functional vascular described in myopia, it is important to comprehend the molecular and cellular changes taking place. The most extensive genetic myopia pathway analyses to date are clinical studies (meta-GWAS from 23andMe and the Consortium of Refractive Error And Myopia, CREAM) (129–134) and studies in common marmosets (*Callithrix jacchus*), a well-established non-human primate model of myopia (18).

Genetic meta-GWAS studies using human specimens have identified several signaling pathways involved in myopia, many of which were previously known, such as the extracellular matrix and ion channel pathways, while others were new, like those involved in angiogenesis. The following genes have been recently identified in meta-GWAS studies and found to have a role in vascular homeostasis: BMP2 and BMP4, CD34, CD55, Flt-1 and TGF-β receptor 1. BMP2 and BMP4 bone morphogenetic proteins (BMPs), named for their bone and cartilage formation ability (135, 136), are increasingly recognized as multifunctional regulators of angiogenesis. BMP2 has a pathological role in the development of vascular inflammation (137, 138), and induces retinal endothelial cell barrier dysfunction in diabetic macular edema and pathological retinal neovascularization (135). Over-expression of BMP4 inhibits experimental choroidal neovascularization by modulating VEGF and MMP-9 (139). CD34 is a transmembrane protein expressed in endothelial cells that promotes the formation of invasive vessels during neovascularization (140). The membrane-bound complement regulator CD55 is highly expressed in the retinal vascular endothelium (141), and significantly decreased in hyperoxic retinas (142). VEGF receptor–1 (also known as Flt-1) is needed for adequate blood vessel patterning on retinal astrocytes and can modulate VEGF-A activation of endothelial cells (143, 144). Flt-1 has unique and important roles in coordinating endothelial sprouting (145, 146), blood vessel anastomosis (147), and genetic loss of *flt-1* leading to vascular overgrowth and reduced network complexity (148). TGF-β receptor 1 inhibits and deep vascular plexus formation (149, 150), and its

endothelial loss leads to aberrant contractile pericyte differentiation and hemorrhagic vascular malformations, and is essential for maintaining the integrity of mature vessels (151).

The analysis of retinal transcriptomes in marmosets induced with myopia has identified major molecular pathways activated during myopic eye growth (18). Some of the key pathways described are involved in vascular signaling and include the beta-adrenergic pathway, cyclic adenosine monophosphate (cAMP), Ca^{2+}, relaxin (152), G protein-coupled receptor and nNOS. Beta-adrenergic signaling, for instance, is involved in hypoxia (153); there is a 90% increase in noradrenaline levels during hypoxia (154, 155), and beta-adrenorceptor activation is followed by an upregulation of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF), both involved in neovascularization (156, 157). The cAMP pathway regulates neuronal, vascular, and inflammatory components of diabetic retinopathy (158). Calcium signaling is involved in capillary - but not arteriole - retinal blood flow as seen by the active dilation observed following astroglial Ca^{2+} signaling (159, 160). Relaxin, a peptide found at high concentrations during pregnancy, is found in endothelial and smooth muscle cells in arteries and veins, supporting its vasodilating role (161–163). G protein-coupled receptors 91 and 81 (GPR91and GPR81), localized in ganglion cells and Muller cells respectively, are involved in the pathogenesis of diabetic retinopathy (DR) and hypoxic retinal diseases such as retinopathy of prematurity (ROP), inner vascular network development and restoration of the vasculature in response to injury (152, 164). The neuronal isoform of nitric oxide (nNOS) is present in the vascular endothelium and contributes to the maintenance of homeostasis in the cardiovascular system. NO contributes to both retinal and choroidal neovascularization (165).

In terms of vascular cellular anatomy, the neurovascular interplay between neuronal, vascular, and glial cells, which is crucial for retinal structural and nutritional support and ion and neurotransmitter homeostasis, appears to be affected by myopia. Marmosets with induced myopia show a lower astrocyte density, increased GFAP-immunopositive staining, lower peripheral capillary branching, and increased numbers of string vessels compared to controls. These changes suggest an activation and reorganization of the astrocyte and vascular templates during myopia development and progression (166). Whether or not these adaptations are beneficial or harmful to the developing retina remains to be investigated.

8. Myopia-associated conditions showing vascular alterations

Myopic macular degeneration, glaucoma, choroidal neovascularization, retinal detachment, posterior staphyloma and cataract amongst the most prevalent myopia complications (167). In this section we review the vascular features of these myopia-associated conditions to help understand the vascular nature of myopia.

8.1. Myopic macular degeneration

Myopic maculopathy is the most common cause of vision loss in myopic eyes (5, 168), but its etiology remains unclear. The distinctive elongation and deformation of the myopic eye, along with its characteristic neovascularization, suggest that vascular pathways likely contribute to the degenerative process. Evidence for a vascular etiology

of myopic maculopathy include a significant choroid thinning, enlarged foveal avascular zone, smaller choriocapillaris flow area, vascular dropout, lower fractal dimension, and a more profound decrease in deep but not superficial retinal capillary plexus density, suggesting that microvascular alterations appear crucial for myopic maculopathy (169–171). In addition, choroidal watershed zones, which are areas situated at the edge of end-arteries usually exhibiting a delayed choroidal filling, have been proposed to play a vascular role in the etiology of myopic maculopathy (172).

8.2. Glaucoma

Glaucoma is a complex neuropathy that preferentially affects the ganglion cell complex (GCC) (173) and exhibits features of vascular etiology and dysfunction (174). The relationship between myopia and glaucoma has been confirmed by several large population-based studies (175–180). Yet, the nature of the myopia-glaucoma relationship remains unknown. Low ocular perfusion has been identified as a risk factor for glaucoma progression independent of intraocular pressure (181–183). Both glaucomatous and myopic eyes show parallel vascular changes: retinal microvasculature attenuation (184), decreased capillary density (63, 66, 184–186), and reduced retinal and ONH blood flow and vascular dysregulation (56, 57, 65, 68, 89, 91, 187–189). In fact, the longer the axial eye length and the thinner the ocular wall in glaucoma patients, the greater the retinal microcirculation reduction (190). In addition, when the vascular features of glaucomatous patients with and without myopia were compared, myopic glaucomatous eyes exhibited greater vascular changes than non-myopic glaucomatous eyes: larger reductions in choroidal blood flow and velocity (191), lower macular and peripapillary capillary density (184, 192), and impaired peripapillary vasoreactivity (127). Therefore, it has been hypothesized that the relationship between myopia and glaucoma might partly be vascular in nature, specifically microvascular, and may be present before the glaucomatous degeneration is evident. In addition, the study of vascular reactivity in glaucomatous patients with and without high myopia has confirmed that the retinal vasoreactivity of the peripapillary capillaries is compromised in glaucomatous eyes with high myopia (127).

8.3. Choroidal neovascularization

Choroidal neovascularization (CNV) is characterized by an atypical choroidal vasculature growth into the retinal pigment epithelium potentially leading to fluid and blood accumulation in the macula (50). Eyes with lower foveolar choroidal blood volume and flow have been identified to be at a higher risk of developing CNV. This reduced choroidal blood supply appears greater than any changes observed in eyes without CNV, suggesting that alterations in the foveal choroidal circulation might precede be part of CNV etiology (193). In addition, the choroidal thinning and capillary density reduction observed in degenerative pathological myopia is believed to trigger RPE and glial cells hypoxia, resulting in an upregulation of VEGF expression (194).

8.4. Retinal detachment

The most prevalent form of neurosensory retina separation from the retinal pigment epithelium (RPE) is the rhegmatogenous retinal detachment. This type of detachment disrupts the retinal vasculature leading to smaller vascular diameters, tortuosity, and vascular density (195). Capillary dilatation, hyperpermeability and fluorescein leakage have also been observed with fluorescein angiography on the detached retina, and have been proposed to originate from tissue hypoxia (196, 197).

8.5. Posterior staphyloma

Peripapillary posterior staphyloma (PPS) is one of six types of posterior staphylomas identified in degenerative myopia (198). Eyes with PPS have an increased macular vessel density in the deep plexus, reduced macular choriocapillaris and radial peripapillary capillary density, and thinner choroids (199). In addition, a retrospective study also identified reduced choriocapillaris flow and thinner subfoveal choroidal thickness, confirming that eyes with posterior staphyloma have thinner choroids and lower perfusion (200).

8.6. Cataract

A relationship between lens opacity and hypertension was identified in the initial cross-sectional phase of the Beaver Dam Eye Study (201). However, this relationship was not confirmed once the longitudinal 5-year Beaver Dam Eye Study was completed (202). There is, however, evidence of lower ocular blood velocity in cataract patients that requires further evaluation to understand the nature of the changes (203).

9. Conclusion

Adequate blood flow is fundamental for tissue homeostasis (204). In view of the findings described in the literature and discussed in this review, studying the haemodynamics and vascular autoregulation features of healthy myopic eyes may be crucial to identify early markers of associated degeneration and help develop novel vascular interventions to preserve the health of myopic eyes.

Author contributions

AB-P conceived, designed, wrote and reviewed the manuscript.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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