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Neurovascular Dysfunction in Retinal Diseases: Biological Mechanisms and Emerging AI-based diagnostic approaches

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ABSTRACT

In the world, retinal diseases are one of the most important causes of permanent vision loss, and they are now known to be more than just vascular diseases; these are diseases of complex interaction between the neuronal, vascular, glial, and immune elements. The retinal neurovascular unit, which consists of retinal neurons, endothelial cells, pericytes, Müller glia, astrocytes and microglia, is a unit that is pivotal to maintaining the homeostasis of the retina via coordinated neurovascular coupling and blood-retinal barrier integrity. This highly integrated system is disrupted in the pathogenesis of major retinal diseases such as diabetic retinopathy , age-related macular degeneration, glaucoma and retinal vein occlusion. Recent data indicates that neurovascular dysfunction usually occurs before clinically apparent vascular lesions, leading to a paradigm change from a vascular to a model of early neuronal damage, inflammation, oxidative stress, and impaired cellular communication. Research for decades pointed to the retinal neurovascular unit as a target for early therapeutic interventions in diabetic retinopathy. The development of new imaging techniques for the retina, such as optical coherence tomography angiography (OCTA), adaptive optics and hyperspectral imaging, have made it possible to visualize micro-vascular and micro-neural changes in the retina like never before. At the same time, artificial intelligence (AI), especially deep learning, multimodal learning, and explainable AI (XAI), has revolutionized retinal diagnostics with automated detection of retinal diseases, their severity, and prediction of the disease prognosis and management. The recent advances in foundation models and multimodal AI systems that combine fundus photography, OCT, OCTA, and clinical metadata, signify a significant leap in precision ophthalmology. This review explores the biological mechanisms involved in retinal neurovascular dysfunction, reviews its contribution to the major retinal diseases, and critically analyzes recent advances, current limitations, and future prospects for the computational intelligence in clinical retinal care.

Keywords: Retinal neurovascular unit, diabetic retinopathy, age-related macular degeneration, glaucoma, optical coherence tomography angiography, artificial intelligence, deep learning, retinal biomarkers, explainable AI.

1. INTRODUCTION

The retina is among the most metabolically active tissues in the human body and is essential for visual function, which is dependent on constant balance and interplay between neural activity and blood flow (Joyal, Gantner, and Smith 2018). Retinal neurons have limited ability to regenerate and strict demands for oxygen delivery, glucose metabolism and vascular integrity. Thus, impairment of retinal neurovascular homeostasis leads to retinopathy, as well as to a progressive degeneration of the retina's neurons and permanent vision loss (Fevereiro-Martins et al. 2023). The traditional concept of retinal diseases has been dramatically changed in the last decade by the growing evidence that in many retinal diseases, including diabetic retinopathy (DR) and glaucoma, there is often a neuronal dysfunction prior to any apparent clinically detectable vascular damage. This paradigm shift has led to an increase in interest in the retinal neurovascular unit (NVU) as a key player in regulating retinal physiology and disease (Zhou and Chen 2023).

The retinal NVU is a complex structure that contains endothelial, pericytes, vascular smooth muscle cells, neurons, Müller glial cells, astrocytes, microglia, and extracellular matrix (Grimes et al. 2024). These cells act together to control the retinal vascular flow, blood-retinal barrier function, synapse transmission and metabolic exchange. A disruption in function of any part of this network can start inflammatory cascades, cause oxidative stress, impair endothelial function, cause non-perfusion of the capillaries, cause apoptosis of neurons, and cause leakage of the vessels, all of which contributes to retinal degeneration. Recent reviews have highlighted that neurovascular impairment should be considered a key pathogenic mechanism and not just the result of a vascular disease (Yemanyi et al. 2021).

Diabetic retinopathy is the most well studied model of neurovascular dysfunction among retinal diseases. DR is an increasingly understood disease and is now known not only as a microvascular problem of diabetes but also as a disease of early neurodegeneration, early glial activation, and early neurovascular coupling dysfunction prior to the development of microaneurysms or hemorrhages (Sinclair and Schwartz 2019). It has since been found that there are similar mechanisms in age related macular degeneration (AMD), glaucoma, retinal vein occlusion (RVO) and inherited retinal dystrophies, indicating that the neurovascular dysfunction is a common pathway in multiple retinal diseases. This has led to a shift from morphology based diagnosis to functional and molecular biomarkers that can diagnose disease much earlier (Wu, Cao, and Liu 2026).

This change has been greatly aided by advances in ophthalmic imaging. In the past few years, optical coherence tomography (OCT), and OCT angiography (OCTA) along with adaptive optics, fluorescence lifetime imaging and hyperspectral retinal imaging have enabled detailed imaging of retinal neurons, microvasculature and blood flow without the need for any invasive procedures (Kostanyan, Wollstein, and Schuman 2015). Such imaging modalities produce vast amounts of high dimensional data that is beyond the scope of conventional manual analysis, which opens up opportunities for approaches based on artificial intelligence (AI) (Pinto-Coelho 2023).

AI has become one of the most powerful technologies in the field of ophthalmology today. Machine learning (ML), CNNs, transformer, and multimodal foundation models have been shown to be highly accurate in the identification of retinal disease from fundus photographs, OCT images, and OCTA datasets (Lim et al. 2024). Multiple standalone AI systems have already been approved for DR screening, and recent studies have been added to AI's role in glaucoma progression, AMD prediction, retinal vascular disease, and systemic disease detection from retinal images.

In more recent developments, multimodal AI systems combining structural OCT, OCTA, fundus imaging, clinical history and genetic data have demonstrated significant potential in enhancing diagnostic precision and personalized risk prediction. Explainable AI (XAI) techniques, attention maps, federated learning, and foundation vision-language models are all simultaneously tackling issues of model transparency, data privacy, and clinical use (Nimmy et al. 2025).

However, there are still several hurdles to overcome before neurovascular biomarkers and AI-driven diagnostics can be seamlessly integrated into standard clinical practice. However, the use of AI in medical imaging remains hindered by biological heterogeneity, the standardization of imaging modalities and pipelines, limited external validation, bias in training datasets, algorithm transparency, and regulatory concerns. Additionally, AI shows great diagnostic performance in a controlled setting, but the potential to improve patient outcomes with earlier intervention and personalized treatment must be validated in a prospective clinical setting (Hassan et al. 2025).

This review aims to detail the biological mechanisms of retinal neurovascular dysfunction and critically discuss the recent advancements in AI applications in retinal imaging and disease management. Special focus is given on the intersection of mechanistic biology and computational intelligence, with an eye on novel opportunities for precision diagnostics, individualized risk assessment and future therapeutic development.

2. STRUCTURE AND FUNCTION OF THE RETINAL NEUROVASCULAR UNIT

The retina is an extension of the central nervous system (CNS), and has one of the highest oxygen consumption rates of any tissue in the human body. Thus, for the maintenance of visual function, neurons, glial cells, and retinal blood vessels must communicate continuously. This concerted interaction is controlled by a well-organized, multicellular structure, the retinal neurovascular unit (NVU), which controls vascular tone, neuronal metabolism, immune surveillance, and blood-retinal barrier (BRB) integrity. In contrast to the prevailing understanding of retinal diseases as being predominantly vascular, modern evidence highlights the role of the NVU as the main functional unit to maintain homeostasis within the retina. These pathological changes can start with the disruption of any of the components of the NVU and eventually lead to irreversible visual impairment (Zhang and Jin 2023).

The retinal NVU is composed of many cell types such as vascular endothelial cells (VEC), pericytes (Per), vascular smooth muscle cells (VSMC), retinal ganglion cells (RGC), bipolar cells, photoreceptors, Müller glia (MG), astrocytes (Ast), microglia (Mi), and extracellular matrix (Ext). These cells

communicate with each other by way of neurotransmitters, cytokines, nitric oxide (NO), vascular endothelial growth factor (VEGF), angiopoietins, transforming growth factor-β (TGF-β), ATP and glutamate, and calcium signaling pathways. These cellular components do not act alone but rather act as an integrated signaling network that is able to quickly adjust the blood flow in the retina to the local metabolic demands of the neurons (Sweeney, Ayyadurai, and Zlokovic 2016).

A key feature of the retinal NVU is neurovascular coupling, where an increase in neuronal activity causes localized vasodilation and increased blood perfusion. Retinal neurons release glutamate in response to visual stimulation initiating calcium signaling in the Müller glial cells and astrocytes. These glial cells in turn secrete vasoactive substances like prostaglandins, nitric oxide and epoxyeicosatrienoic acids that control the diameter of the vessels and adjust the delivery of oxygen to metabolically active areas of the retina. Recent research indicates that dysfunction of neurovascular coupling is one of the earliest detectable abnormalities in the retinal disorders of several patients, and that it precedes detectable structural degeneration (Bose et al. 2025).

The blood vessels in the retina are highly specialised. The retina has 3 capillary plexuses: superficial vascular, intermediate vascular, and deep vascular, which serve different layers. Astrocytes are the cells that mainly envelop the vessels in the superficial vascular plexus, and Müller glia are the cells that support the deeper vessels in the retina structurally and metabolically. Recent ultrastructural studies have shown significant differences in the glial coverage and neuronal contacts between different layers, indicating that each of the retinal vascular plexuses has different susceptibility to disease. These results have led to substantial changes in the understanding of the organization of the retinal vascular system and provide insights into the selective involvement of specific retinal vascular layers in various diseases of the retina (Jobling et al. 2025).

The NVU's other critical role is to maintain the inner blood-retinal barrier (iBRB). The proteins of tight junctions such as claudins, occludins, and zonula occludens-1 create highly selective endothelial barriers that control the passage of molecules between the circulating blood and the retinal tissue. Pericytes stabilize endothelial cells, while Müller cells control the levels of extracellular potassium, neurotransmitter recycling and metabolic support. Disruption of these processes can lead to abnormal blood vessel leakage, inflammation and swelling of the retina and damage to retinal cells, which are typical of late-stage retinal disease (Díaz-Coránguez, Ramos, and Antonetti 2017).

There is also growing evidence that the retinal NVU reflects neurovascular events within the brain. The non-invasive nature of visualizing retinal vessels has made neurovascular dysfunction of the retina an attractive biomarker of cerebral small vessel disease, Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases. Hence, retinal imaging is now considered a "window to the brain" giving access to information about a person's general neurovascular health (Shen 2025). (Figure 1)

As a whole, these studies highlight the importance of coordinated function between neurons, glia, immune

cells and microvasculature to preserve retinal function. Neurovascular dysfunction thus is not merely vascular damage, but rather a failure of interconnected systems in multiple cellular pathways.

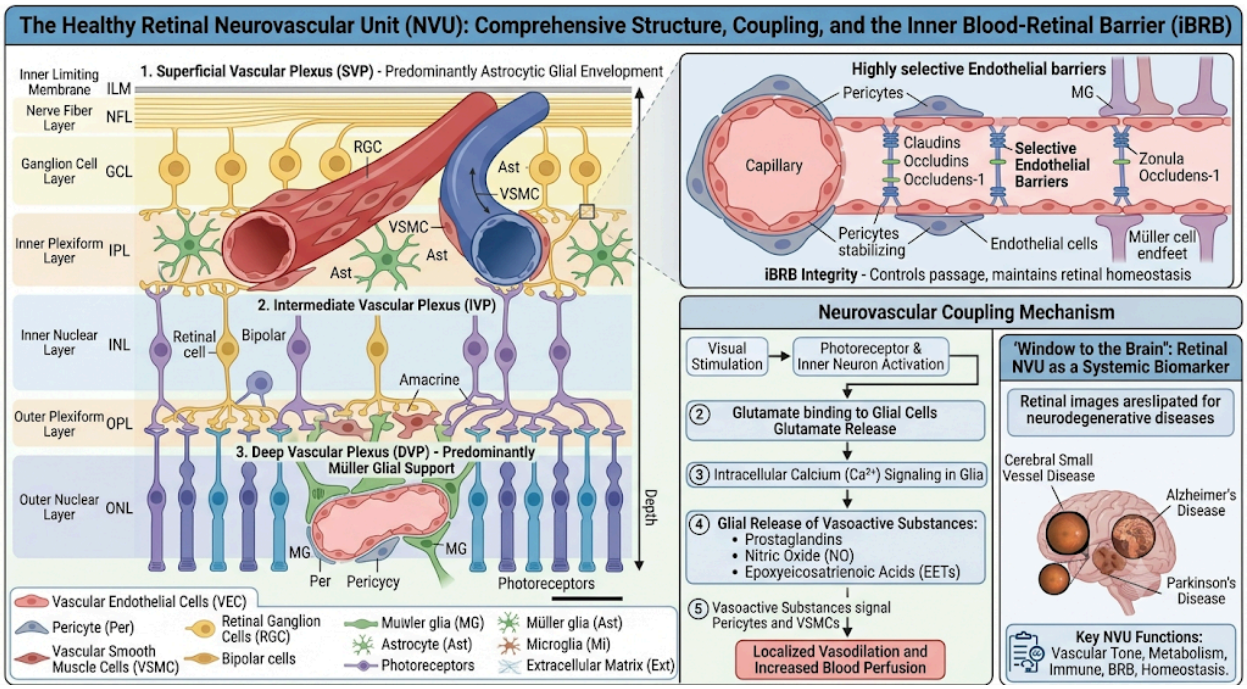


Figure 1: Comprehensive Schematic of the Healthy Retinal Neurovascular Unit (NVU)

3. CELLULAR AND MOLECULAR MECHANISMS OF NEUROVASCULAR DYSFUNCTION

After a gradual loss of synchronization of NVU communication, neurovascular function is lost. Retinal diseases are not a single pathogenic mechanism, but are related to oxidative stress, chronic inflammation, mitochondria dysfunction, endothelial injury, glia activation, vascular remodeling and neuronal degeneration. These biological processes often feed into each other and create vicious circles of retinal damage (Presa et al. 2020). (Figure 2)

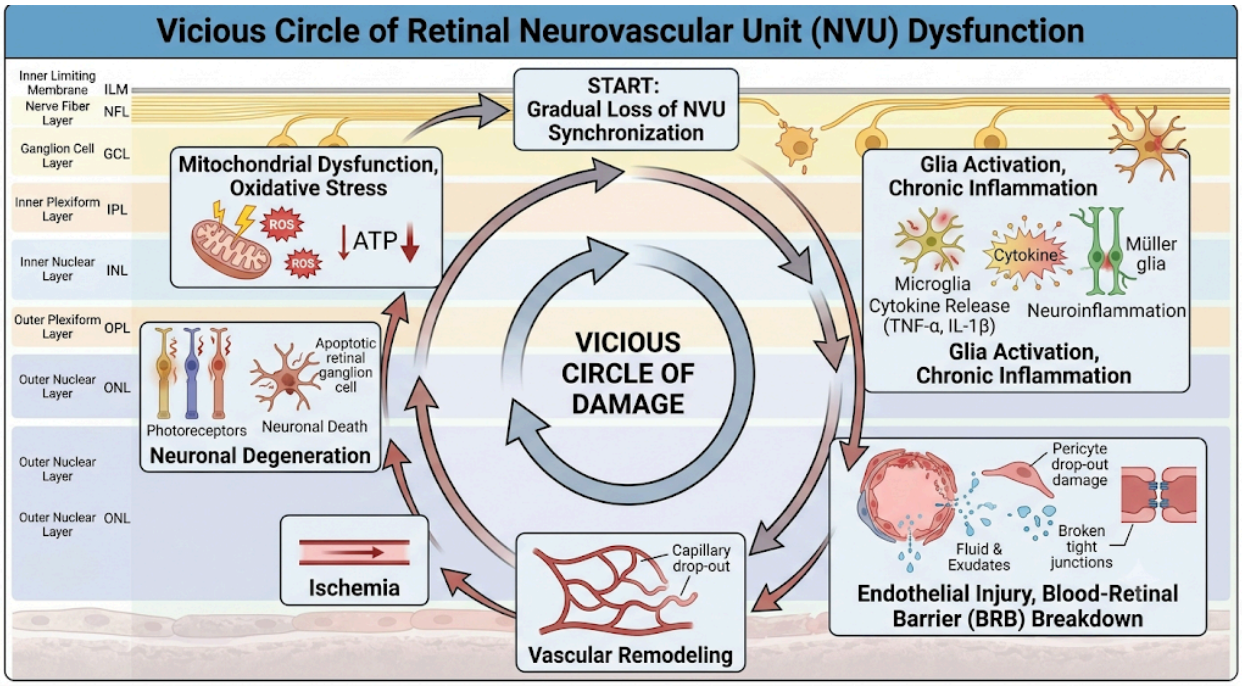


Figure 2: The Vicious Circle of Retinal Neurovascular Unit (NVU) Dysfunction in Disease

3.1 Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is believed to be amongst the earliest molecular events in retinal neurovascular injury. Due to the high oxygen consumption and high density of mitochondria in the retina, it is highly vulnerable to excessive production of reactive oxygen species (ROS). Antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase help to regulate the intracellular redox balance in physiological conditions. These protective mechanisms, however, cannot cope with chronic hyperglycemia, aging, ischemia, and inflammatory signaling, leading to oxidative stress on DNA, proteins, and lipids (Masuda, Shimazawa, and Hara 2017).

Oxidative stress is exacerbated by mitochondrial dysfunction, which results in slower ATP production and contributes to perturbed calcium regulation. Loss of mitochondrial membrane potential leads to intrinsic apoptosis pathways by cytochrome c release, caspase activation, and neuronal cell death. The high metabolism of retinal ganglion cells and photoreceptors makes them especially susceptible. Recent studies indicate that mitochondrial dysfunction has been observed long before the onset of clinically apparent vascular disease and could be useful as biomarkers for early detection of disease and for therapeutic intervention (Zong et al. 2024).

3.2 Neuroinflammation and Glial activation

Inflammation has become a common denominator in the correlation of neuronal injury and vascular dysfunction. Once chronically activated, retinal microglia and Müller glia continuously secrete

inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and interferon-γ.

Müller cells under normal physiological conditions are responsible for recycling of neurotransmitters, potassium buffering and metabolic homeostasis. As the disease progresses, however, these cells become reactive, with an increase in their expression of glial fibrillary acidic protein (GFAP), hypertrophy, altered secretion of cytokines, and disruption of support of neurons. Activated Müller cells also increase the production of VEGF, which causes vascular leakage and pathological angiogenesis (Rashid, Akhtar-Schaefer, and Langmann 2019).

The activation of microglia also plays a role in disease progression. Microglia continuously monitor the retinal environment, and activated microglia will move towards damaged neurons and secrete inflammatory mediators that exacerbate endothelial dysfunction and neuronal apoptosis. The experimental data now strongly indicate that in many instances, glial activation often occurs before the vascular pathology, supporting the notion that neurovascular dysfunction is initiated by disruption in cellular communication and not just vascular injury. (Ramirez et al. 2017)

3.3 Blood-Retinal Barrier Breakdown

The blood-retinal barrier integrity is critical for maintaining retinal immune privilege and metabolic homeostasis. Tight junctions (TJs) keep plasma proteins and inflammatory mediators from diffusing into retinal tissues.

Endothelial junctional proteins are disrupted by multiple pathological stimuli such as: VEGF overexpression, oxidative stress, advanced glycation end products (AGEs), inflammatory cytokines and matrix metalloproteinases (MMPs). Excessive permeability of the vessels enables plasma proteins, leukocytes and inflammatory molecules to leak into the tissue of the retina, causing edema and secondary neuronal damage.

In diabetic retinopathy, the apoptosis of pericytes also causes microaneurysms to form and capillaries to drop out. The same impairment of barrier function is thought to play a role in the development of exudative AMD via choroidal neovascularization and retinal edema in retinal vein occlusion. Therefore BRB disruption is a common mechanism for a number of retinal diseases (Katamay and Nussenblatt 2012).

3.4 Impaired Neurovascular Coupling

The precise timing between neuronal activity and local blood flow is crucial for healthy function of the retina. Neurovascular coupling ensures that metabolically active areas of the retina are supplied with oxygen and glucose.

Neurovascular coupling impairment in disease is caused by impaired communications between neurons, Müller cells, astrocytes, endothelial cells and pericytes. These all contribute to a decreased vascular responsiveness: reduced nitric oxide bioavailability, altered calcium signaling, endothelial dysfunction and impaired glial communication. This results in chronic hypoxia in metabolically active neurons although the retinal vessels are normal.

Diabetics before the onset of retinopathy have been shown to have decreased neurovascular coupling, in recent clinical studies using dynamic vessel analysis and OCT angiography. Abnormalities of this kind have been observed in glaucoma and Alzheimer's disease, thus strengthening the idea that the decrease in neurovascular coupling is an early sign of retinal and brain degeneration (Gerhard et al. 2020).

3.5 VEGF Signaling and Pathological Angiogenesis

Vascular endothelial growth factor (VEGF) serves two functions in the retina. VEGF is responsible for the survival of neurons and maintenance of vessels under physiological conditions. However, in chronic hypoxia, HIF-1α (hypoxia-inducible factor-1α) is activated, leading to an excess production of VEGF, and to pathological angiogenesis and vascular leakage.

While anti-VEGF drugs are the mainstay of treatment for neovascular retinal diseases, there is increasing evidence that anti-VEGF treatment alone is insufficient to restore neurovascular function since vascular stabilization does not prevent neuronal degeneration, inflammation or glial dysfunction. Therefore, novel therapeutic approaches are increasingly directed towards targeting multiple NVU elements and not only at angiogenesis (Penn et al. 2008).

3.6 Crosstalk between Neurodegeneration and Microvascular Injury

The most significant conceptual leap of the last 10 years was the understanding that neuronal degeneration and vascular pathology are a vicious circle, and not independent events. Injured neurons release inflammatory mediators, causing endothelial dysfunction and ischemic microvasculature contributing to neuronal hypoxia and oxidative stress.

This is a two-way street; and this is why there is often poor correlation between visual function and structural vascular abnormalities. A significant degree of neuronal dysfunction can occur with relatively mild vascular pathology, and others can have a considerable amount of microvascular changes and still maintain good visual acuity. This has led to the growing importance of multimodal biomarkers that combine neuronal, vascular, inflammatory and metabolic information, as opposed to the use of vascular imaging alone (Cerquera-Jaramillo et al. 2018).

One of the most important paradigm shifts in modern-day ophthalmology is the concept that retinal disease is a disorder of the whole neurovascular unit. It also serves as the biological underpinning for the development of next generation imaging technologies and artificial intelligence (AI) based diagnostic algorithms to enable detection of disease at an earlier stage than ever before.

4. NEUROVASCULAR DYSFUNCTION IN MAJOR RETINAL DISEASES

Neurovascular dysfunction is a shared pathological process of many retinal diseases, but the molecular events triggering the disease and the subsequent disease progression vary with etiology. Recent studies have shown that neuronal injury, glial activation, vascular remodeling, and inflammatory signaling are much earlier than previously thought, allowing the possibility of earlier diagnosis and intervention through neurovascular biomarkers. The biological mechanisms of neurovascular dysfunction in four major retinal diseases like diabetes retinopathy (DR), age-related macular degeneration (AMD), glaucoma and retinal vein occlusion (RVO) are reviewed.

4.1 Diabetic Retinopathy

Diabetic retinopathy (DR) is still the biggest cause of preventable blindness in people of working age in the world. DR has traditionally been considered a microvascular complication of chronic hyperglycemia with microaneurysms, retinal hemorrhages, microvascular non-perfusion and pathological neovascularization. But, mounting experimental and clinical data now suggest that the retinal neurodegeneration and neurovascular changes occur before clinically observable vascular changes, altering the paradigm of disease pathogenesis (Kropp et al. 2023).

Oxidative stress is caused by persistent hyperglycemia, which leads to increased levels of reactive oxygen species (ROS), activation of protein kinase C (PKC), increased levels of advanced glycation end-products (AGEs) and stimulation of the polyol pathway. These metabolic disturbances affect the endothelial cells, the retinal neurons and the Muller glia simultaneously and cause a progressive disruption of the retinal neurovascular unit (González et al. 2023).

Pericyte loss is one of the earliest pathological events in DR which leads to destabilization of retinal capillaries and microaneurysm formation. At the same time, endothelial tight junction proteins, like occludin and claudin-5, are then disrupted, which results in an increase in vascular permeability and breakdown of the inner blood-retinal barrier (iBRB). These vascular changes go hand-in-hand with the activation of the Müller glial cells and retinal microglia, leading to persistent secretion of inflammatory cytokines such as TNF-α, IL-6, IL-1β, MCP-1 and VEGF. The endothelial dysfunction, neuronal apoptosis and capillary degeneration is further exacerbated by chronic inflammation (Beltramo and Porta 2013).

Apoptosis of retinal ganglion cells has been found prior to the onset of clinical retinopathy, indicating that neuronal injury is one of the earliest signs of diabetes. Studies using optical coherence tomography (OCT) have consistently shown that diabetic patients without apparent retinopathy exhibit thinning of the ganglion cell-inner plexiform layer (GCIPL), which has suggested that there is early retinal neurodegeneration (Barber 2025).

Another mechanism is failure of neurovascular coupling. Retinal vessels dynamically respond to neuronal metabolic needs but this adaptive vascular response is highly impaired in diabetes. Reduced vessel density

in both superficial and deep capillary plexuses has been found prior to clinical DR by OCT angiography (OCTA) studies. Such vascular abnormalities are highly associated with functional deficits in the retina detected by multifocal electroretinography and contrast sensitivity testing (Fletcher et al. 2022).
More recent molecular studies also point to the importance of the role of extracellular vesicles, long non-coding RNAs (lncRNAs), microRNAs and exosomes for endothelial cells to communicate with retinal neurons. These signaling molecules could ultimately be used as markers in the blood to detect early diabetic retinal disease.

Currently, treatment is predominantly anti-VEGF agents injected intravitreally in order to inhibit the development of new blood vessels. However, the greater understanding of early neurodegeneration has spurred the research of neuroprotective strategies that focus on oxidative stress, inflammation, mitochondrial dysfunction, and glial activation. Currently, there is emphasis on neurovascular function preservation prior to vascular irreversible damage and several clinical trials are testing topical neuroprotective agents and antioxidant therapies (Born, Harmon, and Jay 2020).

4.2 Age-Related Macular Degeneration

The most common cause of permanent sight loss in older age groups in developed countries is age-related macular degeneration (AMD). AMD is different from DR in that it affects the outer retina, retinal pigment epithelium (RPE), Bruch's membrane and the choroidal circulation. However, the involvement of neurovascular dysfunction in the initiation and progression of the disease has become of paramount importance.

The mitochondria of RPE cells progressively become dysfunctional with aging, resulting in decreased oxidative phosphorylation and greater production of reactive oxygen species. Simultaneously, chronic inflammation, complement activation, and lipid accumulation promote formation of drusen between the RPE and Bruch's membrane. They disrupt the interface between the choroidal circulation and the photoreceptors, leading to a gradual loss of photoreceptors (Chaudhuri et al. 2023).

Among the most important findings of the last 10 years is the discovery that choriocapillaris impairment occurs before the loss of photoreceptors. OCTA studies show choriocapillaris flow deficits which are very prominent even in the early AMD stage and may be a primary disease mechanism of retinal degeneration, not just a secondary effect of tissue damage.

Inflammation, mediated by the complement system, is especially relevant in the pathogenesis of AMD. Genetic polymorphisms in complement factor H (CFH), complement factor I (CFI) and complement factor C3 are associated with a high susceptibility to disease as a result of the induction of chronic inflammatory activation in the neurovascular unit. Activated microglia migrate to the subretinal space where they secrete inflammatory cytokines, matrix metalloproteinases, and the angiogenic mediators which play a role in retinal degeneration (Kar et al. 2023).

In the case of neovascular AMD, hypoxia causes an overproduction of VEGF, which leads to the

development of abnormal choroidal neovascularization (CNV) that causes bleeding, leakage, scarring and sudden sight loss. Anti-VEGF therapy works well to stop the formation of new vessels, however many patients still see the progressive growth of geographic atrophy which demonstrates that stopping neovascularisation is not enough to stop the degeneration of neurons.

Recent research is now focused on treatments to inhibit complement, protect mitochondria, inhibit senescence pathways, and restore choroidal perfusion, indicating a general acknowledgment of AMD as a multifaceted disease and not simply one of abnormal angiogenesis (Yeo, Chan, and Cheung 2019).

4.3 Glaucoma

Classically glaucoma is described as an optic neuropathy caused by high intraocular pressure (IOP). Recent evidence, however, shows that vascular dysfunction or neurovascular dysfunction plays a significant role in retinal ganglion cell degeneration even in those who have normal-tension glaucoma.
These factors of reduced OPP, endothelial dysfunction, impaired autoregulation, and chronic ischemia all work to allow less blood supply to the ONH. These vascular abnormalities result in decreased oxygen supply to retinal ganglion cell axons leading to mitochondrial dysfunction, excitotoxicity, oxidative stress and apoptosis (Rusciano et al. 2017).

Astrocytes in the ONH become reactive, with up-regulation of GFAP, deposition of extracellular matrix and changes in cytokine production. Activated microglia also exacerbate inflammation by releasing nitric oxide, complement proteins and TNF-α, which help to promote a chronic neuroinflammatory state that hastens retinal ganglion cell (RGC) degeneration.

OCTA studies have consistently shown that glaucoma patients have decreased peripapillary vessel density, even before a visual field deficit is detected. Based on these findings, retinal microvascular abnormalities could be useful biomarkers for early diagnosis and monitoring of glaucoma progression.
Recent studies have also found that retinal vessels exhibit abnormal functional changes in neurovascular coupling during visual stimuli, before structural changes occur. These signals contribute to the development of dynamic vascular biomarkers, as opposed to just static structural imaging (Cekanaviciute and Buckwalter 2016).

4.4 Retinal Vein Occlusion

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy. Central retinal vein and branch retinal vein occlusion (CRVO) results in abrupt loss of retinal perfusion with venous congestion, ischemia, and macular edema.

While vascular obstruction is the initiating event, neurovascular dysfunction plays an important role in the severity of the disease. VEGF is produced very quickly in response to ischemia by activation of hypoxia-inducible factor-1α (HIF-1α) leading to vascular permeability, recruitment of leukocytes, and

inflammatory signaling. Müller cells are activated and directly involved in retinal edema by dysregulated potassium and water transport.

Retinal ganglion cells (RGC) and bipolar neurons are most vulnerable to ischemic injury, and neuronal apoptosis can happen within a few hours. Experimental studies have shown that the accumulation of excitotoxic glutamate, mitochondrial dysfunction and oxidative stress play a major role in the loss of retinal neurons after vascular occlusion.

Visualization of non-perfusion in the superficial and deep capillary plexus has added significantly to the understanding of retinal ischemia by OCTA. The impairment of deep capillary plexus has high correlation with visual acuity, emphasizing the role of neurovascular integrity, not just vascular occlusion.
Newer therapies are emerging that involve a combination of anti-VEGF therapy with corticosteroid and anti-inflammatory agents and experimental neuroprotective approaches to help maintain retinal neuronal function after ischemic injury (Jonas and Lam 2012).

4.5 Shared Neurovascular Pathways Across Retinal Diseases.

Although these different retinal diseases appear different clinically, the mechanisms of neurovascular dysfunction are strikingly similar in diabetic retinopathy, AMD, glaucoma, and retinal vein occlusion. Common pathways include: Oxidative stress and mitochondrial dysfunction, Chronic neuroinflammation, Müller cell gliosis, Microglial activation, Blood-retinal barrier breakdown, Endothelial dysfunction, VEGF overexpression, Impaired neurovascular coupling, Progressive neuronal apoptosis.

These common mechanisms have therapeutic implications. Future therapies might instead involve maintaining integrity of the entire retinal neurovascular unit rather than treating vascular abnormalities in isolation. This systems-based approach is also leading to the development of multimodal imaging biomarkers that can non-invasively evaluate neuronal, vascular and inflammatory changes at the same time.

Moreover, these biological insights give rationale for the use of AI in retinal imaging. AI algorithms are well suited to detect complex imaging patterns that might be missed during clinical interpretation, as neurovascular dysfunction is reflected in subtle changes in structure and function that span several layers of the retina (Ruan et al. 2020).

While there is ample evidence of neurovascular dysfunction in the retina in many diseases, it is unclear if neuronal degeneration invariably leads to vascular dysfunction in all diseases. In diabetic retinopathy and glaucoma it is usually accepted that the initial neuronal dysfunction occurs prior to manifesting as overt vascular disease, whereas in retinal vein occlusion and neovascular AMD the sequence is not as well defined. Therefore, imaging studies that provide all three parameters structural, vascular, and functional along the time dimension are needed to better characterize the disease-specific pathogenic time courses.

5. NEW AI DIAGNOSTIC STRATEGIES IN NEUROVASCULAR DYSFUNCTION

In the last 10 years, there have been many significant advances in retinal imaging that have made ophthalmology one of the most data-rich specialties in medicine. With the advent of high-resolution imaging modalities, vast amounts of structural, vascular and functional information are now obtained that cannot be qualitatively assessed with traditional methods. At the same time, AI has become a powerful analytical tool that is able to pick out subtle imaging markers related to the dysfunction of the retina's neurovasculature. AI algorithms can identify complex multidimensional patterns that indicate early microscopic changes in cells and microvessels, which are not visible on a traditional image; they can detect these patterns even before any clinical symptoms appear. As a result, AI is increasingly becoming an essential part of precision ophthalmology.

5.1 AI-Assisted Retinal Imaging

The application of AI in the diagnosis of retinal diseases is based on retinal imaging, which is a non-invasive way to visualize the neurovascular unit of the retina. Optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) have emerged as two highly promising imaging tools for the study of neurovascular dysfunction.

However, conventional OCT offers micron level cross sectional visualization of the retinal architecture, and enables quantitative assessment of retinal thickness, ganglion cell complex (GCC), retinal nerve fiber layer (RNFL) and photoreceptor integrity. OCTA adds to this the ability to create 3D maps of the microvasculature in the retina and choroid without the use of intravenous dye. OCTA overcomes this limitation and allows for the separate imaging of the superficial vascular plexus (SVP), intermediate capillary plexus (ICP), deep capillary plexus (DCP) and choriocapillaris, allowing for comprehensive assessment of retinal neurovascular integrity.

Recent studies have shown that AI-aided analysis of OCTA images significantly increased the detection of early DR, including subtle decreases in vessel densities, increases in the foveal avascular zone (FAZ), capillary non-perfusion, and changes in vascular tortuosity which are not possible to see with the naked eye.

In addition to OCTA, ultra-widefield imaging, adaptive optics scanning laser ophthalmoscopy (AOSLO), hyperspectral retinal imaging, fluorescence lifetime imaging ophthalmoscopy (FLIO), and retinal oximetry are extending the range of measurable neurovascular biomarkers. AI algorithms are now incorporating data from several imaging modalities, to give a more thorough characterization of the retinal pathology than any individual imaging modality can offer (Yang et al. 2025).
Although OCTA has revolutionized imaging of retinal microvasculature, without injection of dye, it still has the potential for projection artifacts, segmentation errors, and motion-related artifacts, especially in eyes with severe retinal disease. Fluorescein angiography is still the best method for detecting vascular leakage, although it is an invasive technique, while conventional OCT offers excellent structural resolution although it does not directly visualize blood flow. Although near-cellular resolution, adaptive

optics is currently used primarily in research environments due to its limited availability and high acquisition price. Hyperspectral imaging can be used to obtain metabolic information, which might precede structural abnormalities, but standardized acquisition protocols and solid clinical validation are still missing. Hence, it seems that there is no single imaging modality that provides a comprehensive assessment of retinal neurovascular dysfunction, contributing to the increasingly prevalent use of multimodal imaging strategies.

5.2 Deep Learning for the Detection of Retinal Diseases

The diagnosis of the retina has been revolutionised by deep learning, which captures features directly from imaging data. In the field of retinal image classification, segmentation, and disease grading, convolutional neural networks (CNNs), particularly ResNet, DenseNet, EfficientNet, U-Net and inception architectures, have shown outstanding performance.

One of the first clinical successes was Google's deep learning system which was able to detect diabetic retinopathy at a level comparable to retinal specialists, based on color fundus photographs. This pioneering study has proven that AI is a clinically viable diagnostic tool and spurred a sharp growth of ophthalmic AI research. In the research conducted by Gulshan et al, the deep learning algorithm had an AUC value of more than 0.99 for referable diabetic retinopathy (DR) and sensitivity and specificity of more than 90% on independent validation sets. Similarly, AI systems like autonomous IDx-DR have shown sensitivities over 85% and specificities between 87–90% in prospective primary care settings, which has resulted in the FDA approving such systems as tools for diabetic retinopathy screening.

Later studies have been able to apply deep learning to almost all major retinal diseases. Now CNN-based algorithms identify: diabetic retinopathy severity, age-related macular degeneration, glaucoma, retinal vein occlusion, retinal detachment, inherited retinal dystrophies, optic disc edema, macular edema, epiretinal membranes, and choroidal neovascularization.

Deep learning automatically detects the hierarchical imaging features associated with vascular branching, retinal layer organization, microaneurysms, hemorrhages, exudates, capillary dropout, and neuronal degeneration, unlike handcrafted feature-based approaches. As a result, these algorithms often achieve better performance than traditional machine-learning techniques that rely on manual feature engineering.
More recently, researchers have shown that deep learning can be used to directly predict systemic measures such as age, sex, cardiac risk, renal disease, anemia, hypertension, and dementia from the retina (Muchuchuti and Viriri 2023).

5.3 Vision Transformers and Foundation Models

Transformer-based models have recently become the new generation of retinal image analysis despite CNN's domination in the field for almost a decade.

Vision Transformers (ViTs) use a self-attention mechanism to model long-range spatial relationships

within images from the retina, which allows for better characterization of diffuse pathological changes occurring across the different layers of the retina. Transformers are especially useful for integrating multimodal data and large-scale self-supervised learning, which is a task in which CNNs struggle.

Among the recent advances, one of the most crucial is the introduction of RETFound, a retinal foundation model trained on millions of unlabeled retinal images via a self-supervised method. RETFound was seen to enhance performance for many downstream ophthalmic applications, such as diabetic retinopathy, glaucoma, AMD and systemic disease prediction, and significantly reduces the number of images required for training with labels. In its downstream ophthalmic tasks, RETFound showed stable gains across a range of tasks, with a reported AUC gain of 2–6% over conventional supervised CNN architectures and with significantly fewer labeled training images.

Likewise, other backbone models, like VisionFM, and MedSAM, show impressive generalisation performance on a variety of ophthalmic imaging datasets. These models are a step towards universal ophthalmic foundation models that can be used for multiple diagnostic purposes, instead of specific AI models for each specific disease.

These advances are especially pertinent to the analysis of neurovascular dysfunction as transformer architectures enable the simultaneous analysis of structural, vascular, inflammatory, and functional imaging biomarkers, offering a comprehensive characterization of retinal disease (J.-H. Wu et al. 2023).

5.4 Multimodal Artificial Intelligence

Neurovascular dysfunction is fundamentally multi-faceted. All these factors: structural retinal abnormalities, vascular remodeling, inflammatory activity, genetic predisposition and systemic metabolic disturbances contribute to disease progression. Thus, the diagnostic capability of one imaging modality is limited.

Multimodal AI aims to change this by combining various forms of data such as: Fundus photography, Structural OCT, OCT angiography, Fluorescein angiography, Adaptive optics, Clinical records, Laboratory investigations, Electronic health records, Genomic information

Recent multimodal deep learning systems show superior performances to unimodal systems for diabetic retinopathy progression, AMD conversion, and glaucoma severity prediction. Multimodal models such as OCT and OCTA have been able to show the potential in the detection of early diabetic retinal neurovascular dysfunction, evaluating together the retinal thickness, capillary perfusion, FAZ morphology, and vessel density. The same method, which combines retinal imaging with systemic clinical parameters, has greatly enhanced prediction of diabetic kidney disease, cardiovascular events and cognitive decline (Kłodnicka et al. 2025) (Figure 3).

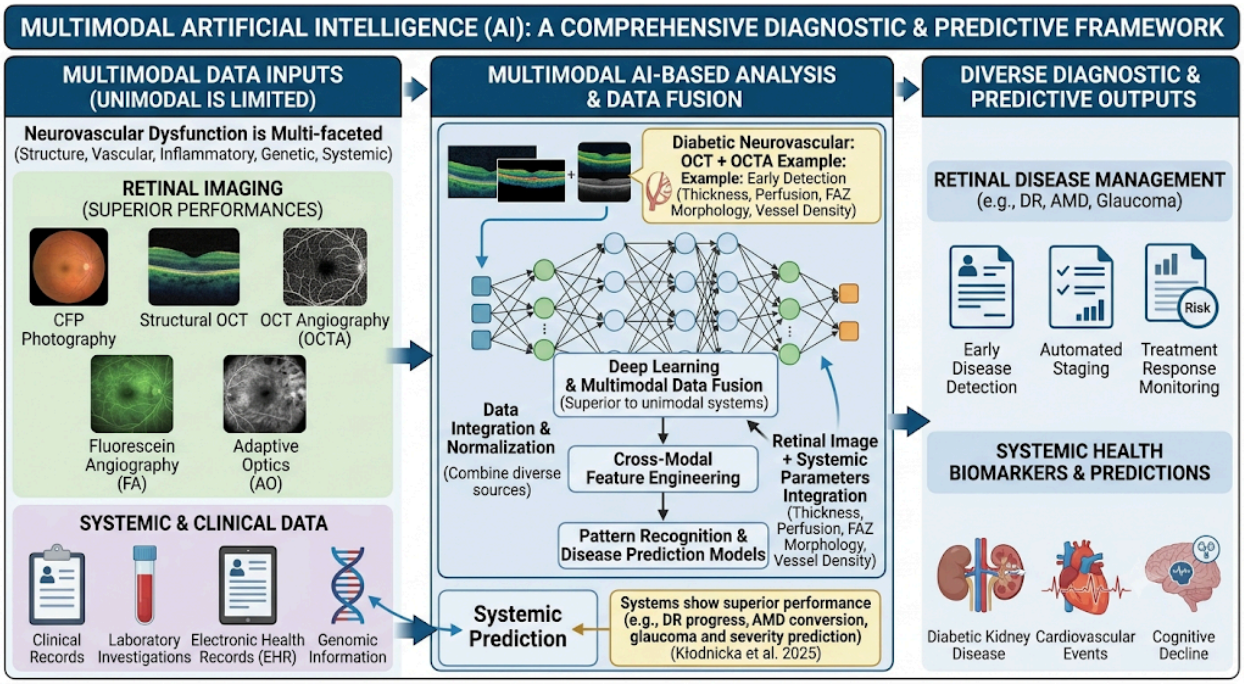


Figure 3: Comprehensive Framework Utilizing Multimodal Artificial Intelligence (AI) for Retinal and Systemic Health

5.5 Explainable Artificial Intelligence (XAI)

Thus, although deep learning models can perform very well in the diagnosis task, they are still often referred to as "black boxes. Clinicians' confidence, regulatory approval and patient acceptance are limited by lack of interpretability.

To overcome this limitation, explainable AI aims to pinpoint imaging regions for which model predictions are made. Common approaches include:

Gradient-weighted Class Activation Mapping (Grad-CAM) is a method that generates a saliency map for each category. SHAP (SHapley Additive exPlanations), Integrated Gradients, Attention visualization, Saliency mapping. Recent ophthalmic studies show that XAI often identifies biologically relevant areas of the retina such as: microaneurysms, ischemic capillary zones, RNFL defects, ganglion cell thinning, choriocapillaris flow deficits and. Importantly, XAI can help to increase the level of trust in a clinician, showing that the predictions made by the algorithm are consistent with known pathological features, and not imaging artifacts. AI's explainability is expected to become a regulatory requirement for deployment in healthcare systems as it takes on greater roles in clinical decision-making (Ennab and Mcheick 2024).

5.6 Federated Learning and Privacy-Preserving AI

One major obstacle to clinical AI development is limited access to large, diverse retinal imaging datasets because of patient privacy regulations. This challenge can be overcome using federated learning, which allows collaborative training of the model among multiple institutions without moving patient data. Each hospital keeps the local data, and only shares the parameters of the model, greatly increasing the security of the data. Since 2023, several multicenter ophthalmic studies have shown that federated learning can provide a similar diagnostic accuracy as centralized learning while offering better generalizability between ethnic groups and imaging modalities. Retinal disease presents significant demographic variation and federated learning is a key technique for mitigating algorithmic bias and translating algorithms to the clinic (Luis Filipe Nakayama et al. 2023).

5.7 AI solutions for the prediction of disease progression.

The traditional way of diagnosing the retina is mostly towards detection of the current pathology. Prediction of future progression of disease has become more accentuated in recent AI research. Estimates are currently made with longitudinal deep learning models: conversion from non-proliferative to proliferative diabetic retinopathy, Conversion of intermediate AMD to geographic atrophy, glaucoma progression, treatment response, recurrence after anti-VEGF therapy, visual acuity outcomes. These prediction models allow for individualized surveillance plans and individualized treatment plans. The incorporation of longitudinal imaging data from multiple clinical visits, using emerging recurrent neural networks (RNNs), temporal transformers, and survival deep learning models, further enhances prediction (Pratap et al. 2024).

5.8 Digital Twins and Precision Ophthalmology

Perhaps the most exciting frontier in ophthalmic AI is the development of digital twins. The retinal digital twin is a virtual model of the neurovascular system of a specific patient's retina generated and updated with multimodal imaging data, genetic data, laboratory studies, and clinical data. In the future, digital twins could model the progression of a disease over time given various treatment options to optimize the treatment for that individual before acting. Digital twin technology is still at an early stage of development, but has been identified as a key element of precision ophthalmology in several recent reviews. Digital twins, coupled with foundation AI models, wearable retinal monitoring devices and cloud-based analytics, could revolutionise the management of retinal diseases over the next decade (Chen and Bai 2025).

5.9 Current Challenges

Although significant strides have been made, there are still several challenges that hinder the widespread adoption of AI in retinal diagnostics. These include: limited external validation, dataset imbalance, demographic bias, inconsistent imaging protocols, device variability, regulatory uncertainty, algorithm

interpretability, cybersecurity concerns, clinician acceptance, reimbursement issues.
Although some impressive diagnostic performance is reported in retrospective data sets, relatively few AI systems have been strictly validated in prospective multicentre studies. One of the main difficulties is domain shift, where the performance of the algorithms decreases significantly when applied to images acquired with different imaging devices, different acquisition protocols, lower image quality, ethnic differences, prevalence of the disease, and different clinical settings. This has led to the need for external validation in geographically and demographically heterogeneous populations as an indispensable pre-requisite for clinical implementation.

Additionally, for successful clinical translation, the study product would need to be approved, usable within current ophthalmic workflows, preferred by clinicians, reimbursed, protected by cybersecurity measures and proven to be cost-effective relative to traditional screening methods. While some autonomous diabetic retinopathy screening technologies are already approved in several countries, there are still many emerging technologies such as retinal foundation models, multimodal generative AI systems and digital twins which need to be subjected to prospective clinical testing before they can be offered to healthcare consumers (Table 1).

AI Method	**Primary Application**	**Advantages**	**Limitations**	**Clinical Readiness**
CNN	Disease detection	Mature technology	Limited multimodal capability	High
Vision Transformer	Global feature learning	Better contextual representation	Computationally expensive	Moderate
Foundation Models	Transfer learning	Requires fewer labelled images	Limited prospective validation	Emerging
Multimodal AI	Integrates OCT + OCTA + Fundus	Highest diagnostic accuracy	Complex data harmonization	Emerging
Explainable AI	Clinical interpretation	Improved transparency	May not fully explain predictions	Moderate
Federated Learning	Privacy-preserving collaboration	Better generalizability	Infrastructure challenges	Emerging
Digital Twin	Personalized prediction	Precision medicine	Early research	Experimental

Table 1: Summary of different AI methods

6. EMERGING TRENDS IN NEUROVASCULAR RESEARCH AND ARTIFICIAL INTELLIGENCE

The methodologies currently in use represent the state-of-the-art of AI, but there are a number of emerging technologies that will shape the future of precision ophthalmology. These new paradigms are not just for the detection of diseases but also for the prediction of all diseases for an individual and for supporting clinical decision-making, as well as for the development of integrated models of the neurovascular system. Over the past four years, there have been significant advancements in retinal neurovascular function and the use of artificial intelligence in ophthalmic diagnostics. Research on retinal disease has transitioned from description of pathology to predictive, personalized, and mechanistic medicine, with the help of several advances. Perhaps the most important advancement is a new category of retinal foundation models based on the self-supervised learning of large amounts of unlabeled retinal images, notably RETFound. Foundation Models, unlike traditional convolutional neural networks trained independently for each disease, are able to learn a general representation of the retina that can be fine-tuned for various ophthalmic and systemic conditions with limited number of labelled images. RETFound has shown excellent performance in diabetic retinopathy (DR), glaucoma, age-related macular degeneration (AMD), retinal vein occlusion (RVO), and cardiovascular risk prediction, marking a significant step forward in the field of universal retinal artificial intelligence (Danese et al. 2023).

Moving from a single modality imaging approach to a multimodal approach to retinal analysis is another important trend. While the previous AI models were mainly based on color fundus photos, recent AI algorithms combine structural OCT, OCT angiography (OCTA), ultra-widefield imaging, FA, and clinical metadata. A combination of neuronal, vascular, inflammatory and structural biomarkers within these multimodal systems better captures the biological complexity of the retinal neurovascular unit. Recent comparative studies have shown that multimodal deep learning can always boost the diagnostic accuracy of the single imaging modality (Grzybowski et al. 2024).

The usage of Vision Transformers (ViTs) has also seen tremendous growth. Diffuse neurovascular abnormalities can be identified better by self-attention in the spatial dimension of retinal images, as used in the Transformer architecture. Transformers excel in the segmentation of retinal vessels, detection of capillary non-perfusion, and analysis of OCTA vascular networks, especially when compared to traditional CNNs.

More recently, quantitative OCT angiography markers have been further highlighted in investigations. Among the emerging objective measures of early neurovascular dysfunction are the vessel density, vessel skeleton density, perfusion density, fractal dimension, vessel tortuosity, choriocapillaris flow deficits and foveal avascular zone (FAZ) morphology. The extraction of these biomarkers using AI has significantly enhanced the early detection of diabetic retinopathy, glaucoma and age-related macular degeneration (Aburass et al. 2025).

Another key area of research is explainable artificial intelligence (XAI). The demand for transparency

prior to clinical deployment of autonomous AI systems is growing amongst regulatory agencies. Therefore, it is common practice to include the Grad-CAM, SHAP analysis, attention visualization, and saliency mapping in the ophthalmology deep learning model to facilitate the model's interpretability and boost the clinician's confidence.

More recently, federated learning has been investigated, which allows for models to be built jointly between different institutions without compromising patient privacy. This method overcomes some key drawbacks of retinal AI, which involve making datasets more diverse without having to store sensitive medical images centrally. As international ophthalmic databases keep growing, federated learning is expected to be more and more significant in the future.

Another new trend is the combination of the omics technologies and the retinal imaging techniques. Multi-modal retinal imaging when combined with transcriptomics, proteomics, metabolomics, and genomics can lead to the identification of molecular signatures related to neurovascular dysfunction. The incorporation of imaging biomarkers into machine learning models is helping to move the field of precision medicine forward by predicting not only disease progression but also treatment response (Mienye et al. 2024).

The notion of digital ophthalmology has also gone far beyond automated diagnosis. There are now cloud-based screening platforms to facilitate continuous monitoring of high-risk patients in a community setting, as well as smartphone fundus imaging, portable OCT devices, wearable retinal monitoring systems and teleophthalmology. AI-powered DRS can significantly enhance access to ophthalmic care, especially in areas where specialists are scarce.

These advances collectively point towards the future of retinal diagnostics in which the evaluation of structural, vascular, molecular and clinical information, rather than imaging information alone, can be done on an integrated computational platform.

7. CHALLENGES AND RESEARCH GAPS

Although significant progress has been made, there are still a number of scientific and clinical challenges. First, there is a great deal of biological heterogeneity in retinal diseases. Abnormal findings in the image can be caused by different molecular processes, which makes the generalisation of AI algorithms trained with small data sets difficult. Larger multicenter datasets containing different ethnicities, imaging devices and severity of disease are still critical.

Second, the existing imaging of the retina mainly assesses the structural abnormalities. Biomarkers of neuronal metabolism, oxygen consumption, mitochondrial function and neurovascular coupling are relatively underdeveloped. Future research directions include integration of functional imaging with AI.

Thirdly, many of the published AI models show good performance on the retrospective data, but poor

validation in the prospective data. To translate into clinical practice, external validation in other health care systems, standard imaging procedures, regulatory clearance, and ongoing post-deployment surveillance are needed.

Issues of interpretability are also significant. While explainable AI approaches have enhanced transparency, many models remain rather 'black boxes'. Clinicians need biologically interpretable outputs which complement and not replace clinical judgment.

Lastly, the ethical implications, such as algorithmic bias, patient privacy, and cybersecurity, data ownership, informed consent, and equitable access to AI technologies, are ongoing concerns. Overcoming these hurdles will be crucial for the successful adoption of AI in everyday ophthalmic care.

8. CONCLUSION

It has become apparent that neurovascular dysfunction plays a key role in the pathogenesis of many major retinal diseases, such as diabetic retinopathy, age-related macular degeneration, glaucoma and retinal vein occlusion. These diseases are not simply vascular diseases, but are diseases with complex interplay of neurons, endothelial cells, pericytes, müller glia, astrocytes, microglia, and inflammatory mediators, which constitute the retinal neurovascular unit. Recent progress in molecular biology shows that this oxidative stress and mitochondrial dysfunction, neuroinflammation, blood-retinal barrier breakdown, and retino-vascular coupling disturbances are often already present before any structural changes can be detected clinically, and therefore early detection of disease is important.

At the same time, the diagnosis in the field of ophthalmology has changed significantly thanks to the rapid developments in retinal imaging and artificial intelligence. The automated identification of subtle neurovascular biomarkers is becoming increasingly possible with remarkable accuracy thanks to the expertise of deep learning methods, multimodal AI, transformer-based architectures, explainable AI, and retinal foundation models. These technologies are not only used for diagnosis of disease but can also predict the risk of disease, model disease progression and plan personalised treatment. While there are still significant hurdles to address, such as validation, interpretability, standardization, and ethical use, AI holds the promise to transform the landscape of retinal healthcare by enabling earlier diagnosis, personalized treatment, and better visual outcomes. The future will see the combination of multimodal imaging, molecular biomarkers, and computational intelligence pave the way for a new era in precision ophthalmology, with a focus on protecting retinal neurovascular integrity.

9. FUTURE PERSPECTIVES

The next steps in research should include extensive studies of the retinal neurovascular unit through multimodal imaging and molecular characterization as well as through longitudinal clinical investigations. Future studies combining OCT, OCT angiography, adaptive optics, hyperspectral imaging and retinal oximetry with genomics, proteomics and metabolomics will add a further layer of understanding to

disease mechanisms and help identify strong neurovascular biomarkers. Progress in the areas of foundation AI models, digital twins, federated learning, and explainable AI are likely to enhance the ability for individualized disease prediction and mitigate data privacy and clinical interpretability concerns. Potential multicenter validations with different sub-populations will be key to prove reliability and generalization of AI-supported diagnostic systems. In conclusion, with continued advances in biological knowledge and cutting-edge computational technology, it will be possible to intervene earlier, treat more precisely and preserve vision for longer in patients with retinal disease.

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