

The Retina's Whisper: Early Signals of Brain Disease

**Dr. Anshumalee Patel¹, Dr. Priyadarshree Patel², Dr. Gita Patel³,
Dr. Yogesh Patel⁴**

¹MS (Ophthalmology), Senior Resident, M & J Western Regional Institute of Ophthalmology, B.J. Medical College, Ahmedabad, Gujarat, India

²MD (Neurointerventional Surgery), Faculty, Willis Knighton Neurovascular Institute, Louisiana, USA

³MS (General Surgery), Senior DNB Consultant, VS Hospital, Ahmedabad, Gujarat, India

⁴MS, M Ch (Plastic Surgery), Consultant, Ananya Medical College and Hospital, Ahmedabad, Gujarat, India

Abstract

The human retina, as an anatomical extension of the brain, provides a uniquely accessible window into cerebral microvascular and neurovascular integrity. This review synthesizes current evidence linking retinal microvascular structure and function with brain health and neurodegenerative disease. Literature from PubMed, Scopus, Google Scholar, and Cochrane databases was reviewed, emphasizing anatomical and physiological parallels between retinal and cerebral vasculature and clinical correlations in Alzheimer's disease, vascular dementia, Parkinson's disease, and related disorders.

Advanced imaging modalities such as OCT-A, adaptive optics, and AI-based analytics now enable quantitative assessment of retinal microvasculature. Structural and functional biomarkers—including vessel density, foveal avascular zone parameters, and fractal dimension—show consistent associations with cognitive decline and cerebral pathology.

Retinal vascular imaging thus offers a practical, reproducible, and non-invasive approach for early detection and monitoring of neurodegenerative disease. Future work integrating multimodal imaging, longitudinal data, and artificial intelligence may establish the retina as a validated biomarker for brain health and disease progression.

Keywords: Retina; Optical Coherence Tomography Angiography; Neurodegeneration; Alzheimer's Disease; Biomarkers; Cerebral Microvasculature

INTRODUCTION

Because of its transparent media and high spatial resolution, the retinal vasculature serves as a living model of neural and vascular interactions, reflecting systemic and neurodegenerative processes that affect the brain. Recent advances in imaging technologies—including optical coherence tomography angiography (OCT-A), adaptive optics, and artificial intelligence–assisted analytics—have transformed our capacity to visualize, quantify, and interpret microvascular changes with remarkable precision. These innovations have expanded the clinical and research frontier beyond ophthalmology, establishing the retina as a powerful biomarker platform for the diagnosis, monitoring, and prognostication of neurodegenerative

diseases such as Alzheimer's disease, vascular dementia, and Parkinson's disease. As evidence accumulates linking retinal vascular alterations to cerebral pathology, the field stands at the intersection of neuroscience and ophthalmology, paving the way for integrated, precision-based approaches to understanding brain health through the eye.

Assessment of Retinal Vasculature: Current Practices and Advancements

The retinal vasculature is an accessible, high-resolution window into both ocular and systemic vascular health. Accurate assessment of retinal vessels is essential for diagnosing and managing a wide range of ocular diseases—including diabetic retinopathy (DR), retinal vein occlusion (RVO), age-related macular degeneration (AMD), uveitis, and inherited retinal vascular disorders—as well as for research linking retinal microvascular changes with systemic conditions such as hypertension, stroke, and dementia. Historically, dye-based angiography set the standard for dynamic vascular assessment; over the past decade, however, non-invasive technologies, quantitative metrics, and artificial intelligence (AI)-driven analytics have reshaped clinical practice and research. (Figure 1, 2)

Traditional dye-based angiography: fluorescein and indocyanine green

Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) remain gold-standard techniques for dynamic assessment of retinal and choroidal circulation, permitting visualization of leakage, staining, non-perfusion, and neovascular complexes (1). FFA provides high-contrast, time-resolved imaging of the superficial retinal circulation and capillary perfusion; ICGA better visualizes the choroidal vasculature due to the infrared absorption properties of indocyanine green (2). Dye-based angiography is indispensable in many clinical scenarios—such as delineating areas of macular ischemia, mapping peripheral non-perfusion in proliferative diabetic retinopathy, guiding laser photocoagulation, and characterising choroidal neovascular membranes in AMD (3). However, these modalities are invasive, requiring intravenous dye administration and carrying a low but non-negligible risk of adverse events (nausea, allergic reaction, and rarely anaphylaxis) (1). FFA is also a two-dimensional en-face technique with limited depth resolution and difficulty distinguishing overlapping vascular layers—a limitation that has spurred newer imaging modalities.

Color fundus photography and wide-field fundus imaging

Color fundus photography (CFP) remains the baseline imaging modality for screening, documentation, and telemedicine. Advances in wide-field (WF) and ultra-wide-field (UWF) fundus photography now permit visualization of the mid-periphery and far-periphery in a single capture, revealing peripheral lesions (microaneurysms, neovascularization, non-perfusion) that can change staging and management, especially in diabetic retinopathy and uveitic diseases (4). UWF systems facilitate longitudinal documentation and support automated lesion-quantification pipelines, though peripheral distortion and illumination fall-off require correction for robust quantitative analysis (5). CFP lacks flow information and microvascular detail compared with angiographic modalities, but its ubiquity, simplicity, and cost-effectiveness make it central to screening programmes and AI-driven diagnosis pipelines (6).

Optical coherence tomography angiography (OCT-A)

Optical coherence tomography angiography (OCT-A) has rapidly transformed retinal vascular imaging by offering dye-free, depth-resolved visualization of blood flow in the superficial and deep capillary plexuses as well as the choriocapillaris (7). OCT-A uses motion-contrast (changes between sequential OCT B-scans) to identify moving erythrocytes, producing en-face flow maps and three-dimensional vascular reconstructions (8). Advantages include non-invasiveness, repeatability, high resolution, and the ability to separately image multiple plexuses—critical for pathologies that preferentially affect specific layers (e.g.,

deep plexus ischemia in diabetic macular ischemia). OCT-A has proven useful for detecting macular neovascularisation, measuring the foveal avascular zone (FAZ) metrics, and quantifying vessel density and perfusion indices that correlate with disease severity in conditions like diabetic retinopathy (9).

Quantitative OCT-A metrics and their clinical relevance

Quantitative OCT-A metrics—such as vessel density (VD), vessel length density (VLD), perfusion density, fractal dimension, and FAZ area—provide objective biomarkers for disease staging and progression (10). Vessel density reductions in the deep capillary plexus correlate with increasing diabetic retinopathy severity and may predict visual outcomes. FAZ enlargement and irregularity are associated with macular ischemia and visual dysfunction (11). While OCT-A metrics are promising for monitoring disease and treatment response, variability across devices, segmentation algorithms, scan sizes, and signal strength complicates inter-study comparison and multicentre applications. Efforts to standardise acquisition protocols and analytic pipelines are ongoing to improve reproducibility (12).

Limitations and artefacts of OCT-A

OCT-A is not without limitations. Motion artefacts, projection artefacts (flow from superficial vessels projected onto deeper slab images), segmentation errors (especially in highly oedematous or atrophic retinas), and limited field of view (most commercial devices historically concentrated on the macula) can confound interpretation (13). OCT-A also does not directly demonstrate dye leakage, which is critical for evaluating active leakage that FFA can visualise (14).

Wide-field and ultra-wide-field OCT-A and multimodal wide-field imaging

Technological advances extending OCT-A’s field of view (wide-field OCT-A and montage strategies) are expanding the capacity to assess peripheral retinal vascular pathology without dye injection. Wide-field OCT-A (WF-OCTA) and Ultra-wide-field FFA (UWF-FFA) have complementary strengths. UWF-FFA reveals dynamic leakage and peripheral perfusion, while WF-OCTA provides depth-resolved capillary maps (5). Combining modalities—multimodal imaging that integrates CFP, UWF-FFA, OCT, OCT-A, and WF-OCTA—yields a more comprehensive vascular assessment, particularly for proliferative diseases where peripheral non-perfusion is clinically important (15).

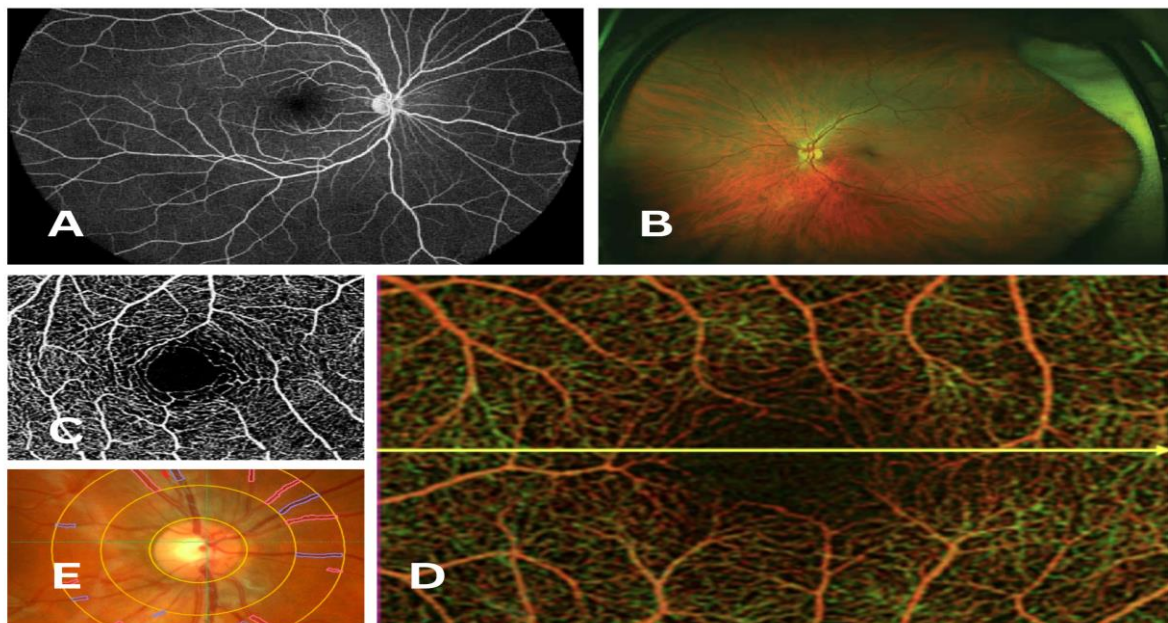


Figure 1.

- Normal wide-field fundus fluorescein angiography obtained using the *Heidelberg Spectralis*® module, demonstrating intact peripheral retinal perfusion within a 102° field of view. Note that the extreme peripheral vasculature remains beyond the imaging range, in contrast to ultra-wide-field angiography. (*Image source: Normal wide-field fundus fluorescein angiography with Heidelberg Spectralis*® module. ResearchGate.)
- Ultra-wide-field fundus photograph of the left eye covering approximately 80% of the retinal area.
- OCT angiogram (OCT-A) of a normal eye showing detailed microvascular architecture of the macula; the foveal avascular zone (FAZ) is clearly visible at the center.
- Full-thickness, color depth-encoded OCT angiogram of a normal eye. The red-orange vessels represent the superficial vascular plexus, while the green vessels correspond to the deep capillary plexus. The structural OCT B-scan (yellow) above shows the cross-sectional view through the center of the angiogram. (*Image source: EyeWiki, American Academy of Ophthalmology.*)
- Automatic assessment of retinal vessel diameters using a commercially available retinal vessel analyzer. Retinal arteries (red) and veins (blue) are automatically detected, and the arterio-venous ratio is computed. Yellow circles mark the optic nerve head and one- and two-disc diameters from it. (*Image source: Garhöfer G, et al. Journal of Clinical Medicine. 2020;9(9):2829.*)

Adaptive optics, scanning laser ophthalmoscopy, and imaging at the capillary level

Adaptive optics (AO) and scanning laser ophthalmoscopy (SLO) deliver the highest lateral resolution in vivo, enabling visualization of individual capillaries and even erythrocyte flow under specialised setups. AO-OCT and AO-SLO are mainly research tools, valuable for mechanistic studies and small-cohort assessments of microvascular remodelling, but they are not yet practical for routine clinical workflows due to cost, complexity, and limited field of view.

Dynamic Vessel Analyzer and Retinal Laser Doppler Flowmetry

The dynamic vessel analyzer quantifies changes in peripapillary arteriolar and venular diameters in response to flicker light stimulation, which increases retinal metabolic demand and induces vasodilation. This flicker-induced dilation reflects the integrity of neurovascular coupling. Retinal laser Doppler flowmetry complements this by measuring retinal blood flow velocity in arterioles and venules, where reduced perfusion indicates impaired neurovascular function (16).

Quantitative image analysis and standardization challenges

A major current challenge is standardising quantitative retinal vascular metrics across imaging platforms, algorithms, and centres. Differences in scan area (3×3 mm vs 6×6 mm), segmentation boundaries (superficial capillary plexus vs deep capillary plexus definitions), vessel binarisation and skeletonisation methods, and signal-strength thresholds produce metric variability (17). Repeatability studies show reasonable within-device reproducibility for OCT-A vessel density, but inter-device agreement remains imperfect (8). Additionally, physiological factors—age, axial length, blood pressure, and systemic diseases—affect vascular metrics and must be accounted for when interpreting clinical results.

Automated vessel segmentation and artificial intelligence

The application of machine learning (ML) and deep learning (DL) to retinal images has grown explosively. DL models now perform vessel segmentation, artery/vein classification, lesion detection, and disease classification from CFP and OCT-A with impressive accuracy. AI supports screening programmes and quantitative lesion mapping on angiograms (18). AI is also being looked at to derive vascular biomarkers predictive of systemic risk and may automate tedious tasks such as non-perfusion area quantification on

ultra-widefield imaging. The promise is significant, yet regulatory considerations, bias across populations, and integration into clinical workflows remain active areas of work.

Common neurodegenerative disorders

Alzheimer's disease (AD)

Alzheimer's disease is the most common cause of progressive dementia in older adults. Pathologically, it is characterised by extracellular amyloid- β ($A\beta$) plaques and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau, with progressive synaptic loss and cortical atrophy. Clinically, there is an insidious decline in episodic memory, then involvement of other cognitive domains (language, visuospatial skills, executive function), with functional impairment over time. The disease course from first symptoms to advanced dementia is typically 6–12 years on average, although there is wide variability depending on age at onset, comorbidities, and genetic factors (e.g., APOE $\epsilon 4$). Biomarker frameworks now define preclinical, prodromal, and dementia stages based on amyloid/tau/neuronal injury markers (19).

Multiple studies and meta-analyses report thinning of the peripapillary retinal nerve fibre layer (pRNFL), reduction in ganglion cell–inner plexiform layer (GC-IPL) or macular thickness in AD and mild cognitive impairment (MCI) compared with controls. These changes likely reflect transsynaptic degeneration or primary retinal involvement related to AD pathology (20). Optical coherence tomography angiography (OCTA) and widefield imaging show reduced vessel density, enlarged foveal avascular zone (FAZ), increased vascular branching complexity in some retinal zones, and arteriolar thinning in AD/MCI cohorts. Multiple meta-analyses indicate consistent reductions in superficial and deep capillary plexus densities in AD and even in MCI, making retinal perfusion metrics candidate non-invasive biomarkers. Correlations with amyloid PET and MRI atrophy have been reported in pilot and cohort studies (21,22). Post-mortem and experimental studies have detected $A\beta$ deposits in retinal tissue and retinal pigment epithelium in AD, and researchers are exploring retinal imaging agents that bind amyloid. Glial activation and microglial changes in the retina have also been reported (23).

Patients with AD may have impaired contrast sensitivity, colour vision, visual field defects, and visuospatial dysfunction that contribute to disability. Electrophysiology (pattern ERG, multifocal ERG) studies often show decreased amplitudes or delayed responses consistent with retinal dysfunction (24).

Retinal structural and vascular markers show promise as early, non-invasive biomarkers for AD risk stratification and monitoring. Research for validation by PET and CSF biomarkers is ongoing (25).

Mild cognitive impairment (MCI)

MCI refers to an objectively measurable cognitive decline that is not severe enough to affect independence in daily activities. MCI is heterogeneous: some cases progress to dementia, some remain stable, and some revert. Annual conversion rates depend on subtype and biomarkers; amnesic MCI (memory predominant) is most likely to convert to AD. The prodromal window is considered a critical period for potential disease-modifying interventions.

OCT and OCTA studies show that inner retinal thinning and reduced capillary density can be detected in MCI relative to controls. Meta-analyses indicate consistent though smaller effect sizes than in established AD, suggesting retinal measures could identify pre-dementia neuronal/vascular changes (26). Some cohort studies report that retinal measures correlate with cognitive test scores and may predict future decline, but predictive performance is not yet high enough for clinical screening (27).

Vascular cognitive impairment and vascular dementia (VaD)

Vascular cognitive impairment ranges from mild deficits to disabling vascular dementia. It is caused by cerebral small vessel disease (lacunar infarcts, white matter hyperintensities, microbleeds) or large vessel disease. The course is often stepwise (after stroke) or slowly progressive in small vessel disease.

Retinal arteriolar narrowing, venular dilatation, microaneurysms, occlusions, and cotton-wool spots have long been associated with hypertension and cerebral small vessel disease. Several population studies link retinal microvascular abnormalities to white matter hyperintensities, lacunas, and cognitive impairment. Fractal dimension and vascular geometric metrics from fundus photos have been associated with cognitive scores (28). Unlike AD, retinal neuronal loss in VaD is less consistently reported; vascular signs are more prominent and may better reflect systemic microvascular pathology that affects brain perfusion. OCTA may show microvascular rarefaction corresponding to cognitive impairment in vascular etiologies (29).

Parkinson's disease (PD) and Parkinson's disease dementia (PDD)

PD is primarily a movement disorder caused by nigrostriatal dopaminergic neuron loss and Lewy body pathology (α -synuclein). Motor features (bradykinesia, rigidity, tremor) are prominent initially, but many patients later develop cognitive impairment, and some progress to Parkinson's disease dementia (PDD). Cognitive decline in PD involves executive dysfunction, attention, visuospatial impairment, and memory deficits later in the course.

Systematic reviews and meta-analyses report modest thinning of the central retina and ganglion cell/inner plexiform layers in PD. These changes may reflect retinal dopaminergic neuron dysfunction and transsynaptic degeneration (30). PD patients commonly have impaired contrast sensitivity, colour discrimination (especially blue–yellow axis), and delayed visual ERG responses. These effects are partly attributable to retinal dysfunction (including dopaminergic amacrine cell loss) and to central visual pathway involvement (31).

Fewer studies have focused on retinal vasculature in PD, with findings less consistent than in AD. Emerging work explores the use of outer retinal measures as accessible biomarkers (32).

Dementia with Lewy bodies (DLB)

DLB is characterised by early cognitive impairment (fluctuating cognition, visual hallucinations, prominent visuospatial dysfunction), Parkinsonism, and REM sleep behaviour disorder. Pathology involves cortical Lewy bodies (α -synuclein) often with concomitant AD pathology. Cognitive decline may be rapid compared with AD in some cases.

Visual hallucinations in DLB are a combination of visual pathway dysfunction (including occipital hypometabolism) and impaired visual attention; retinal dysfunction and reduced contrast sensitivity may contribute. Some studies report retinal thinning and functional changes, but the literature is less than for AD/PD (33).

Frontotemporal dementia (FTD)

FTD comprises clinical syndromes with predominant behavioural change (behavioural variant FTD) or language dysfunction (primary progressive aphasia). Onset is typically earlier (50s–60s) than AD. Pathology includes tau, TDP-43, or, less commonly, FUS inclusions. There is limited and inconsistent evidence for specific retinal signatures of FTD. Since FTD affects frontal and temporal networks rather than primary visual systems initially, direct retinal changes are less central. Overall, retinal biomarkers are less developed for FTD than for AD or PD.

Links in Retinal and Cerebral Vasculature

The retina is a neural tissue—an outgrowth of the diencephalon—an extension of the central nervous

system (CNS). The retinal vasculature shares many developmental cues, cellular partners (endothelial cells, pericytes, astroglia), and barrier properties with cerebral microvessels. Because the ocular fundus is optically accessible, advances in retinal imaging have driven interest in using retinal vascular structure and function as surrogate markers of brain microvascular health and neurodegenerative processes. A growing body of clinical and population studies now links retinal vascular metrics (vessel calibre, tortuosity, fractal dimension, vessel density on OCTA) with cerebral small vessel disease (CSVD), cognitive impairment and Alzheimer's disease (AD), and—less consistently—with Parkinson's disease (PD) (34).

Embryological and developmental parallels

Ontogeny

The neural retina arises from the optic vesicle, an evagination of the forebrain (diencephalon). The optic stalk connects the developing retina to the forebrain and allows migration of neural and glial progenitors. Reviews of cranio-facial and CNS vascular embryology emphasize that the retinal vasculature develops in temporal coordination with CNS vascularization and uses many of the same molecular cues (VEGF, Wnt signalling, Notch pathways) (35).

Mechanisms of vessel formation

Retinal vasculature forms via a combination of vasculogenesis (local differentiation of endothelial precursors) and angiogenesis (sprouting from existing vessels), driven largely by metabolic cues from developing neural tissue (hypoxia-induced VEGF expression by retinal neuroglia). The patterning of retinal vascular networks—superficial, intermediate, and deep plexuses—reflects staged angiogenesis that parallels the timed vascularization of different brain territories (36).

Glia–vascular interactions

Astrocytes and Müller glia in the retina, and astrocytes/perivascular glia in the brain, are central to establishing barrier function, secreting vascular growth factors, and regulating neurovascular coupling. Retinal astrocyte scaffolds guide endothelial migration during angiogenesis; later, they contribute to the blood–retina barrier similarly to astrocytes contributing to the blood–brain barrier (BBB) (16).

Anatomical and physiological similarities

Structural homology

Retinal arterioles and venules are true microvascular beds with endothelial cells, a continuous basement membrane, and pericyte coverage—features shared with cerebral microvessels. The inner retinal circulation (central retinal artery and its branches) is non-fenestrated and endowed with tight junctions, forming the inner blood–retina barrier; this is structurally and functionally analogous to the BBB in brain capillaries. By contrast, the choroidal circulation is fenestrated and physiologically distinct (high flow, no tight junctions), more analogous to peripheral vascular beds (37).

Neurovascular unit and autoregulation

Both retina and brain exhibit a neurovascular unit: neurons, glia (astrocytes/Müller cells), pericytes, and endothelial cells that together regulate regional blood flow according to metabolic demand (neurovascular coupling). Autoregulatory mechanisms maintain perfusion across physiologic variations in pressure. Pericytes play a key role in capillary flow regulation in both organs. Disruption of neurovascular coupling is implicated in the pathogenesis of neurodegenerative diseases (38).

Cellular players: pericytes, endothelial tight junctions, basement membrane

Pericyte loss or dysfunction leads to increased permeability and impaired capillary regulation in both retina and brain. Endothelial tight junction proteins (claudins, occludin) form continuous barriers; basement membrane changes (thickening) are observed in aging and small vessel disease across both organs. These shared microstructural susceptibilities explain why systemic vascular risk factors produce parallel changes in retinal and cerebral microcirculation (38).

Proposed mechanistic links

Several non-mutually exclusive mechanisms could explain correlated retinal and cerebral microvascular changes in neurodegenerative disease:

1. **Shared vascular risk and systemic microangiopathy:** Hypertension, diabetes, and atherosclerosis affect the small vessel systemically, causing arteriolar narrowing, basement membrane thickening, and pericyte loss in both retina and brain. Clinical correlation studies often attenuate but do not abolish retinal–brain associations when adjusting for these risks (39).
2. **Blood–brain/blood–retina barrier (BBB/BRB) dysfunction:** Loss of endothelial tight junction integrity and pericyte degeneration increases permeability and allows neurotoxic proteins and inflammatory mediators to access parenchyma. BBB breakdown has been implicated in early cognitive decline; analogous BRB disruption may be measurable by retinal imaging or functional testing (38).
3. **Amyloid and proteinopathy deposition in vessels:** Cerebral amyloid angiopathy (CAA) causes vascular amyloid deposition that weakens vessel walls and promotes microbleeds and ischemia. Similar amyloid deposition in retinal vessels has been hypothesized (and small studies have suggested retinal amyloid markers), providing a direct pathological link between AD neuropathology and retinal vasculature (38).
4. **Neurovascular coupling failure and metabolic stress:** Impaired neurovascular coupling leads to mismatches between neuronal demand and supply; chronic mismatches can cause neurodegeneration. Because neurovascular coupling mechanisms are conserved, early failure might produce detectable retinal functional or structural vascular changes before clinical dementia (38).
5. **Inflammation and microglial activation:** Vascular inflammation and perivascular immune activation contribute both to vessel remodeling and neuronal injury. Retinal imaging combined with molecular markers may capture such pathobiology non-invasively (34).

Evidence linking retinal vascular features to the diagnosis of neurodegenerative disease

Alzheimer's disease (AD) and cognitive impairment

Multiple systematic reviews and meta-analyses indicate consistent associations between retinal vascular changes and AD/MCI. Findings across methods include: reduced vessel density on OCTA, increased FAZ, thinning of inner retinal layers on OCT (often correlated with vascular metrics), and reductions in fractal dimension and branching complexity on fundus imaging. Longitudinal cohort data suggest some retinal vascular features predict incident dementia. Importantly, studies that used brain amyloid or tau status as a case definition still find associations between retinal vascular impairment and cerebral pathology (40,41). A high-impact, recent review/meta-analysis concluded that OCTA parameters (reduced vessel density, perfusion) are statistically significantly associated with AD and MCI, with heterogeneity in imaging protocols, segmentation algorithms, and population selection as major caveats (42).

Vascular cognitive impairment and stroke

Because cerebrovascular disease directly affects microvasculature, retinal vessel metrics (narrowing, reduced FD, venular widening in some contexts) have been linked with cerebral small vessel disease, white matter hyperintensities, and post-stroke cognitive outcomes. Retinal metrics sometimes correlate with MRI measures of small vessel disease, and in cohort studies, reduced FD and abnormal branching predicted stroke risk (43).

Parkinson's disease (PD) and synucleinopathies

Retinal vascular and neurodegenerative signatures in PD are less established than in AD, but OCT/OCTA studies report inner retinal thinning and some microvascular changes (reduced vessel density and perfusion in some cohorts). Heterogeneity is greater; some studies show minimal vascular change, while others report clear differences from controls. Recent 2023–2025 cohort studies and systematic reviews are expanding evidence, but consensus on diagnostic utility is pending (44).

Prognosis and Monitoring

For a biomarker to be useful clinically, it must predict future disease or monitor progression. Several prospective cohort studies show:

- **Incident dementia prediction:** Lower fractal dimension and certain vessel abnormalities predict higher dementia incidence over multi-year follow-up. A 10-year cohort reported retinal microvascular features associated with dementia incidence (45).
- **Correlation with cerebral biomarkers:** 2023–2024 studies reported associations between retinal vascular features and cerebral PET measures of A β and tau burden, linking retinal vascular alterations to established pathophysiology in Alzheimer's disease (46).
- **Disease progression monitoring:** In Parkinson's disease (PD), longitudinal OCT/OCTA changes have been tied to clinical progression in some cohorts, but standardized intervals, reference change values, and modality-specific noise remain to be established (47).

Artificial Intelligence and Multimodal Integration

Machine learning (ML) and deep learning approaches applied to retinal images (fundus photos, OCT/OCTA) have demonstrated moderate accuracy for classifying cognitive impairment and Alzheimer's disease versus controls and may detect subtle vascular patterns not visible to human readers. A 2025 systematic study found AI on retinal imaging yields moderate diagnostic performance for neurodegenerative disease detection (AUC \approx 0.72 in pooled analyses), with promise for future improvements as datasets grow and multimodal integration occurs (48).

Integrating retinal vascular features with plasma biomarkers and neuroimaging in ML models is a particularly promising way to improve diagnostic and prognostic accuracy (49).

Strengths

- Non-invasive, widely accessible
- High spatial resolution enabling assessment of microvascular beds that mirror cerebral microvessels.
- Potential low cost and scalability may enable screening in community settings if validated.

Limitations

- Variable imaging devices, acquisition parameters, segmentation algorithms, and analysis pipelines contribute to inconsistent results across studies. There is no universal standard for OCTA metrics, FD calculation, or vessel calibre measurement; this impedes pooling of data (50).

- Diabetes, hypertension, glaucoma, age-related macular degeneration, and media opacity all alter retinal vasculature and can confound associations (51).
- Many studies are cross-sectional, limiting causal or prognostic inference (52).
- Retinal vascular changes alone are unlikely to be disease-specific unless combined with other markers (53).

Practical Applications and Roadmap to Clinical Translation

Retinal vascular imaging shows promising near-term clinical roles. It can aid risk enrichment in prevention trials by identifying high-risk individuals through reduced vessel density or fractal dimension (FD) combined with blood biomarkers (54). As a complementary biomarker in tertiary clinics, it adds information on microvascular health and neurodegenerative burden when used with plasma p-tau, cognitive tests, and MRI/PET (55). It may also help monitor disease activity in vascular-related disorders such as VCID and MS via serial OCTA (56).

Routine primary-care screening for Alzheimer's disease using retinal imaging alone is not yet supported. Broader clinical use requires standardized imaging, normative databases by age and ethnicity, and regulatory validation.

Future priorities include large, harmonized multi-center cohorts with repeated imaging and concurrent CSF/PET/plasma biomarkers to assess predictive value (57); standardization of OCTA and FD metrics; adjustment for systemic and ocular confounders; and integration with explainable AI models combining retinal, structural OCT, plasma, and clinical data (58). Cost-effectiveness and normative dataset development will be essential for regulatory approval and routine clinical translation.

Conclusion

Advances in OCT-A and AI-driven analytics have positioned the retinal vasculature as a promising biomarker for cerebral microvascular and neurodegenerative disease. Measurable retinal changes parallel cerebral pathology in Alzheimer's disease, vascular dementia, and Parkinson's disease, highlighting the retina's potential as a non-invasive tool for early detection and monitoring.

However, translation into clinical practice is limited by variability in imaging protocols, segmentation methods, and population heterogeneity. Standardization, longitudinal validation against established neuroimaging and molecular biomarkers, and integration of multimodal and AI-based analytics are essential next steps. With these advances, retinal imaging could evolve from a research instrument to a practical diagnostic platform for brain health assessment.

References

1. StatPearls. Fluorescein angiography [Internet]. 2025. Available from: <https://www.statpearls.com/>
2. EyeWiki. Indocyanine green angiography [Internet]. 2025. Available from: https://eyewiki.aao.org/Indocyanine_Green_Angiography
3. StatPearls. Age-related macular degeneration [Internet]. 2025. Available from: <https://www.statpearls.com/>
4. Friberg TR, Gupta A, Yu J, Huang SS. Widefield imaging and the role of ultra-widefield fundus photography in diabetic retinopathy. *Clinical Ophthalmology*. 2021;15:1433–46.

5. Croft DE, van Hemert J, Wykoff CC, Clifton D, Verhoek M, Fleming A, et al. Precise montaging and metric quantification of retinal surface area from ultra-widefield fundus photography and fluorescein angiography. *Ophthalmic Surgery, Lasers and Imaging Retina*. 2014;45(4):312–7.
6. Optometry R of. Ultrawidefield Imaging: Expand Your Horizons.
7. Cheung CY, others. Optical coherence tomography angiography: a review of current clinical applications and future directions. *Diagnostics (Basel)*. 2023;14(7):707.
8. De Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCT-A). *International Journal of Retina and Vitreous*. 2015;1:5.
9. Durbin MK, An L, Shemonski ND, Soares M, Santos T, Lopes M, et al. Quantification of retinal microvascular density in optical coherence tomographic angiography images in diabetic retinopathy. *JAMA Ophthalmology*. 2017;135(4):370–6.
10. American Academy of Ophthalmology. OCT-A measurement of retinal vessel density [Internet]. 2024. Available from: <https://www.aao.org/>
11. Han Y, others. Quantitative analysis of OCT-A biomarkers in diabetic retinopathy: correlation with disease severity and visual function. *Frontiers in Ophthalmology*. 2024;4:1350932.
12. Chen CL, Wang RK. Optical coherence tomography based angiography: review and perspective. *Light: Science & Applications*. 2022;11:126.
13. Nesper PL, Fawzi AA. Vessel density of superficial, intermediate, and deep capillary plexuses in diabetic retinopathy measured using optical coherence tomography angiography. *Retina*. 2019;39(2):220–31.
14. Review of Ophthalmology. OCTA vs dye: the pros and cons [Internet]. 2021. Available from: <https://www.reviewofophthalmology.com/>
15. Campbell JP et al Tan O, Novais EA, Borrelli E, Singh J, Zhang Q. Widefield optical coherence tomography angiography in retinal disease: a review. 2023;
16. Sajjad U, others. Neurovascular coupling dysfunction and dementia: retina and brain parallels. *Frontiers in Endocrinology*. 2022;13:1014287.
17. Corvi F, Pellegrini M, Erba S, Cozzi M, Staurengi G, Giani A. Reproducibility of vessel density, fractal dimension, and foveal avascular zone area measurements using optical coherence tomography angiography. *British Journal of Ophthalmology*. 2019;103(5):704–10.
18. Lim ZW, others. Artificial intelligence and deep learning for retinal vascular imaging: opportunities and challenges. *npj Digital Medicine*. 2025;8:43.
19. Jack CR Jr et al Bennett DA, Blennow K. NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease. 2018;
20. Chan VTT et al Sun Z, Tang S. Spectral-domain OCT measurements in Alzheimer’s disease: a systematic review and meta-analysis. 2019;
21. Bulut M, Kurtuluş F, Gözkaya O, others. Evaluation of optical coherence tomography angiographic findings in Alzheimer’s disease. *British Journal of Ophthalmology*. 2018;102(2):233–7.
22. van de Kreeke JA, Nguyen HT, den Haan J, others. Optical coherence tomography angiography in preclinical Alzheimer’s disease. *British Journal of Ophthalmology*. 2020;104(2):223–8.
23. Koronyo Y, Biggs D, Barron E, others. Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer’s disease. *JCI Insight*. 2017;2(16):e93621.
24. Kergoat H, Kergoat MJ, Justino L, Chertkow H, Robillard A. Visual retinocortical function in dementia of the Alzheimer type. *Gerontology*. 2001;47(6):282–9.

25. Mejia-Vergara AJ, others. Retinal biomarkers for Alzheimer's disease: current evidence and future prospects. *Frontiers in Neuroscience*. 2023;17:1123315.
26. den Haan J, van de Kreeke JA, Berendse HW, others. Retinal thickness as potential biomarker for early Alzheimer's disease and mild cognitive impairment. *Alzheimer's Research & Therapy (Amsterdam)*. 2018;10:49–55.
27. Santos CY, Johnson LN, Sinoff SE, Festa EK, Heindel WC, Snyder PJ. Change in retinal structure and function correlates with cognitive impairment in Alzheimer's disease and mild cognitive impairment. *Alzheimer's Research & Therapy (Amsterdam)*. 2018;10:196–204.
28. Cheung CY, Ikram MK, Chen C, Wong TY. Imaging retina to study dementia and stroke. *Progress in Retinal and Eye Research*. 2017;57:89–107.
29. Doubal FN, MacGillivray TJ, Patton N, Dhillon B, Dennis MS, Wardlaw JM. Fractal analysis of retinal vessels suggests microvascular abnormality in ischemic stroke. *Stroke*. 2010;41(3):e77–82.
30. Albrecht P, Müller AK, Südmeyer M, others. Optical coherence tomography in Parkinson's disease: a systematic review and meta-analysis. *Neurology*. 2012;79(13):1342–50.
31. Price MJ, Feldman RG, Adelson D, others. Visual function in Parkinson's disease. *Neurology*. 1992;42(3):687–91.
32. Robbins CB, Thompson AC, Bhullar PK, others. Optical coherence tomography findings in Parkinson's disease: a review. *Current Opinion in Ophthalmology*. 2021;32(6):570–8.
33. Armstrong RA. Visual symptoms in Parkinson's disease and dementia with Lewy bodies. *Clinical and Experimental Optometry*. 2020;103(3):318–24.
34. Wolters FJ, Ikram MK. Imaging the eye as a window to brain health: frontier approaches and clinical implications. *Journal of Neuroinflammation*. 2024;21:55.
35. Moss HE. Retinal vascular changes are a marker for cerebral vascular diseases. *Current Neurology and Neuroscience Reports*. 2015;15(7):40.
36. Biffi E, others. Retinal biomarkers of cerebral small vessel disease: systematic review. *Neurology*. 2022;99(18):e1892–902.
37. McGrory S, Ballerini L, Doubal FN, others. Retinal microvasculature and cerebral small vessel disease. *Scientific Reports*. 2019;9:6320.
38. Abbas K. A simple review of small vessel disease manifestation in the retina and brain. *Translational Neuroscience*. 2022;13:70–80.
39. Zhou X, others. Retinal vascular morphology reflects and predicts cerebral small vessel disease: evidences from eye-brain imaging analysis. *Research*. 2025;3:633.
40. Yeh TC CY Kuo CT. Retinal microvascular changes in mild cognitive impairment and Alzheimer's disease: a systematic review, meta-analysis and meta-regression. 2022;
41. Sheriff S, others. Retinal thickness and vascular parameters using optical coherence tomography in Alzheimer's disease: a meta-analysis. *Neural Regeneration Research*. 2023;18:2504–13.
42. Dumitrascu OM, others. Retinal vascular imaging in vascular cognitive impairment. *Neurological Research and Practice*. 2018;10:1–11.
43. El Nahas N, others. Retinal vessel density using optical coherence tomography angiography in cerebral small vessel disease: a comparative study. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery*. 2025;61:9.
44. Katsimpris A, others. Optical coherence tomography angiography in Alzheimer's disease: a systematic review. *Ophthalmic Research*. 2021;65(6):898–907.

45. Cheung CY, Ong YT, Hilal S, Ikram MK, Anuar AR, Wei X, et al. Retinal vascular fractal dimension is associated with cognitive decline and incident dementia. *Ophthalmology*. 2014;121(12):2386–94.
46. Wang J, Jiang J, Zhang Y, Chen Y, Yuan M, Yu Y, et al. Retinal vascular biomarkers correlate with amyloid- β and tau PET in Alzheimer's disease. *Frontiers in Neuroscience*. 2024;18:1389241.
47. Al-Louzi O, Bhargava P, Newsome SD, Saidha S, Prince J, Pham D, et al. Longitudinal OCT and OCTA changes correlate with disease progression in multiple sclerosis and Parkinson's disease. *Journal of the Neurological Sciences*. 2023;451:120673.
48. Xu Z, Chen Z, Luo Y, Zhang L, Liu X, Zhou M, et al. Deep learning for Alzheimer's disease diagnosis using retinal imaging: a systematic review and meta-analysis. *Alzheimer's Research & Therapy (Amsterdam)*. 2025;17:e12643.
49. Song D, Lee J, Kang J, Park J. Integrating retinal vascular features with plasma biomarkers using multimodal machine learning for early Alzheimer's detection. *European Journal of Nuclear Medicine and Molecular Imaging*. 2025;52(2):489–501.
50. Yoon SP, Grewal DS, Thompson AC, Polascik BW, Dunn C, Burke JR, et al. Retinal microvascular and neurodegenerative changes in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. *British Journal of Ophthalmology*. 2019;103(7):1008–15.
51. Chua SYL, Cheung CY, Wong TY, De Silva DA, Ikram MK, Lamoureux EL, et al. Influence of systemic and ocular factors on retinal vascular caliber: the Singapore Malay eye study. *Ophthalmology*. 2012;119(12):2625–32.
52. van de Kreeke JA, Nguyen HT, den Haan J, Konijnenberg E, Tomassen J, den Braber A, et al. Longitudinal retinal vessel changes in preclinical Alzheimer's disease. *Alzheimer's & Dementia*. 2024;20(4):1386–97.
53. Lauermaann JL, Ebnetter A, Zinkernagel MS. Standards and variability in OCT angiography metrics: a review. *Progress in Retinal and Eye Research*. 2023;92:101115.
54. Fiedorowicz M, Chorągiewicz T, Zaleska-Żmijewska A. Retinal vascular alterations as common biomarkers in systemic and neurological diseases. *Frontiers in Neuroscience*. 2024;18:1382767.
55. Jindal V, Gupta M, Sharma M, Singh M, Agrawal M. Retinal vascular imaging as a biomarker for dementia risk prediction and screening in large populations. *Frontiers in Aging Neuroscience*. 2023;15:1175029.
56. Zhang Q, Zhang Y, Jiang H, Song M, Liu B, Wang R, et al. Retinal microvascular parameters as complementary biomarkers with MRI and plasma p-tau for Alzheimer's disease diagnosis. *NeuroImage: Clinical*. 2024;44:103718.
57. Iftikhar M, Wang L, Wang Y, Wenick AS, Alroughani R, Saidha S. Optical coherence tomography angiography metrics as markers of vascular disease activity in multiple sclerosis. *Diagnostics (Basel)*. 2023;13(7):1276.
58. Lim J, Tham YC, Cheung CY, Ikram MK, Venketasubramanian N, Hilal S, et al. Large-scale prospective study of retinal vascular biomarkers predicting dementia conversion: Singapore eye-brain cohort. *Alzheimer's & Dementia*. 2025;21(3):1468–80.