# Retinal Vascular Imaging in Vascular Cognitive Impairment: Current and Future Perspectives

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**ABSTRACT:** Vascular cognitive disorders are heterogeneous and increasingly recognized entities with intricate correlation to neurodegenerative conditions. Retinal vascular analysis is a noninvasive approach to study cerebrovascular pathology, with promise to assist particularly during early disease phases. In this article, we have systematically summarized the current understanding, potential applications, and inevitable limitations of retinal vascular imaging in patients with vascular cognitive impairment. In addition, future directions in the field with support from automated technology using deep learning methods and their existing challenges are emphasized.

**KEYWORDS:** Retinal vessels, automated analysis, vascular cognitive impairment

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Cognitive disorders are heterogeneous conditions with increasing incidence and major burden for the health care system and society.[1] Scientific literature provides a well-characterized relationship between vascular dysfunction, neurodegeneration, and cognitive decline[2] and describes various neurovascular mechanisms of dementia.[3] Vascular disease in the brain plays pivotal roles not only in vascular dementia but also in Alzheimer disease (AD) and other dementia types.[2,4]

Vascular cognitive impairment (VCI) includes a broad range of cognitive disorders attributable to diverse cerebrovascular pathology.[5] Various vascular clinic-radiologic entities and vascular brain injury pathologies are described as VCI,[6] caused by diverse systemic or cerebral large or small vessel diseases affecting cerebral circuits involved in cognition, behavior, or both. Brain imaging is routinely used in clinical practice to characterize the radiologic VCI phenotypes, such as multi-infarct encephalopathy, small vessel and strategic infarct type dementias, subcortical arteriosclerotic leukoencephalopathy, multi lacunar state, mixed cortico-subcortical type, granular cortical atrophy, postischemic encephalopathy, cerebral microbleeds, possible or probable cerebral amyloid angiopathy (CAA), or any combination of those entities.[6,7] In early stages of VCI, however, conventional brain imaging features of cerebral vasculopathy have limited diagnostic accuracy. Retinal vessel imaging may be used as an alternative and direct method to assess the health of the cerebral vasculature as retinal and cerebral small vessels have similar embryological origins, anatomical features, and physiological properties.[8] Dysfunction of blood-retina barrier and blood-brain barrier occurs simultaneously and thus plays a central role in the development of retinal and cerebral microangiopathy.[9] Furthermore, retinal vasculopathy may be identified noninvasively and early in the disease process, whereas cerebral vasculopathy usually remains undetected until significant brain damage has occurred to warrant brain imaging performance.

Ocular fundus photography was proposed as a tool to study cerebrovascular disorders and dementia[10] based on reported associations between retinal vascular abnormalities and small vessel brain disease, global cognitive function,[11] and amyloid-β deposition in AD.[12] Other retinal vascular imaging modalities such as optical coherence tomography angiography (OCTA) and scanning laser Doppler flowmetry are also investigated in this patient population.[13,14] To describe the relationship between retinal vascular abnormalities and VCI, we conducted a systematic review with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[15]

A comprehensive literature search of 3 databases was performed through July 2018, using the combination of search terms provided in the Appendix. The search resulted in 159 (PubMed), 129 (Web of Science), and 0 (Cochrane) studies. 72 duplicates were removed, leaving 216 articles for review. Titles and abstracts were first screened for relevance and bibliographies of seminal articles and reviews manually searched for eligible publications. 165 records were excluded, leaving 51 full-text articles that were assessed for eligibility. Of these, 33 were included in the synthesis. The PRISMA flow diagram[15] of trial selection, including the exclusion criteria, is reported in the Appendix. Articles were not excluded based on year or language of publication. All study designs were allowed, including randomized trials, clinical trials, and observational studies, prospective and retrospective, with cross-sectional and longitudinal designs. Eligible studies were included if they reported retinal vascular imaging findings in patients on the VCI spectrum of pathologies. The retinal vascular imaging modality, reported retinal vascular parameters, and subtype of VCI were collected and are summarized in Table 1.

**Table 1.** Summary of the manuscripts included in the mini-review.

| AUTHOR (YEAR) | VCI TYPE | RETINAL IMAGING MODALITY | RETINAL VASCULAR PARAMETERS |
|---|---|---|---|
| Alten et al (2014)[16] | CADASIL | SLO<br>SD-OCT<br>FA | AVN, venous diameter (SLO)<br>Mean arterial and mean venous outer diameter and wall thickness (SD-OCT) |
| Bettermann et al (2012)[17] | SVD | High-frequency flicker light stimulation | Retinal arterial and venous vasoreactivity to light stimulation |
| Bulut et al (2018)[18] | AD | SD-OCTA | Retinal vascular density, foveal avascular zone, retinal outer retinal flow, choroidal flow |
| Cavallari et al (2011)[19] | CADASIL | Digital retinal photography | Mean fractal dimension |
| Cavallari et al (2015)[20] | CADASIL | Retinal fundus photography | AV ratio, tortuosity index, mean fractal dimension |
| Cheung et al (2014)[21] | AD | Retinal fundus photography | Arterial and venous caliber, fractal dimension, vessel tortuosity, and bifurcation |
| Cheung et al (2014)[22] | VCI | Retinal fundus photography | Retinal vascular fractal dimension, branching angle, tortuosity, and caliber |
| Csincsik et al (2018)[23] | AD | Ultrawide field scanning laser ophthalmoscopy | Venular diameter, arterial fractal dimension, venular width gradient |
| Cumurciuc et al (2004)[24] | CADASIL | Retinal fundus photography, FA | Retinal vascular caliber, microaneurysms, retinal hemorrhages, cotton wool spots, hard exudates |
| de Jong et al (2011)[25] | VaD | Retinal fundus photography | Retinal venular caliber and arteriolar caliber |
| Deal et al (2018)[26] | VCI | Retinal fundus photography | Loss of vascular integrity, FAN, AVN, GAN, arteriolar diameter |
| Ding et al (2011)[27] | VCI | Retinal fundus photography | Retinal arteriolar and venular caliber |
| Fang et al (2017)[28] | CADASIL | EDI-OCT | Subfoveal choroidal thickness, arterial and venous wall thickness and diameters, AV ratio |
| Frost et al (2017)[29] | AD | Digital retinal photography | Retinal arteriolar central reflex and vessel width |
| Frost et al (2013)[30] | AD | Retinal fundus photography | CRAE, CRVE, AV ratio, fractal dimension, curvature tortuosity, branching |
| Golzan et al (2017)[31] | AD | Retinal fundus photography<br>Flicker-induced light stimulation | Retinal arterial and venous pulsations amplitude; retinal vascular dilatory response in response to flicker |
| Hanff et al (2014)[32] | SVD | Retinal fundus photography | Retinal microaneurysms, hemorrhage, AVN, FAN, CRAE, CRVE, any retinopathy (retinal microaneurysms, hemorrhages, soft exudates, hard exudates, macular edema, or optic disk swelling) |
| Haritoglou et al (2004)[33] | CADASIL | Retinal fundus photography | Peripapillary arteriolar sheathing, arteriolar narrowing, AVN |
| Harju et al (2004)[14] | CADASIL | SLO<br>Scanning laser Doppler flowmetry | Retinal arterial and venous caliber, retinal capillary flow |
| Jiang et al (2018)[34] | AD, MCI | Retinal function imager | Retinal blood flow rate and blood flow velocity of precapillary arterioles and postcapillary venules |
| Jiang (2017)[13] | AD, MCI | OCTA | Retinal vascular network, superficial vascular plexus, and deep vascular plexus |
| Jinnouchi et al (2017)[35] | VaD | Retinal fundus photography | GAN, FAN, AVN, arteriolar wall reflex |
| Liu et al (2008)[36] | CADASIL | Retinal fundus photography | Retinal arteriolar narrowing |
| Nelis et al (2018)[37] | CADASIL | OCTA | Vessel density of the macular region, foveal avascular zone size, superficial and deep retinal plexus density; optic nerve head and in the choriocapillaris vessel density |

**Table 1.** (Continued)

| AUTHOR (YEAR) | VCI TYPE | RETINAL IMAGING MODALITY | RETINAL VASCULAR PARAMETERS |
|---|---|---|---|
| Nunley et al (2018)[38] | VCI | Retinal fundus photography | CRAE, CRVE |
| Ong et al (2014)[39] | VCI | Retinal fundus photography | Retinal arteriolar and venular fractal dimensions |
| Pretegiani (2013)[40] | CADASIL | Retinal fundus photography | Retinal arteriolar narrowing and AVN |
| Qiu et al (2010)[41] | VaD | Retinal fundus photography | Retinopathy (retinal blot hemorrhages, soft exudates, microaneurysms, hard exudates, macular edema, and optic disc swelling) |
| Roine et al (2006)[42] | CADASIL | Retinal fundus photography | Retinal arteries and venules diameter, AVR, arteriolar wall reflex, arterial tortuosity, retinal hemorrhages |
| Rufa et al (2004)[43] | CADASIL | Scanning laser Doppler flowmetry | Optic nerve head blood flow, volume, and velocity |
| Ryan et al (2016)[44] | VCI | Retinal fundus photography | Retinal arteriolar and venular diameters |
| Schrijvers et al (2012)[45] | VaD, AD | Retinal fundus photography | Retinopathy (dot/blot hemorrhages, microaneurysms, cotton wool spots or evidence of laser treatment for retinopathy) |
| Taylor et al (2015)[46] | VCI | Retinal fundus photography | Retinal vascular fractal dimension |

Abbreviations: AD, Alzheimer disease; AVN, arteriovenous nicking; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venous equivalent; VCI, vascular cognitive impairment; EDI-OCT, enhanced depth imaging-optical coherence tomography; FA, fluorescein angiography; FAN, focal arteriolar narrowing; GAN, generalized arteriolar narrowing; MCI, mild cognitive impairment; SD-OCT, spectral domain-optical coherence tomography; SD-OCTA, spectral domain-optical coherence tomography angiography; SLO, scanning laser ophthalmoscopy; SVD, small vessel disease; VaD, vascular dementia.

Various retinopathy signs (such as arteriovenous nicking, microaneurysms, retinal hemorrhages, and focal arteriolar narrowing) were shown to be associated with cognitive impairment due to brain microvascular disease[27] and to predict cognitive decline over time.[26,32] Fractal analysis of the retinal vessels showed that rarefaction of the vessels and decreased retinal vessels branching complexity is associated with cognitive dysfunction.[22] In particular, vascular caliber changes, such as retinal venular widening, were shown to be associated with vascular dementia,[25] whereas generalized arteriolar narrowing was found to correlate with disabling dementia.[35] In Atherosclerosis Risk in Communities Study, any retinopathy was associated with accelerated rates of 20-year cognitive decline.[26]

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is one of the most commonly encountered hereditary causes of VCI.[36] Its associated retinal vascular manifestations (eg, increased arteriovenous ratio, venous diameter, and vessel tortuosity) correlate with the brain small vessel disease.[20,24] Fractal analysis was likewise described as a sensitive tool to assess alteration in retinal vessel branching, reflecting early brain microvessel alterations in CADASIL patients.[19] Moreover, multimodal retinal vascular analyses were conducted using scanning laser ophthalmoscopy and spectral domain-optical coherence tomography (OCT).[16] In addition to the retinal macrovessels, microcirculation was also studied using scanning laser Doppler flowmetry and diminished retinal capillary flow and optic nerve head blood flow were noted.[14,43]

Cerebral amyloid angiopathy is associated with age-related small vessel dysfunction and VCI and characterized by deposition of amyloid-β peptide in the walls of penetrating arterioles and capillaries of the leptomeninges and cortex.[47] Dot and blot retinal hemorrhages and microaneurysms were identified on retinal fundus pictures and fluorescein angiography in a small study including 7 patients with sporadic noninflammatory CAA.[48] Cerebral microbleeds and concomitant retinopathy were associated with slower processing speed, poorer executive function, and an increased odds ratio of vascular dementia.[41]

Retinal vascular analysis is also anticipated to serve as a biomarker for early detection of AD.[30] Vascular attenuation, increasing standard deviation of the vessel widths, reduced complexity of the branching pattern, reduced optimality of the branching geometry, increase in venular width gradient, and decrease in arterial fractal dimension were noted in patients with AD.[22,23,29] Adding to the central retinal vessels, abnormalities of choroidal circulation are also appreciated in AD.[18] A retinal function imager study showed lower retinal blood flow rate and velocity in precapillary arterioles and postcapillary venules in patients with AD and mild cognitive impairment (MCI) compared with controls.[34] Diminished retinal vasoreactivity to high-frequency flicker light stimulation was reported in both VCI and AD.[17,31]

Most recently, retinal microvascular abnormalities are being characterized using OCTA,[13] which is a novel method of retinal tridimensional microvasculature imaging. The advantages of OCTA over classical retinal imaging modalities (fundus photography and fluorescein angiography) are that the blood

**Table 2.** Advances and limitations in retinal vascular analysis.

| ADVANCES | LIMITATIONS |
|---|---|
| Deep-learning based methods | Lack of centrally available reference sets of retinal images |
| Artificial intelligence | Difficult automated identification of multiple retinal vascular features simultaneously |
| Automated analysis techniques | Inadequate retinal imaging quality and lack of standardized imaging protocols and devices |
| Semi-automated software<br>SIVA, VAMPIRE | Poor interrater agreement<br>Additional manual steps |

Abbreviations: SIVA, Singapore "I" Vessel Assessment; VAMPIRE, Vessel Assessment and Measurement Platform for Images of the Retina.

vessels are imaged based on flow characteristics, allowing flow visualization in various layers of the retina and choroid, with high resolution and without using an injected dye.[49,50] This technique is becoming widely applied in retinal vascular disorders associated with common ocular pathologies. In neurological disorders, its application to target various cerebrovascular pathologies is under active consideration. The OCTA analysis of patients with migraines with aura showed decreased foveal and peripapillary vascular densities.[51] A small European study including patients with AD showed decreased outer retinal and choroidal flow rates and larger foveal avascular zones compared with controls.[18] The retinal vascular superficial and deep plexuses densities were noted to be lower in AD than in MCI subjects.[13] Apart from one study analyzing retinal vasculature and subfoveal choroidal thickness with enhanced depth imaging OCT[28] and one OCTA study quantifying macular and optic nerve head plexuses in CADASIL patients,[37] the OCTA analysis of the retinal and choroidal blood flow in human VCI is not yet reported. Therefore, OCTA institutes a promising tool for assessing the retinal microvascular networks in this patient population due to its micron-level resolution, increased sensitivity, and large field of view.[52]

Vascular contributions to other neurodegenerative disorders that develop cognitive impairment are well recognized in the literature. For instance, vascular comorbidity has significant association with cognitive impairment in patients with early Parkinson disease, which has prognostic and treatment implications.[53] Similarly, vascular comorbidity is associated with a substantially increased risk of disability progression in multiple sclerosis,[54] whereas cerebrovascular small vessel disease is associated with diagnostic delay and disability at the time of multiple sclerosis diagnosis.[55] Whether retinal microvascular abnormalities predict cognitive impairment in multiple sclerosis or Parkinson disease is still unknown.

Despite increased recognition that cerebrovascular disease and neurodegeneration are advancing together, retinal vascular abnormalities specific for early vascular cognitive decline, which are present irrespective of the comorbid traditional vascular risk factors, as well as their individual or combined predictive value for dementia remain unidentified. Similarly, retinal features which are specific for different VCI clinic-radiologic phenotypes, and various stages of the respective phenotypes, are still unknown. For instance, hypertension and CAA jointly play an important role in vascular cognitive deterioration. Despite this, specific retinal vascular features differentiating hypertensive and amyloid angiopathy are minimally explored. A recent meta-analysis concluded that the potential of ocular fundus image analysis in differentiating between dementia subtypes should be investigated using larger and well-characterized samples.[56]

Current advances in retinal imaging analysis and their limitations are summarized in Table 2. Semi-automated computer-based methods to assess retinal vessel morphology are being developed,[20] which provide quantification of the arteriole-to-venule ratio, tortuosity index, and mean fractal dimension, between other parameters. Automatic techniques are also developed for retinal fundus photographs to serve retinal vessels identification,[57] segmentation,[58] quantitative assessment of retinal arteriolar central light reflex and vessel width,[29,59] hard exudates,[60] and retinal arteriovenous nicking.[61] Artificial intelligence methods demonstrate diabetic retinopathy detection and are potentially ready for prime use for retinal screening in patients with diabetes mellitus in primary care settings.[62] In a similar fashion, automated retinal analysis could come in handy to directly assess cerebral microvascular status and diagnose VCI early.[63] The semi-automated software Singapore "I" Vessel Assessment (SIVA) demonstrated narrowed venular caliber, smaller arteriolar and venular fractal dimensions, and higher arteriolar and venular tortuosity in patients with dementia.[22] However, 2 software applications, the SIVA and the Vessel Assessment and Measurement Platform for Images of the Retina (VAMPIRE) were recently compared and the agreement between the applications was poor.[64]

Investigating multiple aspects of vascular behavior including arteriovenous nicking, vascular caliber changes, and vascular attenuation depends on a preliminary step of accurately specifying boundaries of retinal vessels in retinal fundus images. Therefore, it is very important to develop efficient techniques with as high precision as possible when extracting image-based information, such as the true boundaries of vessel walls. Till date, the automated techniques[65] developed are challenged by the complexities in retinal images including inconsistent contrast, fuzzy boundaries, and missing edges. This leads to

incorrect measurements of vascular features. Same is the case for automated identification and classification of other heterogeneous retinopathy features, such as instance retinal hemorrhages,[66] microaneruysms,[67] and exudates.[68] These methods are not yet being established for other retinal vascular imaging modalities such as OCTA. Furthermore, the lack of centrally available reference sets of retinal images creates uncertainty when improving state of the art.

Deep learning-based methods[69] could provide more precision in measurements and reliable information extraction tools. The right choice of deep learning architecture may offer insight into hidden features and patterns of vessels' behavior that may not only assist automated tools during vessel segmentation, identification, and classification process but may also provide more pathophysiological information about the association of retinal vascular changes and VCI phenotypes. In addition, the automated techniques and tools developed till date are mostly designed to focus and perform single tasks (such segmenting retinal vessels, classifying retinal vessels, and identifying and segmenting lesions) independently. A technique designed to simultaneously perform multiple tasks may provide an opportunity to find and study the association of multiple pieces of information, for example, the size, location, and magnitude of hemorrhages and microaneurysms with respect to retinal arteries and veins, concomitant to fractal vascular analysis.

To conclude, although retinal fundus photography and OCT are proposed tools to study VCI,[70,71] they are not widely used with respect to objective standardized assessments and specific prediction models. Early vascular disease identification is, however, critical because asymptomatic vascular changes in midlife are associated with cognitive decline later in life.[72] Further systematic longitudinal studies should focus on identifying highly specific retinal vascular abnormalities as a screening tool in patients with mild cognitive concerns. Fully automated and standardized retinal vascular measurements are necessary before this application can be routinely applied in clinical practice for screening. Once optimized, this method may find application for monitoring the progression of retinal vascular changes over time, as well as for the quantification of their response to various established or experimental therapeutic interventions.

## Author Contributions

OMD contributed to the conception, design, acquisition, analysis, interpretation of data, drafting the work and revising it critically for important intellectual content. She gave final approval of the version to be published.
TAQ contributed to the conception and drafting of the work and critical revision for important intellectual content. He gave final approval of the version to be published.

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