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REVIEW

Reflections on the Utility of the Retina as a Biomarker for Alzheimer's Disease: A Literature Review

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ABSTRACT

As a part of the central nervous system, the retina may reflect both physiologic processes and abnormalities related to diseases of the brain. Indeed, a concerted effort has been put forth to understand how Alzheimer's disease (AD) pathology may manifest in the retina as a means to assess the state of the AD brain. The development and refinement of ophthalmologic techniques for studying the retina in vivo have produced evidence of retinal degeneration in AD diagnosed patients. In this review, we will discuss retinal imaging techniques implemented to study the changes in AD retina as well as highlight the recent efforts made to correlate such findings to other clinical hallmarks of AD to assess the viability of the retina as a biomarker for AD.

Keywords: Alzheimer's disease; Fundus camera imaging; Optical coherence tomography; Optical coherence tomography angiography; Retina; Retinal biomarker

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Key Summary Points

Why carry out this study?

Biomarkers of AD and other neurodegenerative diseases are greatly needed to enhance clinical trials design and recruitment. Presently neuroimaging and CSF biomarkers are expensive and invasive to perform and are considered impractical for large-scale studies. The field has focused on blood-based biomarkers and is now currently working on the identification of proteins in plasma/serum that may reflect neuropathology in brain. The retinal presents a readily accessible tissue for monitoring the brain and could potentially be used in combination with or as a substitute for current AD biomarkers.

Our review focused on currently available data on the retina and AD. We summarize what has been found to date and discuss potential problems and benefits that the data currently generated has yielded.

What was learned from the study?

The human retina may be an important CNS location to detect Alzheimer's pathology.

Data on retinal involvement in AD and neurodegenerative diseases have been controversial and inconsistent. The reasons behind this may be technical or procedural in nature.

Standardization, round-robin studies and additional scientific meetings are needed to determine how the retinal can be used to denote neurodegenerative disease pathology.

INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disease that is characterized by memory loss and cognitive deficits in elderly adults, usually > 65 years of age. Post-mortem analysis of the brain for amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFT) comprised of the microtubule protein tau remains the gold standard for AD diagnosis [1, 2]. There is sufficient evidence to suggest that abnormal Aβ expression and tau precede cognitive deficits, resulting in the addition of biomarkers to the AD clinical guidelines set forth by the National Institute of Aging/Alzheimer Association (NIA/AA) [3]. Currently, AD biomarkers are quantified through positron emission tomography (PET) or concentration in cerebral spinal fluid (CSF). While these biomarkers provide information regarding Aβ plaque load and neurodegeneration, such tests are invasive and expensive. Additional biomarkers that are non-invasive and inexpensive would only serve to support an early diagnosis of AD.

Cognitive visual changes manifest in patients in the early stages of AD, including difficulty reading and finding objects [4, 5], depth perception, perceiving structure from motion [4–6], color recognition [4, 7] and impairment of spatial contrast sensitivity [7, 8]. Previously, these defects were thought to be due to pathologic changes in the cortex. Analysis of post-mortem retinal tissue identified retinal ganglion cell loss and optic nerve head thinning in AD patients [9, 10]. The retina is thought of as a "window to the brain" as it stems from the same embryonic precursor as the central nervous system (CNS) and exhibits similar characteristics to the brain [11, 12]. Changes in neuronal and vascular structures in the retina as determined by in vivo clinical measures are evident in multiple neurologic diseases, highlighting the retina as a potential biomarker for the CNS [13].

Studies in transgenic mice heavily suggest that the abundant expression of Aβ and tau results in neurodegeneration and visual loss. Aβ accumulates within cell bodies and along the microvasculature in transgenic mouse models of AD 10–15 and Octodon degus, a natural model of sporadic AD [14]. Retinal Aβ plaques appear at 2.5 months of age in APP(SWE)/PS1(ΔE9) mice, 2–3 months before plaques form in the brain [15]. These animal models also demonstrated a significant reduction in visual function and visuospatial recognition

compared with healthy controls [16–18], mirroring deficits reported in AD patients. Aβ was shown to exert its neurotoxic effect in the retina by upregulating the expression of an inflammatory cytokine (MCP-1), a microglial (F4/80) and apoptotic marker in the ganglion cell layer [19], consequently inducing microglia infiltration and astrogliosis in the retina [20, 21]. As a result, retinal ganglion cell dendritic atrophy precedes cell loss, inner retinal thinning, reduction of axonal density in the optic nerve and reduced scotopic threshold response amplitudes measured through electroretinogram [16, 22, 23]. While the studies in mouse models simulate symptoms observed in AD patients and suggest a potential mechanism for the visual alterations observed in humans, it is unclear if similar processes occur in the human retina, as disease progression between species may utilize different pathways and therefore bias results.

This review will discuss the multiple retinal imaging methods used to evaluate the human retina in AD patients. We will discuss significant findings as well as outstanding issues with the currently used retinal imaging techniques. Also, we will reflect on how alterations of the retina corroborate with other biomarkers of AD, such as protein load in the brain as well as CSF. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

METHODS

We performed a literature search in PubMed and Web of Science for studies published before June 2019. Keywords included "Alzheimer's disease," "retina" and "imaging." A total of 112 articles were identified. Studies in our review investigated changes in the retina between Alzheimer's disease diagnosed patients and healthy controls, through the retinal thickness, vascular alterations or in vivo inclusion detection. Studies conducted in mice as well as repeats were discarded. The identification of subsequent articles occurred throughout the literature review process. Our review discusses previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RETINAL THICKNESS

Numerous studies into AD-mediated retinal changes evaluated the thinning of the retinal nerve fiber layer, as histopathologic analysis of postmortem ocular tissue from AD patients identified optic nerve degeneration and retinal ganglion cell (RGC) loss compared with controls [9, 10]. Non-invasive retinal imaging technology such as optical coherence tomography (OCT) uses low-coherence interferometry to produce high-resolution cross-sectional scans of the retinal architecture [24]. While other ocular techniques reported similar findings [25–28], OCT produced data with higher diagnostic value compared with semiquantitative methods such as red-free photography [29], and the reliability and reproducibility of OCT retinal scans have been assessed in normal and cognitively impaired individuals [30, 31]. Thinning of the peripapillary retinal nerve fiber layer (pRNFL), the retinal layer around the optic nerve head, is associated with other retinopathies and neurodegenerative diseases [32]. The pRNFL around the optic head is segmented into four quadrants: superior, inferior, nasal and temporal. Previous meta-analyses have concluded that retinal thinning, particularly around the pRNFL, may be a reliable indicator of neurodegeneration in AD patients [33–37]. Thinning of the pRNFL was apparent in the inferior [38–48] or superior peripapillary quadrant in AD patient retinas [26, 40–43, 45–56]. Meta-analysis of studies performed on patients diagnosed with mild cognitive impairment (MCI) suggest retinal thinning may also occur but to a lesser extent than in AD-diagnosed patients [33, 35, 36]. Kesler and colleagues found significant inferior quadrant pRNFL thinning in MCI-diagnosed patients, while the superior and inferior quadrants were thinner in AD patients, suggesting a potential retinal diagnostic index to differentiate between MCI and AD [44]. However, subsequent studies in MCI patients report thinning in the temporal

[46] and nasal quadrant [53]. Thinning of the pRNFL may be an indication of cognitive impairment associated with AD, yet signs indicative of early disease progression remains inconclusive.

The macula may also be a potential AD biomarker because of the high density of RGCs around the fovea [57]. Histopathologic studies quantified as much as 25% RGC loss within the macula in post-mortem AD retinal tissue [58]. Retinal cells are organized in layers within the retina to optimize the processing of visual stimuli, with RGCs contained within the ganglion cell-inner plexiform layer (GC-IPL). Recent OCT studies indicate that the macular GC-IPL is reduced in AD patients compared with age-matched controls [33, 43, 53, 59, 60]. These data support the observation of fewer RGCs in the AD retina, further implicating retinal neurodegeneration in AD. As seen in the pRNFL, decreased macular retinal thickness is less prevalent in MCI patients. Further assessment of macular thickness may provide additional insight into RGC degeneration in AD.

While evidence for the association of pRNFL thinning and late stage AD is prevalent, recent studies contradict previous findings when assessing retinal thickness in the earlier stages of AD progression [61–66]. A majority of these studies were performed on a spectral-domain OCT (SD-OCT) machine, a newer generation of OCT technology that improved scan time and resolution over the previous time-domain OCT (TD-OCT) machines [67]. As noted by den Haan and colleagues in 2017, there are discrepancies between previous generations of OCT, as studies using TD-OCT machines reported greater differences in pRNFL thickness between AD and healthy controls [35]. While OCT studies highlight changes observed in AD patients, similar degeneration occurs in other retinopathies. Current imaging modalities cannot distinguish retinal changes caused by glaucoma or dementia, as a recent study using SD-OCT failed to report significant differences in pRNFL thinning between AD and preperimetric glaucoma patients [68]. Although SD-OCT improved resolution may eventually identify features unique to AD, a diagnosis using OCT alone is not sufficient.

RETINAL VASCULAR CHANGES IN AD

Vascular diseases are a risk factor of dementia, and evidence suggests AD pathophysiology includes a vascular component [69, 70]. For example, abnormally reduced cranial blood flow is observed in AD patients through transcranial Doppler analysis [71]. Disruptions in the cerebral vasculature, such as infarcts and hemorrhages, are also documented in AD post-mortem tissue [69]. The brain and retina share anatomical and physiologic similarities, and alterations in the retinal microvasculature may emulate changes in the brain [72]. Disruptions of the retinal vasculature are reported in cognitively impaired individuals [72]. Abnormal retinal blood flow has also been measured in AD, implicating the retinal vasculature as another potential AD retinal biomarker [50]. While other techniques exist, two primary ocular imaging modalities used to study AD-related vascular structural changes are retinal fundus imaging and OCT angiography (OCTA).

Retinal fundus imaging is a standardized technique that allows for the quick assessment of the retinal vasculature [73]. Semiautomated analysis of retinal photographs provides quantification of prominent vasculature changes associated with blood pressure such as inner vessel width (caliber), tortuosity and global branch patterning (fractal dimension) [74]. Retinal vasculature assessment from two population-based cohorts identified changes in vessel caliber were associated with dementia in hypertensive individuals [75] and individuals diagnosed vascular dementia but not AD [76]. Various alterations in the retinal vasculature were observed in individuals diagnosed with AD compared with control [77]. However, an independent study reported significant differences in retinal fraction in individuals diagnosed with vascular impairment but not early stage AD [78]. The *APOE* ε4 allele is associated with small vessel disease and a genetic risk factor for AD [79, 80]. Vessel structure and composition measured through retinal vessel central reflex were significantly associated with *APOE* ε4 status [77]. The association between vessel central reflex and AD was not significant when *APOE* ε4 status was taken

into account. Collectively, these data suggest that vascular retinal measurements could be a reliable indication of vascular infarctions often comorbid with AD. Meta-analysis of retinal fundus imaging studies concluded retinal fractal dimensions were consistently altered in AD patients, suggesting measuring vascular complexity may be a viable biomarker when using retinal fundus imaging [81–83].

The retinal vasculature is organized into distinct networks within the retinal layers, and each vascular network comprises a unique set of microvessels [84]. As cerebral microvasculature distortions in AD brains lead to disrupted blood flow, the retinal microvasculature may reflect similar malformations. Retinal fundus imaging lacks the resolution to discern between the superficial and deep capillary networks [85]. Advances in OCT technology have allowed for the detailed analysis of the retinal vascular networks through OCTA [86]. The movement of objects, such as red blood cell flow, creates variations in the OCT signal, making it an ideal contrast agent for vascular imaging. Repeated scans are analyzed in OCTA to subtract regions of static OCT signal and highlight regions of varying OCT signal, producing an in-depth visualization of the retinal microvasculature.

Several groups demonstrated retinal vessel density reduction of the superficial capillary plexus (SCP), the vascular network within the GC-IPL, in AD-diagnosed patients [87–91]. Jiang and colleagues noted a marginal decrease in GC-IPL thickness in AD compared with MCI and healthy controls [88]. Reduced GC-IPL thickness was correlated with the deep capillary plexus (DCP), a vascular network located in the inner retina mainly composed of capillaries [88]. Because capillary dysfunction is associated with AD-mediated neurodegeneration, it is possible that the DCP dysfunction is highly susceptible in the AD retina and may indicate disease progression [92]. Retinal microvessel density of the DCP was also significantly lower in AD and MCI patients from the same study [88]. However, subsequent OCTA analyses did not observe DCP vessel density reduction in MCI [91, 93] or AD [87, 93]. Additional analysis of the SCP and DCP through OCTA may provide more information about the specific vascular networks altered in AD and MCI.

The fovea avascular zone (FAZ) is a specialized region of the fovea that lacks retinal blood vessels in order to reduce light scattering [94]. The FAZ can indicate disease progression, as the width and circumference of the FAZ correlate with capillary nonperfusion [95]. A few studies utilizing OCTA observed larger FAZ in AD [89, 90]. While increased areas of FAZ were reported in one study that had screened their population with AD biomarkers [96], other groups failed to observe similar changes in their preclinical AD cohort [91, 97]. One possible explanation for the positive result could be the variation in AD biomarkers used to identify experimental subjects. An alternative explanation may be that increased FAZ may be indicative of later stages of AD.

As oxygen metabolism is likely perturbed in AD [98], another possible retinal vascular measurement is oxygen consumption using retinal oximetry [99]. Hemoglobin saturated with oxygen is sensitive to wavelengths at 600 nm but not 570 nm. Optical densities are calculated in the retinal vessels to measure relative vessel oxygenation [100]. The first study to analyze AD retinas with retinal oximetry detected elevated venous oxygen saturation in AD patients compared with control individuals, suggesting that less oxygen is leaving the blood [101]. Similar results were observed in patients diagnosed with MCI, hinting that faulty oxygen metabolism occurs early on in AD [102]. Decreased venous blood flow was also seen in MCI patients as well as AD patients, possibly contributing to the disruption of retinal oxygen consumption [50, 90]. In summary, these results suggest that the retinal vasculature is impaired in such a way to ultimately reduce blood flow. One vascular measure may not suffice as a definitive sign of AD; however, quantifying a few key measures such as oxygen saturation and retinal vessel density may contribute to developing a distinct profile of AD progression in the retina.

DETECTING AD PATHOLOGY IN THE RETINA

Retinal neural fiber layer degeneration and retinal vasculature configuration are also characteristic of other retinopathies independent of

AD [103–105]. The possibility of detecting the classic AD hallmarks such as fibrillar Aβ plaques or NFTs in the retina alongside other retinal changes could further support an AD diagnosis. However, Aβ and tau are also implicated in other age-related retinopathies. Inclusions that resemble the extracellular inclusions called drusen associated with early stage age-related macular degeneration (AMD) [106] were detected in the retinal periphery of AD patients through ultra-widefield fundus imaging [107]. Several studies report the presence of Aβ within the retinal pigmented epithelium (RPE) cells and drusen in AMD patients [108–110]. Reduction of the outer retina such as the photoreceptor layer is associated with early AMD progression [111–113]. One study failed to detect differences in any of the outer retinal layers among MCI, AD and healthy controls, implying that photoreceptor layer thinning is unique to early AMD [114]. Loss of RGCs is observed in both glaucoma and AD, implying a relationship between the two diseases [115]. In animal models of glaucoma, apoptosis of RGCs is associated with increased production of amyloid [116], and inhibiting aggregation may prevent RGC loss [117]. Tau-mediated pathogenic mechanisms may be involved in retinal degeneration, as suggested by decreased tau levels in the retina [118] and increased levels of tau in the vitreous body of patients with glaucoma and diabetic retinopathy [119]. Elevated intraocular pressure (IOP) present in glaucoma may play a role in tau phosphorylation [118]. However, no differences in IOP were detected in AD patients compared with controls [51, 120]. It is possible that although Aβ and tau may be present in glaucoma and AMD, key differences may be sufficient to distinguish the different forms of retinopathy from AD.

The work from the Koronyo-Hamaoui laboratory has provided evidence for detecting retinal Aβ detection in vivo. A pilot study administering curcumin, a turmeric-derived fluorophore known to bind to Aβ plaques [121], to AD and AMD patients reported abundant curcumin-positive objects in the peripheral retina of AD and AMD patients [15]. Histologic analysis of postmortem retinas performed by the same group detected Aβ-positive inclusions using curcumin and a panel of Aβ-specific antibodies in AD diagnosed patients compared with controls [15, 52, 122]. Of note, they showed that Aβ-positive inclusions were more frequently found in the periphery of the superior quadrant and were uncommon in the macula. Diverse Aβ deposits often associated with blood vessels were found predominantly in the ganglion cell layer [122]. In contrast, other groups have been unsuccessful in detecting retinal Aβ deposition in AD patients. Williams et al. were unable to detect any Aβ, tau inclusion or deposits in the retinas of 17 AD-related cases [123]. Schön and collaborators did not find fibrillary accumulations of Aβ in six post-mortem AD retinas [124]. Similarly, Ho et al. examined eyes from 11 AD cases and 6 age-matched controls and did not observe amyloid deposits in the lens, retina or other ocular structures in AD eyes [125]. Hinton and colleagues also failed to find amyloid in the retinas of four AD patients [126], and Leger et al. did not find intraretinal amyloid in eyes of older patients or two AD patients [127]. Lastly, Jiang et al. completed a meta-analysis of five of the aforementioned studies and found significant statistical heterogeneity between their results, which was thought to be due to the fact that the first study by Koronyo-Hamaoui and coworkers used five antibody clones in contrast to the other four studies, which used only one clone [128]. The authors concluded that this meta-analysis did not provide sufficient evidence to suggest whether pathologic accumulation of retinal Aβ could be used as a diagnostic tool for AD. The inability to reproduce Aβ human retinal staining can be attributed to technical inconsistencies such as the tissue preparation or immunohistochemical protocol [129]. Our laboratory has performed immunohistochemical analysis on post-mortem AD and control retinal tissue and observed diffuse Aβ staining. While promising, we would like to refine our technique. More importantly, the variation in Aβ staining as well as the other retinal markers discussed above may lie in the heterogeneity of the sample population.

Detection of retinal tau is promising as it is known to play a pivotal role in retinopathy progression by interacting with axonal

transport signaling pathways and bridging various signaling protein complexes [130]. AT8-positive detecting phosphorylated tau inclusions were observed in post-mortem retinal tissue from six AD cases as well as retinal tissue from two progressive severe palsy cases [124]. Using several antibodies to characterize the presence of Aβ and tau in post-mortem brain and retina, den Haan and colleagues detected phosphorylated tau in the inner and outer plexiform layers of retinal tissues from AD cases and Aβ signal in both AD and control cases [131]. Additionally, phosphorylated tau but not Aβ staining was present in both brain and retinal tissue of AD cases. Two cognitively normal cases also exhibited retinal phosphorylated tau staining. To summarize, retinal tau may indicate tauopathy in the brain, but interpretations may also be complicated by retinal diseases such as glaucoma.

Fluorescent live imaging ophthalmoscopy (FLIO) is an emerging technology that measures the autofluorescence of the retinal fluorophores, calculating the overall fluorescent lifetime of a fluorophore. The fluorescent lifetime, or the time elapsed from peak excitation of the fluorophore to ground state, can be used to detect abnormalities in the retina. A couple of FLIO studies observed a significant correlation between AD diagnosis as well as AD CSF biomarker concentrations with fluorescence lifetime [132, 133]. Fluorescence lifetime measurements also correlated with GC-IPL thickness measured through OCT as well as with Aβ and tau CSF levels [132]. While additional studies are needed to further validate these finding, the use of FLIO in AD retinal diagnosis is promising.

USING RETINAL ALTERATIONS IN CONJUNCTION WITH ESTABLISHED AD BIOMARKERS

Age is a risk factor of AD and other retinopathies that may confound the use of the retina as a biomarker for AD. The retinal nerve fiber layer naturally decreases with age at a rate of 0.44 μm per year [134]. A thinner GC-IPL and retinal nerve fiber layer was detected in individuals ≥ 50 years [135–137]. Retinal layer thickening is observed in the outer retina of older individuals, possibly because of decreased activity of the RPE [135, 138, 139]. While studies include an age-matched healthy control group to account for these issues, it is difficult to conclude with high confidence whether changes in the retina are inflicted by AD pathology or a result of the normal aging process. Longitudinal studies would provide information about retinal thickness and disease progression over time to account for these potential cofounders.

Early longitudinal studies have focused on assessing retinal thickness in elderly cohorts to assess the relationship of retinal degeneration and disease progression. In a 25-month study following a cohort of nondemented elderly individuals, significant thinning in the inferior pRNFL quadrant was observed in individuals whose cognitive abilities had declined [38]. Reduction of the pRNFL was observed after 12 months in patients diagnosed with mild to moderate AD [41]. Drusen-like inclusions in the peripheral retina increased over a 2-year period in clinically diagnosed AD patients, suggesting the continued development of retinal inclusions may occur late in the disease [107]. Recent studies have utilized other biomarkers such as functional imaging and CSF Aβ and tau concentrations to further understand the relevance of retinal thinning to AD progression. After individuals were sorted into preclinical AD or control groups based on Aβ PET imaging, Santos et al. reported a decrease in retinal layer thickness in the preclinical group as well as an inverse relationship between retinal layer thickness and Aβ accumulation in the preclinical AD group [140]. In another study, elderly individuals determined to be cognitively normal at the beginning of the study were assessed by magnetic resonance imaging and OCT to correlate retinal thickness to cingular cortical thickness. Decreased retinal thickness in the inferior peripapillary quadrant was associated with cortical atrophy as well as episodic memory 12 months after initial examination [39]. In summary, longitudinal studies have provided

support for using the retina as a feasible biomarker for the early diagnosis of AD.

However, other studies implementing Aβ PET [97], CSF [87] or both AD biomarkers [141] failed to repeat retinal changes observed in clinically diagnosed AD populations. Although alterations in macular vessel density were observed in the biomarker-positive group, Lahme and colleagues concluded that they were not due to AD pathology, but vascular diseases comorbid with AD [87]. In a comprehensive study using multiple ophthalmologic techniques to quantify various retinal vasculature parameters, no significant vascular changes were reported between AD biomarker-positive and -negative groups [141]. A similar study conducted between Aβ-positive patients converted to AD and Aβ-negative patients diagnosed with vascular cortical impairment found a reduced fractal dimension in the Aβ-negative group diagnosed with vascular impairment [78]. Furthermore, retinal thinning and parietal cortical atrophy were observed in both Aβ-positive and -negative individuals, leading the authors to conclude thinning of the retina correlates with the parietal lobe independent of the presence of Aβ [60]. These observations suggest that the alterations in the retina are not directly due to Aβ accumulation but through other mechanisms that are comorbid with AD.

Prognostic studies using AD biomarkers have provided new insight into retinal changes in the preclinical stages of AD. Asymptomatic individuals with high levels of Aβ-PET signal exhibit higher retinal vessel densities as well as larger vascular widths [97, 142], suggesting higher blood flow in the retina with Aβ accumulation. Increased retinal blood flow can be induced by hypoxia, increasing the vascular density observed in OCTA [143]. A recent study tracking retinal vessel dynamics identified vasculature impairment in MCI-diagnosed patients. Further analysis correlated arteriole dilation with CSF Aβ levels, with the authors proposing Aβ levels in brain and retina may impede retinal vascular function [93]. Taken together, these results support the hypothesis that inflammation instigated by Aβ accumulation induces the retina to go into a hypoxic state similar to the brain [144]. Activated microglia were detected in the retinas of pre-symptomatic triple-transgenic mice, implicating that Aβ plaques and NFTs can induce gliosis in the retina [145]. In a case-controlled cross-sectional study, retinal thickening was revealed in MCI patients through multivariate regression analysis [66]. The authors speculate that retinal thickness temporarily increases as an inflammatory response in the early stages of AD [66, 146]. The dynamic state of the retina due to gliosis may partially explain the varied results previously reported in the prodromal population.

Larger prospective longitudinal studies may provide a more comprehensive assessment of the utility of ocular markers to diagnose AD. Retinal imaging studies can be added on to existing larger studies. One such example of this is the A4/LEARN clinical trial, an ongoing study that has enrolled over 1500 asymptomatic individuals screened through PET for elevated Aβ levels. Added onto the study is a retinal imaging component that has two objectives: (1) determine the incidence of Aβ accumulation in retina relative to brain AD pathology and (2) correlate retinal Aβ and Aβ brain PET to cognitive measures across both arms. All participants in the retinal imaging add on are administered curcumin and scanned by fundus camera for curcumin-positive inclusions. After the completion of the double-blind portion of the study, participants of the A4 trial will be offered the opportunity to continue treatment on the open-label extension. The open-label extension will provide valuable information with regard to delayed start analysis. Amendments to studies such as the one described above will provide further data to determine if the retina is a reliable biomarker for early AD diagnosis.

CONCLUSION

The retina may serve as a "window into the brain" that may potentially provide a non-invasive and simple method to diagnose AD. Studies have highlighted distinct changes in the ocular and vascular structure in AD patients as well as uncovered distinct retinal changes in early stages of AD indicative of inflammation. However, several inconsistencies are reported

questioning the utility of the retina as a reliable biomarker for diagnosing AD. While small sample sizes may be influencing results, another concern is the variation in techniques used to measure the retina. Although technology may provide higher resolution and ease of data acquisition, one also needs to remember that such techniques should be reproducible and also scalable to previous iterations. Furthermore, other factors such as retinopathy and aging similarly alter the retina, confounding the retinal alterations possibly due to AD. Future studies should consider measuring the retinal vasculature, retinal fiber layer as well as potential Aβ retinal inclusions to compare disease progression, ideally in individuals pre-screened through other biomarkers.

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