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REVIEW

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The Retina as a Biomarker for Parkinson's Disease: A Systematic Review

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ABSTRACT

Parkinson's disease is the second most common neurodegenerative condition in the world. Due to the absence of a single definitive diagnostic test, there has been increasing emphasis on identifying reliable biomarkers. This systematic review investigates the potential use of the retina as a biomarker for Parkinson's disease, with a focus on its utility for diagnosis, early detection, or monitoring disease progression. We conducted a comprehensive search using systematic review methodology and tools across multiple databases (PubMed, Embase via OVID and Cochrane), limiting publications to the last five years, in the English language, and to human studies. Of the 13 studies submitted to critical appraisal after systematic filtering, 11 used optical coherence tomography (OCT), 4 used optical coherence tomography angiography (OCT-A), 3 used contrast sensitivity, 7 used best corrected visual acuity (BCVA), 2 used electroretinography (ERG), and 2 visually evoked potential (VEP) to compare between Parkinson's disease patients and healthy controls. The results varied across different techniques, with OCT and OCT-A showing inconsistent statistical significance in multiple studies. Contrast sensitivity demonstrated statistical significance, while BCVA showed no significant difference. ERG and VEP each exhibited some degree of statistical significance. Among the techniques, contrast sensitivity, ERG, VEP, and vessel density (measured with OCT-A) showed the most consistent statistical significance as potential biomarkers. These findings provide early evidence supporting the retina's potential as a biomarker for Parkinson's disease.

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KEYWORDS
Retinal biomarker; parkinson's disease; optical coherence tomography (OCT); retinal nerve fiber layer (RNFL); retinal ganglion cell (GCL)

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative condition, affecting 1% of the global population over 60 years old and approximately 153,000 people in the UK.[1,2] It is due to the dysfunction and eventual death of dopaminergic neurons in the substantia nigra, resulting in a variety of impairments, including muscle movement and walking, stiffness, tremors, impaired balance alongside difficulties with speech, loss of smell, sleep, visual hallucinations, cognitive impairment and other basic tasks as the disease progresses.[3–5]

Alongside these symptoms, patients with PD may experience a range of visual impairments, including contrast sensitivity, difficulty with reading, double vision, and spatial awareness.[6,7] Dry eye disease, affecting 60% of patients, is also common, alongside a reduced blink rate, ptosis and Meibomian gland dysfunction.[8]

How is PD currently diagnosed?

Currently, no single clinical test can be used alone to make a definitive diagnosis. The UK Parkinson's Disease Society Brain Bank's diagnostic criteria for Parkinsonian syndrome define three steps, step one being the presence of bradykinesia along with muscle rigidity, 4-6 Hz rest tremor or postural instability. Step two comprises the exclusion of other neurological conditions, whereas step three is the presence of three or more of a list of criteria (Supplementary Table S1).[9]

Alternatively, the alpha-synuclein seed amplification assay – a diagnostic tool under development– tests for alpha-synuclein within spinal fluid and accurately identifies PD in 87.7% cases.[10] The gold standard test, a postmortem assessment, will demonstrate an accumulation of α-synuclein and formation of Lewy bodies within the brain. α-synuclein deposits may also thicken the inner retina,

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detectable by imaging techniques like optical coherence tomography (OCT).[11,12]

MRI, CT and DaTSCAN (dopamine transporter scan) can be used to assess brain structures and identify areas with a loss of dopamine-producing cells. However, none of these methods are diagnostic on their own or definitive early in the disease.[13,14]

PD may also be assessed in terms of severity and progression, which using the Hoehn and Yahr (H&Y) scale and the Unified Parkinson's Disease Rating Scale (UPDRS), which consists of 3–4 parts: mood and behavior (part 1), daily living activities (part 2), motor examination (part 3) and motor complications (part 4).[15]

How can the retina be used as a biomarker?

Given the absence of a single definitive diagnostic test, there has been a growing focus on identifying reliable biomarkers that can aid in the early detection and monitoring of disease, with one of them being the retina. Different techniques may be used to assess this, which include visual acuity, color vision, contrast sensitivity, visual fields, optical coherence tomography (OCT), optical coherence tomography angiography (OCT-A) and electroretinography (ERG).

Summary

This systematic literature review gathers the most up to date information on using retinal structure or retinal function as a biomarker for PD to help early diagnosis of the disease, which would potentially improve quality of life, reduce treatment costs and aid future research.[16]

Methods

Search strategy

A systematic search of literature was conducted to identify studies investigating the use of retina as a biomarker in PD. Databases searched included Pubmed, Embase via OVID and Cochrane, with filters for including only English language papers, human studies and studies within the last five years to ensure only up-to-date information are included. (See Table 1 for the search conducted on the 7 February 2024 for the number of articles found). Keywords used as search terms involved all possible methods of investigations, which resulted in a list of different imaging, psychophysical and electrophysical techniques. This included: "visual acuity," "visual fields," "perimetry," "colour vision," "contrast sensitivity," "OCT," "OCT-A" and "electroretinography." "retina" in combination with the term "Parkinson's" and associated terms "alpha synuclein" and "dopamine."

Table 1. Number of papers found within each database.

SEARCH TERMS	Pubmed	Embase	Cochrane
(Visual Acuity) and (Parkinson's)	22	61	10
((Visual Field*) OR (perimetry)) AND (Parkinson's)	12	37	26
(Color Vision) AND (Parkinson's)	3	9	3
(contrast sensitivity) AND (Parkinson's)	17	49	11
(Dopamine*) AND (retina*) AND (Parkinson's)	34	73	1
(alpha synuclein) AND (retina*) AND (Parkinson's)	20	31	0
((OCT) OR (Optical Coherence tomography)) AND (Parkinson's)	88	253	8
((OCT-A) OR (Optical Coherence tomography angiography)) AND (Parkinson's)	16	44	0
(electroretinography) AND (Parkinson's)	6	9	0
Total	218	566	59

Data extraction and critical appraisal

Two reviewers independently assessed titles and abstracts for relevance, and any disagreements were resolved through discussion. Full texts were then reviewed, in which critical appraisal was completed with the use of Joanna Briggs Institute checklist.[17] Table 2 shows the Joanna Biggs Institute (JBI) checklist for the first study – the remaining can be found in the supplemental materials. Data extraction and verification were conducted by using an adapted version of the Cochrane Effective Practice and Organization of Care (EPOC) 2017 to extract important information from each study. Both authors independently verified all entries and double-checked to ensure completeness and accuracy. The same form was used for each study to reduce bias and allow all the relevant information to be gathered. Table 3 is the data collection for the first study (the remaining can be found in the supplemental materials).

Table 2. JBI critical appraisal checklist for analytical cross-sectional studies for Zhou et al.'s paper.

JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies				
Reviewer: Abigail Gardner, Rosa Li			Date:	12/07/24
Author: Min Zhou, Lei Wu, Quiyuan Hu, Congyao Wang, Jiacheung Ye, Tingting Chen and Pengxia Wan			Year:	2021
Record Number: 1				
	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	√			
2. Were the study subjects and the setting described in detail?	√			
3. Was the exposure measured in a valid and reliable way?	√			
4. Were objective, standard criteria used for measurement of the condition?	√			
5. Were confounding factors identified?	√			
6. Were strategies to deal with confounding factors stated?			√	
7. Were the outcomes measured in a valid and reliable way?	√			
8. Was appropriate statistical analysis used?	√			

Results

In total, there were 843 papers found in Pubmed, Embase and Cochrane, with 218 in Pubmed, 566 in Embase and 59 in Cochrane. The papers were exported into Endnote and an excel sheet for duplication screening, leaving 420 remaining. These were then screened for suitability according to their titles and abstracts, leaving 107 papers for full text screening.

No full text was available for 46 of these papers. Of the remaining papers, 12 were excluded for the lack of relevance, 1 for no control group, 16 for mismatching of the control groups, 3 for unsuitable study design, 1 for the lack of data measured as mean with standard deviation and 15 for having PD patients without clinical diagnosis via the UK Brain Bank criteria. This left 13 papers for critical appraisal. The results of the above search and filtration can be seen in the PRISMA flowchart. (Figure 1).

Demographics

Table 4 shows the demographics of the studies included in this review. The studies in this review were conducted in a variety of different countries, underscoring the global impact of PD. Majority of the studies were conducted in neurology, ophthalmology or movement disorder clinics, except for two studies which did not specify the study locations.

All studies in this review were either cross-sectional or case-control, classified as level 3 or level 4 evidence. Given the observational nature of the research question, the inclusion of higher-quality experimental studies such as randomized controlled trials were not expected.

The majority of participants were male, which reflects the prevalence of PD in the male biological sex. The mean age of the patients ranged from 52.5–69 years old, with no significant difference in ages between PD patients and healthy controls.

The mean number of years since diagnosis of PD varied drastically between the studies used in this review, with Sung et al[18] and Yildiz et al[19] not specifying this information. Among all studies, the mean values ranged from a minimum of 1.83 years to a maximum of 9.1 years. It should be noted that Sung et al[18] only included "de novo" patients, which may explain why this information was not considered relevant for inclusion.

The smallest number of people included within a study was by Mello et al[20], which included 21 patients with PD and 19 healthy controls (HC). Conversely, the largest number was 52 patients with PD and 100 HCs included in Zhang et al.[21] Overall, the number of participants in each study varied greatly (see Table 4).

The studies that used OCT and OCT-A are included in Table 5. Spectral domain OCT was the most common type used of the three main OCT technologies (spectral domain, time domain and swept source). The studies that used OCT-A either used spectral domain or swept source OCT, with half of the studies using swept source and half using spectral domain.

JBI checklists

All 13 studies included within this review were appraised by the JBI critical appraisal checklist. Seven of 13 studies scored seven out of eight (higher quality), whereas four others scored six and two scored five (medium quality).

Table 3. Summary of data extracted from "visual impairments are associated with retinal microvascular density in patients with Parkinson's disease" by Zhou et al.

Review Title	The retina as a Biomarker for Parkinson's disease
Date Form completed	14/07/24
Reviewers Conducting Data Extraction and Validation	Abigail Gardner, Rosa Li
General information	
Study name	Visual Impairments Are Associated With Retinal Microvascular Density in Patients with Parkinson's Disease
Authors	Min Zhou, Lei Wu, Quiyuan Hu, Congyao Wang, Jiacheung Ye, Tingting Chen and Pengxia Wan
Publication Year	2021
Record Number	1
Study Characteristics	
Participants	24 eyes of 24 patients with PD and 23 eyes of 23 controls
Inclusion	Diagnosed with Idiopathic Parkinson's diagnosed by an experienced neurologist using UK Brain Bank criteria, Eligible patients were aged 40 years or older and only received drug treatment without any surgical intervention
Exclusion	Patients with psychiatric or neurological diseases other than PD, such as dementia or multiple sclerosis; diabetes, uncontrolled hypertension, or other systemic diseases which could affect the visual system; history of ocular trauma or surgery; family history of glaucoma; high refractive error (±6.00D spherical equivalent); intraocular pressure (IOP) > 21 mmHg; media opacifications; concomitant ocular diseases such as corneal disease, glaucoma, or retinal disease
Sample recruitment method	Consecutive patients were recruited from the neurology outpatient clinic of the First Affiliated Hospital of Sun Yat-sen University, and healthy subjects were recruited from the patients' non-consanguineous families or friends via asking for their willingness to participate
Methods	
Aim of study	"This study aimed to evaluate retinal microvascular density in patients with Parkinson's disease (PD) and its correlation with visual impairment"
Design	Cross sectional Study
Risk of bias	
Exposure	Stage of Parkinson's disease- average stage 2 (H&Y), no comparisons made Currently on Parkinson's medications – not documented
Confounding factors	Age, different scan protocols- discrepancy of macular VD, higher quality OCTA images in healthy controls- bias interpreting results
Attrition	7 PD and 4 controls removed due to ocular condition or px noncompliance 8 PD and 3 controls excluded because if insufficient image quality

Results

	PD Mean (SD)	HC Mean (SD)	*p* Value
BCVA	0.0880 (0.122)	0.097 (0.117)	0.591
Statistical test	t-test, Mann – Whitney U-test as appropriate		
Nasal macular microvascular density	17.4 (3.5)	19.4 (2.6)	**0.029***
Temporal macular microvascular density	17.2 (3.6)	19.7 (1.9)	**0.009***
Superior macular microvascular density	17.1 (4.1)	19.4 (2.6)	**0.049***
Inferior macular microvascular density	17.1 (3.1)	18.8 (2.5)	**0.049***
Central macular microvascular density	6.6 (2.6)	8.2 (2.3)	**0.032***
Inner ring macular microvascular density	17.2 (3.2)	19.3 (2.1)	**0.011***
Full area macular microvascular density	16.0 (3.0)	18.0 (2.0)	**0.010***
FAZ	0.31 (0.10)	0.28 (0.10)	0.464
Statistical test	Spearman correlation		
Additional Information			
OCT-A used	Zeiss Cirrus HD-OCT 5000 with AngioPlex OCTA 3 mm diameter region		
Correlation	No statistical significance between PD history or UPDRS and BCVA, P100 latency or P100 amplitude.		

Narrative synthesis

The 13 studies included in this review used a variety of methods for assessing any differences between the retina of those with and without PD. Statistical significance in all of the studies was used with the *p*-value of <0.05.

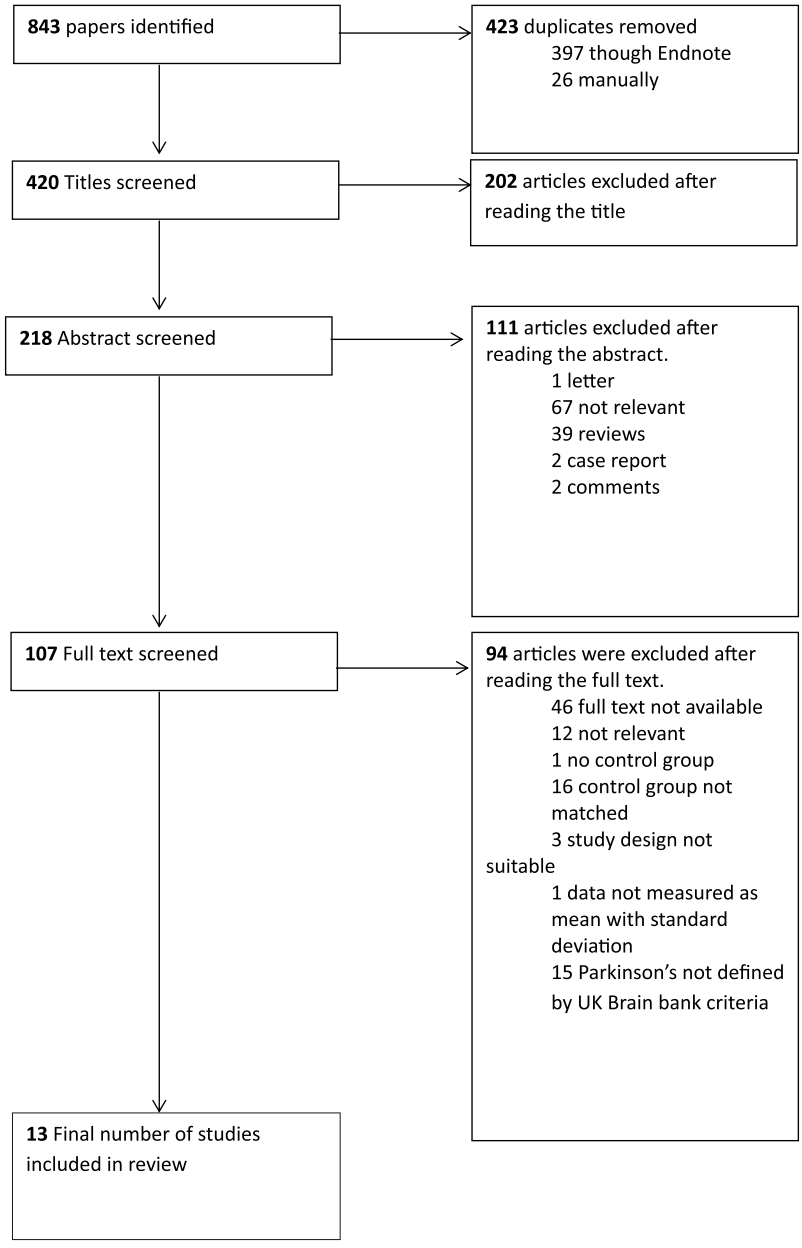

Figure 1. PRISMA flowchart.

A variety of different techniques were used to assess the retina. Figure 2 shows the equipment used over all of the studies.

Optical coherence tomography (OCT)

In this review, 11 of 13 studies used an OCT to compare PD patients to HCs. Among the 13 studies included within this review, 10 studies measured retinal layers. RNFL was measured in all these studies, with 8 studies measuring peripapillary retinal nerve fiber layer (pRNFL) specifically (see Table 6). Varying results were reported, with Sung et al[18], Elkhatib et al[22], Zou et al[23] and Elanwar et al[24] all reporting different significance within the measurements of average, superior, inferior, temporal and nasal pRNFL. The remaining pRNFL studies showed no statistical significance.

Zhang et al[25] measured RNFL in 1 mm, 3 mm and 6 mm circles, in which measurements at 3 mm (p = .004) and 6 mm (p = .024) showed significant difference. Similarly, Shafiei et al[26] reported significance for the average superior (p = .021) and inferior

Table 4. Demographic information of all papers included within this review.

Study ID	Study Design	Masked	Country	Location	PD diagnosis years (SD/min-max)	no. of PD patients included (controls)	Male PD %	Age years ±SD
1	cross sectional	No	China	Hospital (neurology)	5.3 (4.2)	24 (23)	75	65.88 ± 6.50
2	cross sectional	No	South Korea	Hospital (movement disorder clinic)	–	74 (53)	33.8	65.30 ± 8.38
3	cross sectional	No	China	–	2.04 (1.23)	42 (75)	44.6	55.92 ± 7.53
4	cross sectional	No	Brazil	Hospital (movement disorder clinic)	9.1 (6.6)	21 (19)	57.9	52.5 ± 8.3
5	cross sectional	No	Turkey	Hospital (Neurology)	–	22(22)	45.5	67.5
6	cross sectional	No	Iran	Hospital (neurology)	6.52 (4.08)	23(23)	78.3	61.30 ± 11.57
7	cross sectional	No	China	Hospital (neurology)	3.2 (2.0)	35 (35)	84.2	61.86 ± 5.46
8	cross sectional	No	Turkey	Hospital (movement disorder clinic)	6.45 (4.58)	50 (50)	70	65.10 ± 9.81
9	cross sectional	No	China	Hospital	2.47 (1.51)	52 (100)	50	57.92 ± 8.14
10	case control	No	Egypt	Hospital (neurology)	3.64 (2.32)	50(50)	68	60.36 ± 11.38
11	cross sectional	No	Turkey	Hospital	2(0–18)	41(29)	65.9	65.58 ± 9.89
12	case control	No	Egypt	Hospital (Neurology/ ophthalmology)	6.53 (3.07)	20(20)	50	63.2 ± 5.50
13	case control	No	South Korea	Hospital (movement disorder clinic)	1.83 (1.83)	48(27)	35.4	69 ± 9

(p = .045) measurements. Despite there being statistical significance found within individual RNFL studies, there was no trend overall, hence no overall conclusion can be made.

Ganglion cell complex (GCC) thickness was a parameter measured in five studies included within this review (see Table 7). Their GCC results differed, with Sung et al[18] and Batum et al[27] finding a statistically significant difference in average (p = .001, p < .001) and minimum (p < .001, p < .001) GCC measurements, while Zou et al[23] and Tuncer et al[28] reported no significant findings. Interestingly, Elanwar et al[24] reported an average GCC demonstrating statistical significance within the right eye (p = .02) but not the left.

Ganglion cell layer (GCL) was measured in two separate studies, with both Mello et al[20] and Yildiz et al[19] using different categories for their measurements. Collectively, they reported no statistical significance in any of their GCL measurements.

Table 5. Types of OCTs used within studies included.

	Type of OCT			Type of OCT-A	
Study ID	SD-OCT	Time Domain OCT	SS-OCT	SD OCT-A	SS OCT-A
1				1	
2	1				
3			1		1
4	1				
5	1				
6	1				
7	1			1	
8		1			
9			1		1
10	1				
11	1				
12	1				

Mello et al[20] and Zhang et al[25] also measured inner plexiform layer (IPL) and inner nuclear layer (INL), respectively, with Mello et al[20] categorizing measurements at the fovea, inner ring, and outer ring, while Zhang et al[25] used 1 mm, 3 mm, and 6 mm concentric circles. Mello et al[20] found no statistically significant differences, whereas Zhang et al[25] reported significance in INL measurements within the 1 mm (p = .001) and 3 mm circles (p = .026).

Sung et al[18] measured the ganglion cell-inner plexiform layer (GCIPL) (see Table 7) and found statistical significance in all areas, whilst Zou et al[23] reported significance in the average value (p = .046). Zhang et al[25] reported no statistical significance.

It should be noted that a later study found significant differences in outer retinal thickness across all regions, while choroidal thickness differed in most areas except superior and nasal.[21]

The macula was measured in four studies. Significant differences were found by Zou et al[23] in the total macular volume (p = .005) and macular retinal thickness (p = .008), but not in central macular thickness. Batum et al[27] detected significance in five out of nine areas of the macula measured- fovea, nasal inner quadrant, superior inner quadrant, nasal outer quadrant and superior outer quadrant. Similarly, Sung et al[18] found statistical significance in central foveal thickness (p = .016), average macular thickness (p = .013) and overall macular cube volume (p = .034). However, Tuncer et al[28] and Mello et al[20] detected no

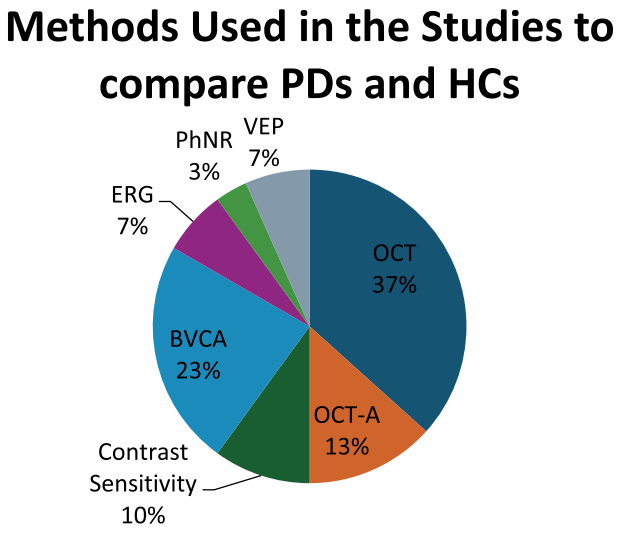

Figure 2. Pie chart showing methods used within studies included in this systematic review.

statistical significance in foveal thickness nor macular volume, contradicting findings found by the other papers included within this study.

Contrast sensitivity

Three studies included information of the difference between PD and HCs using contrast sensitivity. Zhang et al[21] and Hong et al[29] both used instruments that measure the contrast sensitivity at different special frequencies (See Table 8). The results of these studies showed statistical significance at 3, 6, 12 and 18 cpd in both studies, with Hong et al[29] reporting the same but with significance at 1.5 cpd ($p < .01$). Mello et al[20] used a Pelli-Robson chart to measure contrast sensitivity for both monocular and binocular tests, in which both demonstrated statistical significance.

Best corrected visual acuity

Table 8 shows the difference in best corrected visual acuity (BCVA) between PDs and HCs. In the studies that measured this, there was no statistical significance found.

Optical coherence tomography angiography (OCT-A)

Four studies used OCT-A to compare between PD patients and HCs.

The foveal avascular zone (FAZ) was measured by two studies. Zhou et al[30] and Zou et al[23] both measured the FAZ area and neither found any statistical significance between PDs and HCs. Zou et al[23] also measured the perimeter of the FAZ, which showed no statistical significance, and FAZ circularity, which showed statistical significance of both groups ($p = .037$).

Four studies measured the vessel density. Zhang et al[21] measured 1 mm, 3 mm and 6 mm circles at the macular and also the superior, temporal, inferior and nasal quadrant, with significance in all except temporal and nasal quadrants. Zhang et al[25] further analyzed superficial and deep flow densities with flow ratios across the same parameters. Statistical significance was shown in most of these areas, with no significance in the temporal superficial flow density, 1 mm circle and temporal superficial flow ratios, nasal deep flow density, and 1 mm deep circle flow ratios. Similarly, Zhou et al[30] reported significant microvascular density in all quadrants (nasal, temporal, superior, and inferior) and zones (1 mm, 1–3 mm, 3–6 mm). Zou et al[23] found significance in the same sections, including the full 6 mm area.

Vessel length density (VLD) was measured by Zou et al[23] in the central (1 mm diameter), inner

Table 6. Summary of study results measuring pRNFL.

Study ID	Type of OCT	Average pRNFL (*p*-value)	Superior pRNFL (*p*-value)	Inferior pRNFL (*p*-value)	Temporal pRNFL (*p*-value)	Nasal pRNFL (*p*-value)
2	SD-OCT	.001	.091	.015	.462	<.001
4	SD-OCT	.566	.947	.924	.842	.1
5 (RE)	SD-OCT	.838	.697	.826	.825	.606
5 (LE)	SD-OCT	.632	.642	.918	.202	.973
7	SD-OCT	.358	.98	.695	.002	.583
8	time domain OCT	.711	.225	.494	.378	.391
10 (RE)	SD-OCT	.003	<.001	<.001	–	–
10 (LE)	SD-OCT	<.001	<.001	<.001	–	–
11 (RE)	SD-OCT	–	.499	.686	.107	.119
11 (LE)	SD-OCT	–	.8	.265	.939	.766
12	SD-OCT	<.0001	<.0001	.003	.02	.72

Table 7. Summary of *p* values measuring GCC and GCIPL.

		GCC				GCIPL									
study ID	OCT	average	min	superior	inferior	average	1 mm	3 mm	6 mm	Supero-nasal	superior	Supero-temporal	Infero-temporal	inferior	Infero-nasal
2	SD-OCT	**<0.001**	**<0.001**	–	–	–	–	–	–	**0.007**	**0.048**	**0.004**	**0.002**	**0.001**	**<0.001**
3	SS-OCT	–	–	–	–	–	0.695	0.869	0.109	–	–	–	–	–	–
7	SD-OCT (ROC)	0.072	–	–	–	**0.046**	–	–	–	–	–	–	–	–	–
8	time domain OCT	**<0.001**	**<0.001**	–	–	–	–	–	–	–	–	–	–	–	–
10 (RE)	SD-OCT	**0.02**	–	–	–	–	–	–	–	–	–	–	–	–	–
10 (LE)	SD-OCT	0.09	–	–	–	–	–	–	–	–	–	–	–	–	–
11 (RE)	SD-OCT	–	–	0.384	0.259	–	–	–	–	–	–	–	–	–	–
11 (LE)	SD-OCT	–	–	0.409	0.361	–	–	–	–	–	–	–	–	–	–

$p < .001$, $p < .001$.

(1–3 mm diameter), outer (3–6 mm diameter) and full (6 mm diameter) areas. All sections, except for the outer area, demonstrated statistical significance.

Zhang et al[21] measured the choroidal vessel index in various areas (0-1 mm, 0-3 mm, 0-6 mm diameters and superior, temporal, inferior and nasal quadrant), with statistical significance found in most areas, other than the 0-1 mm diameter and nasal quadrant. The same study measured the choroidal vascular volume is the same areas, which demonstrated statistical significance in the 0-6 mm diameter and the superior, temporal, and inferior quadrants.

Pattern visual evoked potential (PVEP)

Three studies in this review included information on PVEP. Zhou et al[30], Tuncer et al[28] and Batum et al[27] all measured P100 latency, with Zhou et al[30] and Batum et al[27] finding statistical significance, whilst Tuncer et al[28] reported none. Zhou et al[30] also measured P100 amplitude which found no statistical significance. Tuncer et al[28] and Batum et al[27] also measured N75 latency, both finding no statistical significance. Additionally, they measured N135 in both eyes and N145 latency, respectively, with no statistical significance reported for all measurements. However, Batum et al[27] did find the N75-P100 amplitude statistically significant ($p < .001$).

Electroretinography (ERG)

Two studies included ERG recording as a way of distinguishing between PDs and HCs. Mello et al[20] found statistical significance in the photopic response of b-wave amplitude ($p = .002$) and the photopic negative response of the ERG (PhNR) ($p = .025$). Elanwar et al[24] found that in both dark and light adapted ERGs, both a and b wave latency showed statistical significance (all $p < .001$) between the PD and HCs. No statistical significance was found in any of the other electroretinography results in this study.

Disease duration and severity

A number of studies included within this review assessed the role of biomarkers in the progression

Table 8. Summary of study results measuring BCVA and contrast sensitivity.

			CPD						
Study ID	BCVA *p*-value	Test used	1.5	3	6	12	18	Pelli-Robson Monocular	Pelli-Robson Binocular
1	.591	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2	.136	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
3	1	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
4	.329	Pelli-Robson	n/a	n/a	n/a	n/a	n/a	**<0.001**	**<0.001**
7	.388	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
8	.798	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
9	.3191	CSV-1000E instrument	n/a	**<0.001**	**<0.001**	**<0.001**	**<0.001**	n/a	n/a
13	n/a	Vistech Vision Contrast Test System 6500	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**	n/a	n/a

of PD. Elanwar et al[24] established no correlation between OCT measurements and either the H&Y scale or UPDRS score. Similarly, Tuncer et al[28], Zhou et al[30] and Sung et al[18] found no connection between UPDRS scores and their measured biomarkers – mean VEP values, P100 (latency and amplitude) and retinal thickness, respectively.

However, there were a number of studies that established significant correlations: Sung et al[18] linked the H&Y scale to superior GCIPL thickness. Yildiz et al[19] found UPDRS inversely correlated with left-eye superior GCC, specifically in the superior, inferior and total quadrants. Shafiei et al[26] associated UPDRS score with total and temporal RNFL. Elkhatib et al[22] associated superior RNFL thickness to both duration of the illness and H&Y scale.

Discussion

PD is characterized by the aggregation of misfolded alpha-synuclein, which results in the dysfunction and ultimately, death, of dopaminergic neurons within the substantia nigra pars compacta.[5] This neuronal loss disrupts modulation of the fronto-thalamostriatal circuit, which contributes to visual perception deficits in patients.[31] In addition, however, PD can lead to dopaminergic neurodegeneration in the retina, retinal nerve fiber layer thinning, and hence changes in retinal blood flow, which can potentially contribute to visual disturbance in PD patients.

Given the retina is an embryological extension of the central nervous system, it has been postulated as a potential site of early detection of PD.[32] Multiple techniques could be used to assess the retina, some of which are outlined above. Taking these into consideration, this systematic literature review aimed to evaluate if the retina could be used as a biomarker in PD.

Eleven studies used OCT to measure various structures within the retina. Whilst there were some studies which measured the same structure in the same way, the majority only had one study assessing a particular feature or layer of the retina. This made it difficult to make any definitive conclusions about using this measure as a biomarker.

There were several parameters that showed no statistical significance: pRNFL showed no consensus, and the nine studies measuring BCVA – two studies utilizing OCT-A measuring FAZ and the one study that measured retinal vessel diameter – showed no statistical significance.

Conversely, three studies established significance with PVEP-P100 latency. One study reported significant photopic b-wave and another for PhNR differences, while another found significant dark- and light-adapted ERG a- and b-wave latency changes.

Contrast sensitivity was found to be statistically significant across all methods (the Pelli-Robson and charts using sine-wave gratings) in all three studies. All three OCT-A studies of macular vessel density – across varying diameters – showed significant differences, though only the superior quadrant reached unanimous significance.

Overall, there was no complete agreement; however, a decrease in the superior quadrant of the RNFL/GCC seems to be linked with duration of PD.

Limitations

This is the first systematic literature review that attempts to cover all aspects of the retina as a biomarker for PD. Within this systematic literature review, there are several limitations. The English-only inclusion may have omitted relevant non-English studies, while the 5-year publication window could exclude older significant findings. Heterogeneous retinal parameters complicated cross-study comparisons, and small sample sizes – often including younger patients – limit generalizability. Furthermore, comorbidities of participants may have also further confound retinal findings presented within this review, such as hypertension and diabetes mellitus. Additionally, this study's younger participant age range- 52.5–69 years whilst average onset of PD has been described to be around 70 years – may limit the generalizability of the findings to older PD populations.[33]

It should be acknowledged that published studies are more likely to include results of statistical significance. Unpublished works may disagree with some the results found in this review.

Another possible weakness may be the inclusion criteria for this review, which were to only include studies which used the UK Brain Bank criteria for PD (criteria to ensure standardization of diagnosis). This approach may have led to a selective sampling of papers, not fully capturing the breadth of known studies on the topic.

Moreover, the exclusion of 46 papers due to full text unavailability may have increased selection bias, which may have indirectly impacted on the views presented in this paper.

Additionally, no meta-analysis was conducted due to the heterogeneity and breadth of techniques investigated.

Results in context

There are currently no other systematic literature reviews that we know of that cover the use of contrast sensitivity, vessel length density, PVEP or ERG as biomarkers for PD.

In this systematic literature review, contrast sensitivity was found to be a useful tool for differentiating between patients with and without PD, a result that is in line with findings of impaired contrast sensitivity in PD established by Weil et al[6]. It has been postulated that impaired contrast sensitivity is associated with retinal ganglion cell layer thinning.[34]

Systematic reviews and meta-analyses have reported statistically significant RNFL thinning in PD, with significant changes particularly in the superior and inferior quadrants.[35,36] Huang et al[36] also found a significant decrease in combined thickness of the inner plexiform and ganglion cell layer for those with PD. Atypical PD also showed significant RNFL thinning when compared to HCs or typical PD patients.[37] A specific pattern of RNFL thinning- "inferotemporal thinning most and nasal quadrant thinning least," has also been reported by Huang et al[38] Similarly, a review by Zhou et al[30] also reports statistical significance in RNFL, noting it across "all quadrants of the pRNFL, macular foveal thickness, all outer sector thickness at the macula, macular volume and macular ganglion cell complex thickness." However, this did not correspond with the results of this review, which revealed no consensus. It should be noted that only one study was included for assessing this parameter for comparison.

Beyond RNFL measurements, it has also been reported by Deng et al[35] that statistical significance was present in vessel density in the superficial retinal capillary plexus, although none in the deep retinal capillary plexus. Katsimpris et al[39] also used OCT-A to measure the vessel density, particularly in the "whole superficial vascular plexus (SVP), foveal SVP, parafoveal SVP and foveal avascular zone." However, they only found statistical significance when comparing the whole superficial vascular plexus. This matched with the results found in this review, which reveals variations in the statistical significance of vessel density depending on the depth and position.

Future scope

The use of contrast sensitivity, PVEP, ERG, and vessel density have all produced results which show strong statistical significance. While this reveals promising associations, future studies should aim to be conducted with unified designs including multimodal imaging to reduce variability and heterogeneity for further confirmation. Further studies should also aim to establish whether retinal biomarkers can reliably detect PD in its early or prodromal stages through prospective, longitudinal studies involving at-risk populations.

Since most retinal tests are noninvasive, and OCT is widely available in optometry practices across the UK, using the retina as a biomarker for PD could be efficient and cost-effective. It may have a role in helping with early diagnosis in community optometry, referral to hospital services for assessment and definitive diagnosis, monitoring disease progression prior to starting any therapeutic intervention or in future monitoring progression during treatment.[16]

Conclusion

In conclusion, this systematic review demonstrates the potential of using the retina as a biomarker for PD, with statistical significance found in the measurements of different retinal functions and structure (contrast sensitivity, visual evoked potential, electroretinography and vessel density). Further studies with unified designs are required for comparison, and more studies that separately analyze retinal changes in relation to disease stages would be beneficial in helping establish clear associations between retinal changes and disease progression.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Ethical approval

Ethics approval was not required for this systematic review.

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