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REVIEW

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Optical coherence tomography and optical coherence tomography angiography in multiple sclerosis

Adel Hassanein Elsayed Gad[1], Nouran Alaa Abd El Hamid[1], Randa Mohamed Abdel-Moneim El-Mofty[2] and Lobna Ahmed Talaat El Ghoneimy[1*]

Abstract

Background In multiple sclerosis (MS), optical coherence tomography (OCT) has become a sensitive tool for evaluating retinal and optic nerve diseases. Optical coherence tomography angiography (OCT-A) is a novel technique that can assess the density of retinal vascular networks. Vascular changes caused by MS play a chief role in the development and progression of the MS lesions giving the idea and goal of this study which aimed to assess vascular anomalies in MS using OCT and OCT-A, determine their relationship to clinical characteristics, and determine if vasculopathy may play a role in MS causation. This research also looked at whether the retinal vasculature can be used as a biomarker for neurodegeneration and disease progression. A total of 30 MS patients with and without history of optic neuritis (ON), as well as 10 healthy volunteers, were included in the study. OCT-A and spectral domain. (SD-OCT) were performed on all of them. The data included clinical history, the Expanded Disability Status Scale (EDSS), illness duration, visual function assessment, and investigations.

Results When comparing MS patients to controls, OCT-A revealed a drop in the arterial density in the eyes of MS patients. When compared to control eyes, all SD-OCT and OCT-A parameters indicated a statistically significant drop in MS eyes (with and without ON). Results showed a direct association ($p = 0.001$) between vascular density metrics and SD-OCT parameters ($p \leq 0.001$).

Conclusions Results showed a reduction in retinal vascular density (VD) in MS patients. The clinical link between VD and SD-OCT characteristics is highlighted, implying that OCT-A may be a useful marker of illness and impairment in MS.

Keywords Multiple sclerosis, Retinal vascular anomalies, Optical coherence tomography angiography

Background

In MS, the optic nerve affection and the loss of retinal ganglion cells (RGC) have been documented by OCT which revealed significant weakening of the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) despite the absence of myelin. In MS, inflammatory demyelination causes injury to the optic nerve axons and loss of RGC that can be seen in the presence or absence of clinical ON, this might be due to subclinical optic nerve irritation or retrograde degeneration [1].

Optical coherence tomography (OCT), which is a non-invasive, quick, and relatively cheap and easy to use technique that uses near-infrared light to create images of the retina. The images produced via OCT are of very high resolution and highly reproducible. Assessment of the

*Correspondence:
Lobna Ahmed Talaat El Ghoneimy
lobna85@hotmail.com
[1] Neurology Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[2] Ophthalmology Department, Faculty of Medicine, Cairo University, Cairo, Egypt

RNFL and GCL using OCT potentially allows us to assess axonal and neuronal degeneration [2].

OCT has been utilized to study the pathophysiology of MS; correlation between OCT findings and MS, both with ON (MSON) and without preceding ON (MSNON), has been studied, where the thickness of both the RNFL and GCL is statistically significantly decreased [3].

OCT-A is complementary to OCT in neurology. OCTA captures the location of blood vessels by detecting blood mobility utilizing intrinsic signals. Despite its low sensitivity to leakage and restricted field of vision, OCT-A offers the potential to advance our understanding of vascular ocular physiology and pathology [4].

In 2016, Roisman and colleagues demonstrated using OCT-A, a lower optic nerve head (ONH) perfusion in individuals with MS, particularly those with a history of ON. They emphasized that combining OCT-A with other OCT parameters can increase the diagnostic accuracy of detecting MS in eyes with ON [5].

In 2015, Kuehlewein and colleagues found a reduced VD in both the superficial vascular plexus (SVP) and deep vascular plexus (DVP) in the perifoveal area in MS patients which can be linked to volume reduction of the corresponding retinal layers compared to healthy control group; they found an increase in choriocapillaris density that was explained by the inflammation within the previous 24 months; they also found a correlation between the reduction in both SVP and DVP capillary density shown in OCTA and retinal neuroaxonal thinning seen by OCT [6].

Methods

The current prospective cross-sectional comparative study was conducted at a tertiary referral center. The study included 30 patients with relapsing remitting multiple sclerosis (RRMS), diagnosed according to the 2017 criteria of diagnosis of MS [7].The control group included ten age matched healthy volunteers. The study protocol was approved by the institutional review board of Faculty of Medicine, Cairo University (MS-1902-2019). Informed consent to participate in the study was obtained from all participants.

The participants were divided into two groups: **Group 1** included 30 patients with RRMS who were diagnosed using the 2017 McDonald criteria. The eyes of those patients were then subdivided into two groups based on their history of ON; **Group 1a**: eyes with history of ON ($n=25$) and **Group 1b**: eyes without history of ON ($n=35$). **Group 2** included 10 healthy volunteers (control group).

Participants of both groups had undergone thorough neurological and ophthalmological examinations along with disability evaluations using the expanded disability status scale (EDSS).

SD-OCT and OCT-A were performed by ophthalmologists at Ophthalmic Diagnostic Laser Unit (ODLU), using an Optovue RTVue XR Avanti TM Optical Coherence Tomography equipment (Optovu, inc. Fremont, CA, USA).

For the OCT, two protocols were used in both eyes; the macular map allowing fast macular scan for ganglion cell complex (GCC) measurements and the peripapillary RNFL protocol measuring RNFL thickness around the ONH.

In OCT-A, the macular capillary network was visualized by performing a 6×6 mm scan over the macular region. VD was defined as the percentage area occupied by the large vessels and microvasculature in the analyzed region. According to the early treatment diabetic retinopathy study, OCT software applied to all angiograms using a grid centered on fovea dividing the macular region into foveal and parafoveal areas and further dividing the parafovea into superior and inferior hemispheres, temporal, nasal, inferior and superior sections. For each eye analyzed, the software automatically calculated VD in whole scan area and in all sections of applied grid. Poor-quality images were excluded from the analysis.

SPSS (statistical package for social sciences) version 18.0 was used for data management and data analysis. Quantitative data were described using mean, standard deviation and median with range when necessary. Qualitative data were described using numbers and percentage.

For comparing mean values of two independent groups, parametric and non-parametric *t* test were used. For comparing mean values of more than two independent groups one-way ANOVA (analysis of variance) and Kruskal Wallis ANOVA were used. However, for comparing the mean values of 2 dependent groups, paired *t* test was used. *p* value was used to represent significance and its significant value is when ≤ 0.05.

Results

This study included 40 participants, Group 1: thirty patients diagnosed with clinically definite RRMS; it included 19 patients with history of ON and 11 with no history of ON. Group 1 (60 eyes) was further subdivided into two subgroups: Group 1a: 25 eyes with ON (41.7%) and Group 1b: 35 eyes without ON (58.3%). Group 2: ten healthy volunteers.

The EDSS score for both patients with and without ON ranged from 2 to 6 with a median of 3.5.

When comparing SD-OCT findings, there was a significant difference between Group 1 and Group 2, where all

the RNFL and GCC values in Group 1 were considerably lower than in Group 2 ($p=0.001$), see Table 1, Fig. 1.

There was significant difference between SD-OCT findings between eyes of Group1a and Group 1b and those of Group 2 (p value $=0.001$), see Table 2.

Table 1 Comparison of SD-OCT parameters between all patients (group 1) and controls (group 2)

SD-OCT parameters	All patients (mean ± SD)	Controls (mean ± SD)	Patients vs. controls (p value)
Average RNFL(μm)	87.4 ± 11.7	104.3 ± 8.3	< 0.001*
Superior RNFL(μm)	89.1 ± 12.3	104.2 ± 8.1	< 0.001*
Inferior RNFL(μm)	85.7 ± 12	103.1 ± 9	< 0.001*
Average GCC(μm)	85.7 ± 12.2	101.8 ± 4.4	< 0.001*
Superior GCC(μm)	84.9 ± 12	101.2 ± 4.7	< 0.001*
Inferior GCC(μm)	86.4 ± 12.7	101.8 ± 4.9	< 0.001*
FLV (%)	3.8 ± 3.1	0.68 ± 0.24	< 0.001*
GLV (%)	11.1 ± 9.9	1.2 ± 0.5	< 0.001*

SD-OCT spectral domain optical coherence tomography, *SD* standard deviation, *RNFL* retinal nerve fiber layer, *GCC* ganglion cell complex, *FLV* focal loss volume, *GLV* global loss volume

*Significant

There was a significant lower SVP density percentage in OCT-A between eyes of Group 1 and Group 2 in whole scan and in all grid sectors (fovea and parafovea). ($p \leq 0.001$), see (Fig. 2).

A significant lower DVP density percentage in eyes of Group 1 when compared to Group 2 in whole scan, superior hemisphere, superior and inferior sectors. On the other hand, the fovea and the rest of grid sectors showed no statistical significance between the two groups, see (Table 3)

There was a lower SVP VD percentage, by OCTA-, in Group 1a compared to Group 2 and also between eyes of Group 1b compared to Group 2. The difference was statistically significant both in whole scan and in all grid sectors (fovea and parafovea). ($p = < 0.001$).

There was a statistically significant lower DVP density percentage, by OCT-A, in eyes of Group 1a than that of Group 2 in whole scan superior hemisphere, superior and inferior sectors. However, the fovea and the rest of grid sectors showed no statistical significance between eyes of Group1a and Group2. The comparison between eyes of Group1b and Group 2 showed a statistically significant findings only in the whole scan.

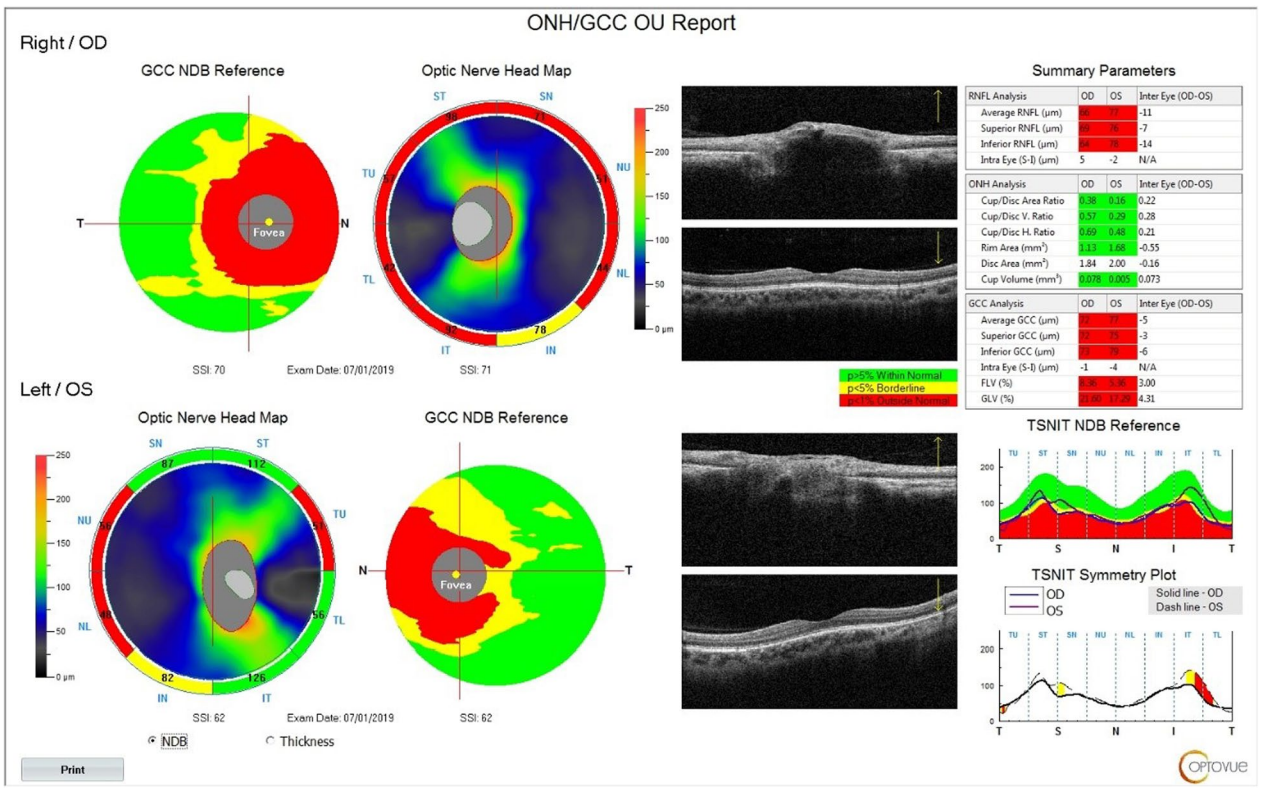

Fig. 1 Average retinal nerve fiber layer and average Ganglion cell complex are markedly affected in the right eye with history of optic neuritis and also the left eye which has no history of optic neuritis

Table 2 Comparison of SD-OCT parameters between eyes with optic neuritis (ON) (group 1a), eyes without ON (group 1b) and controls (group 2)

SD-OCT parameters	Eyes with ON (mean ± SD)	Eyes without ON (mean ± SD)	Controls (mean ± SD)	Eyes with ON vs. controls (*p* value)	Eyes without ON vs. controls (*p* value)
Average RNFL (μm)	84.60 ± 9.8	89.51 ± 12.75	104.3 ± 8.3	< 0.001*	< 0.001*
Superior RNFL (μm)	85.68 ± 10	91.60 ± 13.3	104.2 ± 8.1	< 0.001*	< 0.001*
Inferior RNFL (μm)	83.44 ± 10.5	87.43 ± 12.96	103.1 ± 9	< 0.001*	< 0.001*
Average GCC (μm)	81.73 ± 12.1	88.57 ± 11.69	101.8 ± 4.4	< 0.001*	< 0.001*
Superior GCC (μm)	80.85 ± 11.7	87.91 ± 11.56	101.2 ± 4.7	< 0.001*	< 0.001*
Inferior GCC (μm)	82.83 ± 12.64	89.03 ± 12.34	101.8 ± 4.9	< 0.001*	< 0.001*
FLV (%)	4.74 ± 3.56	3.14 ± 2.73	0.68 ± 0.24	0.001*	0.001*
GLV (%)	14.38 ± 10.85	8.81 ± 8.6	1.2 ± 0.5	< 0.001*	< 0.001*

SD-OCT spectral domain optical coherence tomography, *SD* standard deviation, *RNFL* retinal nerve fiber layer, *GCC* ganglion cell complex, *FLV* focal loss volume, *GLV* global loss volume

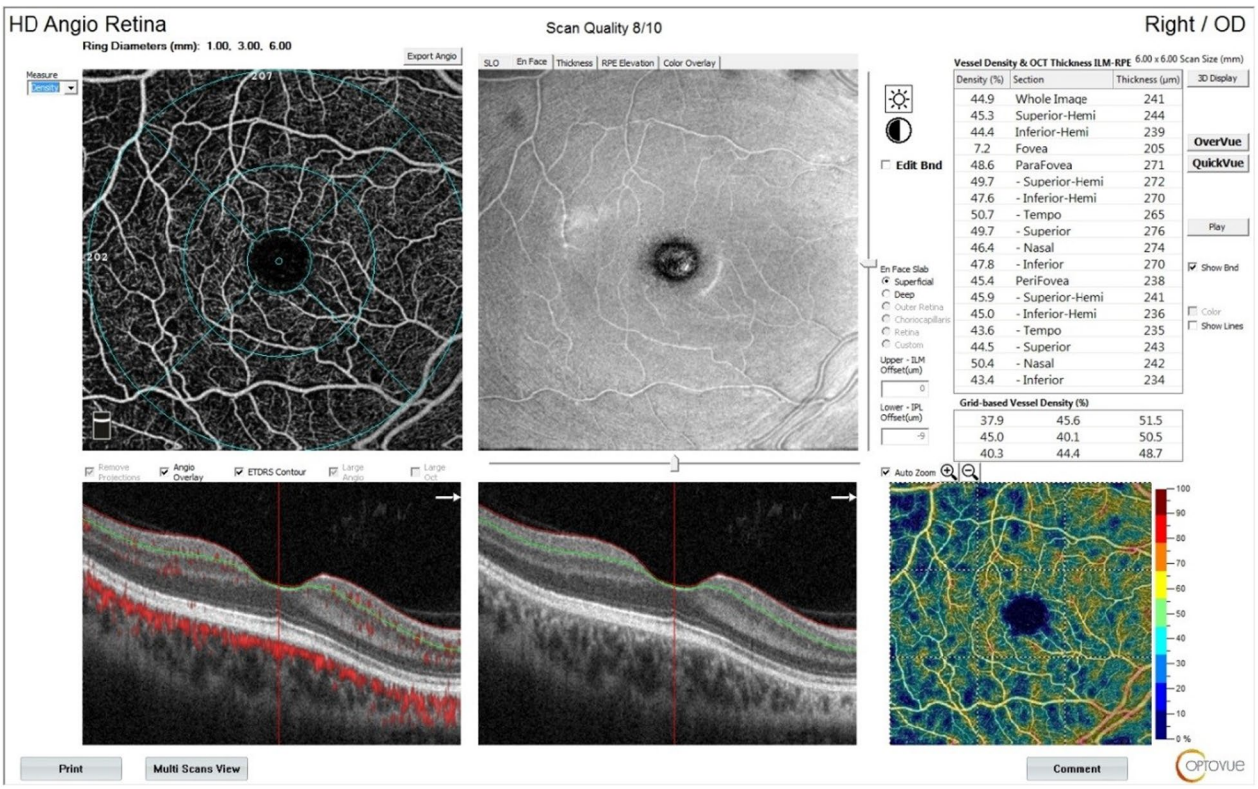

Fig. 2 OCT-A shows reduced superficial vascular plexus density in the right eye

There was a significant negative correlation between EDSS score and all SD-OCT parameters except for the focal loss volume (FLV).

Also, a significant negative correlation between visual acuity (VA) and all SD-OCT parameters and between VA and both SVP and DVP density in all OCT-A grid sectors.

Our study correlated the patients' age at onset of MS and disease duration with both SD-OCT parameters and VD detected by OCT-A in the SVP and DVP. A significant negative correlation was found between duration of MS and all SD-OCT parameters. None of the other correlations were significant.

Table 3 Comparison between deep vascular plexus density in patients and controls

OCT-A grid sectors	All patients (mean ± SD)	Controls (mean ± SD)	Patients vs. controls (*p* value)
Whole image	52.5 ± 6.7	58.4 ± 3.5	**< 0.001***
Fovea	33.5 ± 8.17	37.6 ± 4.7	0.067
Parafovea	58 ± 4.9	60.8 ± 1.3	0.066
Superior hemisphere	58.1 ± 5.19	61.5 ± 1.6	**0.023***
Inferior hemisphere	57.9 ± 4.7	60.6 ± 1.69	0.066
Temporal sector	58.9 ± 4.36	60.6 ± 0.67	0.294
Superior sector	57.2 ± 6.13	61.6 ± 1.73	**0.017***
Nasal sector	59 ± 4.4	60.7 ± 1.6	0.283
Inferior sector	57.1 ± 5.7	60.4 ± 1.99	**0.018***

OCT-A optical coherence tomography angiography, *SD* standard deviation, *significant

There was a statistically significant positive correlation between all SD-OCT parameters and SVP density detected by OCT-A in all grid sectors except for FLV % and global loss volume (GLV) % which showed a negative correlation with VD.

Finally, a statistically significant positive correlation between all SD-OCT parameters and DVP density detected by OCT-A in all grid sectors except for FLV % and GLV % which showed a negative correlation with VD.

Discussion

MS is a demyelinating inflammatory disorder of the CNS associated with a progressive neurodegeneration [8].

ON represents the initial manifestation in about 25% of MS patients and occurring in around 50% of patients at some point of the disease course [9].

The goal of our study was to compare retinal VD between MS patients and healthy volunteers, and to explore whether vasculopathy could be part of MS pathogenesis. Our study also aimed at correlating between the nerve thickness detected by OCT and the VD detected by OCT-A to provide a possibility that the retinal vasculature may be a biomarker of neurodegeneration and disease progression. This study included 30 RRMS patients (60 eyes) and 10 healthy volunteers (20 eyes). The MS group was further subdivided into two subgroups, MS with ON (25 eyes) and MS without history of ON (35 eyes). Our results showed that SD-OCT parameters were significantly different between the 2 groups of MS and control. We found that all RNFL and GCC parameters were significantly lower in MS group than in control group ($p = < 0.001$).

Many previous studies reported a similar significant finding in patients when compared to control.

Lanzillo and colleagues in 2018 carried a study, using SD-OCT, on a total of 50 MS patients with and without history of ON and 46 healthy control. The study revealed that all GCC and RNFL parameters were lower in patients than in controls [8].

Khalil and colleagues in 2017 carried a similar study on 68 MS patients and 23 healthy controls, they found that the thickness of RNFL and GCC were significantly lower in MS eyes when compared to controls. Progressive axonal loss could explain the RNFL thinning found in eyes of MS patients with and without a history of ON [10].

In a study by Soufi and colleagues in 2015, MS patients' eyes showed statistically significantly lower values of the total RNFL than the Healthy Control eyes [11].

Pillay and colleagues showed in their study in 2018 that the mean values of average RNFL thickness and values in superior, temporal, and inferior quadrant were significantly reduced when compared to control groups. As well as overall mean values of average GCL-inner plexiform layer thickness and values in superior, superonasal, superotemporal, inferonasal, and inferotemporal quadrant were significantly reduced in all groups except Fellow eye of ON group when compared to control group. In addition, in the inferior and superonasal quadrant, thickness was reduced even in Fellow eye of ON group [12].

In our study, when comparing between SD-OCT parameters of MS patients with ON and those without ON, there was no significant difference in all RNFL and GCC parameters between the two subgroups; there was a statistically significant negative correlation between SD-OCT parameters and both EDSS ($R = -0.377$, $P = 0.003$) and disease duration ($R = -0.314$, $P = 0.014$).

Most prior studies found a similar significant correlation. Khalil and colleagues in 2017 found a statistically significant negative correlation between the average RNFL thickness of MS eyes and disease duration; the longer the disease duration, the thinner the RNFL, this could be explained by with longer disease duration there is more axonal degeneration. They also found a statistical negative correlation between the average RNFL thickness and neurological disability quantified by EDSS; when the EDSS score increased the RNFL thickness decreased [10].

Another study by Garcia-Martin and colleagues in 2014 showed that the retinal nerve fiber layer and ganglion cell layer thicknesses were inversely correlated with the functional disability score in patients with MS. The ganglion cell layer and inner plexiform layer thicknesses could predict axonal damage in patients with MS [13].

Also, Soufi and colleagues in 2015, studied 62 MS eyes with and without ON, they found a negative correlation

between the total RNFL thickness and both EDSS and disease duration [11].

Our study also showed a significant correlation between VA and all SD-OCT parameters.

This was similar to the studies done by Soufi and colleagues in 2015 [11] and Siepman and colleagues in 2010 [14] who proved that reduction in RNFL thickness was associated with a decrease in VA.

In our study we used OCT-A to measure retinal SVP and DVP densities. We found that there was a lower SVP density percentage in eyes of RRMS when compared to control group; this difference was statistically significant in the whole scan and in all grid sectors (fovea and parafovea). There was also a strong statistical significance when comparing eyes with ON to controls and eyes without ON to controls.

A study by Farci and colleagues in 2020 showed a reduction of retinal perfusion in a significant portion of MS patients independently if they had a previous history of optic nerve inflammation or not on performing an OCT-A at the optic nerve head level and at the macular region [15].

Our study was similar to the study by Murphy and colleagues in 2019 [16] conducted on 42 MS eyes and 26 healthy control eyes; the results showed that SVP density was lower in MSON and MSNON, when compared to healthy controls.

Those findings were also similar to results by Lanzillo and colleagues in 2018 [8] who found a lower SVP density in MS eyes with and without history of ON when compared to control group.

In 2019, Murphy and colleagues had a potential explanation as vascular abnormalities in the retina were not just a transient effect, but represented a process possibly contributing in the pathophysiology of MS [16].

In our study, there was no significant difference between SVP density between eyes with ON and eyes without ON.

This was concordant with the results of Lanzillo and colleagues in 2018 [8], where there were no statistically significant differences found regarding OCT-A measurements, except for VD in inferior sector.

On the contrary, Murphy and colleagues in 2019 revealed significant reductions in SVP density in MSON eyes when compared to MSNON eyes. It was explained as ON could cause more inflammation, neurodegeneration and accordingly more decreased VD [16].

In our study, regarding DVP density, when comparing eyes with RRMS to the control group, there was lower DVP density percentage in eyes of RRMS which was statistically significant in whole scan, superior hemisphere, superior and inferior sectors. On the other hand, the fovea and the rest of grid sectors showed no statistically significant difference between the 2 groups. Again, when comparing eyes with ON to the control group, there was a statistically significant difference in the whole scan, superior hemisphere, superior and inferior sectors. However, when comparing eyes without ON to control, there was only statistical significance in the whole scan. When we compared the density of DVP in eyes with ON and eyes without ON, we found no statistical significance in any of the grid sectors.

In the study of Murphy and colleagues in 2019, the results showed no difference in the mean DVP density between MS eyes and those of control group, or between the MSON eyes when compared to MSNON eyes [16]. The study proposed two theories to explain the variation between SVP and DVP; the first was that the DVP is only supplied by anastomoses from the SVP which makes the vessels less prominent in the DVP. The second hypothesis stated that SVP supplies RNFL, GCC, and inner plexiform layer, while DVP supplies inner nuclear layer (INL) and outer plexiform layer (OPL). MS causes atrophy of the inner retinal layers (RNFL and GCC) but not to INL and outer retinal layers [17].

Consequently, this variable degree of neurodegeneration among the retinal layers in MS patients explains why SVP density is affected unlike DVP. The study emphasized that those two theories need further research.

A review by Mihai and colleagues in 2023 showed that the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) were significantly lower in MS patients compared to controls, and correlated with clinical and paraclinical variables, such as visual function, disability, and magnetic resonance imaging (MRI). The superficial capillary plexus (SCP) was the best OCT-A microvasculature parameter for the detection of MS. The reduced retinal vessel density (VD) was correlated with the disability in MS [18].

Our study found a significant correlation between VA and VD of both SVP and DVP. This was similar to the results of the study of Murphy and colleagues in 2019 [16] who stated that lower SVP densities in MS patients are associated with worse visual function. The study stated that those findings were similar to collective studies done with SD-OCT. This proves that the affection of the retinal structure in patients with MS also affects the retinal function and results in decreased visual function. One important finding of our study, is the presence of strong significant correlation between all SD-OCT parameters and the densities of retinal vessels of both the SVP and DVP in all OCT-A grid sectors.

Conclusion

In conclusion, this study proved the significant reduction in vascular plexus density between MS eyes and controls. It also proved that the density decreases in correlation with the nerve thickness. Accordingly, our study suggests that OCT-A could increase the insight into understanding the pathophysiology of MS and it could be a good marker of disease and of disability of the disease.

Our study had several limitations; the small sample size, the study population included RRMS subtype and did not include progressive MS types and finally the study population showed relatively low EDSS values. Thus, it remains to be determined whether similar findings also apply for MS patients with longer standing disease and more severe disability.

Finally, we only analyzed associations of OCT-A measures with patients in remission.

So, it is necessary to correlate OCT-A measures with disease activity.

Abbreviations

DVP	Deep vascular plexus
EDSS	Expanded disability status scale
FLV	Focal loss volume
GCL	Ganglion cell layer
MS	Multiple sclerosis
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography angiography
ON	Optic neuritis
ONH	Optic nerve head
RGC	Retinal ganglion cells
RNFL	Retinal nerve fiber layer
RRMS	Relapsing remitting multiple sclerosis
SD	Spectral domain
SVP	Superficial vascular plexus
VD	Vascular density

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Author contributions

AH: research idea, data analysis, manuscript reviewing, NA: data acquisition, data analysis, interpretation, writing, RM: research idea, manuscript reviewing, writing, LG: data interpretation manuscript writing and reviewing.

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Availability of data and materials

All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Faculty of Medicine, Cairo University (MS-1902–2019).
All participants signed an informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

No conflict to disclose.

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