Multiple sclerosis (MS) is a chronic complex neurodegenerative disease that attacks the central nervous system and mostly has autoimmune nature.[1] The main pathological feature of MS is the periventricular inflammatory lesions with a subsequent formation of demyelinating plaques.[2] Earlier in the disease, axons are not affected followed by irreversible axonal damage and finally neurological insults occur.[3] Relapsing-remitting multiple sclerosis (RRMS) is the most common presentation of MS, representing about 85% of MS patients. It is characterized by relapses or exacerbations followed by periods of partial or total inactivity of the disease that are called remissions.[4] The activity of the disease can be assessed by the expanded disability status scale (EDSS); it consists of 20 steps with 0.5 increment, 0 indicates normal, and 10 means death.[5] Optic neuritis (ON) may be the first presentation of MS in 20% of patients.[6,7] Furthermore, it may occur in about 50% of cases during the disease, so assessment of the conversion to MS is essential in these patients.[8]

Multiple studies reported that vascular abnormalities exist in patients with MS. Moreover, such vascular malformations are usually associated with progressive disability in MS patients.[9,10]

Optical coherence tomography (OCT) is an essential tool in the diagnosis of MS. It can detect structural abnormalities in MS patients in the form of thinning of the retinal nerve fiber layer (RNFL) and the retinal ganglion cell layer (GCL).[11] Recently OCT angiography (OCT-A) is a noninvasive technique that can assess vessel density and flow velocity in the optic disc and macula.[11,12]

The present study aims to evaluate the hemodynamic changes in the optic nerve in MS patients by OCT-A and correlates them with the structural damage detected by OCT.

Methods

This prospective noninterventional study included 30 eyes of clinically diagnosed (RRMS). Patients were recruited from inpatient and outpatient clinics from May 2019 to December 2019.

Three groups were included in the study, group (1): 10 eyes with MS with history of optic neuritis (MS+ON), group (2): 10 eyes with MS without any history of optic neuritis (MS-ON), and group (3) is the control group formed of 10 eyes of normal age/sex/refraction matched participants not suffering from any ocular or systemic disease.

Purpose: To evaluate optical coherence tomography angiography findings in patients with multiple sclerosis (MS). Methods: This prospective noninterventional study was conducted on 30 eyes of relapsing-remitting MS patients. Group (1) included 10 eyes with a history of optic neuritis (ON), group (2) included 10 eyes without any history of optic neuritis (MS-ON), and group (3) included 10 eyes of normal age/sex/refraction matched participants. Optical coherence tomography (OCT) and OCT-A (ZEISS Cirrus™ HD-OCT Model 4000 (Carl Zeiss-Meditec, Dublin, CA) of the optic disc were done for all patients. Results: The best-corrected visual acuity was diminished in MS cases, especially in patients with ON with P value <0.001. The retinal nerve fiber layer (RNFL) thickness showed a significant decrease in the average thickness and in all quadrants, notably the temporal quadrant in group 1 (P < 0.001). Ganglion cell layer thickness was diminished in average thickness and in all quadrants in both groups of MS, but only the first group showed statistical significance with P value <0.001). In respect to optic disc perfusion, Average, superficial, and deep vascular density index (AVDI, VDI 1, VDI 2) were statistically significantly lower in groups 1, 2 with (P-value < 0.001). Conclusion: Decreased vascular perfusion of the optic nerve in MS patients, especially in those with ON is strongly correlated with the damage of RNFL and ganglion cell layer detected by OCT.

Key words: Ganglion cell layer, multiple sclerosis, optic neuritis, optical coherence tomography, optical coherence tomography angiography, retinal nerve fiber layer, vascular density index
The study included patients diagnosed with RRMS of more than 18 years old diagnosed according to McDonald’s criteria 2017. In the first group of patients with MS with ON, we included only patients at least 3 months after resolution of the attack. The patients were recruited by cooperation between Neurology and Ophthalmology Department in Tanta University; once the case that fulfill the inclusion criteria was diagnosed in the Neurology department, data was sent to the Ophthalmology department to evaluate the case. The study did not include consecutive patients.

Patients with any media opacity as corneal opacity or dense cataract that interferes with the quality of imaging, patients with any other retinal disease as diabetic retinopathy, high myopia, retinal degeneration, and dystrophy, and patients diagnosed with any other causes of optic neuropathy like Table 1: RNFL thickness in all groups

| OCT RNFLT | Groups | ANOVA | TUKEY’S test | I&II | I&III | II&III |
|-----------|--------|-------|-------------|------|-------|-------|
| Superior  | Range  | 54-123| 99-133      | 108-120 | 6.176 | 0.006 | 0.015 | 0.013 | 0.999 |
|           | Means±SD | 92.30±23.10 | 113.00±12.08 | 113.30±4.92 | 5.519 | 0.010 | 0.021 | 0.020 | 0.999 |
| Inferior  | Range  | 52-125| 98-140      | 97-140  | 3.561 | 0.042 | 0.582 | 0.035 | 0.246 |
| Nasal     | Range  | 46-72 | 51-71       | 56-75   | 31.542| <0.001| <0.001| <0.001| 0.122 |
| Temporal  | Range  | 35-63 | 50-65       | 58-68   | 31.542| <0.001| <0.001| <0.001| 0.246 |
| Average   | Range  | 51-89 | 80-95       | 81-96   | 12.859| <0.001| <0.001| <0.001| 0.741 |
|           | Means±SD | 70.00±12.60 | 85.00±5.43 | 87.80±4.49 |

RNFLT: Retinal nerve fiber layer thickness, MS: Multiple sclerosis, ON: Optic neuritis.*: Significant

Table 2: GCL thickness in all patients

| OCT GCLT | Groups | ANOVA | TUKEY’S test | I&II | I&III | II&III |
|----------|--------|-------|-------------|------|-------|-------|
| Superior | Range  | 49-74 | 68-91       | 68-86 | 15.555| <0.001| <0.001| <0.001| 0.413 |
|          | Means±SD | 61.20±8.53 | 74.10±7.21 | 78.20±5.18 |
| Inferior | Range  | 49-70 | 61-83       | 72-83  | 23.658| <0.001| <0.001| <0.001| 0.487 |
| Nasal    | Range  | 44-69 | 66-84       | 70-89  | 34.812| <0.001| <0.001| <0.001| 0.439 |
| Temporal | Range  | 47-70 | 70-92       | 76-87  | 30.576| <0.001| <0.001| <0.001| 0.538 |
| Average  | Range  | 49-71 | 65-85       | 71-86  | 25.761| <0.001| <0.001| <0.001| 0.381 |
|          | Means±SD | 59.60±7.42 | 76.40±5.43 | 80.00±6.07 |

GCLT: Ganglion cell layer thickness, MS: Multiple sclerosis, ON: Optic neuritis *: Significant

Table 3: OCT-A of the optic disc in all cases in all levels (VDI 1, VDI 2, VDI 3, VDI 4, and average VDI)

| OCT_A ONH % | Groups | ANOVA | TUKEY’S test | I&II | I&III | II&III |
|-------------|--------|-------|-------------|------|-------|-------|
| VDI 1       | Range  | 48.17-55.75 | 50.43-64.95 | 60.85-68.91 | 46.171| <0.001| <0.001| <0.001| <0.001 |
|             | Means±SD | 51.60±2.58 | 57.1±4.54 | 65.84±2.42 |
| VDI 2       | Range  | 60.59-71.74 | 63.39-76.83 | 68.21-79.9 | 12.584| <0.001| <0.001| <0.001| 0.989 |
|             | Means±SD | 67.08±3.35 | 67.32±4.14 | 74.56±3.82 |
| VDI 3       | Range  | 3.7-13.92   | 7.48-16.79  | 8.26-16.21 | 0.820 | 0.451   | -     | -     | -    |
|             | Means±SD | 10.02±3.00 | 10.98±2.72 | 11.75±3.35 |
| VDI 4       | Range  | 48.69-56.67 | 50.34-66   | 52.82-60.73 | 1.168 | 0.326   | -     | -     | -    |
|             | Means±SD | 54.38±2.64 | 54.25±4.66 | 56.39±2.87 |
| AVDI %      | Range  | 41.51-47.66 | 44.74-52.72 | 49.97-55.08 | 22.070| <0.001| 0.184 | <0.001| <0.001 |
|             | Means±SD | 45.77±1.91 | 47.56±2.87 | 52.14±1.65 |

OCT-A: Optical coherence tomography angiography, MS: Multiple sclerosis, ON: Optic neuritis, VDI: Vascular density index, *: Significant
glaucoma, ischemic, and compressive optic neuropathy were excluded from the present study. Also, patients with other types of MS as progressive MS or patients with other demyelinating diseases like neuromyelitis optica or acute disseminating encephalomyelitis were excluded from the study. Also, patients with acute attacks of ON were not enrolled in this study as optic nerve head (ONH) edema will prevent the proper measurement of RNFL. Eyes with refraction with spherical equivalent less than -6.00 Dioptries and more than +2.00 Dioptries were excluded.

The neurological examination was done to evaluate the type and the severity of MS using the EDSS Score. A thorough ophthalmic evaluation was performed for all patients including the best-corrected visual acuity (BCVA) by Snellen chart that was converted to logMAR for statistical analysis, intraocular pressure assessment using applanation tonometry, slit-lamp examination of the anterior segment, retinal assessment by slit-lamp biomicroscopy using +78 D lens. OCT and OCT-A (ZEISS Cirrus™ HD-OCT Model 4000 (Carl Zeiss-Meditec, Dublin, CA) (which uses a superluminescent diode) were performed for all patients.

**Optical coherence tomography (OCT)**

OCT of the optic disc: Circular profile 3.4 mm centred on the optic disc that was manually adjusted to the optic disc margins was taken to assess the RNFL thickness. The thickness of the mean peripapillary RNFL area and the four quadrants were evaluated. OCT of the GCL: Macular GCL complex, including the average and 3 mm circular area, was evaluated in the study. OCT-A: of ONH was performed using a 3 × 3 mm scan centered on ONH and was assessed in four levels to determine vascularity at different levels. The average vascular density index (VDI) was calculated. The superficial papillary level (VDI-1) was determined to extend from a point at the level of the internal limiting membrane to a point at the outer boundary of the inner plexiform layer. The deep papillary level (VDI-2) was determined to extend from a point at the level of the outer boundary of the inner plexiform layer to a point at the outer edge of the outer plexiform layer. Outer retina level (VDI-3) extends from a point at the level of the outer boundary of the outer plexiform layer to an end at the level of Bruch’s membrane.

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**Figure 1:** (a and b): Right eye of a female patient 39 years old diagnosed with MS 10 years ago with a history of ON since 9 years. (a) RNFL thickness protocol, peripapillary RNFL thickness shows thinning of all quadrant with average thickness 51 µm. (b) Macular GCLT protocol showing significant thinning in all quadrants detected by color coding, with 3 mm average thickness 49 µm.

**Table 4: Correlation between BCVA and OCT-A optic disc findings**

| Correlations                      | BCVA LogMAR |
|-----------------------------------|-------------|
| OCT_A ONH % VDI_1                 | -0.748      |
| OCT_A ONH % VDI_2                 | -0.044      |
| OCT_A ONH % VDI_3                 | -0.342      |
| OCT_A ONH % VDI_4                 | -0.316      |
| OCT_A ONH % AVDI                  | -0.576      |

OCT-A: Optical coherence tomography angiography, BCVA: Best-corrected visual acuity, VDI: Vascular density index, ONH: Optic nerve head, *significant
All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical analysis of the present study was conducted using the mean, standard deviation, student’s t-test, Chi-square, linear correlation coefficient, and analysis of variance [ANOVA] tests by (Statistical Package for the Social Science; SPSS, Chicago, IL, USA). Unpaired Student t-test was used to compare between two groups in quantitative data. Chi-square indicates that the row and column variables are independent without indicating the strength or direction of the relationship. The linear Correlation coefficient was used to detect the correlation between two quantitative variables in one group. ANOVA test was used to compare the different times in the same group in quantitative data. P value >0.05 is nonsignificant, and P value ≤0.05 is considered significant.

Results
The mean ± SD of age in group 1 is 31.700 ± 6.395 years, while that of group 2 and 3 is 30.000 ± 5.207 and 30.000 ± 2.981 years, respectively, with no detected statistical significance between the three groups with P value 0.690, P values between groups 1, 2 (0.654), between groups 1, 3 (0.627), and between groups 2, 3 (0.642) with no statistical significance. Mean ± SD of disease duration was 4.900 ± 2.846 years in group 1, while that of group 2 was 3.700 ± 1.636 years, no statistical significance was recorded regarding the disease duration between the two groups of patients of MS with P value = 0.263. Concerning BCVA by logMAR, it was diminished in cases of group 1 (0.978 ± 0.472), if compared to patients of group 2 (0.366 ± 0.133) and group 3 (0.108 ± 0.093) with P value <0.001. Moreover, it was found that the average RNFL thickness and the thickness in all quadrants, notably the temporal quadrant, were significantly reduced in group 1 (P < 0.001). Furthermore, the average thickness was decreased in group 2 if compared to group 3, but without any detected statistical significance (P = 0.741); this is shown in Table 1.

Also, GCLT was decreased in average thickness and all quadrant thickness in both groups of MS. Still, only group 1 showed statistical significance with a P value <0.001, as regarding the average thickness, no statistical significance was recorded between group 2 and 3 with a P value 0.381 as illustrated in the Table 2. In respect to optic disc perfusion, average, superficial, and deep vascular density (AVDI, VDI 1, VDI 2) were statistically significantly lower in groups 1, 2 (P < 0.001); this is shown in Table 3.

It was reported that there was a significant negative correlation between BCVA by logMAR and the average VDI of ONH (P = 0.008) and VDI 1 (P < 0.001) as shown in Table 4. Moreover, RNFLT correlates significantly with GCLT, AVDI, and VDI-1 with P values <0.001*, 0.018*, 0.004*, respectively. In addition, the BCVA was significantly correlated with RNFL thickness in all quadrants except the nasal quadrant and significantly correlated with GCL thickness in all quadrants. Moreover, GCLT was positively correlated with AVDI with statistical significance with P value 0.004, r-value 0.608.

Fig. 1a and b shows RNFL thickness protocol and macular GCLT protocol of the right eye of a female patient 39 years old.
diagnosed with MS 10 years ago with a history of optic neuritis since 9 years. Fig. 2a-e shows OCT-A of ONH of the same case with VDI at all levels.

Fig. 3a and b shows RNFL thickness protocol and macular GCLT protocol of the right eye of a female patient 37 years old diagnosed with MS 6 years ago without any history of optic neuritis. Fig. 4a-e shows OCT-A of ONH of the same case with VDI at all levels.

**Discussion**

As the retina is devoid of myelin, changes in the RNFL thickness will be only caused by axonal damage. Assessment of the RNFL can be performed by OCT which is considered as a useful tool of disease activity and can be used as a part of the routine imaging of patients to monitor MS complementing MRI. RNFL thickness is affected by age; this has been documented using OCT. To avoid this source of bias, we selected a control group that was age-matched with MS patients, also the study excluded patients with acute attacks of ON as there is optic disc edema that may interfere with proper evaluation of axonal damage.

The present study evaluated the RNFLT in all quadrants in the three groups and reported a significant reduction in MS patients when compared with the control group. Other studies done by Henderson AP et al.,[17] Graves JS et al.,[18] and Winges KM et al.,[19] detected similar results of RNFL thinning in MS patients. Significant reduction in average RNFL thickness in cases of group 1 compared to groups 2 and 3 ($P < 0.001$).

These results coincide with Winges KM et al.[19] and Fisher JB et al.[20] who reported significant RNFL thinning in this population compared to the control group. Also, the present study reported a reduction in the average RNFL thickness in group 2 patients in comparison with group 3, but with no statistical significance ($P = 0.741$). This finding agrees to Jasek L et al.,[21] Trip SA et al.,[22] and Winges KM et al.,[23] that reported that even patients with MS without a history of ON showed thinner RNFL than controls providing evidence that at baseline, patients with MS have abnormal optic nerves.

The present study reported that the average GCL thickness was significantly reduced in patients of group 1 with $P = 0.001$; studies performed by Huang-Link YM et al.,[24] Graves JS et al.,[18] and Nguyen J et al.,[25] stated that the RNFL and GCL were thinner in MS patients. Still, the change was more pronounced in group 1. Furthermore, group 2 patients showed a reduction in average GCL thickness as compared to the group 3 but with no statistical significance ($P = 0.381$). The last finding agrees with other reports by Graves JS et al.,[18] Huang-Link YM et al.,[24] and Oberwahrenbrock T et al.,[26] who detected decreased GCL complex thickness even in patients without ON. GCL complex has functional superiority than RNFL. Moreover, it is less prone to be influenced by optic disc swelling and can detect damage before RNFL. Furthermore, GCL atrophy correlates well with whole-brain and gray matter atrophy in MS.[27]

Regarding ONH perfusion, the vascular density of the superficial and deep capillary plexus and the average vascular density (VD1 1, VDI 2, AVDI) were significantly

![Image of RNFL Deviation Map](Figure_3a.png)

![Image of RNFL Deviation Map](Figure_3b.png)

![Image of RNFL Deviation Map](Figure_3c.png)

**Figure 3:** (a and b): The right eye of a female patient 37 years old diagnosed with MS 6 years ago. No history of ON. (a) RNFL thickness protocol, peripapillary RNFL thickness is within the accepted normal range in all quadrants except inferior quadrant with an average thickness of 82 $\mu$m. (b) Macular GCLT protocol showing within normal thickness detected by color coding except superior, with 3 mm average thickness 73 $\mu$m.
detected reduced perfusion of the superficial capillary plexus. Also, the vascular density of the deep capillary plexus was significantly reduced, especially in the group 1 compared with healthy controls. This finding agrees with Feucht N et al.[34] In contrast, Murphy OC et al.[35] and Ulusoy MO et al.[32] reported the same results with no statistical significance. The possible explanation for reduced vascular densities is that the superficial vascular plexus (SVP) that supply the RNFL and GCL is affected by damage in MS patients; since anastomoses from superficial vessels supply the deep vascular plexus, the deep capillary plexus can also be affected.[35]

According to the present study, worse visual function was associated with a reduction of ONH perfusion ($P = 0.008$) especially with superficial capillary plexus and the average VDI ($P < 0.001$). Furthermore, regarding the correlation between vessel density and SD-OCT parameters, reduction of both average RNFL thickness was strongly associated with a decrease of ONH perfusion especially with the decrease in average VDI and the superficial capillary plexus (VDI 1) with ($P = 0.018$, 0.004) respectively. Moreover, the average GCL thickness was strongly correlated with average VDI with $P$ value = 0.004, which confirms the alteration of both cellular and vascular structure of the retina in MS patients. The finding coincides with Murphy OC et al.[35] Lanzillo R et al.[29] and Ulusoy MO et al.[32] who found that the SVP density was reduced as long as RNFL and GCL thicknesses were diminished. In contrast to Spain RI et al.[31] who reported no statistically significant correlation between ONH perfusion and the structural OCT measures, the present study reported that peripapillary RNFL and GCL thinning correlates with decreased visual acuity, which is similar to other studies done by Winges KM et al.[15] Nguyen J et al.[25] and Spain RI et al.[31]

The present study has some limitations, first the small number of patients, in addition, some technical limitations of the new technique by which assessment of retinal vessel density from OCT-A images was done including many imaging artefacts as motion and projection artefacts. Furthermore, ocular dysmetria in MS patients may result in loss of focus artefact and falsely reduced vascular densities. Moreover, OCT-A cannot provide a quantitative evaluation of the blood flow velocity, vessel morphology, or alterations of the vessel barrier. Further studies with a more significant number of patients and more extended periods of follow-up are required to understand the mechanisms of ONH microcirculation changes.

**Conclusion**

Due to the small sample size, the manuscript should only conclude that there was a concordance between OCT and OCT-A optic disc parameters in MS denoting that both cellular layer and vasculature of the retina are altered in MS, not secondarily to the inflammatory injury of the optic nerve, but probably primarily due to the disease status suggesting that OCT-A could be a useful marker of MS.

**Ethics approval and participants’ consents**

The Ethical Committee of the Faculty of Medicine, Tanta University, Egypt approved the research (approval code 33024/03/19). Written consent was obtained from all participants.

**Data availability**

The data sets used during the current study are available from the corresponding author on a reasonable request.

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**Figure 4:** (a-e): OCTA of ONH of the previous patient of Figure 3 (3 x 3 mm): (a) OCTA of superficial papillary level with VDI 1 = 62.317%. (b) OCTA of deep papillary level with VDI 2 = 63.386%. (c) OCTA of outer retina level with VDI 3 = 12.423%. (d) OCTA of choroidal level with VDI 4 = 57.753%. (e) Density flow map of superficial papillary level showing within normal ONH perfusion with AVDI = 47.660%
Authors’ contribution
SAK performed the ophthalmic clinical evaluation and follow-up of all patients, AEN performed ophthalmic investigations including OCT, OCT-A for all patients, AAG performed neurological clinical diagnosis and assessment of all patients, AMG performed data collection for all patients and statistical analysis, and all authors contributed in writing, editing approval, and revision of the manuscript.

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Conflicts of interest
There are no conflicts of interest.

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