

Association of Retinal Nerve Fiber Layer Thickness with Disability in Patients with Multiple Sclerosis

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ABSTRACT

Background: Retinal nerve fiber layer (RNFL) thinning has been observed on histopathology and time-domain optical coherence tomography in many diseases of the central nervous system. In this study, with a higher resolution of optical coherence tomography (OCT), we detected RNFL changes in patients with multiple sclerosis (MS, and compared RNFL thickness between eyes without optic neuritis (ON). **Aim:** Evaluation the role of OCT in detecting the thickness of RNFL in MS patients without history of optic neuritis and correlate our findings with disease duration and disease disability. **Subjects and methods:** The study was conducted in Neurology Department, Faculty of Medicine, Zagazig University. 34 MS patients were included in the study. RNFL was measured using OCT and results were compared to controls. **Results:** Our results revealed that Mean $\pm$ SD. of average RNFL was 69.24 ± 10.71 in study group, and was 101.61 ± 7.25 in control group, with highly statistical significant difference between groups, and as regard Rim area, Mean $\pm$ SD. was 1.16 ± 0.19 in case study group and was 1.23 ± 0.17 in control group, with no statistical significant difference between groups, and as regard RNFL Symmetry; Mean $\pm$ SD. was 0.66 ± 0.16 in study group, and was 0.91 ± 0.09 in control group, with highly statistical significant difference between groups, and there is highly significant positive correlation between Average RNFL in study group and each of Rim area and RNFL Symmetry, also there is highly significant positive correlation between Average RNFL in control group and each of Rim area and RNFL Symmetry ($p < 0.001^*$). **Conclusion:** Retinal nerve fiber layer (RNFL) thickness was inversely correlated with disease duration and disability (EDSS). The OCT scan represents a high-resolution, objective, noninvasive and easily quantifiable in vivo biomarker of MS.

Keywords: OCT, RNFL, Multiple Sclerosis, Optic Neuritis.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by both demyelination and axonal degeneration. Although multiple sclerosis (MS) has long been considered a primary demyelinating disease, axonal loss is of critical importance since this pathologic change appears to correlate with a patient's ultimate disability^[1]. Axonal loss is increasingly thought to occur early in the disease course and is thought to be associated with neurologic deficits and predictive of progression to permanent disability^[2].

However, the pathogenetic mechanism of MS is still unknown. The retina is the only place where a tissue layer made up of unmyelinated axons can be imaged directly, so the changes in the retinal architecture require a unique model^[3]. A single biomarker for diagnosing MS does not exist at present. Oligoclonal bands, magnetic resonance imaging (MRI) and optical coherence tomography (OCT) are all used in clinical practice^[4]. However,

MRI is the most widely used in the diagnosis of MS, the lesions shown in the images only explain a small fraction of the patient's clinical symptoms (known as the clinico-radiological paradox). It is, therefore, highly worthwhile to seek new biomarkers capable of determining progression of the disease^[5].

The visual system is an extension of the central nervous system and the neurodegenerative processes of MS frequently manifest in visual pathways, making the analysis of them a means of diagnosing the disease and evaluating its progress. Quantification of the retinal nerve fiber layer (RNFL) has the potential to open a diagnostic window for monitoring the axonal and neuron injury^[6].

Retinal nerve fiber layer thickness (RNFLT) is of particular interest in MS, because optic neuritis (ON) is often a pivotal event in establishing the diagnosis. Moreover, optic nerve dysfunction, which is routinely assessed by optic disc pallor, loss of contrast sensitivity, visual field defects, and delayed latency of visual-evoked potentials (VEPs); may occur subclinically in many other patients^[7]. It is estimated that nearly 20% of all patients with MS present initially with ON, and overall 30–70% of MS patients develop ON during their disease course^[8]. Many studies have found a loss of RNFLT in ON, likely due to axonal destruction in optic nerve. Axonal loss in the RNFL, as measured by OCT, has the potential to become a model to study axonal loss throughout the central nervous system (CNS) in patients with MS^[9].

Optical coherence tomography (OCT) is a relatively technology capable of imaging histologically identifiable layers of the retina in real-time with highly refined resolution, accuracy and reproducibility. Its sensitivity allows direct visualization and measurement of RNFLT and macular volume with micron-scale resolution^[10]. Over the past 2 decades, the technique of OCT has developed tremendously. Spectral-domain optical coherence tomography (SDOCT) has been widely applied in clinical ophthalmology. Compared to the third generation, i.e. time-domain optical coherence tomography (TDOCT) which has significantly lower axial resolution and limited image acquisition, SDOCT, with axial resolutions of 2–3 μm , is characterized by markedly increased image acquisition speed and improved imaging quantification^[11]. It also uses the same anatomical area in the follow-up examinations of the eye, which makes it possible to monitor neurological deterioration in neurodegenerative pathologies, thereby serving as a reliable progression biomarker. Some authors consider its reliability to be as high as or higher than serial MRI^[12].

PATIENTS AND METHODS

I. Technical design

This study was a case control study carried out on 34 patients with clinically definite relapsing remitting multiple sclerosis (RRMS) and 34 age and sex matched patients (other than MS) served as the controls, were selected from the inpatients wards and outpatients Clinic of Neurology department, Zagazig University Hospitals, during the period from June 2020 to December 2020.

The study was approved by the institutional review board of Faculty of Medicine, Zagazig University and informed written consent was obtained from patients or written assent from a relative.

To participate in this study, patients had to fulfill the following inclusion criteria:

- Thirty four patients aged ≥ 18 years of both sexes.
- Patients with clinically definite RRMS according to the revised McDonald's criteria 2017.

Control group:

- Thirty four age-matched and sex-matched healthy controls.
- Visual acuity (VA) of 20/30 or better.
- No ophthalmic or neurologic diseases or a medical history of diabetes mellitus, hypertension, or renal or liver diseases.

Exclusion criteria:

- Patients with a refractive error of $\pm \geq 5.0$ D.
- Patients with clinical diagnosis or history of optic neuritis (ON).
- Patients with a history of eye disease that may impact significantly on OCT measures such as glaucoma, anterior ischemic optic neuropathy, congenital abnormalities of the optic nerves, history of ocular surgery or penetrating trauma.
- Patients with other medical diseases such as hypertension or diabetes mellitus.
- Patients with a VA 20/200 (Snellen scale) or less in both eyes.

All patients were subjected to the following:

(A) Clinical assessment which includes:

1. Full history taking including

Including age, sex, past history of other medical conditions, detailed history of current illness including the number and time of relapses, duration of illness, detailed drug history, and symptoms of the current relapse.

2. Complete general examination including:

3. Neurological examination.

According to multiple sclerosis assessment sheet of neurology department, Zagazig University.

4. Assessment of disease disability was done using the Expanded Disability Status Scale (EDSS).

Clinical scales encompassing: Kurtz Expanded Disability Status Score (EDSS). It is a scale used to quantify disability in eight function systems, pyramidal, cerebellar, brain stem, sensory, visual, bowel and bladder and other functions was performed to the patients.

(B) Investigations:

1. Laboratory investigations: Routine laboratory investigation which include complete blood count (CBC), fasting blood glucose, lipid profile, kidney and liver function tests, C-Reactive protein (CRP), erythrocyte sedimentation rate (ESR).

2. Spectral domain OCT examination using the Heidelberg Engineering Spectralis (Heidelberg Engineering, Heidelberg Germany).

- RNFL images were acquired by taking three circular 3.4-mm-diameter scans, centered on the optic disc, the mean of which was used to express RNFL thickness in four quadrants (temporal, superior, inferior, and nasal).
- The thicknesses of the quadrants were automatically calculated by the OCT device software.

3. Radiological Investigation: Magnetic resonance imaging (MRI) of brain and / or spinal cord was done for all patients. A standardized protocol of MRI comprising T2-weighted, T1-weighted gadolinium enhancing (T1Gd+), FLAIR images and gadolinium (Gd) enhancement images were performed using 1.5 Tesla superconducting MR imager (Achieva, Philips Medical System).

MRI activity was defined as a presence of new/ newly enlarged T2 lesion and/ or one or more Gd enhancing lesions.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 15 for Windows® (SPSS Inc, Chicago, IL, USA). Qualitative data was presented as number and percent. Comparison between groups was done by Chi-Square test. Quantitative data was tested for normality by Kolmogorov-Smirnov test. Normally distributed data was presented as mean $\pm$ SD. $P < 0.05$ was considered to be statistically significant.

RESULT

Table (1): Comparison between the two studied groups according to demographic data

Demographic data	RRMS (N = 34)		Controls (N = 34)		Test of Sig.	p
	No.	%	No.	%		
Sex					$\chi^2=$ 0.249	0.618
Male	12	35.29	14	41.18		
Female	22	64.71	20	58.82		
Age (years)					0.251	0.802
Mean $\pm$ SD.	34.56 $\pm$ 8.79		34.03 $\pm$ 8.79			
Median (IQR)	41.0 (29.0 – 51.0)		35.50 (28.0 – 44.0)			
Age of Disease Onset	27.94 $\pm$ 6.94		NA			
Disease duration						
Mean $\pm$ SD.	6.62 $\pm$ 4.05		NA			
Median (IQR)	12.0 (9.0 – 14.0)					
EDSS	2.01 $\pm$ 1.78		NA			

N: number; SD: standard deviation; EDSS: Expanded Disability Status Scale; IQR: Interquartile range; NA: not applicable; χ^2 : Chi square test; t: Student t-test

*: Statistically significant at $p \leq 0.05$

This table shows that 64.71 % were female and 35.29% were male in MS patients, while in controls 58.82% were female and 41.18% were male, and there was non-statistical significant difference between groups as regard sex.

As regard age, mean $\pm$ SD of age is 34.56 $\pm$ 8.79 years in MS patients and 34.03 $\pm$ 8.79 years in controls and there was non-statistical significant difference between groups as regard age.

This table shows that mean $\pm$ SD of age of disease onset was 27.94 $\pm$ 6.94 and disease duration in MS patients was 6.62 $\pm$ 4.05 years. The mean $\pm$ SD of EDSS is 1.78 $\pm$ 1.48.

Table (2): Distribution of the RRMS patients according to MRI and VEP (N=34).

Parameters	N	%
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MRI brain finding		
Non active form of M.S	20	57.1
Active form of M.S	14	39.9
VEP		
Prolongal p100 lateray in bilateral eyes	19	54.3

N: number; MRI:Magnetic Resonance Imaging; VEP:visual evoked potential

This table shows MRI findings; Non-active form of M.S is present in 57.1% and active form of MS in 39.9%. As regard VEP 42.9% is with delay of p100 wave in bilateral eyes, , and Prolongal p100 lateray in bilateral eyes in 54.3%.

Table (3):Comparison between the RRMS and Controls according to RNFL thickness and BCVA

Parameters	RRMS (N = 34)	Controls (N = 34)	Test of Significance	P
Temporal Min. – Max. Mean ± SD. Median (IQR)	25.80 – 63.10 42.44 ± 13.09 38.70 (30.40 – 55.70)	71.30 – 91.40 81.20 ± 6.35 82.60 (75.20 – 85.80)	t =15.53	<0.001*
Nasal Min. – Max. Mean ± SD. Median (IQR)	49.50 – 68.40 58.11 ± 5.60 58.65 (52.20 – 61.70)	64.60 – 81.40 74.80 ± 5.17 76.30 (71.0 – 79.30)	t =12.76	<0.001*
Superior Min. – Max. Mean ± SD. Median (IQR)	73.30 – 112.4 92.47 ± 13.09 90.25 (80.90 – 104.6)	104.4 – 142.6 121.7 ± 10.14 121.9 (112.6 – 128.8)	t =10.29	<0.001*
Inferior Min. – Max. Mean ± SD. Median (IQR)	65.60 – 102.3 83.93 ± 11.52 85.40 (73.60 – 92.90)	119.2 – 142.9 128.7 ± 7.73 126.5 (121.9 – 135.6)	t =18.81	<0.001*
BCVA < 0.1 0.1-0.5 > 0.5	3 (8.8%) 9 (26.5%) 22 (64.7%)	0 (0%) 6 (17.6%) 28 (82.4%)	F=3.91	0.148

N:number; RNFL: retinal nerve fiber layer; RRMS:Relapsing-remitting multiple sclerosis; t: Student t-test; F: Fisher Exact; SD:Standard deviation; IQR:interquartile range; BCVA: Best Corrected Visual Acuity

*: Statistically significant at $p \leq 0.05$

Table three and figure four show that in temporal part, Mean $\pm$ SD. was 42.44 ± 13.09 in case group and was 81.20 ± 6.35 in control group, and in nasal part; mean $\pm$ SD. was 58.11 ± 5.60 in case group and 74.80 ± 5.17 in control group, while in superior part; Mean $\pm$ SD. was 92.47 ± 13.09 in case group, and 121.7 ± 10.14 in control group, and in inferior area, Mean $\pm$ SD. was 83.93 ± 11.52 in case group, and was 128.7 ± 7.73 in control group, and there was highly statistical significant difference between case and control groups as regard RNFL thickness in all parts (temporal, nasal, superior and inferior). Majority of cases in each group shows that BCVA was > 0.5 , and there was non- statistical significant difference between case and control group as regard BCVA.

Table (4):Comparison between R.R.M.S, controls according to R.N.F.L average thickness, Rim zone, R.N.F.L symmetry

	RRMS (n = 34)	Controls (n = 34)	t	p
Average RNFL				
Min. – Max.	73.55 – 106.55	89.88 – 114.58		
Mean $\pm$ SD.	89.24 ± 10.71	101.61 ± 7.25	5.577	$<0.001^*$
Median (IQR)	68.25 (59.28 – 78.72)	101.8 (95.18 – 107.4)		
Rim area				
Min. – Max.	0.90 – 1.40	1.0 – 1.50		
Mean $\pm$ SD.	1.16 ± 0.19	1.23 ± 0.17	1.552	0.125
Median (IQR)	1.20 (1.0 – 1.40)	1.20 (1.10 – 1.40)		
RNFL Symmetry				
Min. – Max.	0.40 – 0.90	0.80 – 1.0		
Mean $\pm$ SD.	0.66 ± 0.16	0.91 ± 0.09	7.578	$<0.001^*$
Median (IQR)	0.70 (0.50 – 0.80)	0.90 (0.80 – 1.0)		

RRMS: Relapsing-remitting multiple sclerosis; RNFL: retinal nerve fiber layer ; t: Student t-test

*: Statistically significant at $p \leq 0.05$

Table four and figure four show that mean $\pm$ SD of Average RNFL is 89.24 ± 10.71 in study group, and was 101.61 ± 7.25 in control group, with highly statistical significant difference between groups. As regard Rim area, Mean $\pm$ SD. was 1.16 ± 0.19 in case study group and was 1.23 ± 0.17 in control group, with no statistical significant difference between groups, and as regard RNFL Symmetry; Mean $\pm$ SD. was 0.66 ± 0.16 in study group, and was 0.91 ± 0.09 in control group, with highly statistical significant difference between groups.

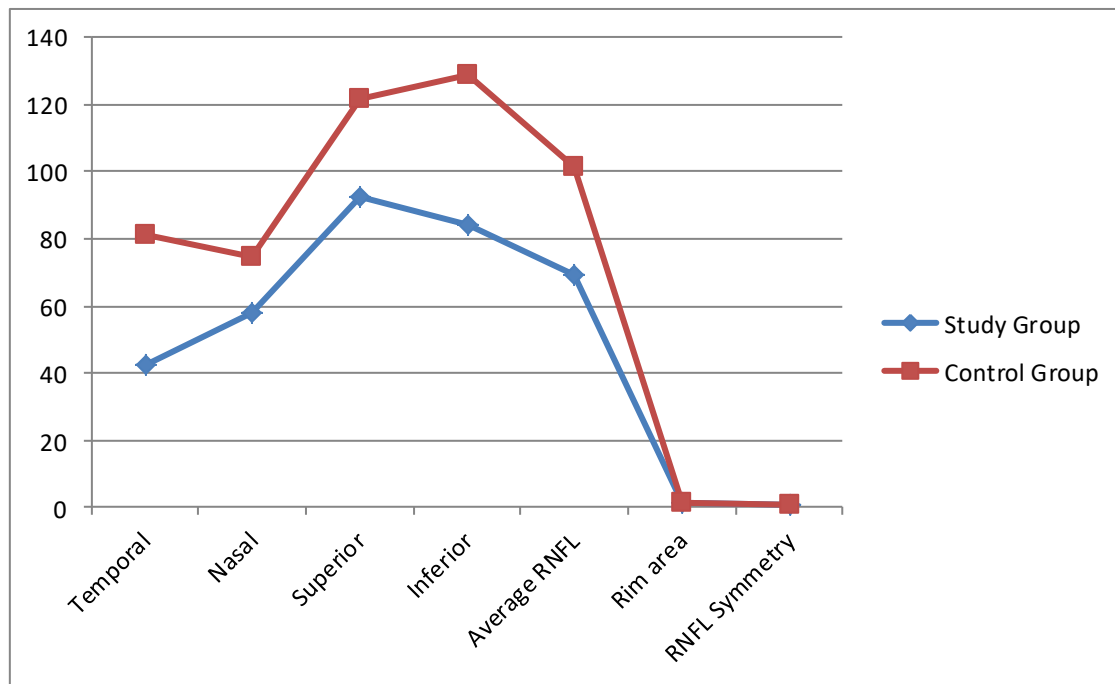


Fig (4): bar charts show distribution of two studied group according to different parameters

Table (5):Comparison between the two studied gatherings according to VF

VF	RRMS (n = 34)		Control (n = 34)		Fisher exact	p
	N	%	N	%		
Normal	10	29.4	34	100.0	37.091	<0.001*
Defect	24	70.6	0	0.0		

N: number; VF: visual field

*: Statistically significant at $p \leq 0.05$

This table shows that there is highly statistical significance difference between RRMS patients and controls as regard VF.

Table (6): Univariable analysis of characteristics of RRMS patients with RNFL.

Characteristics	RNFL		
	Mean $\pm$ SD	t	P
Gender:			
Male	69.12 $\pm$ 10.86	0.073	0.94
Female	69.39 $\pm$ 10.89		
Medication			
Yes	90.89 $\pm$ 11.68	0.841	0.41
No	87.76 $\pm$ 9.87		

RRMS:Relapsing-remitting multiple sclerosis; SD: standard deviation ; RNFL: retinal nerve fiber layer ; EDSS: Expanded Disability Status Scale

This table shows that there is no statistically significant difference in RNFL as regard gender and patients under medication.

Table (7): Correlation between RNFL with parameters in RRMS patients.

Parameters	RNFL	
	r	P
Age	0.310	0.074
Disease duration	-0.380	0.027*
EDSS	-0.524	0.001*

RNFL: retinal nerve fiber layer; EDSS:Expanded Disability Status Scale

*: Statistically significant at $p \leq 0.05$

This table shows that there is no statistically significant as regard age. There is statistically significant negative correlation between RNFL thickness in MS patients with disease duration and EDSS.

Table (8): Correlations between quadrant measurements, retinal nerve fiber layer (RNFL), and central macular thickness (CMT) in RRMS patients.

Quadrant measurements	RNFL	CMT
Superior		
r	0.542	0.321
p	0.001	0.019
Inferior		
r	0.735	0.423
p	<0.001	0.004
Nasal		
r	0.594	0.284
p	0.001	0.112
Temporal		
r	0.564	0.311
p	0.001	0.041

RNFL: retinal nerve fiber layer; CMT: central macular thickness

*: Statistically significant at $p \leq 0.05$

This table showed that thinning of RNFL was correlated with all field quadrants in MS patients, whereas CMT thinning significantly correlated with all field quadrants, sparing the nasal one.

DISCUSSION

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disease of the central nervous system. It may cause demyelination and axonal degeneration. During the past decade, the contributions of axonal and neuronal loss to disability in MS have been increasingly recognized^[13].

Visual loss has been recognized for decades as one of the most common and disabling clinical manifestations of multiple sclerosis. Visual symptoms can result from a variety of pathological processes, including inflammation, demyelination, and axonal degeneration in the afferent visual pathway (retina, optic nerves, chiasm, and tracts). The visual pathway is now recognized as a model for structure-function correlation in MS for studying the pathophysiology of disease and for testing both novel and standard therapies that involve neuroprotection and repair^[14,15].

Optical coherence tomography (OCT) is a noninvasive imaging technology that provides high-resolution cross-sectional images of tissue microstructures in vivo. OCT studies in MS have primarily focused on evaluation of the RNFL. The application of nonconventional MRI techniques has led to only modest achievements in linking imaging data with clinical measures of disease severity for MS. Cross-sectional studies show more thinning of RNFL in progressive forms of MS compared with the relapsing-remitting disease course (RRMS) form. However, it remains unsure whether these differences are due to the disease subtype per se, or are related to disease duration, lesions, or severity. The aim of our study is to evaluate the role of OCT in detecting the thickness of RNFL in RRMS patients and correlate our findings with disease duration and disease disability^[16,17].

According to demographic data, our results showed that 64.71% were females and 35.29% were males in RRMS patients, while in controls 58.82% were females and 41.18% were males, and there was non-statistical significant difference between patients and controls. Moreover, the mean $\pm$ SD age of MS patients was 34.56 ± 8.79 years, and in control group was 34.03 ± 8.79 years with no statistical significant difference between groups.

Our results showed that female to male ratio was 1.8:1. This is in agreement with other Egyptian studies and other Arab countries confirmed female dominance in MS. However, some studies in the Middle East region showed lower female: male ratio as in Kingdom of Saudi Arabia (1.32:1), Iraq (1.2:1) and in Qatar (1.33:1). Other literatures reported higher ratio (F:M) up to 3:1 and 3.34: 1 in Iran. Furthermore, X chromosome inactivation in women (skewed X chromosome) resulting in over representation of MS. Women and men might also have different responses to environmental factors, like sun exposure and vitamin D supplements^[17].

The clinical data of the MS patients in this study showed that the mean age of MS onset ($\pm$ SD) was $27.94 (\pm 6.94)$ years. This was in agreement with the reported overall estimate in a meta-analysis of 52 studies in the Middle East and North Africa (MENA) region (27.61–29.48 years). Moreover, the relatively recent large Egyptian epidemiological MS study found that the mean age of onset ($\pm$ SD) was $26.17 (\pm 7.6)$ years. However, our result was younger than that reported in the North American Research Committee on Multiple Sclerosis registry, where the mean age of onset was 31.4 ± 9.7 years and in European MS registries where MS symptoms starting around the mid-30s. It seems that these differences between studies originated from diverse inclusion criteria, distinctive ethnic and geographical variations. In this study, the mean disease duration was $6.62 (\pm 4.05)$, and this was in accordance with other studies. In contrast, a study show a higher disease duration that was 10.3 ± 9.7 years among MS patient.

To assess the clinical disability of MS patients, we have chosen a reliable, validated and well accepted clinical score. The Expanded Disability Status Scale (EDSS) is the most commonly used rating scale to evaluate the disability of patients with MS. It is not particularly difficult or time consuming to perform. The mean EDSS score of our patients was $2.01 (\pm 1.78)$. This is in agreement with the results of many Arab countries such as

Kingdom of Saudi Arabia, Dubai and Qatar but was lower compared with the result in Jordan (3.9).

According to RNFL thickness measurement, there was decrease in all parameters in RRMS patients compared to control with high statistical significant difference. Moreover, the mean $\pm$ SD of average RNFL was 89.24 ± 10.71 in RRMS patients and was 101.61 ± 7.25 in controls with highly statistical significant difference between groups. This is in agreement with other studies demonstrated significant reduction in RNFL thickness in patients of multiple sclerosis without ON compared to controls **Zamzam et al.**,^[18] **Khalil et al.**, 2017^[19] evaluated retinal nerve fiber layer thickness measured by optical coherence tomography in Moroccan patients with multiple sclerosis. Total RNFL, Temp-RNFL, mNFL and the GC-IPL thicknesses were significantly lower in MS eyes compared to healthy control eyes.

In the present study, there were significant correlations between quadrant measurements with RNFL and central macular thickness (CMT) in multiple sclerosis patients. Thinning of RNFL was correlated with all field quadrants, whereas CMT thinning significantly correlated with all field quadrants, sparing the nasal one. This is in agreement with the results of other studies^[18].

The majority of MS patients and controls showed that BCVA was > 0.5 but with no statistical significant difference between them. **Khalil et al.**^[19] reported a decrease in mean ($\pm$ SD) of BCVA in multiple sclerosis patients (0.41 ± 0.33) compared to controls (0.09 ± 0.09) and this was statistically significant ($p < 0.001$).

As regard duration, RNFL was inversely correlated with disease duration in MS patients. Our finding of significant negative correlation between RNFL thickness and disease duration was consistent with **Khalil et al.**^[19]. In addition, RNFL was inversely correlated with Extended Disability Status Score (EDSS) in MS patients. This is in agreement with previous studies showed an inverse correlation^[19]. However, other studies didn't identified a relationship between RNFL thickness and EDSS^[20].

CONCLUSION

The present study showed that the RNFL thickness detected by OCT in MS patients is significantly decreased than healthy controls. In addition, RNFL thickness was inversely correlated with disease duration and disability (EDSS).

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