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Retinal neurodegeneration in diabetic patients without diabetic retinopathy

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Abstract
Background: Spectral-domain optical coherence tomography (SD-OCT) is a non-invasive technology that has become an essential instrument for precise assessments of retinal thickness with high resolution and increased definition of the various retinal layers. Our objective was to assess the retinal neurodegeneration in cases with type 2 diabetes mellitus (T2DM) without diabetic retinopathy (DR) using OCT.
Methods: This prospective cohort trial was performed on two groups: 25 eyes of diabetic patients with no signs of DR, 25 eyes of non-diabetic individuals with normal retina as a control group. We included cases with T2DM who doesn't show signs of DR, eyes with clear ocular media, best corrected visual acuity (BCVA) of 0.4 or more for both groups. BCVA, intraocular pressure, fundus examination measurements and OCT were performed on the cases.
Results: Macular thickness was significantly decreased in diabetic group compared to non-diabetic group in all sectors except central 1mm zone. Ganglion cell layer thickness was significantly decreased in diabetic group compared to non-diabetic group in all sectors as regards: superotemporal, superonasal, superior, average, inferotemporal, inferonasal and inferior sectors. RNFL thickness was significantly decreased in diabetic group compared to non-diabetic group as regards: average, nasal and temporal quadrants. A significant negative correlation was reported between duration of DM and ganglion cell layer thickness and RNFL in all sectors. A significant negative correlation was reported between HbA1c and ganglion cell layer thickness as regards (average, superior, superonasal, and superotemporal sectors), furthermore, a significant negative correlation was found between HbA1c and RNFL thickness in (average, superior quadrant).
Conclusions: Retinal neurodegeneration including macular GCL, peripapillary RNFL and macular thinning are early events in DR before vascular events.

Keywords: Retinal, neurodegeneration, diabetes, retinopathy

Introduction
Diabetic retinopathy (DR) is one of the most severe effects of diabetes that leads to irreversible blindness and is classified as a micro-vasculopathy. In addition to micro vasculopathy, neuropathy in diabetes mellitus can also trigger retinal degeneration [1]. Research has shown that retinal neurodegeneration occurs in very early stages of the disease and it may precede micro-vascular changes [2].
Retinal neurodegeneration described as apoptosis of many retinal cells (bipolar cells, photoreceptors, astrocytes, ganglion cells) with reduced thickness of several layers of the retinal in early stage of DR or even when routine ophthalmologic examination cannot detect DR [3-6]. Retinal ganglion cells have the highest rate of apoptosis along with being the earliest affected cells, also higher rate of apoptosis has been monitored in the outer retinal layer (photoreceptors) and the retinal pigmented epithelium (RPE) [7-9].
Spectral-domain optical coherence tomography (SD-OCT) is a non-invasive technology that has become an essential instrument for precise assessments of retinal thickness with high resolution and increased definition of the various retinal layers.
Our objective was to assess the retinal neurodegeneration in cases with type 2 diabetes mellitus (T2DM) without DR by using OCT.

Materials and Methods
This prospective cohort trial was conducted on 25 eyes of diabetic cases showing no signs of DR (group A), 25 eyes of non-diabetic individuals with normal retina as a control group (group B).

Cases were selected from the outpatient clinic of Tanta Ophthalmology Hospital during the period from October 2020 to October 2021. The local research ethics committee, Faculty of Medicine, Tanta University, Egypt provided approval for conducting this trial. Informed consents were obtained from all study participants.

Inclusion criteria
Cases with T2DM showing no signs of DR, eyes with clear ocular media, best corrected visual acuity (BCVA) 0.4 or more for both groups.

Exclusion criteria
Cases with DR, hypertension, other ocular diseases such as uveitis or glaucoma, trauma, eyes that underwent prior ocular surgeries, photocoagulation or intraocular injection, and high refractive errors (hypermetropia >+4.00 dioptres or myopia >-6.00 dioptres).

Full ophthalmic examination
Including testing visual acuity by Snellen chart and for statistical analysis it is converted to log MAR. Anterior segment examination by slits lamp. Posterior segment was examined by slit lamp biomicroscopy with non-contact Volk® +90 dioptre, and direct and indirect ophthalmoscope.

Investigations
OCT: images were obtained (The Zeiss Cirrus 5000 HD-OCT), it has a 5µm axial resolution with a scanning depth of 2 mm and an A-scan velocity of 27,000 scans/sec. Only scans with signal strength equal to 6 or more were used.

Fig 1: The Zeiss Cirrus 5000 HD-OCT

For the macula, this scan generates a 6 × 6 mm macular cube data centred on the fovea. The 512 × 128 grid was used, which consists of 128 horizontal B-scans each composed of 512 A-scans. Nine subfields matching to Early Treatment of Diabetic Retinopathy Study (EDTRS) regions were chosen for macular measurements. ETDRS regions are defined by three concentric circles with diameters of 1, 3, and 6 mm centred to the fovea. The central subfield thickness represented the central ring (the average thickness of the central 1 mm). Two intersecting lines were dividing the two outer rings into quadrants. Every sector was designated C, S3, S6, T3, T6, I3, I6, N3, and N6. The SD-OCT software automatically positioned the ETDRS grid, allowing for macular thickness values' capture and extraction.
Cirrus HD-OCT measures the inner plexiform layer (IPL) and ganglion cell layer (GCL) together, the thickness map reveals the measurements of the IPL+ GCL thickness in a 6 × 6 mm cube focusing on an elliptical annulus centred to the fovea. The thickness table displays the minimum and mean measurements of the GCL+IPL thickness.
In predetermined sectors, the thickness of the macular GCL was estimated automatically. The ganglion cell analysis algorithm that identifies inner retinal layers' segmentation automatically summarizes the GCL and the IPL based on the three-dimensional (3D) data obtained from the protocol of the macular cube. The difference between the outer boundary of the macular RNFL and IPL yields the segmented GCL-IPL (Fig. 20 B). The minimum, mean, and six sectors - superotemporal, superonasal, superior, inferotemporal, inferonasal and inferior, - defined for the thickness map of the ganglion cell analysis are measured within an elliptical annulus excluding the fovea [10].
Optic Disc Cube 200 × 200 scanning algorithm was used for scanning optic nerve head and peripapillary RNFL. It consists of 200 horizontal linear B-scans, each consisting of 200 A-scans, which spans a 6 × 6 mm area. For RNFL thickness, Cirrus HD-OCT uses measurements from a 3.46 mm diameter calculation circle centred on the BMO (Bruch's membrane opening). The data obtained are summarized in quadrant and clock hour's pie charts.

Statistical analysis
SPSS v27 was used for performing the statistical analysis (IBM©, Armonk, NY, USA). To assess the normality of the distribution of data, histograms and Shapiro-Wilks test were used. Categorical data were presented as frequency and percentage (%) and Chi-square test or Fisher's exact test (when appropriate) were used in the analysis. Numerical parametric variables were presented as mean and standard deviation (SD) and unpaired student t-test was used for the analysis. Numerical non-parametric variables were presented as the median and interquartile range (IQR) and Mann Whitney-test was used for the analysis. A two-tailed P value < 0.05 was deemed statistically significant.

Results
As regards the macular thickness in central 1mm zone, no significant variation (p = 0.106) was reported between diabetic group and non-diabetic group.
A significant decrease in the GCL thickness in diabetic group was reported compared to non-diabetic group as regards: average thickness (p<0.001), superior sector thickness (p<0.001), superonasal sector thickness (p=0.003), superotemporal sector thickness (p=0.001), inferior sector thickness (p<0.001), inferonasal sector thickness (p<0.001) and inferior- temporal sector thickness (p<0.001).
A significant decrease in RNFL thickness was reported in diabetic group compared to nondiabetic group as regards: average thickness (p=0.006), nasal quadrant thickness (p=0.049) and temporal quadrant thickness (p=0.005) Table 1.

1-Correlation between duration of DM (years) and HbA1c (%) with Macular thickness, GCL thickness and RNFL thickness in diabetic group. Table2
A-Correlation between duration of DM (years) with macular thickness, ganglion cell layer thickness and RNFL thickness

in diabetic group: it showed a significant negative correlation between duration of DM and ganglion cell layer thickness in all sectors, a significant negative correlation was reported between duration of DM and the RNFL thickness in all quadrants, so the higher duration of DM was, the thinner ganglion cell layer and RNFL. No significant correlation was reported between duration of DM and macular thickness.

B-Correlation between HbA1c (%) with Macular thickness, Ganglion cell layer thickness and RNFL thickness in diabetic group: it showed a significant negative correlation between HbA1c and ganglion cell layer thickness in (average, superior, superonasal and superotemporal sectors), and RNFL thickness in (average, superior quadrant). No significant correlation was found between HbA1c and macular thickness.

Cases with DM duration longer than 10 years showed reduction in GCL thickness in all sectors, and significant reduction in GCL thickness in average (p=0.017), superior sector (p=0.046), inferior sector (p=0.018) compared to cases with DM duration <10 years.

cases with DM duration longer than 10 years showed reduction in RNFL thickness in all sectors, there was significant reduction in RNFL thickness in average (p=0.001), nasal quadrant (p<0.001) and inferior quadrant (p<0.001) compared to those with DM duration <10 years. Table 3

Cases who have poor metabolic control (HbA1c>7%) showed significant reduction in GCL thickness in all sectors [Average (p=0.005), superior (p=0.005), superonasal (p=0.002), supero temporal (p=0.012), inferior (p=0.002), inferonasal (p=0.017) and inferotemporal (p=0.002)] compared to cases who have good metabolic control (HbA1c<7%). Table 4

Cases who have poor metabolic control (HbA1c>7%) had a reduced RNFL thickness in all sectors with significant reduction in average (p=0.050), temporal quadrant (p=0.048), compared to those cases who have good metabolic control (HbA1c<7%). Table 4

Table 1: Comparison according to macular thickness, GCL thickness and RNFL thickness between the two studied groups

Macular thickness	Diabetic group (n = 25)	Non-diabetic group (n = 25)	T	P
Center				
Min.-Max.	219.0-281.0	217.0-286.0	1.645	0.106
Mean ± SD.	246.9 ± 17.13	255.6 ± 20.05		
Median (IQR)	242.0 (237.0-264.0)	260.0 (248.0-265.0)		
Inner-Superior				
Min.-Max.	231.0-337.0	302.0-354.0	3.733*	0.001*
Mean ± SD.	306.1 ± 21.39	324.2 ± 11.46		
Median (IQR)	312.0 (295.0-319.0)	323.0 (321.0-328.0)		
Inner-Nasal				
Min.-Max.	276.0-350.0	307.0-358.0	3.642*	0.001*
Mean ± SD.	309.7 ± 19.28	325.9 ± 11.08		
Median (IQR)	306.0 (293.0-319.0)	325.0 (320.0-327.0)		
Inner-Inferior				
Min.-Max.	274.0-337.0	297.0-346.0	2.905*	0.006*
Mean ± SD.	310.1 ± 14.91	320.6 ± 10.16		
Median (IQR)	308.0 (302.0-314.0)	320.0 (318.0-323.0)		
Inner-Temporal				
Min.-Max.	261.0-381.0	283.0-340.0	2.128	0.040*
Mean ± SD.	303.8 ± 22.95	314.84 ± 12.10		
Median (IQR)	300.0 (289.0-308.0)	315.0 (313.0-318.0)		
Outer-Superior				
Min.-Max.	245.0-298.0	248.0-307.0	2.137*	0.038*
Mean ± SD.	274.4 ± 10.78	282.40 ± 15.19		
Median (IQR)	277.0 (273.0-279.0)	278.0 (272.0-295.0)		
Outer-Nasal				
Min.-Max.	257.0 – 311.0	271.0 – 310.0	2.262*	0.028*
Mean ± SD.	283.6 ± 12.83	291.0 ± 10.29		
Median (IQR)	283.0 (276.0 – 291.0)	293.0 (286.0 – 295.0)		
Outer-Inferior				
Min.-Max.	229.0-280.0	245.0-281.0	2.104*	0.041*
Mean ± SD.	260.3 ± 11.22	266.52 ± 9.70		
Median (IQR)	260.0 (258.0-268.0)	269.0 (263.0-272.0)		
Outer-Temporal				
Min.-Max.	238.0-286.0	230.0-293.0	2.032*	0.048*
Mean ± SD.	257.7 ± 11.07	265.44 ± 15.43		
Median (IQR)	258.0 (251.0-262.0)	268.0 (262.0-275.0)		
Ganglion cell layer thickness	**Diabetic group (n = 25)**	**Non-diabetic group (n = 25)**	**T**	**P**
Average				
Min.-Max.	64.0-90.0	76.0-90.0	4.404*	<0.001*
Mean ± SD.	76.04 ± 7.67	83.92 ± 4.60		
Median (IQR)	75.0 (70.0-82.0)	85.0 (80.0-88.0)		
Sector-Superior				
Min.-Max.	65.0-87.0	68.0-96.0	3.870	<0.001*
Mean ± SD.	76.92 ± 7.30	84.32 ± 6.17		

Median (IQR)	76.0 (72.0-85.0)	84.0 (82.0-89.0)		
Sector-Superionasal				
Min.-Max.	64.0-95.0	76.0-91.0	3.255*	0.003*
Mean ± SD.	77.04 ± 9.18	83.60 ± 4.16		
Median (IQR)	79.0 (69.0-84.0)	83.0 (81.0-87.0)		
Sector-Superiotemporal				
Min.-Max.	62.0-102.0	77.0-90.0	3.897*	0.001*
Mean ± SD.	75.40 ± 10.25	83.80 ± 3.33		
Median (IQR)	75.0 (67.0-80.0)	84.0 (82.0-86.0)		
Sector-Inferior				
Min.-Max.	65.0-87.0	75.0-91.0	4.647*	<0.001*
Mean ± SD.	75.32 ± 6.44	82.76 ± 4.75		
Median (IQR)	77.0 (69.0-81.0)	83.0 (80.0-86.0)		
Sector-Inferionasal				
Min.-Max.	55.0-89.0	68.0-92.0	3.951*	<0.001*
Mean ± SD.	74.80 ± 9.19	83.84 ± 6.82		
Median (IQR)	75.0 (69.0-82.0)	85.0 (83.0-88.0)		
Sector-Inferiotemporal				
Min.-Max.	55.0-87.0	69.0-92.0	4.374*	<0.001*
Mean ± SD.	73.56 ± 9.31	83.64 ± 6.79		
Median (IQR)	75.0 (65.0-82.0)	86.0 (81.0-88.0)		
RNFL thickness	**Diabetic group (n = 25)**	**Non-diabetic group (n = 25)**	**T**	**P**
Average				
Min.-Max.	78.0-100.0	85.0-102.0	2.892*	0.006*
Mean ± SD.	89.04 ± 6.56	94.0 ± 5.52		
Median (IQR)	90.0 (83.0-95.0)	94.0 (90.0-98.0)		
Sector-Superior				
Min.-Max.	88.0-133.0	102.0-139.0	1.564	0.125
Mean ± SD.	108.8 ± 15.02	114.6 ± 10.86		
Median (IQR)	105.0 (95.0-121.0)	112.0 (107.0-119.0)		
Sector-Nasal				
Min.-Max.	52.0-80.0	54.0-87.0	2.018*	0.049*
Mean ± SD.	67.96 ± 8.15	73.04 ± 9.59		
Median (IQR)	71.0 (63.0-74.0)	74.0 (64.0-82.0)		
Sector-Inferior				
Min.-Max.	94.0-153.0	106.0-142.0	0.596	0.554
Mean ± SD.	118.0 ± 12.59	120.0 ± 11.07		
Median (IQR)	118.0 (113.0-123.0)	116.0 (113.0-127.0)		
Sector-Temporal				
Min.-Max.	49.0-71.0	50.0-87.0	2.912*	0.005*
Mean ± SD.	61.04 ± 6.07	67.72 ± 9.73		
Median (IQR)	61.0 (57.0-65.0)	67.0 (61.0-73.0)		

*Significant as $p<0.05$. RNFL: Retinal nerve fiber layer, GCL: Ganglion Cell Layer.

Table 2: Correlation between duration of DM (years) and HbA1c (%) with Macular thickness, GCL thickness and RNFL thickness in diabetic group

	Duration of DM (years)		**HbA1c (%)**	
	R	**p**	**R**	**P**
Macular thickness				
Center	-0.140	0.504	-0.208	0.319
Inner-Superior	-0.103	0.623	-0.085	0.687
Inner-Nasal	-0.165	0.432	-0.344	0.093
Inner-Inferior	-0.069	0.744	-0.326	0.112
Inner-Temporal	-0.158	0.450	-0.166	0.427
Outer-Superior	-0.286	0.166	-0.149	0.479
Outer-Nasal	-0.125	0.552	-0.265	0.200
Outer-Inferior	-0.090	0.669	-0.205	0.326
Outer-Temporal	-0.252	0.225	-0.173	0.407
Ganglion cell layer thickness				
Average	-0.592	0.002*	-0.492	0.013*
Sector-Superior	-0.569	0.003*	-0.461	0.020*
Sector-Superior nasal	-0.536	0.006*	-0.567	0.003*
Sector-Superior temporal	-0.519	0.008*	-0.487	0.014*
Sector-Inferior	-0.529	0.007*	-0.392	0.052
Sector-Inferior nasal	-0.411	0.041*	-0.333	0.104
Sector-Inferior temporal	-0.461	0.020*	-0.325	0.113
RNFL thickness				
Average	-0.715	<0.001*	-0.442	0.027*

Sector-Superior	-0.411	0.041*	-0.397	0.049*
Sector-Nasal	-0.579	0.002*	-0.152	0.467
Sector-Inferior	-0.425	0.034*	-0.218	0.295
Sector-Temporal	-0.425	0.034*	-0.286	0.167

*Significant as $p<0.05$. HbA1c: Glycated haemoglobin, RNFL: Retinal nerve fiber layer, DM: Diabetes mellitus, GCL: Ganglion Cell Layer.

Table 3: Correlation between duration of DM (years) with Ganglion cell layer thickness and RNFL thickness in diabetic group

		Duration of DM (years)		T	P
		<10 (n = 13)	≥10 (n = 12)		
Ganglion cell layer thickness	**Average**				
	Mean ± SD.	79.46 ± 5.98	72.33 ± 7.78	2.580*	0.017*
	Median (Min. – Max.)	81.0 (70.0 – 90.0)	69.50 (64.0 – 85.0)		
	Sector-Superior				
	Mean ± SD.	79.69 ± 5.33	73.92 ± 8.15	2.114*	0.046*
	Median (Min. – Max.)	81.0 (72.0 – 86.0)	71.50 (65.0 – 87.0)		
	Sector-Superior nasal				
	Mean ± SD.	80.23 ± 7.54	73.58 ± 9.83	1.906	0.069
	Median (Min. – Max.)	80.0 (70.0 – 95.0)	69.0 (64.0 – 90.0)		
	Sector-Superior temporal				
	Mean ± SD.	78.92 ± 9.38	71.58 ± 10.14	1.881	0.073
	Median (Min. – Max.)	79.0 (65.0 – 102.0)	67.0 (62.0 – 91.0)		
	Sector-Inferior				
	Mean ± SD.	78.15 ± 5.98	72.25 ± 5.63	2.536*	0.018*
	Median (Min. – Max.)	79.0 (65.0 – 87.0)	69.50 (67.0 – 82.0)		
	Sector-Inferior nasal				
	Mean ± SD.	77.31 ± 10.65	72.08 ± 6.71	1.453	0.160
	Median (Min. – Max.)	82.0 (55.0 – 89.0)	72.0 (59.0 – 83.0)		
	Sector-Inferior temporal				
	Mean ± SD.	76.31 ± 10.0	70.58 ± 7.82	1.584	0.127
	Median (Min. – Max.)	81.0 (55.0 – 87.0)	69.0 (62.0 – 82.0)		
	Median (Min. – Max.)	61.0 (55.0 – 71.0)	60.50 (49.0 – 71.0)		
		Duration of DM (years)		**T**	**P**
		<10 (n = 13)	**≥10 (n = 12)**		
RNFL thickness	**Average**				
	Mean ± SD.	92.85 ± 5.11	84.92 ± 5.45	3.753*	0.001*
	Median (Min. – Max.)	92.0 (82.0 – 100.0)	84.0 (78.0 – 96.0)		
	Sector-S				
	Mean ± SD.	109.08 ± 15.97	108.58 ± 14.63	0.080	0.937
	Median (Min. – Max.)	101.0 (92.0 – 133.0)	108.0 (88.0 – 133.0)		
	Sector-N				
	Mean ± SD.	74.15 ± 2.70	61.25 ± 6.52	6.365*	<0.001*
	Median (Min. – Max.)	74.0 (70.0 – 80.0)	62.50 (52.0 – 71.0)		
	Sector-I				
	Mean ± SD.	125.77 ± 10.42	109.58 ± 8.88	4.163*	<0.001*
	Median (Min. – Max.)	123.0 (111.0 – 153.0)	113.50 (94.0 – 118.0)		
	Sector-T				
	Mean ± SD.	61.85 ± 5.61	60.17 ± 6.67	0.683	0.501
	Median (Min. – Max.)	61.0 (55.0 – 71.0)	60.50 (49.0 – 71.0)		

*Significant as $p<0.05$. DM: Diabetes mellitus, RNFL: Retinal nerve fiber layer.

Table 4: Correlation between HbA1c (%) with Ganglion cell layer thickness and RNFL thickness in diabetic group

		HbA1c (%)		T	p
		≤7 (n = 8)	>7 (n = 17)		
Ganglion cell layer thickness	**Average**				
	Mean ± SD.	82.0 ± 3.59	73.24 ± 7.52	3.108*	0.005*
	Median (Min. – Max.)	82.0 (75.0 – 86.0)	71.0 (64.0 – 90.0)		
	Sector-S				
	Mean ± SD.	82.63 ± 3.50	74.24 ± 7.12	3.134*	0.005*
	Median (Min. – Max.)	83.0 (77.0 – 87.0)	72.0 (65.0 – 86.0)		
	Sector-SN				
	Mean ± SD.	84.75 ± 4.56	73.41 ± 8.57	3.489*	0.002*
	Median (Min. – Max.)	86.0 (79.0 – 90.0)	70.0 (64.0 – 95.0)		
	Sector-ST				
	Mean ± SD.	82.63 ± 6.07	72.0 ± 10.16	2.721*	0.012*
	Median (Min. – Max.)	82.50 (73.0 – 91.0)	68.0 (62.0 – 102.0)		
	Sector-I				
	Mean ± SD.	79.63 ± 2.39	73.29 ± 6.79	3.422*	0.002*
	Median (Min. – Max.)	80.0 (75.0 – 82.0)	70.0 (65.0 – 87.0)		

	Sector-IN				
	Mean ± SD.	81.0 ± 4.24	71.88 ± 9.51	2.571*	0.017*
	Median (Min. – Max.)	81.50 (75.0 – 87.0)	73.0 (55.0 – 89.0)		
	Sector-IT				
	Mean ± SD.	80.0 ± 4.38	70.53 ± 9.54	3.403*	0.002*
	Median (Min. – Max.)	82.0 (71.0 – 84.0)	72.0 (55.0 – 87.0)		
		HbA1c (%)		**t**	**p**
		≤7 (n = 8)	**>7 (n = 17)**		
RNFL thickness	**Average**				
	Mean ± SD.	92.75 ± 6.07	87.29 ± 6.19	2.068*	0.050*
	Median (Min. – Max.)	93.50 (82.0 – 100.0)	87.0 (78.0 – 98.0)		
	Sector-S				
	Mean ± SD.	116.0 ± 11.72	105.47 ± 15.51	1.698	0.103
	Median (Min. – Max.)	116.0 (93.0 – 130.0)	98.0 (88.0 – 133.0)		
	Sector-N				
	Mean ± SD.	69.0 ± 5.21	67.47 ± 9.33	0.430	0.671
	Median (Min. – Max.)	70.50 (62.0 – 74.0)	71.0 (52.0 – 80.0)		
	Sector-I				
	Mean ± SD.	121.50 ± 13.37	116.35 ± 12.27	0.952	0.351
	Median (Min. – Max.)	117.50 (111.0 – 153.0)	118.0 (94.0 – 134.0)		
	Sector-T				
	Mean ± SD.	64.50 ± 5.53	59.41 ± 5.76	2.086*	0.048*
	Median (Min. – Max.)	65.50 (55.0 – 71.0)	59.0 (49.0 – 71.0)		

*Significant as $p<0.05$. HbA1c: Glycated haemoglobin, RNFL: Retinal nerve fiber layer.

Discussion

Traditionally, DR in individuals with DM was seen as a vascular condition. However, recent studies suggested that neuropathy could also cause retinal degeneration in DM, not only by vasculopathy [11].

Multiple research have revealed loss of ganglion cell bodies, neural apoptosis, glial reactivity, and reduced thickness of the inner layers of the retina in the earliest stages of DR. Some claim that diabetes induces retinal neuropathy via a micro-vascular mechanism [12].

Our objective was to assess the retinal neurodegeneration in cases with type 2 diabetes mellitus (T2DM) without DR by using OCT.

The present research reported that the analysis of macular thickness as regards the central 1mm zone showed insignificant difference between diabetic group and non-diabetic group. While diabetic group had a significantly decreased macular thickness compared to non-diabetic group as regards: inner superior sector, inner nasal sector, inner inferior sector, inner temporal sector, outer superior sector, outer nasal sector, outer inferior sector and outer temporal sector.

Opposing to our results, Dumitrescu *et al.* [13], who measured retinal vessel caliber and early changes in macular thickness between cases having T2DM without DR compared with healthy controls using OCT, found that at the central 1mm zone, the diabetic group had a significantly thinner mean macular thickness compared to the controls, also, except for the central 1mm zone, the macular thickness in all quadrants was insignificantly different between the diabetic patients and the controls, this discrepancy might be explained by the duration of T2DM in participants in the Dumitrescu study were at least 5 years, but not more than 10 years, however in our study we included the diabetes group with duration of T2DM more than 10 years.

Furthermore, our results revealed a significant decrease in the GCL thickness in diabetic group compared to nondiabetic group as regards: superotemporal, superonasal, superior, average, inferotemporal, inferonasal and inferior sectors.

These findings are in accordance with Carpineto *et al.* [14] who studied the neuroretinal alterations in cases with T2DM without DR or mild non proliferative DR (NPDR) and with no sign of diabetic macular edema using OCT, the results showed that diabetic patients had a significant reduction in GCL thickness regarding the average, superior, superotemporal, inferior, inferonasal and inferotemporal sectors.

This result is not compatible with a study performed by Öztürk *et al.*, [15] who identified early ocular changes in children and adolescents with type 1 diabetes mellitus (T1DM) without DR using OCT and optical biometry, this study found that there was a significant thinner central RNFL thicknesses in T1DM compared to the control group, there were not any significant differences between the nasal and temporal RNFL thicknesses of the groups.

This discrepancy between our result and this result may be due to Öztürk's study being done in children and aldolesent with age ranging from 10 to 18 years old and also that the cases were all suffering with T1DM, however, we included cases with T2DM only.

The current research reported the correlation between the duration of DM (years) with GCL thickness and RNFL thickness in group A, revealing a significant negative correlation between DM duration and GCL thickness and RNFL thickness.

Our results are in harmony with Ezhilvendhan *et al.*,[16] who evaluated macular thickness, RNFL and GCL thickness in cases with T2DM using OCT, they revealed a significant negative correlation between DM duration and the GCL thickness and RNFL thickness.

The present study revealed a significant negative correlation between HbA1c and the GCL thickness in diabetic group as regards (average, superior, supero nasal and superotemporal), also, a significant negative correlation was reported between HbA1c and RNFL thickness in diabetic group as regards (average and superior quadrant).

Our results are compatible with Mikhail *et al.*, [17] who studied correlation of RNFL and ganglion cell complex thickness with HbA1c in diabetic patients, they reported a significant negative correlation between HbA1c and RNFL thickness in diabetic group as regards (average, superior, nasal and inferior quadrants). Moreover, a significant negative correlation was reported between HbA1c and GCL

thickness in diabetic group as regards (average, superior, and inferior sectors).

In the present research, the cases of diabetic group were distributed according to duration of DM, and HbA1c. The relation between the DM duration and RNFL thickness and GCL thickness was investigated. According to RNFL thickness our results revealed that cases with DM duration longer than 10 years had a significant reduction in RNFL thickness in average, nasal sector and inferior sector compared to cases with DM duration < 10 years.

Garcia-Martin *et al*. [11] investigated the neurodegeneration in cases with T2DM without DR using SD-OCT. They focused on measurement of GCL thickness, macular thickness and RNFL thickness, the results reported that the cases with DM duration longer than 10 years had a significant retinal thinning in the RNFL thickness in the average, superior-temporal and inferior-temporal quadrants compared to cases with a DM duration < 10 years. It is suggested that the prolonged hyperglycemia could induce retinal inflammation and hypoxia, causing impairment in the neural function and retinal structures.

The present study showed a relationship between the DM duration (years) and GCL thickness, revealing a significantly reduced GCL thickness in cases with DM duration longer than 10 years as regards (average, superior and inferior sectors) compared to cases with DM duration of < 10 years. Cetin *et al*., [18] showed the same result as they assessed the course of neurodegeneration based on retinal layer thickness and integrity analysis in DM cases without DR and its relation to inner retinal reflectivity. They reported a significant reduction in the GCL thickness in cases with DM duration of longer than 10 years in the pericentral, superior and inferior sectors compared to cases with a DM duration < 10 years.

The current study revealed that the patients with poor metabolic control HbA1c more than 7% presented a significant reduction in RNFL thickness in average and temporal quadrant compared to those patients with good metabolic control HbA1c less than 7%.

Garcia-Martin *et al*.,[11] reported a significant retinal thinning in RNFL thickness in the superior and superior-nasal sectors in cases with poor metabolic control (HbA1C > 7%) compared to cases with controlled HbA1C < 7%.

The current study demonstrated that the patients with poor metabolic control HbA1c more than 7% presented a significantly reduced GCL thickness as regards (average, superior, superonasal, superotemporal, inferior, inferonasal and inferotemporal sectors) compared to those patients with good metabolic control HbA1c less than 7%. Mikhail *et al*., [17]showed similar results in his study which evaluated correlation of RNFL and ganglion cell complex thickness with HbA1c in cases with DM, the results exhibited that cases with poor metabolic control (HbA1c > 7%) presented a significantly reduced GCL thickness in (average, superior, superonasal, superotemporal, inferior sector, inferonasal and inferotemporal sectors) compared to patients with HbA1c < 7%.

Conclusion

Retinal neurodegeneration including macular GCL, peripapillary RNFL and macular thinning are early events in DR before vascular events. We recommended studies with larger number of cases, OCT and FA follow up of diabetic patients with early retinal neurodegeneration every 6monthes to evaluate the time before vascular changes.

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