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ORIGINAL ARTICLE

Evaluation of Neuroretinal Changes in Type II Diabetes Mellitus Without Diabetic Retinopathy Using Optical Coherence Tomography

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Abstract

Background: **Microaneurysm proliferation is the hallmark of the early stages of diabetic retinopathy (DR). It is the mild form of NPDR. with increased severity, the progression to PDR occurs which is characterized by the formation of new blood vessels on the retina and posterior surface of the vitreous, and it develops from moderate or severe NPDR by a process of increased vascular permeability and occlusion.**

Aim: **To assess neurodegeneration in individuals with type II diabetes mellitus (type II DM) who do not have DR.**

Patients and methods: **Full ophthalmic examination and Spectral is optical coherence tomography was performed on 50 eyes of 25 patients with type II DM and do not have DR, and on 50 eyes of 25 healthy controls. The thickness of the peripapillary retinal nerve fiber layer (RNFL) and the macular ganglion cell complex (GCL) were measured. The RNFL thickness in the peripheral retina was measured with a glaucoma application. Comparison was done between patients with DM without DR of different disease duration and healthy control patient.**

Results: **Macular GCL (avg inf, avg sup, avg total) significantly decreased in cases contrasted with controls. The average inf is more affected in the patient than control and in patients with longer duration than with early disease and with higher HBA1C than with lower measures (negative correlation) peripapillary RNFL thickness is significantly reduced in almost all sectors except inferonasal sector in patients (non-significant difference) compared with the controls and decrease more in longer diabetic duration and higher HbA1c.**

Conclusion: **Retinal neurodegeneration occurs early before DR present.**

Keywords: Diabetes mellitus, Diabetic retinopathy, Neuroretinal changes

1. Introduction

One of the most significant complications of diabetes mellitus (DM) is diabetic retinopathy (DR), which is the leading cause of blindness in industrialized nations.[1]

Current DR therapies focus on the latter stages of the illness, but it is more important to assess the effectiveness of screening for diabetic alterations and treating early-stage DR. There is some debate about whether DR originates as a primary microvasculopathy, a neurodegenerative disease, or some mix of the two.[2,3]

Retinal neurodegeneration is now thought to play an important part in the pathogenesis of DR, shifting the focus away from the previously held belief that DR is a microvascular condition.[4,5]

Microvascular anomalies and angiogenesis are currently thought to represent late manifestations of DR, rather than the primary culprit in retinal degeneration.[6]

Current research has suggested that neurodegenerations in the diabetic retina may occur before the onset of microvascular problems. Studies on neurodegeneration in the retina and neuroprotective techniques to protect vision in diabetes cases have increased in recent years.[1,4]

Preceding clinically detectable micro-vascular alterations arise, structural examination of retinal neurodegenerations may be a useful method for

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identifying persons at high risk for developing DR.[7,8]

Optical coherence tomography (OCT) is quick, requires no case preparation and the results may be viewed right away; it is also capable of offering structural information. The quantitative data gleaned from modern macular or peripapillary thickness assessments is helpful in making diagnoses and tracking the course of eye diseases.[9]

2. Aim

The objective of the research is to assess early structural neuroretinal changes in the macular area (outer retinal layer thickness and GCL layer thickness) of cases with type II DM without clinical signs of diabetic retinopathy (i.e., retinal vascular alterations or maculopathy) using OCT.

3. Patients and methods

3.1. Sample size

This research was designed to be prospective case control study including 50 individuals, the cases were randomly selected from attendants to Tanta ophthalmic hospital and divided into two groups: group A, 25 healthy individuals without diabetes or any occular or systemic diseases, they are the control group. Group B, 25 diabetic patients 'type II DM' without clinical diabetic retinopathy macular edema or microvascular changes.

The Inclusion criteria were: Healthy nondiabetic people with normal vision as control group, Type II DM patients without DR i. e macular edema or microvascular changes. While the Exclusion criteria were: diabetic pateints with macular edema, diabetic patients with microvascular changes, people with known systemic diseases affecting the eye, people with occular diseases affecting the retina other than DM, type I DM.

All participants were consented to participate in this study. All patients were evaluated as follows: full history was taken including the duration and the control of diabetes, measurement of HbA1c and careful ophthalmic examination involving: best corrected visual acuity, anterior segment examination, slit lamp biomicroscopy, intraocular pressure, pupillary reflexs and posterior segment examination by slit lamp biomicroscopy using 90 volk lens.

OCT macula was done for all patients by spectral domain optivue machine to measure outer retinal layer thickness and GCL thickness, and compare the findings among diabetic and healthy individuals. Fundus Fluorescein Angiography (FFA) was done for all participants to exclude vascular changes and macular edema. All the patients were rechecked after 1 month as routine follow-up. The patients will be followed-up after one month for a full examination.

3.2. Statistical analysis

Data were gathered, reviewed, and coded before being loaded into version 23 of the Statistical Package for Social Science (IBM SPSS). When the data was determined to be parametric, the mean, standard deviations, and ranges were reported. When the data were revealed to be non-parametric, the median and inter-quartile range (IQR) were presented. Likewise, numerical and percentage representations of qualitative data were provided.

When the predicted count in any cell was discovered to be less than 5, the χ^2 test or the Fisher exact test was used to do the comparison between the groups utilizing the qualitative data.

The comparison of two independent groups with quantitative data and parametric distribution was carried out with the help of the Independent t-test, whilst the comparisons of the groups with nonparametric distributions were carried out with the assistance of the Mann–Whitney test.

When determining whether or not there was a link between two quantitative factors that belonged to the same group, the Spearman correlation coefficient was utilized.

The receiver operating characteristic curve (ROC) was evaluated to determine the optimal cutoff point for the examined marker, taking into consideration its sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC).

The margin of error that was acceptable was set at 5%, and the confidence interval was configured to be 95%. Therefore, the following criteria were used to determine whether or not the *P*-value was significant: If the *P*-value is greater than 0.05, the result is insignificant (NS), if it is less than 0.05, the result is significant (S), and if it is less than 0.01, the result is highly significant (HS).

4. Results

This study included 50 eyes of 25 healthy individuals with ageing range from 48 to 54 years and 50 eyes of 25 DM patients with ageing range from 47 to 57 years.

4.1. Demographic data

4.1.1. Mean age

The mean age for the 25 normal healthy individuals was (50.64 years ± 2.06 SD) ranging from (48–54) years and the mean age for the 25 DM cases was (51.96 years ± 2.76 SD) ranging from (47–57) years. No statistically significant variance was found among control and patients groups concerning mean age (*P*-value 0.061) (Table 1).

4.1.2. Sex distribution

The 25 healthy normal patients included 11 (44%) males and 14 (56%) females. The 25 DM patients included 16 (64%) males and 9 (36%) females. There was no statistically significant variance among the control and the case groups concerning sex distribution (*P*-value 0.156) (Table 1).

4.1.3. Mean duration of DM (years)

The median duration of DM (5.5 years 4.5–7) was ranged from 3 to 8 years (Table 1).

4.1.4. Mean HbA1c (%)

The control group included mean HbA1c (±SD) as (5.12% ± 0.55), ranged from 4.2 to 5.8% and the DM patient group included mean HbA1c (±SD) as (7.87% ± 0.67), ranged from 6.4 to 9%. There was highly statistically significant difference between the control and the patient groups regarding HbA1c *P* value 0.000 (Table 1).

4.1.5. Refraction

The refraction of healthy individuals is of median ± 1.53 (1.5–2.75) ranged from −3.5 to 3.00 and the refraction of DM individuals is of median ± 2 (0.2–3) range from −3.5 to 3.5. There is no significant variance in the refraction among healthy and DM cases (Table 1).

4.1.6. Type of diabetes mellitus

All DM patients group are of type II DM without DR and on diabetic treatment tablets orally.

The previous table displays that there was no statistically significant variance among control and patients group regarding mean age and gender while there was statistically significant variance among both groups regarding HbA1c found greater in patients than control group.

4.2. Ophthalmological examinations

4.2.1. BCVA

The mean best corrected visual acuity (BCVA) (±SD) recorded using E chart in control was (0.93 ± 0.11) and in DM patients was (0.77 ± 0.14) (Table 2). A highly statistically significant variance was found among control and patients group concerning BCVA (*P*-value 0.003).

4.2.2. IOP

The intra occular pressure (IOP) of healthy individuals is of mean 13.7 ± 1.36 and diabetic

Table 1. Comparison among control and cases group concerning demographic data of the investigated subjects.

	Control group No. = 25	Patients group No. = 25	Test value	*P*-value	Significance
Sex					
Female	14 (56.0%)	9 (36.0%)	2.013[a]	0.156	NS
Male	11 (44.0%)	16 (64.0%)			
Age (ye)					
Mean ± SD	50.64 ± 2.06	51.96 ± 2.76	−1.916[b]	0.061	NS
Range	48–54	47–57			
Refraction					
Median (IQR)	1.53 (−1.5–2.75)	2 (0.5–3)	−1.111[c]	0.266	NS
Range	−3.5–3	−3.5–3.5			
Hba1c					
Mean ± SD	5.12 ± 0.55	7.87 ± 0.67	−15.810[b]	0.000	HS
Range	4.2–5.8	6.4–9			
Type of DM treatment					
TAB	0	25 (100.0%)	–	–	–
Diabetic duration (years)					
Median (IQR)	–	5.50 (4.5–7)	–	–	–
Range	–	3–8			

P-value greater than 0.05: Nonsignificant; *P*-value less than 0.05: Significant; *P*-value less than 0.01: Highly significant.

[a] Chi-square test.

[b] Independent t-test.

[c] Mann-Whitney test.

Table 2. Comparison among control and patient groups regarding BCVA and IOP.

	Control group No. = 50	Patients group No. = 50	Test value	*P*-value	Significance
BCVA					
Mean ± SD	0.93 ± 0.11	0.77 ± 0.14	6.707•	0.000	HS
Range	0.7–1	0.5–1			
IOP					
Mean ± SD	13.70 ± 1.36	13.66 ± 1.21	0.156•	0.877	NS
Range	12–16	12–16			

BCVA, best corrected visual acuity; IOP, intra occular pressure.

individuals is 13.66 ± 1.21 both heathy and diabetic ranged from 12 to 16 (Table 2).

The previous table demonstrations a greatly statistically significant variance was found among control and patients group concerning BCVA (*P*-value 0.003) and no statistically significant variance among control and patients groups concerning IOP.

4.3. Structural OCT data

4.3.1. Mean GCC layer thickness (um)

There were significant variances in the thickness of total, sup, inf, ganglion cell complex (GCC) (RNFL + GCL + IPL) thickness values amongst DM group (92.40 ± 4.70 μ, 92.71 ± 6.10, 91.64 ± 4.92, and control group (103.00 ± 10.35 μm) 104.53 ± 12.90, 101.34 ± 8.64 ($P < 0.001$) 0.000 (Table 3). So the total, superior and inferior quadrants of GCC were significantly more thinner in the groups 1 DM in contrast to control healthy group (Table 3) (*P* values < 0.001) (Table 3).

The previous table shows that there were greatly significant variances in the thickness of total, sup, inf, GCC (RNFL + GCL + IPL) thickness values among DM group and control group ($P < 0.001$) 0.000. So the total, superior and inferior quadrants of GCC were significantly more thinner in the groups 1 DM in contrast to the control healthy group (Table 3) (*P* values < 0.001).

The previous table demonstrations that there were statistically significant differences of peripappillary retinal nerve fiber layer (RNFL) thickness using glaucoma application technique in all sectors except inferonasal sector average, superior average, inferior average, superotemporal, superonasal, inferotemporal and inferonasal, temooral upper, temporal lower, nasal upper, nasal lower, average upper, average lower, average temporal, average nasal between the studied two groups (Table 4).

4.3.2. Correlation between the studied parameters and diabetic duration

In the diabetic cases without retinopathy, there was a significant negative association among total, superior and inferior GCC, peripappillary RNFL thickness in all sectors, with duration of DM (Table 5).

Spearman correlation coefficient: The previous table reveals that there was a negative correlation for diabetes duration with GCC average, GCC superior average, GCC inferior average and RNFL average temporal.

4.3.3. Correlation between the studied parameters and HbA1c

In the diabetic cases without retinopathy, there was a significant negative association amongst TOTAL, superior and inferior GCC, peripappillary RNFL thickness all sectors with HBA1c duration of DM (Table 6).

The previous table displays that there was a negative relationship for HbA1c with GCC average, GCC superior average, GCC inferior average and RNFL average temporal.

Table 3. Comparison between control and patient groups regarding GCC thickness total average, superior average and inferior average.

	Control group No. = 50	Patients group No. = 50	Test value	*P*-value	Significance
GCC average					
Mean ± SD	103.00 ± 10.35	92.40 ± 4.70	6.596•	0.000	HS
Range	89.47–132.17	80.42–99.91			
GCC superior average					
Mean ± SD	104.53 ± 12.90	92.71 ± 6.10	5.859•	0.000	HS
Range	89.46–138.82	77.91–101.81			
GCC inferior average					
Mean ± SD	101.34 ± 8.64	91.64 ± 4.92	6.898•	0.000	HS
Range	90.01–125.52	81.02–107.66			

GCC, ganglion cell complex.

Table 4. Comparison of retinal nerve fiber layer thickness sectors between control and patient groups.

	Control group No. = 50	Patients group No. = 50	Test value	*P*-value	Significance
RNFL average					
Mean ± SD	107.42 ± 5.47	93.35 ± 20.68	4.653•	0.000	HS
Range	98.95–115.89	10.37–119.18			
RNFL superior average					
Mean ± SD	112.47 ± 6.73	99.17 ± 14.13	6.009•	0.000	HS
Range	102.15–125.78	70.12–119.6			
RNFL inferior average					
Mean ± SD	102.39 ± 7.13	94.73 ± 11.85	3.915•	0.000	HS
Range	91.98–114.73	72.44–124.06			
RNFL superio-temporal					
Mean ± SD	144.52 ± 9.75	126.38 ± 19.83	5.804•	0.000	HS
Range	126–159	81–160			
RNFL superio-nasal					
Mean ± SD	131.50 ± 17.73	114.22 ± 20.47	4.512•	0.000	HS
Range	104–163	69–155			
RNFL infero-temporal					
Mean ± SD	144.50 ± 7.41	123.32 ± 19.61	7.144•	0.000	HS
Range	134–158	79–166			
RNFL Infero-nasal					
Mean ± SD	115.43 ± 24.14	113.68 ± 19.76	0.397•	0.692	NS
Range	76–155	88–170			
RNFL temporal-upper					
Mean ± SD	85.63 ± 14.98	74.72 ± 21.14	2.977•	0.004	HS
Range	63–107	9–142			
RNFL temporal-lower					
Mean ± SD	76.17 ± 9.05	67.48 ± 9.79	4.608•	0.000	HS
Range	58–96	40–81			
RNFL Nasal-upper					
Mean ± SD	87.18 ± 12.09	77.46 ± 16.40	3.373•	0.001	HS
Range	70–112	41–111			
RNFL Nasal-lower					
Mean ± SD	73.47 ± 8.11	66.04 ± 11.51	3.732•	0.000	HS
Range	59–90	41–87			
RNFL average superior					
Mean ± SD	138.14 ± 9.72	120.30 ± 17.24	6.374•	0.000	HS
Range	120–151	82–149			
RNFL average inferior					
Mean ± SD	130.19 ± 13.06	117.38 ± 15.90	4.402•	0.000	HS
Range	107–155	84–167			
RNFL average temporal					
Mean ± SD	81.19 ± 10.37	72.50 ± 11.86	3.899•	0.000	HS
Range	61–96	47–110			
RNFL average nasal					
Mean ± SD	80.66 ± 9.25	72.14 ± 13.57	3.668•	0.000	HS
Range	67–98	41–99			

4.4. Sensitivity and specificity of these measures to detect early diabetic affection

The area under the ROC, also known as the AUC, was utilized to investigate both the sensitivity and the specificity. In those with diabetes who did not have DR, the widest regions of the ROC curves for GCC thickness were observed in the inferior quadrants (AUC = 0.861, cutoff = 94.28). These quadrants had a sensitivity of 78% and a specificity of 92%. The overall average (AUC = 0.839) was the next largest part of the curve (Table 7).

The widest parts of the ROC curves of peripapillary RNFL thickness in the diabetic patients is at inferotemporal sector and followed by average superior followed by the superior average with AUC of (0.858, 0.821, 0.795), cutoff (131, 124, 102.04) and with sensitivity (80, 68, 54) and specificity (100, 88, 100) (Table 7).

The previous ROC curve displays that the best cut off point for GCC average to detect effect of DM was found less than or equal to 93.37 with a sensitivity of 64%, specificity of 92,% and AUC of 83.9%, GCC superior less than or equal to 98.95, sensitivity of

Table 5. Association among Diabetic duration and other studied parameters among patients group.

	Diabetic duration (years)	
	R	*P*-value
Hba1c	**0.796****	**0.000**
Refraction	0.147	0.310
BCVA	−0.007	0.960
IOP	0.069	0.633
GCC average	**−0.535****	**0.000**
GCC superior average	**−0.349***	**0.013**
GCC inferior average	**−0.394****	**0.005**
RNFL average	−0.108	0.457
RNFL superior average	−0.238	0.097
RNFL inferior average	−0.162	0.261
RNFL superio-temporal	−0.096	0.506
RNFL superio-nasal	−0.129	0.371
RNFL infero-temporal	**−0.382****	**0.006**
RNFL Infero-nasal	0.172	0.232
RNFL temporal-upper	**−0.281***	**0.048**
RNFL temporal-lower	**−0.295***	**0.038**
RNFL Nasal-upper	−0.243	0.089
RNFL Nasal-lower	−0.135	0.351
RNFL average superior	−0.137	0.341
RNFL average inferior	**−0.362***	**0.010**
RNFL average temporal	**−0.360***	**0.010**
RNFL average nasal	−0.184	0.200

BCVA, best corrected visual acuity; GCC, ganglion cell complex; IOP, intra occular pressure.

Table 6. Correlation of HBA1C with different ophthalmologial parameters.

	HbA1c	
	R	*P*-value
Diabetic duration (y)	**0.796****	**0.000**
Refraction	0.103	0.476
BCVA	−0.125	0.388
IOP	−0.123	0.396
GCC average	**−0.702****	**0.000**
GCC superior average	**−0.331***	**0.019**
GCC inferior average	**−0.611****	**0.000**
RNFL average	−0.168	0.244
RNFL superior average	−0.207	0.149
RNFL inferior average	−0.129	0.370
RNFL superio-temporal	−0.114	0.431
RNFL superio-nasal	−0.009	0.950
RNFL infero-temporal	**−0.519****	**0.000**
RNFL Infero-nasal	0.151	0.294
RNFL temporal-upper	**−0.358***	**0.011**
RNFL temporal-lower	**−0.321***	**0.023**
RNFL Nasal-upper	−0.113	0.435
RNFL Nasal-lower	−0.077	0.596
RNFL average superior	−0.084	0.561
RNFL average inferior	**−0.326***	**0.021**
RNFL average temporal	**−0.490****	**0.000**
RNFL average nasal	−0.060	0.680

BCVA, best corrected visual acuity; GCC, ganglion cell complex; IOP, intra occular pressure.

94% and specificity of 66% and AUC of 85.1% also GCC inferior average with sensitivity of 64%, specificity of 92% and AUC of 80.4%.

5. Discussion

Some researchers hypothesized that neuropathy (a distinct mechanism from the common vascular issues seen in diabetic retinopathy) was to blame for ocular deterioration in DM cases.[10]

Nevertheless, the putative relationship between neuropathy and vasculopathy is yet unclear, despite the suggestion that neuropathic changes can precede microvascular modifications in these patients.[7]

Nevertheless, alterations affecting retinal neurons, which involve elevated apoptosis of the retinal ganglion cells and activation of the microglia,[11,12] have also been detected without indications of vascular abnormalities.

Reactive gliosis, apoptosis, thinning of the neural retina, and alterations in neurofilament and macroglia have all been found to occur in diabetic patients before the development of microangiopathy.[13,14]

Possibly preceding the microvascular anomalies in the etiology of DR is the degeneration of retinal neurons.[2,15]

Objectives to evaluate the validity of the investigated measures in predicting early diabetic alterations in the neural retina (GCL, IPL, and RNFL) in diabetic individuals without DR.

Assessment of retinal anatomical anomalies with OCT GCC and RNFL thicknesses analysis is a conventional, objective procedure.[16]

Spectral-domain OCT was used to examine the retinal alterations in 50 eyes of 25 individuals with type II DM who showed no signs of diabetic retinopathy.

In the present investigation, the mean GCC avg total, inf, sup and RNFL avg inf, sup temporal, nasal decreased significantly in the DM group compared with the control group ($P < 0.001$). This was the case despite the absence of microvascular changes in the DM group.

Because the GCL's health is so important to normal vision, these alterations are indicative of compromised retinal neuronal function indicating that diabetics have much worse vision than healthy controls.

Patients with DM (type 1 in Scarinci and Gundogan trials) but no diabetic retinopathy have had their macular GCL reduced in current studies.[17–19] Although the RNFL thickness did not change significantly in the diabetic group following adjusting for age, a separate research published within the past few years did find a decline in the macular RNFL and GCL in type II DM without diabetic retinopathy.[20]

Using the gold standard in Glaucoma applications, we measured the peripapillary RNFL thickness of our cases.

Table 7. Receiver operating characteristic curve for GCC parameters to assess the effect of diabetes.

Variables	Cut off point	Area under the curve	Sensitivity	Specificity	+PV	-PV
GCC average	≤93.37	0.839	64.00	92.00	88.9	71.9
GCC superior average	≤96.76	0.820	72.00	80.00	78.3	74.1
GCC inferior average	≤94.28	0.861	78.00	92.00	90.7	80.7

GCC, ganglion cell complex.

When comparing the diabetes group to the control group, we found that both the macular GCC and the peripapillary RNFL were significantly lower in the diabetic group.

HBA1c and the length of time someone has had diabetes affect GCC and RNFL thicknesses negatively ($P < 0.001$).

We compared GCC and RNFL characteristics for their ability to identify early and the most sensitive and specific alterations in the neural retina.

Regarding GCC: the widest areas of the ROC curves (AUC = 0.861, cutoff 94.82, 92 percent sensitivity, and 78% specificity) occurred during earlier DM stages, when the inferior GCC thickness was altered. Based on these results, it appears that measuring inferior GCC thickness might help detect structural alterations of the neuronal retina at an earlier stage.

Regarding RNFL: the inferotemporal sector thickness is most influenced in the first stages of DM, as seen by the largest sections of the ROC curves (AUC = 0.858, cutoff 131.0, 80% sensitivity, and 100% specificity).

5.1. Conclusion

Reduced macular GCC thickness and peripapillary RNFL thickness are signs of neuronal loss in preclinical DR.

Therefore, neurons in the macular region and axons in various parts of the optic disc are affected by neurodegeneration in individuals with type II DM before they develop diabetic retinopathy. Indicating that neurodegenerative alterations are present in these individuals prior to the onset of microvascular injury.

Our findings indicate that there is neurodegeneration in patients with type II DM who do not have diabetic retinopathy, most notably impacting neurons in the macula and temporal and inferior sectors of the optic disc. Subclinical ischemia, as well as other metabolic variables, may be a significant contribution to neurodegeneration in these patients. More long-term research is required to determine whether or not additional systemic DM problems, particularly ischemia, contribute to the pathophysiology of retinal neurodegeneration.

Conflicts of interest

There are no conflicts of interest.

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