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Assessment of Macular Thickness Using OCT in Patients with Diabetic Retinopathy in Relation to HbA1c

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ABSTRACT

Background: diabetic retinopathy (DR) is the specific micro vascular complication of diabetes mellitus (DM) and affects 1 of 3 with DM. DR remains a leading cause of vision loss in working adult population. Patients with severe levels of DR are reported to have poor quality of life and reduced physical, emotional and social wellbeing.

Objectives: to evaluate the relation of macular thickness to HbA1c in patients with diabetic retinopathy.

Patients and Methods: this study included 30 eyes of 16 patients with a diagnosis of diabetic retinopathy (DR). Patients were recruited from Retinal Clinic in Bab El-Shearyah University hospital and asked to participate in this study. This study was designed as an observational, cross-sectional and non-coherent study in the period from 12/2018 to 5/2019.

Results: the controlled HbA1c group and uncontrolled HbA1c group were comparable in age, sex, type of diabetes mellitus and best corrected visual acuity, but controlled HbA1c group had shorter duration of diabetes mellitus and lower glycosylated haemoglobin level than uncontrolled HbA1c group. Six (40.0%) patients of controlled HbA1c group were hypertensive patients and 11(73.3%) patients of uncontrolled HbA1c group were hypertensive patients.

Conclusion: intensive glycemic control might affect retinal vasculature and decrease ischemia and affect the development and progression of diabetic retinopathy.

Keywords: Macular Thickness, OCT, Diabetic Retinopathy, HbA1c

INTRODUCTION

The world is currently facing an epidemic risk called diabetes, according to WHO estimates. The number of people with diabetes worldwide will rise to 360 million by 2030 [(1)].

Diabetes mellitus is divided into two types, type 1 in which insulin production is predominantly damaged, and type 2 which is characterized by increased resistance to insulin, it's familial and related to limited physical activity and life style. Diabetic retinopathy is the specific micro vascular complication of diabetes mellitus and affects 1 of 3 with DM. DR remains a leading cause of vision loss in working adult population. Patients with severe levels of DR are reported to have poor quality of life and reduced physical, emotional and social wellbeing [(2)].

Diabetic retinopathy affects up to 80% of all patients who have had diabetes for 10 years or more[(3)].

Despite these alarming statistics, research suggests that at least 90% of these new cases can be reduced if there is careful treatment and eye control [(4)].

The longer the person has diabetes the higher his or her chances of developing diabetic retinopathy [(5)]. Each year in United States, diabetic retinopathy accounts for 12% of all new cases of blindness [(6)].

Diabetic retinopathy is a progressive disease predominantly affects the integrity of microscopic vessels found in the retina, DR can be divided into two clinical stages non proliferative and proliferative diabetic retinopathy [(7)].

The significant morbidity and mortality of diabetes mellitus predominantly results from its complications among which the vascular dysfunction leading to macular edema which resembles the most important vision threatening complication [(8)].

Proliferative diabetic retinopathy develops following the occlusion of retinal capillaries leading to retinal ischemia, which promotes the development of neovascularization, a process by which new blood vessels proliferates on the surface of the retina, however these vessels are fragile and bleed easily, The resulting accumulation of blood in the vitreous cavity from these hemorrhaging vessels seriously impairs vision. This may be permanent due to further complications as traction retinal detachment leading to registered blindness. It has been estimated that without treatment for proliferative diabetic retinopathy 50% of patients will become blind within 5 years following diagnosis [(9)].

Optical Coherence tomography (OCT) has become part of the standard care in ophthalmology. It provides cross sectional and three dimensional imaging of the anterior segment, retina and optic nerve head with micrometer scale-depth resolution [(10)].

With the help of (OCT), it's now possible to measure the macular thickness objectively and to follow the progression of diabetic retinopathy quantitatively [(11)].

Periodic glycosylated hemoglobin (HbA1c) measurements can reflect the long term control of hyperglycemia. Intensive glycemic control had been proved to be effective in decreasing incidence rate of development and progression of diabetic retinopathy in type 1 and type 2 diabetes mellitus as demonstrates by diabetes control and complications trials [(12)].

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AIM OF THE WORK

It is to evaluate the relation of macular thickness to HbA1c in patients with diabetic retinopathy.

PATIENTS AND METHODS

This study included 30 eyes of 16 patients with a diagnosis of diabetic retinopathy (DR). Patients were recruited from Retinal Clinic in Bab El-Shearyah University hospital and asked to participate in this study. This study was designed as an observational, cross-sectional and non-coherent study in the period from 12/2018 to 5/2019.

Ethical approval and Written informed consent:

An approval of the study was obtained from Al- Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Study Population:

Patients were divided into 2 groups:

- Controlled HbA1c group: 15 eyes with diabetic retinopathy with controlled glycosylated hemoglobin (HbA1c ≤7 %)
- Uncontrolled HbA1c group: 15 eyes with diabetic retinopathy with uncontrolled glycosylated hemoglobin (HbA1c >7%)

Inclusion criteria:

Type I and type II diabetic retinopathy patients (DR).

Exclusion criteria:

1- Presence of any other vascular or metabolic disease than DM.
2- Opaque cornea.
3- Opaque lens.
4- Refraction more than +6 or -6.
5- Photocoagulation Laser, intra vitreal injection and intra ocular surgery that have been done within 3 months before OCT assessment.
6- Glaucoma.

Study design:

All subjects participating in the study were asked to sign consent before inclusion. Then they were subjected to:

1- Full Medical history.
2- Blood sample was taken on the day of OCT assessment to measure HbA1c level and the patient was asked to fast at least for 6 hours before admission of blood sample.
3- Careful ocular examination on the day of OCT assessment.
4- Blood pressure examination using stethoscope and sphygmomanometer.

Ocular examination included:

a- Best corrected visual acuity (BCVA) using a Snellen chart: the patient was 6 m away from the chart; one eye at a time was tested with the fellow eye occluded. When the patient couldn't read the largest line of the chart, he moved slowly toward the chart until the largest letter could be read. If no letters could be read at any distance, we asked the patient to count fingers at progressively shorter distances. When finger counting was not possible, we checked for the perception of hand motions, then light perception with localization and finally, no light perception.
b- Intraocular pressure by Air Puff tonometer.
c- Anterior and posterior segment examination by a slit-lamp biomicroscopy.

Dilated fundus examination using slit-lamp biomicroscopy with a 90D lens

d- Refraction using Auto Refractometer.

Optical Coherence Tomography (OCT):

The same examiner performed all OCT measurements. Optical Coherence Tomography (OCT) measurement for central macular thickness was performed using the same device using (Topcon DRI OCT Triton plus Swept Source OCT ver 10.11), This OCT system introduce combined anterior and posterior segments examination, it uses super luminescent diodes with a wavelength of 1,050 nm. And a high speed of 100,000 A-scans per second.

Macular Thickness Measurements:

After pharmacological pupillary dilation using tropicamide eye drop 1.0% by putting 1 drop every 5 minutes 3 times, the Patients were asked to fixate on an internal fixation target during the scanning process and if fixation was not central, the external fixation target was used to move the scanning area centrally over the macula.

HbA1c level was measured in Bab El-Shearyah University hospital lab using COBAS INTEGRA 400 plus, the blood sample was taken in the same day of OCT assessment.

Statistical Analysis

The collected patient's data was revised, coded, tabulated and introduced to a PC using statistical package for social sciences (IBM SPSS VERSION 20.0). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. P-value: Level of significance: $P>0.05$: Non significant (NS) - $p<0.05$: Significant (S) - $p<0.01$: Highly significant (HS).

RESULTS

Table (1): Comparison between controlled HbA1c group and uncontrolled HbA1c group regarding age and sex

		Controlled group	Uncontrolled group	Test value	P-value	Sig.
		No. = 15	No. = 15			
Age (years)	Mean ± SD Range	43.87 ± 16.36 17 – 64	61.13 ± 8.68 51 – 76	-3.611•	0.001	HS
Sex	Male Female	6 (40.0%) 9 (60.0%)	6 (40.0%) 9 (60.0%)	0.000*	1.000	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

There was a statistically highly significant difference between controlled HbA1c group and uncontrolled HbA1c group regarding age as mean age for controlled group was 43.87±SD16.36 while mean age for uncontrolled group was 61.13±SD 8.68 and *(p<.05)*, However; there was statistically insignificant difference between controlled HbA1c group and uncontrolled HbA1c group regarding sex and type of DM as (*p*>.05).

Table (2): Comparison between controlled HbA1c group and uncontrolled HbA1c group regarding blood pressure, type & duration of DM, BCVA, HbA1c, CMT and association of other diseases

		Controlled group	Uncontrolled group	Test value	P-value	Sig.
		No. = 15	No. = 15			
Blood pr	Normotensive Hypertensive	9 (60.0%) 6 (40.0%)	4 (26.7%) 11 (73.3%)	3.394*	0.065	NS
Type of diabetes	Type I Type II	6 (40.0%) 9 (60.0%)	0 (0.0%) 15 (100.0%)	7.500*	0.006	HS
Duration of DM (years)	Mean ± SD Range	6.07 ± 4.04 1 – 14	13.80 ± 4.71 7 – 20	-3.817≠	0.001	HS
BCVA	Mean ± SD	0.47 ± 0.32	0.20 ± 0.18	-2.840≠	0.005	HS
HbA1c	Mean ± SD	6.42 ± 0.46	9.61 ± 2.03	-5.943•	0.001	HS
CMT (µm)	Mean ± SD	221.73 ± 69.46	406.80 ± 207.23	-3.279•	0.003	HS
Other associated diseases	Negative Positive	13 (86.7%) 2 (13.3%)	11 (73.3%) 4 (26.7%)	0.833*	0.361	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

There was a highly statistically significant difference between controlled HbA1c group and uncontrolled HbA1c group regarding type & duration of DM, BCVA, HbA1c, and CMT ***(p<0.01).*** Regarding type 1 DM there was 6 eyes with type 1 DM in the controlled group and 0 eyes in the uncontrolled group, and for type 2 DM there was 9 eyes with type 2 DM in the controlled group and 15 eyes in the uncontrolled group.

Regarding duration of DM the mean for the controlled group was 6.07± SD 4.04 while the mean for the uncontrolled group was 13.80 ± SD 4.71. Regarding the BCVA the mean for the controlled was 0.47 ±SD 0.32 while in the uncontrolled group the mean was 0.20 ±SD 0.18. Regarding the HbA1c the mean for the controlled group was 6.42 ±SD 0.46 while the mean for the uncontrolled group was 9.61 ± SD 2.03.

Regarding central macular thickness the mean for the controlled group was 221.73 ± SD 69.46 while the mean for the uncontrolled group was 406.80 ± SD 207.23, but there was statistically insignificant difference between controlled HbA1c group and uncontrolled HbA1c group regarding blood pressure and association of other diseases ***(p>0.05).***

Table (3): Comparison between type 1 diabetic patients and type 2 diabetic patients in both groups regarding age and sex

		Type of diabetes		Test value	P-value	Sig.
		Type I	Type II			
		No. = 6	No. = 24			
Age (years)	Mean ± SD Range	28.00 ± 9.84 17 – 39	58.63 ± 9.44 42 – 76	-7.051•	0.001	HS
Sex	Male Female	2 (33.3%) 4 (66.7%)	10 (41.7%) 14 (58.3%)	0.139*	0.709	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test

There was a highly statistically significant difference between type 1 diabetic patients and type 2 diabetic patients in both groups regarding age as the mean age for type 1 diabetic patients 28.00 ± SD 9.84, while mean age for type 2 diabetic patients58.63 ± SD 9.44 ***(p<0.01),*** but there was insignificant difference between them regarding sex ***(p>0.05).***

Table (4): Comparison between type 1 and type 2 diabetic patients in both groups regarding blood pressure, duration of DM, BCVA, HbA1c, CMT, and association of other diseases

		Type of diabetes		Test value	P-value	Sig.
		Type I	Type II			
		No. = 6	No. = 24			
Blood pr	Normotensive Hypertensive	6 (100.0%) 0 (0.0%)	7 (29.2%) 17 (70.8%)	9.808*	0.002	HS
Duration of DM (years)	Mean ± SD Range	9.33 ± 4.03 5 – 14	10.08 ± 6.27 1 – 20	-0.261≠	0.794	NS
BCVA	Mean ± SD Range	0.44 ± 0.17 0.17 – 0.67	0.31 ± 0.31 0.02 – 1	-1.749≠	0.080	NS
HgbA1c	Mean ± SD	6.57 ± 0.37	8.38 ± 2.29	-1.907•	0.067	NS
CMT (µm)	Mean ± SD	262.50 ± 74.30	327.21 ± 195.37	-0.788•	0.437	NS
Other associated diseases	Negative Positive	4 (66.7%) 2 (33.3%)	20 (83.3%) 4 (16.7%)	0.833*	0.361	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

There was a highly statistically significant difference between type 1 diabetic patients and type 2 diabetic patients in both groups regarding blood pressure as there was 6 normotensive cases with type1 DM and 7 normotensive cases with type 2 DM while there was 0 hypertensive cases with type1 DM and 17 hypertensive cases with type2 DM, the test value was 9.808 ***(p<0.01),*** but there was insignificant difference regarding duration of DM, BCVA, HbA1c, CMT, and association of other diseases ***(p>0.05).***

Table (5): Comparison between BCVA, HbA1c and CMT in all cases regarding age and duration of DM

	All cases					
	BCVA		HgbA1c		CMT (µm)	
	r	P-value	r	P-value	r	P-value
Age (years)	**-0.651****	**0.000**	**0.427***	**0.019**	0.190	0.315
Duration of DM (years)	**-0.439***	**0.015**	**0.695****	**0.000**	0.316	0.089

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant; Spearman correlation coefficient

There was a highly significant reverse relationship between age and BCVA as r value was -0.651 (p<0.01), however there was a significant direct relationship between age and HbA1c as r value was 0.427 (p<0.05), and there was insignificant direct relationship between age and CMT as r value was 0.190 (p>0.05), Also there was a significant reverse relationship between duration of DM and BCVA as r value was -0.439 (p<0.05) while there was a highly significant direct relationship between duration of DM and HbA1c as r value was 0.695 (p<0.01), and a highly significant direct relationship between duration of DM and CMT as r value was 0.316 (p<0.01).

DISCUSSION

Previous studies had shown that many factors may affect the retina like diabetes mellitus (DM)[14].

In our study the center macular thickness (CMT) was significantly lower in controlled HbA1c group than uncontrolled HbA1c group. Also, CMT was significantly lower in normotensive patients than hypertensive patients.

Diabetes is a metabolic disease affecting the systemic vasculature. Although the principal changes in diabetic eyes occur in the retinal vasculature, additional changes are also observed in the choroidal layer, an important vascular tissue that supplies blood to the outer retina [13].

Our study was conducted on two groups of patients, controlled HbA1c group include 15 eyes of diabetic patients with controlled HbA1c (≤7 %) and uncontrolled HbA1c group include 15 eyes of diabetic patients with uncontrolled HbA1c (>7%).

Optical Coherence Tomography (OCT) measurement for macular thickness of patients was performed using Topcon DRI OCT Triton plus Swept Source OCT ver 10.11, it uses super luminescent diodes with a wavelength of 1,050 nm and a high speed of 100,000 A-scans per second

The same examiner performed all OCT examinations for all patients and the 3D macula protocol was used for macular thickness measurements.

In our study the 2 groups were comparable regarding age and the mean age of the 2 group was 52.50 years old. In agreement with our study **Al-Sarraf *et al.*[14]** reported a greater chance of diabetic retinopathy (DR) in individuals aged 50–59 years and ≥60 years and **Raman *et al.*[15]** also reported the significance of age as a risk factor for DR**.**

In contrast to our study **Xie *et al.*[16]** reported no association between age and DR.

In our study the 2 groups were comparable regarding sex but in controlled HbA1c group 9/15 (60%) patients were female and also in uncontrolled HbA1c group 9/15 (60%) patients were female while 6/15 (40%) of patients were male in both groups which reveals that DR is more prominent in the females. In agreement with our study **Kajiwara *et al.*[17]** reported greater chance of DR among females. In contrast to our study **Raman *et al.* [15]** reported greater chance of DR among males.

In our study the 2 groups were comparable regarding BCVA although we used Snellen chart for visual acuity measurement not logMAR method.

In our study the mean duration of DM was longer and HbA1c level was higher in uncontrolled HbA1c group than in controlled HbA1c group and the macular thickness (MT) was thicker in uncontrolled HbA1c group than in controlled HbA1c group. In agreement with our study **Klein *et al.*[18]** reported that the incidence of macular oedema over the 10-year period was associated with higher levels of glycosylated hemoglobin and more severe retinopathy in both younger- and older-onset groups. Also, **Moreira *et al.*[19]** reported that HbA1c was the only variable that showed a significant association with macular edema in diabetic retinopathy patients**.**

Yeung *et al.*[20] also reported that HbA1c level positively correlated with macular thickness in patients with type I and II diabetes of 10 or more year's duration without diabetic macular edema. This study suggests that subclinical macular volume and thickness changes may occur before diabetic macular edema (DMO) becomes clinically evident.

Chou *et al.* [21] also reported that HbA1c level of 8% or above was associated with an increase in macular thickness in diabetic patients with diabetic retinopathy.

So we could suggest that intensive glycemic control is associated with delaying the development and progression of diabetic retinopathy. HbA1c of 7 or above increased the risk of diabetic macular edema (DME).The duration of diabetes is also a risk factor for development of DME, However, the reported duration of type II DM is usually not reliable due to the non-specific symptoms of DM and difficulty of the patient to recall those symptoms. Some patients were diagnosed with known diabetic complications, indicating that they likely had the disease for years before being diagnosed.

In our study in controlled HbA1c group 6/15 (40.0%) patients were hypertensive patients and in uncontrolled HbA1c group 11/15 (73.3%) patients were hypertensive patients.

In agreement with our study **Sivaprasad and Jackson[22]** and **Huang *et al.*[10]** also reported that blood pressure (BP) control is modifiable factor of DM known to reduce vascular complications, so hypertension is also important risk factor in the development of DR and DME**.**

Bourke *et al.*[23] also showed that untreated systemic hypertension is associated with choroidopathy**.** So we could suggest that the presence of hypertension may show correlation with the prevalence of development of DME and diabetic choroidopathy.

Limitations of the study:

The approximately 30 eyes per diabetic group is a relatively small number.

We excluded patients who had laser therapy within 3 months only before OCT assessment but the time between the PRP treatments and when the CT measurements were taken was ignored when it was more than 3 months.

We did not consider the axial length, there is a significant negative correlation between axial length and macular thickness except at the foveal region which shows increased thickness with increase of axial length.

Additional clinical studies on larger populations are needed for a more detailed evaluation of central macular thickness changes, the effect of blood pressure on CMT, effect of HbA1c on NPDR progression and its effect on MT.

CONCLUSION

Intensive glycemic control might affect retinal vasculature and decrease ischemia and affect the development and progression of diabetic retinopathy. Glycosylated hemoglobin of 7 or above increases the risk of macular edema. Optical coherence tomography is a sensitive and noninvasive diagnostic tool in the evaluation of macular thickness. Hypertension is also an important risk factor in the development of diabetic retinopathy, diabetic macular edema. Glycosylated hemoglobin is a great indicator for control of diabetic retinopathy as well as central macular thickness and best corrected visual acuity.

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