Epidemiology and Risk Factors for Development of Diabetic Retinopathy

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Received: 18-5-2021, Accepted: 30-8-2021, Published online:16-9-2021

EJO(MOC) 2021;3:128-137.

Running title: Risk factors of diabetic retinopathy.

Abstract

Background: Diabetic retinopathy (DR) is one of the leading causes of blindness worldwide and patients with this sight-threatening disease are expected to grow as dietary habits are changing especially in developing nations. For the past two decades, optical coherence tomography (OCT) was used as a routine technique for ocular imaging. It is considered as an ideal technique because it is a non-invasive technique and in the same time is able to give high-resolution (1–10 μm), depth-resolved, and cross-sectional images.

Objective: Study the epidemiology and the risk factors of diabetic retinopathy among diabetic retinopathy patients attending the outpatient clinic of Mansoura ophthalmic center through one year.

Patients and methods: This cross-sectional descriptive study included 400 eyes of 200 patients with diabetic retinopathy recruited from Mansoura ophthalmic center, Mansoura University Hospitals, Egypt. After obtaining a written informed consent, the cases were subjected to full history taking and full ophthalmological examination. Spectral domain OCT 2000 was used to obtain retinal images. Laboratory investigations were conducted for all the cases included HBA1C, lipid profile and serum creatinine

Results: The mean macular thickness was statistically significantly higher in the cases with HTN and cases with hepatitis. There was no statistically significant difference in the macular thickness according to sex, smoking or family history of DM. There was a statistically significant difference in the mean macular thickness between the eyes according to the findings of fundus examination. The highest macular thickness was reported with the eyes with stage 3 non-proliferative diabetic retinopathy (NPDR). Linear regression analysis, cholesterol level and best corrected visual acuity (BCVA) had statistically significant predictive ability for macular thickness

Conclusion: Retinopathy is a common complication of diabetes in diabetic patients. DR at the initial stage of diabetes may prevent disability from blindness caused by DR.

Key words: Diabetes, Diabetic retinopathy, Optical coherence tomography, Macular thickness.

Introduction:

Diabetes mellitus (DM) is a major medical problem throughout the world. Diabetes causes an array of long-term systemic complications that have considerable impact on the patient, family, and society, as the disease typically affects individuals in their most productive years [1].

The prevalence of diabetes is increasing throughout the world, and this increase appears to be greater in developing countries mostly due to modernization of life and unhealthy dietary patterns [2].

Patients with diabetes often develop ophthalmic complications, such as corneal abnormalities, glaucoma, iris revascularization, cataract, and neuropathies. The most

common and potentially most blinding of these complications, however, is diabetic retinopathy (DR) [3].

The progression of retinopathy is gradual, advancing from mild abnormalities, characterized by increased vascular permeability, to moderate, severe non-proliferative till proliferative DR characterized by the growth of new blood vessels on the retina and on the posterior surface of the vitreous[4].

Several factors have been identified as determinants for the development of DR and its progression, including the type of diabetes, family history, duration of DM, age, sex, glycemic control, hypertension, Body mass index , smoking, serum lipids, and presence of microalbuminuria [5-8].

Traditionally, diagnosis of DR has been clinical with adjunctive testing, such as fluorescein angiography (FA) and optical coherence tomography (OCT), used to confirm or quantify clinical suspicion of structural complications, such as neovascularization and macular edema. Except for common metrics, such as central macular thickness or macular volume, the interpretation of OCTs in diabetics has been predominantly subjective [9].

Optical coherence tomography (OCT) is an imaging technique similar to ultrasound, but instead of using sound waves it uses light to achieve much higher resolution images (10-100 times better than ultrasound) [10].

To the best of our knowledge, an accurate, automated screening system for DR based on OCT does not exist with lack of studies in this topic.

Patients and methods

This is a cross sectional, observational non-interventional study that was conducted in the period between September 2019 to September 2020 in Mansoura ophthalmic center, Mansoura University, Egypt.

This study included 400 eyes of 200 patients with diabetic retinopathy from both genders and from different ages. The cases with the following conditions were excluded; Patients with impaired glucose tolerance, eyes with ocular abnormality other than diabetic macular edema such as vitreoretinal disease and epiretinal membrane and presence of media opacities interfering with reliability of OCT imaging (dense cataract, corneal opacity, uveitis).

After approval from the institutional review board of Mansoura Faculty of Medicine and obtaining an informed written consent from the participants, all cases were subjected to complete history taking.

Full detailed ophthalmic examination was done for all the cases including assessment of the visual acuity (VA) using Landolt's VA chart and then transformed for statistical analysis to logarithm of minimal angle of resolution units (Log MAR).

slit lamp biomicroscopy (Haag Streit BP 900) (Haag-Streit, Koeniz, Switzerland) was used to assess corneal clarity, anterior chamber depth and regularity, pupil shape, size, regularity and reactivity, state of the lens and complications of diabetes such as (recurrent styes, xanthelasma, accelerated senile cataract, rubeosis iridis).

Posterior segment examination was conducted using indirect ophthalmoscope and slit lamp biomicroscopy with auxillary lenses.

Optical coherence tomography (OCT) using Spectral domain OCT 1000 [Topcon, Inc., Paramus, NJ, USA] was used to measure the central macular thickness and correlate it with different risk factors.

The following laboratory investigations were done for all the cases (HBA1C, lipid profile and serum creatinine,

Results

The current study included 200 patients with diabetic retinopathy. The mean age of the cases was 55.23 ± 9.28 years. Among the cases, there were 72 males (36%) and 128 females (64%). The mean duration of affection with DM among the included cases was 14.17 ± 6.59 years with 7 months as the least duration and 30 years as the maximum duration. There were 40 cases (20%) who received oral antidiabetic as treatment for DM and 160 cases (80%) who received Insulin. The study of the associated comorbidities and risk factors revealed that 20 cases (10%) were smokers, 142 cases (71%) were hypertensive, hepatitis was present in 42 cases (21%) and dyslipidaemia in 129 cases (64.5%). Positive family history of DM was present in 129 cases (64.5%) and glycaemic control was detected in 130 cases (65%).

14% of the included eyes had history of cataract surgery, 27.5% had history of intravitreal injection and 20.5% had history of laser therapy. Data were shown in table (1)

Table (1): Demographic, medical and ophthalmological history in study cases.

Items		Cases (n= 200)
Age (years)	Mean ± SD	55.23 ± 9.28
	Median (min-max)	57 (21-76)
Sex		
Males		72 (36%)
Females		128 (64%)
Duration of the disease (years)	Mean ± SD	14.17 ± 6.59
	Median (min-max)	15 years (7 months-30 years)
Treatment		
Oral antidiabetic		40 (20%)
Insulin		160 (80%)
Medical history		
Smoking		20 (10%)
Hypertension		142 (71%)
Hepatitis		42 (21%)
Dyslipidemia		129 (64.5%)
Positive Family history		129 (64.5%)
Glycemic control		
Controlled (HBA1C ≤ 7.5)		130 (65%)
Uncontrolled (HBA1C > 7.5)		70 (35%)
Ophthalmological history		
History of cataract surgery		56 (14%)
History of IVI		110 (27.5%)
History of LASER therapy		82 (20.5%)

Fundus examination of the included cases revealed that mild NPDR was found in 30.25% of the eyes, moderate NPDR was detected in 42.75% of the cases, while sever NPDR was found in 16% and PDR in 11% of the eyes.

There was no statistically significant difference in the mean macular thickness between the male and female cases (p= 0.112). Also, there was no statistically significant difference in the mean macular thickness between smokers and non-smokers (p=0.236), or between cases with positive and negative family history (p=0.661). The mean macular thickness was statistically significant higher in the cases with hypertension and cases with hepatitis (p=0.031 and 0.015) respectively.

Also, there was a statistically significant difference in the mean macular thickness between the eyes according to the findings of fundus examination. The highest macular thickness was reported with the eyes with sever NPDR. Data were presented in table (2).

Table (2): Effect of the risk factors on macular thickness

Variables	no	Thickness	p-value
Sex			0.112
Males	72	314.89 ± 166.15	
Females	128	275.16 ±123.01	
Smoking			0.236
Yes	20	326.16 ± 158.11	
No	180	286.15 ± 139.25	
HTN			0.031*
Yes	142	300.84± 144.87	
No	58	265.84 ± 136.04	
Hepatitis			0.015*
Yes	42	335.18± 157.34	
No	158	277.34 ± 135.2	
Family history			0.661
Positive	129	289.54± 137.41	
Negative	71	290.26 ± 141.34	
Fundus examination			
Mild NPDR	121(30.25%)	211.89± 63.86	
Moderate NPDR	171(42.75%)	305.7± 139.1	<0.001*
Sever NPDR	64(16%)	405.45± 187.51	
PDR	44(11%)	286.04±102.4	

There was a statistically significant positive correlation between macular thickness with age, disease duration, HBA1C, serum creatinine, cholesterol level and triglycerides level. There was a statistically significant negative correlation between macular-thickness and BCVA. Data was presented in table (3).

Table (3): Correlation between macular thickness and other parameters in the study

		Macular thickness
Age	r	0.195
	p	0.006*
Disease duration	r	0.172
	p	0.015*
HBA1C	r	0.388
	p	<0.001*
Creatinine	r	0.149
	p	0.036*
Cholesterol	r	0.582
	p	<0.001*
Triglycerides	r	0.469
	p	<0.001*
BCVA	r	-0.495
	p	<0.001*

R: Spearman's correlation

P: probability

*: Statistically significant (p< 0.05)

Cholesterol level and BCVA had statistically significant predictive ability for macular thickness by linear regression analysis, as shown in table (4).

Table (4): Linear regression analysis for macular thickness in the cases of the study

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	122.267	77.823		1.571	0.118	-31.257	275.790
Age	-0.491	0.994	-0.033	-0.494	0.622	-2.451	1.469
HBA1C	1.496	5.479	0.019	0.273	0.785	-9.313	12.305
Creatinine	-30.649	42.124	-0.048	-0.728	0.468	-113.748	52.450
cholesterol	1.117	0.175	0.554	6.377	**<0.001***	0.771	1.462
Triglycerides	-0.111	0.214	-0.043	-0.516	0.606	-0.533	0.312
BCVA	-180.583	67.319	-0.278	-2.683	**0.008***	-313.385	-47.782

Discussion:

The current study addressed the epidemiology and the risk factors of diabetic retinopathy among diabetic retinopathy patients attending the outpatient clinic at Mansoura ophthalmic center through one year. This study included 400 eyes of 200 diabetic patients with different stages of diabetic retinopathy.

Similar results were reported by Abdeen et al. (2018) who included 500 eyes of 287 patients with different stages of diabetic retinopathy, 115 males (40.07%) and 172 females (59.93%). Their ages ranged from 20 to 80 years, with mean age 55.98 and standard deviation ± 9.81 [11].

Females constituted nearly about two thirds (64%) of our diabetic population, which is consistent with previous epidemiological studies carried out in Egypt [12, 13].

On the other hand, gender was not found to be an important risk factor for developing DR in most other studies [13-16]. However, other studies found males to be more prone to develop DR than females, as in UAE [6] and Oman [17].

There has been considerable inconsistency of the prevalence of DR from one study to another even within the same country [6, 17-21]. The reason is partly explained by the different methodology used and the different population sample investigated in each study design

In the current study, the mean duration of affection with DM among the included cases was 14.17 ± 6.59 years with 7 months as the least duration and 30 years as the maximum duration. Similar duration was also reported by Tang et al. (2017) who showed that the duration of DM among the included subjects was 13.5 ± 9.37 years [5].

This was shorter than the duration reported in a study conducted in Saudi Arabia by Ahmed and his colleagues where the mean age of onset and mean duration of diabetes were 43.91 and 13.4 years, respectively. The difference could be explained by different criteria of the included subjects.

Regarding the results of fundus examination in the included cases, mild NPDR was found in 30.25% of the eyes, moderate NPDR in 42.75% of the cases, sever NPDR in 16% and PDR in 11% of the eyes.

Similar to our results, the study conducted by Abdeen et al. (2018) showed that mild / moderate NPDR was detected in 11.6% of the eyes, sever NPDR in 31 %, mild / moderate PDR in 28.6%, Sever PDR in 22.2% of the cases and advanced diabetic eye disease in 6.6% of the cases [11].

Furthermore, Tang et al. (2017) showed that among 434 eyes from 286 patients with diabetes included in their study, there were 171 eyes with no DR, 120 eyes with mild NPDR, 114 eyes with moderate NPDR, 25 eyes with severe NPDR and 4 eyes with PDR [5].

Our results also agreed with Ahmed et al. (2016) who showed that the overall prevalence of DR was 146 (36.4%). Mild NPDR was found in 57.5% of the patients, moderate NPDR in 19.9% and severe NPDR in 11.0% while 11.6% of diabetic patients had PDR [8].

The present study showed a higher prevalence of PDR (11%) than that of KSA(6.4%) [22], but lower than that reported from Oman(12.8%) [6, 17].

Our study found no significant gender difference in the development of DR, which is in accord with multiple studies mostly from the middle east and Saudi Arabia [17, 23-26], but it is in contrast to a study from Sweden [27], which documents higher rates for women than men [22]; and studies from KSA, India, and UAE where DR was observed to be more prevalent in male diabetics [6, 28].

In the current study, there was a statistically significant difference in the mean age between the cases according to the findings of fundus examination. There was an increase in the mean age with the increase of the stage of DR. Also, there was a statistically significant positive correlation between macular thickness with age.

This disagreed with Macky et al. who reported that the risk between increasing age and developing DR was only applied to patients > 30 years in their study [12].

This might be explained as their study had higher incidence of type 1 diabetes that is more manifested in younger patients, which could be a stronger influential factor than age and duration of DM

The duration of diabetes could be considered as the single most important and consistent risk factor for the development of DR. In the current study, there was a statistically significant difference in the mean disease duration between the cases according to the findings of fundus examination. There was a reported increase in the disease duration with the increase of the stage of DR with the longest duration was reported with the eyes with sever NPDR. Also, there was a statistically significant positive correlation between macular thickness with disease duration.

This came in accordance with Ahmed et al. (2016) who showed a significant difference in mean duration among the four stages of retinopathy; ($P = 0.001$). *Post-hoc* test revealed that the duration of DM was significantly different for PDR ($P = 0.003$) in comparison to NPDR. Similarly, the total mean cholesterol was different among the four stages ($P = 0.019$)[8].

This agreed with the Egyptian study conducted by Macky et al. who showed that there was a statistically significant increase in the prevalence of DR with longer durations of diabetes from one group to another ($p < 0.001$) [12].

The results of our study indicate that retinopathy increases with younger age at onset of diabetes and showed a significant association between DR and duration of diabetes, which is consistent with most of the previous studies [14, 22, 29, 30]. A study from Sweden documents that prevalence of DR reached 100% after 30 years of diabetes [27].

In the current study, there was a statistically significant difference in the mean HBA1C between the cases according to the findings of fundus examination. There was an increase in the level of HBA1C with the increase of the stage of DR with the highest HBA1C level was reported with the eyes with sever NPDR. Also, there was a statistically significant positive correlation between macular thickness with HBA1C.

The results of our study were similar to the prevalence studies, cohort studies have identified systemic parameters of quality of metabolic control (i.e., hyperglycaemia or the HbA1c level) to be consistently associated with incidence and progression of DR [31-35].

On the contrary, Macky and his colleagues did not find any significant difference in the level of HBA1C with the different stages of DR. This surprising finding was also reported previously for diabetic patients in the UAE [19].

Also, our results disagreed with a longitudinal study by Aiello et al. reported that the prevalence of DR in long-standing diabetes is not dependent on the control of the disease.

However, this could be due to the fact that since HBA1c reflects only the previous 3 months of control, it does not say anything about patients' glycemic control over the years.

In the current study, there was a statistically significant difference in the mean BCVA between the cases according to the findings of fundus examination. There was decrease in the BCVA with the increase of the stage of DR with the lowest BCVA was reported with the eyes with sever NPDR. Also, there was a statistically significant negative correlation between macular thickness with BCVA.

This agreed with the results of the Diabetic Retinopathy Clinical Research Network study conducted by Browning and his colleagues who showed that by analysis of patients in DR treated with laser showed a linear relationship between central

retinal thickness and visual acuity, but there was substantial variation in visual acuities at any given retinal thickness. Many eyes with thickened maculae had excellent visual acuity, and many eyes with maculae of normal thickness had decreased visual acuity. Suggesting macular thickness is just one of several variables affecting visual acuity [36].

In the current study, there was a statistically significant positive correlation between macular thickness with serum creatinine levels.

Similar observations on chronic kidney diseases as factor associated with DR were made in the Korea National Health and Nutrition Examination Survey 2008–2010 [37]. Also, in the Beijing Eye Study, a higher 10-year incidence of DR was significantly associated with higher serum concentration of creatinine (p = 0.02; OR 1.01; 95% CI 1.002–1.022) in a multivariate analysis [38].

In the current study, there was a statistically significant positive correlation between macular thickness with cholesterol level and triglycerides level. Moreover, by linear regression analysis, cholesterol level had statistically significant predictive ability for macular thickness.

Our results came in agreement with Ahmed et al. (2016) who showed that the total cholesterol level was significantly higher in the severe grade of DR, which may indicate that it could be a risk of the progression of DR to severe retinopathy, a finding that emphasizes the importance of good lipid control as a preventive measure for the progression of retinopathy [8].

In a meta-analysis of case-control studies, the mean concentrations of total serum cholesterol (mean difference [mg/dL]: 30.1; 95% CI 21.1–39.0; p < 0.001), low-density lipoproteins (18.6; 95% CI 5.8–31.4; p < 0.05), and serum triglycerides (24.8; 95% CI 9.2–40.4; p < 0.05) were significantly higher in patients with DME than those in individuals without macular oedema [39].

On the other hand, population-based cross-sectional studies did not find any significant associations between dyslipidemia with DR [40, 41].

Interestingly, fenofibrate, which reduces the levels of low-density lipoprotein, very low-density lipoprotein and tri-glyceride and increases high-density lipoprotein levels, as compared to placebo has been reported to reduce the risk of requiring laser treatment for proliferative DR or DME by 31%[42].

The difference between the studies could be explained by different sample size and different characteristic of the included cases.

In the current study, 142 cases (71%) were hypertensive. The mean macular thickness was statistically significant higher in the cases with HTN as compared with non-hypertensive cases (p=0.031).

This agreed with Macky et al. (2011) who showed that 61% of diabetics in their study population were found to be hypertensive of whom 77% were controlled. Diabetic patients with hypertension had about twice the risk of developing DR than non-hypertensive diabetics (25 vs. 13%). Also, diabetics with uncontrolled hypertension had about 3 times the risk of developing DR than those with controlled hypertension (51.5 vs. 17%) [12].

Hypertension has been documented as a risk factor in studies from Jordan [43], Oman [17], and also by a longitudinal UK prospective diabetes study group [44].

While in contrast, some studies were not able to find any significant role of hypertension in the development of DR[45-47].

In the current study, cholesterol level and BCVA had statistically significant predictive ability for macular thickness.

On the other hand, Ahmed et al. (2016) reported that by univariable analysis, the rate of retinopathy was significantly associated with older age group, younger age at onset, longer duration of disease, poorly controlled blood sugar, the presence of hypertension (receiving drug treatment), insulin use, and the presence of multiple complications [8].

Our findings also disagreed with the study in Oman in which similarly aged patients, poor control of diabetes (with HbA1c ≥9), high systolic blood pressure and complications were documented as insignificant after multiple regression analysis [17].

The difference could be attributed to many factors including different sample size, different patients' characteristics, different techniques of assessment and the high prevalence of metabolic syndrome and dyslipidemia (Even if not diagnosed) among our study population.

The limitation of our study is that a predictive inference cannot be drawn from our observational data since a more extensive study is required. Moreover, the relatively small sample size (according to the nature of the study) could decrease the power of the obtained results.

Conclusion:

Our finding clearly demonstrates that the retina of diabetic patient provides a summary measure of lifetime exposure to the effects of hyperglycaemia.

We supported the idea that good control of diabetes will not prevent the occurrence of DR but it can delay the onset, progression and complication of diabetic retinopathy.

Small investments in prevention, awareness and care can dramatically improve the quality of life of patients with long-standing diabetes.

The treating physicians should also be reminded to refer all diabetics to ophthalmologists for examination. Much awareness and attention to this complication is therefore needed in Egypt**.**

Conflict of Interest

Authors declare no conflicts of interest.

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Ethics declarations

Conflict of interest

Amira Kashwa, Amr M Abdelkader, Hossam Eldin Abouelkheir, Hamza Ahmad, all authors have no conflicts of interest that are directly relevant to the content of this review.

Funding: No sources of funding were used to conduct this review.

Reviewer disclosures: No relevant financial or other relationships to disclose.

Declaration of interest: No financial affiliations or financial involvement with any organization or entity with a financial competing with the subject matter or materials discussed in the review.

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