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Risk Factors for Diabetic Retinopathy in Type 2 Diabetes Mellitus

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Abstract
Objectives: To find risk factors to diabetic retinopathy (DR) in type 2 diabetes mellitus (T2DM) patients.**Methods:** A four years cross sectional study involving 386 patients with T2DM conducted at the diabetes clinic in Al-Hindeya General Hospital, Karbala, Iraq. Interviews were done for the participants focused on sociodemographic factors and included general examination with laboratory screening for fasting blood glucose (FBG), glycated haemoglobin (HbA1c), and serum lipids. The participants underwent ophthalmological testing including visual acuity, slit lamp examination, and optical coherence tomography. The patients were divided into retinopathy and non-retinopathy groups involving 109 and 277 patients, respectively. Both groups were screened for risk factors including age, gender, duration of disease, body mass index (BMI), treatment modality, HbA1c, and dyslipidemia. **Results:** The study included 109 patients (62 females, 47 males) with retinopathy and 277 patients (149 females, 128 males) control. Mean age for retinopathy and control groups were 54.76± 7.63 and 54.15± 9.20 years, respectively. Mean duration of disease for retinopathy and control groups were 12.79± 5.91 and 8.51± 5.16 years, respectively. Longer duration of disease and poor glycemic control showed positive association with DR with a P-value of 0.0001 and 0.033, respectively. Gender, BMI, age, treatment modality, and dyslipidemia showed negative association with DR.**Conclusions:** In our study DR significantly associated with longer duration of disease and poor glycemic control while the relation was insignificant for gender, BMI, age, treatment modality, and dyslipidemia.
Keywords: Type 2 diabetes mellitus, Diabetic retinopathy, glycated hemoglobin, risk factor for retinopathy.
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Introduction

T2DM is a worldwide major health problem with multi-systemic involvement. Diabetes is expected to follow the projected increase in the global number of diabetics reaching 629 million by 2045. Such a huge number of patients supposed to associate with a wide range of complications including retinopathy (1).

DR Retinopathy is a well-recognized irreversible microvascular complication of long-standing DM with a variable prevalence in T2DM (2-5). Vision loss due to DR is now the main cause of blindness in developed countries as the prevalence of etiologies like glaucoma and cataract fell down as a result of implementing screening programs and the advancement is surgical techniques (6). It is estimated that 50% of the high-risk diabetic population are unaware of the presence of DR due to the subtle and progressive clinical features of early DR. This fact contributed to the increase visual morbidity in diabetic patients (7, 8).

Risk factors associated with DR had been studied in different geographical areas as an attempt to understand the behavior of the disease and implement programs for its prevention. Age, gender, duration of disease, BMI, treatment modality, HbA1c, and dyslipidemia were frequently screened in assessing DR (3, 9, 10, 11, 12). As with any other illness, modifying risk factors may well reduce the incidence and delay the progression of DR (8).

The study aims to detect risk factors associate with diabetic retinopathy in T2DM patients of the target population.

Methodology

Study design: A cross sectional study involving 386 patients (211 females and 175 males) with T2DM conducted from September 2015 to August 2019.
Study population: The participants were enrolled at the Diabetes Clinic in Al-Hindeya General Hospital, Kabala, Iraq. Following clinical assessment including ophthalmologic examination, the patients were divided in to two groups, namely, retinopathy group regardless of the grade (109 patients) and non-retinopathy group as control (277 patients). Both groups were age and gender matched with the same inclusion criteria
Inclusion and exclusion criteria: All participants were above 35 years of age and received treatment in the form oral anti-diabetes, insulin or mixed, with history of T2DM of more than 3 years.
Patients with non-DM retinal diseases, corneal disease and those with poor pupillary dilatation were excluded.
Participants screening: The participants had to complete a questionnaire about the socio-demographic criteria

including age, gender, occupation, and catchment area. Detailed medical history was obtained including duration of disease, treatment modality, history of eye disease and hypertension.

A general clinical examination was performed on each individual and included blood pressure measurement in the sitting and standing positions using mercury sphygmomanometer. Anthropometric measurements including height and weight were estimated to calculate the BMI using the equation of weight in kilogram divided by height in squared meter. Then the patients were divided according to the BMI in to three groups as normal (BMI <24.9 kg/m2), overweight (BMI 25-29.9 kg/m2), and obese (BMI >30 kg/m2) (13).

Glycemic control for each participant was decided by measuring fasting blood glucose and HbA1c. Fasting serum lipids were also measured. The fasting period was set at 12 hour. The patients were further assigned to three groups according to their HbA1c as: controlled (<7%), borderline (7-9%), and poor control (>9%). The American diabetes association guidelines were used to define abnormal serum lipids as: total cholesterol (TC) ≥ 6.2 mmol/L, low density lipoprotein (LDL-C) ≥ 2.6 mmol/L, height density lipoprotein (HDL-C) < 1.0 mmol/L, and triglyceride (TG) ≥ 1.7 mmol/L (14).

Chemistry analyzer (Cobas integra 400 plus, Roche Diagnostics, Germany) was used for HbA1c and lipid assays, the former done with 2 ml of whole blood by immunoassay, while the latter done with 1 ml of serum by photometric transmission measurement.

All participants verbally consented to share their data in this study.

Eye examination and retinopathy grading: Initial visual acuity, intraocular pressure measurement, refraction followed by slit lamp examination to exclude ocular media opacity, were all performed at our ophthalmology department. For pupillary dilatation Tropicamide 1% eye drops were used and repeated after 10 minutes. After full dilatation, indirect non-contact lens (+90, +78) on slit lamp biomicroscopy were used to grade the retinopathy. KOWA fundus camera (JAPAN VX-10) was used for posterior segment photography. Macular analysis were obtained using Optical Coherence Tomography (OCT) (ZEISS HD 5000 OCT system) to document macular edema detected on clinical examination, identify the type of edema, and measure macular thickness.

DR was classified according to the following grading system: grade 0: no diabetic retinopathy, grade 1: background retinopathy, grade 2: clinically significant macular edema, grade 3: proliferative retinopathy, and grade 4: advanced retinopathy (15).

Statistical analysis: The statistical package of social science SPSS V22 was employed in statistical analysis of the study. Descriptive statistics were presented using frequency distribution table, while Chi square test used to find out associations between studied variables and occurrence of retinopathies. The discrimination point of significance was considered as P-value <0.05.

Results

Of the 386 patients, 109 had retinopathy and the remaining 277 were controls. There was relative female preponderance in both groups with a female to male ratio of 1.31:1 in retinopathy group and 1.16:1 in control group. Most of the patients in both groups were above 40 years. The duration of disease less than ten years in retinopathy group contributed to one quarter (26.6%) in comparison to nearly two thirds in control group (60.6%). About one quarter of patients with retinopathy (26.6%) had BMI less than 25 while only 15.9% in control group. Most of patients were on oral anti-diabetes drugs in both retinopathy group and control group (83.5%, 89.2% respectively) as illustrated in table-1.

Table 1: Socio-demographic characteristics of diabetic retinopathy group and control group

Characteristics	Categories	Retinopathy No. (%)	No retinopathy No. (%)	Total No. (%)
Gender	Female	62(56.9)	149(53.8)	211(54.7)
	Male	47(43.1)	128(46.2)	175(45.3)
Age groups (years)	≤40	2(1.8)	18(6.5)	20(5.2)
	41-59	75(68.8)	163(58.8)	238(61.6)
	≥60	32(29.4)	96(34.7)	128(33.2)
Duration of disease (years)	<10	29(26.6)	168(60.6)	197(51)
	10-19	64(58.7)	99(35.8)	163(42.2)
	≥20	16(14.7)	10(3.6)	26(6.8)
BMI (kg/m^2)	<25	29(26.6)	44(15.9)	73(18.9)
	25-29.9	42(38.5)	118(42.6)	160(41.5)
	≥30	38(34.9)	115(41.5)	153(39.6)
Treatment modality	Oral	91(83.5)	247(89.2)	338(87.5)
	Mixed	13(11.9)	15(5.4)	28(7.3)
	Insulin	5(4.6)	15(5.4)	20(5.2)

BMI= body mass index

Table 2 shows a highly significant association between longer duration of disease and retinopathy (P-value 0.0001), while age and gender revealed no association with retinopathy.

Table 2: Association between socio-demographic variables and retinopathy

Characteristics	Categories	Retinopathy No. (%)	No retinopathy No. (%)	P value
Duration of disease(years)	<10	29(26.6)	168(60.6)	0.0001**
	10-19	64(58.7)	99(35.8)	
	≥20	16(14.7)	10(3.6)	
Gender	Female	62(56.9)	149(53.8)	0.58
	Male	47(43.1)	128(46.2)	
Age groups (years)	≤40	2(1.8)	18(6.5)	0.074
	41-59	75(68.8)	163(58.8)	
	≥60	32(29.4)	96(34.7)	

**= highly significant relationship.

No association was found between BMI and treatment modality with retinopathy as illustrated in table 3.

Table 3: Association between clinical variables and retinopathy

Characteristics	Categories	Retinopathy No. (%)	No retinopathy No. (%)	P value
BMI (kg/m2)	<25	29(26.6)	44(15.9)	0.051
	25-29.9	42(38.5)	118(42.6)	
	≥30	38(34.9)	115(41.5)	
Treatment modality	Oral	91(83.5)	247(89.2)	0.084
	Mixed	13(11.9)	15(5.4)	
	Insulin	5(4.6)	15(5.4)	

BMI= body mass index

The association between participants' laboratory findings and retinopathy is presented in table 4. Poor glycemic control in contrast to dyslipidemia showed a significant association with a P-value of 0.033.

Table 4: Association between laboratory findings and retinopathy

Characteristics	Categories	Retinopathy No. (%)	No retinopathy No. (%)	P value
HbA1c (%)	<7	3(2.8)	20(7.2)	0.033*
	7-9	17(15.6)	66(23.8)	
	>9	89(81.7)	191(68.9)	
TG (mmol/L)	<1.7	37(33.9)	94(33.9)	0.99
	≥1.7	72(66.1)	183(66.1)	
TC (mmol/L)	<6.2	88(80.7)	232(83.8)	0.48
	≥6.2	21(19.3)	45(16.2)	
LDL-C (mmol/L)	<2.6	28(25.7)	79(28.5)	0.58
	≥2.6	81(74.3)	198(71.5)	
HDL-C (mmol/L)	≥1	57(52.3)	133(48)	0.45
	<1	52(47.7)	144(52)	

HbA1c = glycated haemoglobin, TG = triglyceride, TC = total cholesterol, LDL-C = low density lipoprotein, HDL-C = height density lipoprotein, *= significant relationship.

Discussion

We found longer duration of T2DM has strong association with retinopathy (P-value 0.0001) which is supported by most of the reference studies (7, 8, 16, 17, 18). This result shows the impact of longer duration of hyperglycemia on the development and progression of DR. However, the duration of the disease is a major risk factor that cannot be modified.

Sadiq H et al (7), Chatziralli IP et al (9), and Stratton et al (19) reported a significant relation between male gender and DR. While Pedro RA et al (20) and Takuya A et al (21) did not find a relation between gender and DR. Our study showed insignificant association between gender and the development of DR (P-value 0.583). Although there was female preponderance in both retinopathy and control groups in our study, the difference between genders was statistically insignificant.

The majority of patients in both DR and control groups were between 41 to 60 years accounting for 61.65% of the total number of participants. In this study we did not find a significant association between age and DR (P-value 0.059), which is similar to other studies (6, 7, 8, 16, 19, 22). In contrast to our study, Razia A. Ahmed et al (12) and Stratton et al (19) observed a positive relation between age and DR.

Weight disorder is a common problem in T2DM with having an impact on disease management and incidence of complications. Takuya A. et al (21) and V. Narendran et al (24) observed a negative association between BMI and DR while the relation was inconclusive by Cheung N. et al (23). In our study nearly significant relation (P-value 0.51) was found between BMI and DR. Similar result were observed by other Iraqi and UAE studies (25, 22).

Various diabetes treatment modalities (oral, insulin, and mixed) were also evaluated in this study. Insulin therapy was significantly associated with DR in some studies (7, 17, 26, 27) . In our study however we did not find a positive association between insulin use and DR (P-value 0.084) likely due to the small percentage of insulin users (5.18%) compared to those using oral therapy (87.56%).

Poor glycemic control manifested by elevated HbA1c in T2DM indicates chronic exposure to hyperglycemia leading to increased risk of complications. In a previous study done in our hospital 78.3% of patients with T2DM had inadequate glycemic control (28). The Diabetes Control and Complications Trial found a 30-40% decrease risk of DR for each one percent reduction in HbA1c (29). In our study we showed a positive association between increased HbA1c and DR (P-value 0.033), which is consistent with other studies (6, 7, 30, 31). In contrast, non-significant association between HbA1c and retinopathy was found in an Iranian study which may be related to single measurement of HbA1c or designing the study around a group of patients with good glycaemic control (17).

Dyslipidemia frequently combine T2DM with variable presentation and the prevalence may reach up to 73% (33). Multiple studies done in different geographical areas showed diversity in the association between serum lipids and DR. Al-Kharji F et al (3), Sadiq H et al (7), and Rema M et al demonstrated significant association (34). In our study we did not find a significant association between various types of serum lipids and DR. Our results were compatible to Pedro RA et al (20), Takuya A et al (21), Rehab B (15), Wong TY (36), and Tapp RJ et al (37). Furthermore, the anti-lipid fenofibrate found to reduce the progression of DR but did not affect the incidence of retinopathy (32).

Conclusions

Our study found diabetic retinopathy in type 2 diabetes mellitus significantly associated with longer disease duration and poor glycemic control. We did not detect a significant association between diabetic retinopathy and

gender, body mass index, age, type of treatment, and dyslipidemia.

Aknowlegment
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