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Prevalence, characteristics and risk factors of diabetic retinopathy in type 2 diabetes mellitus patients in Jordan: a cross-sectional study

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Abstract

Objectives: To measure the prevalence of diabetic retinopathy in patients with type 2 diabetes, to define their characteristics, and identify the associated risk factors.

Methods: We performed a cross sectional study of 1316 adult patients with type 2 diabetes mellitus who attended an ophthalmology clinic. Demographic, clinical, and laboratory data were analyzed. Diabetic retinopathy (DR) was diagnosed using a complete ophthalmic evaluation, including a fundic examination. Two regression models were constructed to identify the risk factors associated with DR and the parameters associated with the stage of retinopathy.

Results: Men accounted for 774 (58.8%) of the participants. The prevalence of DR was 28.2% (371 participants). DR was significantly more common in participants who were $\geq$60 years old, were women, had had diabetes for $>$10 years, were taking insulin, were not taking metformin, had a body mass index $>30\,kg/m^2$, were current smokers, or had a history of hypertension. Advanced stages of DR were more common in participants in the later stages of nephropathy and with albuminuria.

Conclusions: Poor glycemic control, smoking, and advanced diabetic kidney disease are most closely associated with retinopathy. Further longitudinal studies are necessary to identify the mechanisms underlying these relationships and to guide community-based interventions.

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Introduction

Diabetes mellitus (DM) is a global pandemic that places significant burdens on patients, physicians, and healthcare systems. It is responsible for 67.9 million disability-adjusted life years and ~1 million deaths per year.[1,2] Conventionally, most of the sequelae of DM are placed to two broad pathological categories, microvascular and macrovascular complications. The former includes pathologies that are closely related to glycemic control (neuropathy, retinopathy, and nephropathy) and examples of the latter are cerebrovascular accident, myocardial infarction, and peripheral arterial disease.[3]

Diabetic retinopathy (DR) is one of the most debilitating long-term microvascular complications of DM and is the most common cause of blindness in people of working age worldwide.[4] It is estimated that ~34.6% of individuals with diabetes aged ≥40 years have DR and 10.2% have vision-threatening retinopathy.[5,6] According to the International Clinical Classification System for Diabetic Retinopathy, DR is either proliferative or non-proliferative, according to the presence or absence of numerous abnormal retinal blood vessels.[7] In type 2 DM, macular edema, which can accompany both proliferative and non-proliferative changes, is an important cause of visual impairment.[8]

The reported prevalence of type 2 DM in Jordan in 2020 was 16%, and this is expected to reach 20.6% in 2050.[9] Studies performed in the region have generated estimated prevalences of DR in patients with type 2 DM of 34% to 64%; and shown that older age, a longer duration of diabetes, poor glycemic control, uncontrolled blood pressure, and the presence of nephropathy are significant risk factors.[10,11] However, information regarding the prevalence of DR in Jordan is scarce, with the last study having been published 14 years ago. Therefore, the aims of the present study were to calculate the prevalence of DR in a cohort of patients with type 2 DM in Jordan, to define the characteristics of such patients, and to identify the associated risk factors.

Patients and methods

Study design and ethics approval

We performed a retrospective cross-sectional study of consecutive patients who had been diagnosed with type 2 diabetes using the American Endocrinology Association criteria and visited the ophthalmology clinic at our hospital between January and December 2019. Patients ≥18 years of age were included if they completed at least one official visit to the ophthalmology clinic for the evaluation of diabetic retinopathy within a single year and completed a renal assessment for diabetic nephropathy. We excluded patients with missing laboratory or clinical data, pregnant women, and patients on renal dialysis. Written informed consent was obtained from all the participants and all

the participant data were de-identified. This study was approved by the Institutional Review Board of Jordan University Hospital (# 10/2022/5672, dated 1/3/2022) and complied with principles of the World Medical Association Declaration of Helsinki. The reporting of this study conforms to STROBE guidelines.[12]

Data collection

Data were collected from the medical records of the patients included in the study. The International Clinical Diabetic Retinopathy Disease Severity Scale (ICDR) was used to diagnose and classify DR.[7] All the patients underwent a thorough eye examination by an experienced ophthalmologist utilizing slit-lamp biomicroscopy and a fundic examination with adequate pupillary dilatation achieved using tropicamide 1%. To stage their DR, we used the eye with the most advanced stage of the disease. Participants were deemed to have DR if they had non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), and/or clinically significant macular edema. In addition, the age, sex, general medical history (hypertension, myocardial infarction, coronary artery disease, heart failure, stroke, and smoking status), duration of DM, presence of other microvascular complications, such as peripheral neuropathy, diabetic nephropathy, and microalbuminuria, and current use of medication (antidiabetics, antihypertensives, lipid-lowering agents, and other medications) were recorded. Laboratory data, including the serum creatinine concentration, fasting lipid profile (if available), serum albumin concentration, and extent of urinary albuminuria, were collected within 3 to 6 months of the clinic visit, and the most recent laboratory test results were recorded. Diabetic kidney disease (DKD) was defined using an estimated glomerular filtration rate (eGFR) of $<60\,\text{mL/minute/1.73}\,\text{m}^2$ and/or the presence of albuminuria (microalbuminuria or macroalbuminuria).

Statistical analysis

All analyses were performed using Stata Statistical Software, release 16 (StataCorp LLC, College Station, TX, USA). Categorical data are presented as percentages and continuous data are presented as the mean ± standard deviation. Sociodemographic characteristics, medical history, co-morbidities, and the medication of participants with or without evidence of DR were compared using the chi-square test for categorical data and Student's *t*-test for continuous data. Two regression models were constructed: (i) binary logistic regression was used to identify parameters associated with a higher risk of DR; and (ii) multi-stage ordinal logistic regression analysis was used to identify parameters associated with the stage of DR. Factors that affected the risk of DR and potential confounders DR (sex, lipid profile, waist circumference, body mass index (BMI), hemoglobin A1c (HbA1c) level, chronic kidney disease stage (classified using eGFR), smoking status, and hypertension) were assessed using unit-variable regression analysis, and the significant factors were included in the final multi-variable regression model. The estat vif command was used to exclude variables with high variable inflation factors to minimize multicollinearity. Confidence intervals of 95% are quoted and *p*-values of ≤ 0.05 were considered to indicate statistical significance.

Results

General characteristics of the participants

Of the 1652 candidates, 1316 met the inclusion criteria. Seven hundred seventy-four (58.8%) of the participants were men and

542 (41.2%) were women, and 53% of the cohort were >60 years of age. Most of the participants had been diagnosed with type 2 DM >10 years previously (41.2%), had HbA1c levels ≥7.0 (60.6%), and were taking metformin (77.2%) or insulin (39.4%). Their mean waist circumference was 109.2 cm (±14.4), and most of the participants had a BMI >30 kg/m^2 (66.1%). Hypertension (68.8%) and congestive heart failure (30.12%) were the most prevalent co-morbidities. The prevalences of DKD and diabetic neuropathy were 49.1% and 41.8%, respectively. Only 12.3% of the patients were smokers, 71% had never smoked, and 16.8% were ex-smokers (had stopped smoking within the preceding ≥6 months).

Prevalence of diabetic retinopathy

The prevalence of DR in the sample was 28.2% (371 participants). Specifically, 136 participants had mild NPDR (12.7%), 79 had moderate NPDR (7.4%), 44 had severe NPDR (4.1%), and 84 had PDR (7.9%). Of the participants with PDR, 30 had active PDR and had undergone laser treatment, 28 had stable, treated PDR, and 26 had active PDR despite laser treatment. One hundred forty-eight (11.2%) participants had clinically significant macular edema. DR was significantly more common in participants who were ≥60 years of age, were women, had had DM for >10 years, were taking insulin, were not taking metformin, had a BMI >30 kg/m^2, were current smokers, or had a history of hypertension, myocardial infarction, congestive heart failure, coronary artery disease, stroke neuropathy, or diabetic kidney disease. Table 1 shows the characteristics of the participants, classified according to their DR status, along with the calculated *p*-values.

Factors associated with diabetic retinopathy

Table 2 lists the factors found to be associated with a higher risk of DR, presented with their odds ratios (ORs). High HBA1c level was associated with a significantly higher risk of DR (OR: 1.4, 95% CI: 1.3–1.5, $p < 0.01$). Moreover, all the later stages of chronic kidney disease (classified using eGFR) were associated with significantly higher risks of DR than stage 1. Specifically, chronic kidney disease stages 4 and 5 were associated with the highest risks of DR (OR: 5.8, 95% CI: 2.7–12.3, $p < 0.01$ and OR: 3.5, 95% CI: 1.3–9.7, $p < 0.01$, respectively). Participants who were current smokers were at significantly higher risk of DR than those who had never smoked (OR: 1.7, 95% CI: 1.2–2.4, $p < 0.01$), but ex-smokers were not at higher risk than non-smokers.

Discussion

In the reported cohort of 1316 Jordanian patients with type 2 DM, more than one in four had DR. The prevalences of mild, moderate, and severe NPDR were 12.7%, 7.4%, and 4.1%, respectively. Only 7.9% of the sample had PDR. The multivariable model showed that high HBA1c, poor renal function, and current smoking were all significantly associated with a higher risk of DR.

We found a lower prevalence of DR than previous studies of Jordanians. Salem *et al.* studied 212 patients with type 2 DM between 1995 and 1996, and reported prevalences of DR, NPDR, PDR, and maculopathy of 50%, 38.8%, 11.2%, and 17%, respectively.[13] One major limitation of this study was the relatively small sample size, which meant that its statistical power was fairly low. A study of 986 patients with DM published in 2005 showed even higher prevalences, of 64.1%, 54.8%, 9.3%, and

Table 1. General characteristics of the 1,316 participants with type 2 diabetes, according to their diabetic retinopathy status, with the calculated *p*-values.

Parameter	Category	N (%) 1,316 (100)	Diabetic retinopathy, n (%) 371 (28.2)	No diabetic retinopathy, n (%) 945 (71.8)	*p*-value
Age	<60 years	623 (47.3)	147 (23.6)	476 (76.4)	**<0.01**
	≥60 years	693 (52.7)	224 (32.3)	469 (67.7)	
Sex	Men	774 (58.8)	176 (22.7)	598 (77.3)	**<0.01**
	Women	542 (41.2)	195 (36)	347 (64)	
Duration of DM	<5 years	379 (28.8)	37 (9.8)	342 (90.2)	**<0.01**
	5–10 years	291 (22.1)	50 (17.1)	241 (82.8)	
	>10 years	646 (49.1)	284 (44)	362 (56)	
HbA1c (%)	<7.0	519 (39.4)	79 (15.2)	440 (84.8)	**<0.01**
	≥7.0	797 (60.6)	292 (36.6)	505 (63.4)	
Anti-diabetic medication	Insulin	648 (49.3)	272 (42)	376 (58)	**<0.01**
	Metformin	1,014 (77.2)	257 (25.4)	757 (74.7)	**<0.01**
	Other	590 (45)	138 (23.4)	452 (77)	**<0.01**
Taking ACEIs/ARBs		699 (53.2)	217 (31)	482 (69)	**0.02**
BMI (kg/m^2)	<25	117 (9)	26 (22.2)	91 (77.8)	**<0.01**
	25–29	327 (25)	87 (26.6)	240 (73.4)	
	>30	868 (66.1)	285 (29.7)	610 (70.3)	
Waist circumference (cm)*		109.2 ± 14.4	110.7 ± 12.5	108.7 ± 15	**0.02**
Smoking status	Never a smoker	933 (71)	246 (26.4)	687 (73.6)	0.18
	Current smoker	162 (12.3)	66 (40.7)	96 (59.3)	**<0.01**
	Ex-smoker	221 (16.8)	59 (26.7)	162 (73.3)	
Medical history	Hypertension	906 (68.8)	293 (32.3)	613 (67.7)	**<0.01**
	Congestive heart failure	41 (30.12)	20 (48.8)	21 (51.2)	**<0.01**
	Coronary artery disease	145 (11)	55 (37.9)	90 (62.1)	**<0.01**
	Stroke	85 (6.5)	40 (47.1)	45 (52.9)	**<0.01**
Diabetic complication	DM neuropathy	550 (41.8)	172 (31.3)	378 (68.7)	**<0.01**
	Diabetic kidney disease	646 (49.1)	214 (33.1)	432 (66.9)	**<0.01**

Data are mean ± standard deviation or number (percentage) and were analyzed using Student's *t*-test or the chi-square test, respectively.

DKD, diabetic kidney disease; DM, diabetes mellitus; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index.

30.8%, respectively;[10] but this included patients with type 1 DM, which may explain the high prevalences. Finally, in 2008, Al-Amer *et al.* reported prevalences of DR, NPDR, PDR, and maculopathy of 34.1%, 24.5%, 9.6%, and 7.8%, respectively.[11] Thus, overall, it seems that the prevalence of DR, while still high, is decreasing in the Jordanian population.

A recently published meta-analysis estimated the global prevalence of DR to be 22.27% in patients with type 2 DM.[14] We found a slightly higher prevalence of DR in the Jordanian population, of 28.2% in patients with type 2 DM. In recent years, a standardized protocol for the review of every patient in Jordan with newly diagnosed type 2 DM, which included a fundoscopic examination, was implemented. Moreover, previous studies have shown relatively high levels of awareness regarding DR and the importance of periodic

Table 2. Results of the multivariable binary logistic regression analysis to identify factors associated with diabetic retinopathy in 1,316 participants with type 2 diabetes mellitus.

Parameter	Subgroup	OR	*p*-value	95% CI
HBA1c		1.4	**<0.01**	1.3–1.5
CKD stage	Stage 1 (reference group)			
	Stage 2	1.8	**<0.01**	1.3–2.4
	Stage 3	1.6	**0.01**	1.1–2.3
	Stage 4	5.8	**<0.01**	2.7–12.3
	Stage 5	3.5	**0.02**	1.3–9.7
Smoking status	Non-smoker (reference group)			
	Current smoker	1.7	**<0.01**	1.2–2.4
	Ex-smoker	1	1	0.7–1.4

OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; HBA1c, hemoglobin A1c.

fundoscopic examinations, compared with other parts of the world, although the authors commented that awareness must still be translated into effective patient practices and that there remain socio-economic challenges regarding access to periodic ophthalmic examinations.[15,16] Ideally, a standardized, widely available, and convenient eye screening program should be offered to every patient with DM at a reasonable cost, with the aim of improving their health seeking behaviors.[17]

In the present study, we have demonstrated that having DKD, albuminuria, or a later stage of chronic kidney disease is associated with a higher risk of DR. Furthermore, the multivariable regression model showed a biological gradient (dose-effect relationship) between chronic kidney disease and the stage of DR. DKD is a slowly progressive microvascular complication of DM that may be present at diagnosis in patients with type 2 DM.[18] Given that they share the same pathophysiological basis, it is plausible that DR and DKD share many risk factors, including the duration of diabetes, poor glycemic control, systolic hypertension, and dyslipidemia.[19] Nevertheless, large population-based studies have failed to show that DR is a strong predictor of the progression of DKD or *vice versa*.[19,20] The possibility that DR is an independent risk factor for the progression of DKD has been suggested, mainly because retinal vacsularity can be easily and non-invasively assessed as a marker of microvascular disease, and DR might represent an marker of a concurrent pathological process at an early stage, rather than a predisposing factor for DKD.[21] Conversely, the Chronic Renal Insufficiency Cohort (CRIC) study demonstrated that a low glomerular filtration rate in the general population is associated with more marked retinal vascular changes, independent of other co-morbidities.[22] Although it is unclear whether this potential relationship is confounded by the shared risk factors, more aggressive screening and preventive measures should be implemented in patients with DM and DKD.

Current smokers were found to be at a higher risk of DR in the present study. Interestingly, we found that stopping smoking for $\geq$6 months normalized the risk of DR. The effects of cigarette smoking on the development and progression of DR in patients with type 1 DM are well established, but are less clear for patients with type 2 DM, with some studies not showing a link between DR and smoking and others even suggesting a protective role.[23,24] These unexpected effects of smoking on the risk of DR may be attributable to survival bias

because most smokers who develop type 2 DM die early, and only those smokers with excellent control of their other diabetes and cardiovascular risk factors and excellent compliance with medication survive long enough to develop this long-term complication of DM. Jordan has an extremely high prevalence of smoking, with previous studies showing that 60% to 80% of Jordanian men and 17% to 20% of women are current smokers.[25,26] This high prevalence of smoking might affect the epidemiology of DR in the context of other risk factors under real-world conditions. Moreover, stopping smoking for >6 months reduces the risk of DR, and this might represent a form of response to withdrawal (dechallenge), a criterion for causality.[27] However, this finding might also be attributable to a change in health promoting behaviors: individuals who were motivated to stop smoking may have been more likely to adopt a healthy lifestyle and comply with their prescribed diabetes treatment.[28]

The principal limitation of the present study was its observational, retrospective nature, which precludes the drawing of conclusions regarding cause and effect. Another limitation was the sampling method: the cohort comprised patients attending a tertiary academic center. The capital city, Amman, is highly representative of the ethnic diversity of Jordan, and probably of the Middle East, and owing to the nature of the healthcare system in Jordan, in which the role of general practitioners/family doctors is limited and patients often bypass primary care providers to seek medical care from specialists, we believe that the findings of this study accurately reflect patients with type 2 DM who seek evaluation and treatment in the country.

In conclusion, we have shown that 28.2% of Jordanians with type 2 DM have DR, which remains a high percentage. Poor glycemic control, assessed using HbA1c, current smoking, and advanced diabetic nephropathy were most strongly associated with the presence of DR. Education regarding healthy lifestyles, good glycemic control, and periodic screening should be an essential part of every clinic visit. Moreover, affordable retinal screening programs should be made available across the country. In parallel, additional studies are needed to assess the cost effectiveness and preparedness of healthcare systems and the attitudes of patients towards such programs. Finally, nationwide registries involving longitudinal follow-up are needed to better characterize the natural history of DR in Middle Eastern populations and to help with the formulation of overarching multidisciplinary healthcare policies.

Author contributions

AR, M Al-imam, and M Al-Sabbagh were responsible for the literature review, data acquisition, data analysis, and manuscript preparation. RF was responsible for conceiving and designing the study, data proofing, and manuscript editing. NA supervised the project, contributed to the conception and design of the study, was responsible for data proofing and manuscript review and is the designated guarantor of this work. All the authors take responsibility for the contents of the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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