ORIGINAL RESEARCH

Retinopathy and risk factors in diabetic patients from Al-Madinah Al-Munawarah in the Kingdom of Saudi Arabia

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Background: Diabetes mellitus is accompanied by chronic and dangerous microvascular changes affecting most body systems, especially the eye, leading to diabetic retinopathy. Diabetic retinopathy without appropriate management is emerging as one of the leading causes of blindness. Therefore, it is necessary to improve the early diagnosis of diabetic retinopathy, reduce the risk of blindness, and identify relevant risk factors.

Methods: This descriptive study was designed to estimate the prevalence of retinopathy and its staging in diabetic patients attending the diabetes clinic at King Fahd Hospital in Al-Madinah Al-Munawarah, Kingdom of Saudi Arabia, from 2008 to 2010. Patients completed a questionnaire, underwent a full medical assessment carried out by the treating clinicians, and were examined for evidence of diabetic retinopathy using standard ophthalmic outpatient instruments.

Results: In total, 690 randomly selected diabetic patients of mean age 46.10 ± 11.85 (range 16–88) years were included, comprising 395 men (57.2%) of mean age 46.50 ± 11.31 years and 295 women (42.8%) of mean age 45.55 ± 12.53 years. The mean duration of diabetes mellitus was 11.91 ± 7.92 years in the women and 14.42 ± 8.20 years in the men, and the mean total duration of known diabetes mellitus was 13.35 ± 8.17 years. Glycated hemoglobin was higher in men ($8.53\% \pm 1.81\%$) than in women ($7.73\% \pm 1.84\%$), and this difference was statistically significant ($P \leq 0.0001$). Of the 690 diabetic patients, 249 (36.1%) had retinopathy. Mild nonproliferative diabetic retinopathy was present in 13.6% of patients, being of moderate grade in 8% and of severe grade in 8.1%. A further 6.4% had proliferative diabetic retinopathy.

Conclusion: Regular screening to detect diabetic retinopathy is strongly recommended because early detection has the best chance of preventing retinal complications.

Keywords: diabetic retinopathy, diabetes complications, risk factors

Introduction

Diabetes mellitus is a major public health problem worldwide. Worryingly, the World Health Organization[1,2] has estimated that the number of adults with diabetes worldwide will increase from 135 million in 1995 to 300 million in 2025. Recent studies have shown a significant increase in the prevalence of diabetes mellitus.[3] The prevalence was about 23.7% during 2004 in Saudi Arabia,[4] but by 2011 there has been a significant increase to 30%, with a rate of 34.1% in men and 27.6% in women.[5]

Diabetic retinopathy is a serious complication of the chronic microvascular changes that occur in most body systems in diabetics. Untreated diabetic retinopathy has chronic complications and is emerging as an important cause of blindness. Progression of retinopathy is gradual, advancing from mild abnormalities characterized by increased vascular permeability to moderate-severe nonproliferative diabetic retinopathy, through

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to proliferative diabetic retinopathy characterized by growth of new blood vessels on the retina and posterior surface of the vitreous.[6]

The pathophysiological mechanisms leading to development of diabetic retinopathy are indeed complex and remain unclear, but several theories have been postulated to explain the typical course and history of the disease. Multiple interactive mechanisms may come into play, causing cellular damage and adaptive changes which lead to the development of this devastating complication of diabetes.[7]

Diabetic retinopathy is a leading cause of visual impairment in people with diabetes[8] aged 20–64 years,[9] and more than 77% of patients who survive for over 20 years with diabetes mellitus are affected by the condition.[10] The main risk factors involved in the development of microvascular and macrovascular complications of diabetes include a long disease duration,[11,12] inadequate control of serum glucose levels,[12–16] hypertension,[11,12] dyslipidemia, smoking,[17,18] gender,[13,19] and pregnancy.[20,21] Genetic factors also seem to play a role in predisposition to microvascular and macrovascular disease.[22,23] Diabetic retinopathy occurs in approximately 84.5% of patients with a known disease duration of 15 years.[13,24] The prevalence of retinopathy in type 2 diabetes is 12%.[8,25,26] During the first two decades of the disease, nearly all patients with type 1 diabetes and up to 60% of patients with type 2 diabetes develop retinopathy.[27] In this study, our aims were to estimate the prevalence of retinopathy among diabetics and to investigate the associations between risk factors and stages of diabetic retinopathy.

Materials and methods

The study was part of a general survey carried out to assess the prevalence of retinopathy and blindness as one of the complications of diabetes mellitus among patients with the disease in Al-Madinah Al-Munawarah District, Kingdom of Saudi Arabia, in 2008–2010.

We obtained ethics committee approval, and informed consent was taken from the 690 diabetic men and women recruited for this study. The participants were randomly selected, with 57.2% being male and 42.8% being female, giving a gender ratio of 1.33:1, with a total mean age of 46.1 ± 11.85 years (Table 1).

Risk factors investigated included demographic and clinical parameters. The demographic parameters were age and gender, and the clinical parameters were glycated hemoglobin (HbA_{1C}) levels and coexistence of hypertension, using the World Health Organization definition of hypertension, ie, systolic blood pressure ≥130 mmHg and/or a diastolic blood pressure ≥90 mmHg, or requirement for ongoing treatment with antihypertensive drugs.

The patients were interviewed by clinicians at the diabetic patient center and hospital outpatient clinic to collect information about type of diabetes and years since diagnosis of the disease (treated as an ordinal variable [0, 0–5 years; 1, 5–10 years; 2, 10–15 years; 3, 15–20 years; 4, >20 years]). Data on compliance with treatment as assessed by doctors, associated complications, and comorbidity were also collected. Blood pressure was measured by a nurse early in the morning in the sitting position prior to drawing blood samples, using a standard mercury sphygmomanometer. Height was measured without shoes, and weight was recorded while wearing indoor clothing. Body mass index (BMI, weight in kg divided by height in meters squared) was calculated. The World Health Organization classification of BMI was used to estimate the degree of obesity.[28] Obesity was assessed, and classified as overweight (BMI 25.0–29.9 kg/m²), obese (30.0–39.9 kg/m²), or morbidly obese (40.0 kg/m²).[29]

Blood samples were collected from both controls and patients for a series of laboratory investigations using standard protocols for estimation of fasting and postprandial blood glucose, serum total cholesterol, triglycerides, high-density and low-density lipoprotein cholesterol, serum creatinine, and HbA_{1C} (DiaSTAT Hemoglobin A_{1c} program, Bio-Rad Laboratories, Hercules, CA). The estimated normal range for HbA_{1C} in nondiabetics is 4.4%–6.4%; a value <7% was considered as good glycemic control and >7 was considered as poor control.[30,31] A blood cholesterol level <5.18 mmol/L was considered normal, 5.18–6.18 mmol/L as borderline high, and >6.18 mmol/L as high. Triglycerides <150 mg/dL (<1.7 mmol/L) were defined as normal, 150–200 mg/dL (1.7–2.3 mmol/L) as increased risk, and >200 mg/dL (>2.3 mmol/L) as high-risk. High-density lipoprotein levels >40 mg/dL (>1.04 mmol/L) were taken as normal, 30–40 mg/dL as increased risk, and <30 mg/dL as high-risk. Low-density lipoprotein levels were optimal if <100 mg/dL (<1.3 mmol), borderline high at 130–159 mg/dL (3.3–4.1 mmol), and high at 160–189 mg/dL (>4.1 mmol).[32–35]

All patients were referred to two ophthalmologists working at the two main hospitals of Al-Madinah Al-Munawarah district for a detailed eye examination. After adequate mydriasis, examination of the interior segment was carried out using a slit lamp with a Volk 90 D lens. Intraocular pressure was measured using a Goldman applanation tonometer. Fundus photography was done using a Topcon TRC-NW6 nonmydriatic fundus camera.

Table 1 General characteristics of study population and variables according to gender

Variables	Women (n = 295)	Men (n = 395)	Total (n = 690)
Age (mean ± SD)	45.55 ± 12.5	46.50 ± 11.3	46.10 ± 11.8
Type 1 diabetes	27	31	58 (8.4%)
Type 2 diabetes	268	364	632 (91.6%)
Nonsmokers	295	379	674 (97.7%)
Smokers	0	16	16 (2.3%)
Negative family history of hypertension	203	258	461 (66.8%)
Positive family history of hypertension	92	137	229 (33.2%)
Negative family history of diabetes	125	152	277 (40.1%)
Positive family history of diabetes	170	243	413 (59.9%)
Duration of diabetes (mean ± SD)	11.91 ± 7.9	14.42 ± 8.2#	13.35 ± 8.1
Body mass index	32.00 ± 5.8	33.57 ± 6.8*	32.93 ± 6.5
Systolic blood pressure (mmHg)	128.22 ± 21.9	128.37 ± 19.3	128.31 ± 20.5
Diastolic blood pressure (mmHg)	77.93 ± 10.2	77.83 ± 10.3	77.87 ± 10.3
Glycated hemoglobin (%)	7.73 ± 1.8	8.53 ± 1.8#	8.41 ± 1.9

Notes: *$P \leq 0.001$; #$P \leq 0.0001$.
Abbreviation: SD, standard deviation.

Diabetic retinopathy was clinically graded in accordance with the International Clinical Diabetic Retinopathy guidelines as follows: background retinopathy, if microaneurysms, hemorrhages (dot, blot, or flame-shaped), hard exudates, and/or macular edema was present; proliferative diabetic retinopathy, if cotton wool spots, multiple large blot hemorrhages, neovascularization of the retina or iris, angle, venous beading, loops, and reduplication, arterial sheathing, or an atrophic-looking retina were present; and advanced diabetic eye disease, if vitreous hemorrhage, retinal detachment, rubeosis iridis, or glaucoma was present.[36,37]

Statistical analysis

Differences were considered statistically significant at $P < 0.05$. SPSS statistical software (v 8; SPSS Inc, Chicago, IL) was used to perform the descriptive analysis.

Results

In total, 690 randomly selected diabetic patients were included, with a mean age of 46.10 ± 11.85 (range 16–88) years. There were 395 males of mean age 46.50 ± 11.31 years and 295 females of mean age 45.55 ± 12.53 years. The men and women were matched for age, with no statistically significant differences (independent t-test, $P \leq 0.295$). The patients were investigated for gender, type of diabetes mellitus, smoking status, and family history of hypertension. There were more women than men for all variables investigated, except for smoking status (Table 1).

The mean duration of diabetes mellitus in all patients was 13.35 ± 8.17 years, but was significantly ($P \leq 0.0001$) shorter in women (11.91 ± 7.92 years) than in men (14.42 ± 8.20 years). There was a statistically significant

difference (independent-samples test, $P \leq 0.001$) between women and men for mean BMI (32.00 ± 5.88 and 33.57 ± 6.86, respectively). Both genders were overweight, making them more susceptible to chronic disease, eg, hypertension and diabetes (Table 1).

Men had higher mean blood pressure (systolic 128.37 ± 19.36 mmHg and diastolic 77.83 ± 10.33 mmHg) than women (128.22 ± 21.92 mmHg and 77.93 ± 10.26 mmHg, respectively) but the difference was not statistically significant. Mean HbA$_{1C}$ was significantly higher (≤ 0.0001) in men (8.53 ± 1.81) than in women (7.73 ± 1.84).

One hundred and forty-two (48.13%) of the 295 women and 155 (39.24%) of the 395 men had had known diabetes for up to 10 years, with 114 (38.64%) women and 139 (35.18%) men having had the disease for up to 20 years, and 39 (13.22%) women and 101 (25.56%) men having had it for more than 20 years. In total, 297 (43%) had had diabetes for up to 10 years, 253 (36.7%) for up to 20 years, and 140 (20.3%) for more than 20 years (Table 2).

Figure 1 shows the distribution of diabetic retinopathy according to grade for all patients in our study. A total of 441 (63.9%) of 690 patients were free from diabetic retinopathy, while 249 (36.1%) had the disorder. Ninety-four (37.7%) of the 249 patients had mild nonproliferative diabetic retinopathy (NPDR), representing 13.6% of the total 690 diabetic patients in the study. Fifty-four (22%) of the 249 patients with diabetic retinopathy had moderate NPDR, representing 8% of the total 690 diabetic patients. Fifty-six (22.4%) of the patients with diabetic retinopathy had severe NPDR, representing 8.1% of the total 690 patients. Finally, 44 (17.6%) of the 249 patients had proliferative diabetic retinopathy, representing 6.4% of the total group. Subjects with diabetic

Table 2 Duration of diabetes in men and women according to type of diabetes

Duration of diabetes (years)	Men			Women			Total
	Type 1	Type 2	Total	Type 1	Type 2	Total	
<10	2	153	155	0	142	142	297 (43%)
11–20	19	120	139	12	102	114	253 (36.7%)
>20	10	91	101	15	24	39	140 (20.3%)
Total	31	364	395	27	268	295	690

retinopathy were more likely to be male (155/690, 22.46%) than female (94/690, 13.62%). By gender, the proportion of patients having diabetic retinopathy was 39.24% for men and 31.86% for women (Figure 2).

Diabetes in this study was defined according to self-reporting of a previous diagnosis of the disease or HbA_{1C} ≥6.5%. Two photographs were taken of the fundus of each eye using a digital nonmydriatic camera and were graded using the Airlie House classification scheme and the Early Treatment Diabetic Retinopathy Study severity scale.

Figure 3 shows fundus images indicating the different grades of diabetic retinopathy, ie, a diabetic subject without diabetic retinopathy, a case with mild NPDR, a case with moderate NPDR, a case with severe NPDR, a case of proliferative diabetic retinopathy, a case of advanced proliferative diabetic retinopathy and vitreous hemorrhage, a case of vitreous hemorrhage with previous laser marks, and a case with vitreoretinal traction bands.

Table 3 shows the distribution of patients with diabetic retinopathy according to their gender and percentage of the frequency in the total population according to classification grade of diabetic retinopathy. Two hundred and forty (54.4%) of 441 patients free of retinopathy were men, representing 34.8% of the total study population of 690 patients, and

201 (45.6%) of the 441 patients free of retinopathy were women, representing 29.2% as the total study population. Across the different grades of diabetic retinopathy, the frequency for men was proportionally greater than for women.

Table 4 shows the distribution of patients according to gender and frequency in the total population and grading of diabetic retinopathy and duration of diabetes. Diabetic patients free from retinopathy with a disease duration of less than 10 years comprised 208 of 262 patients, and patients with mild NPDR comprised 51 patients (19.46%); another three were found under the moderate grade and nothing was recorded for severe NPDR or proliferative diabetic retinopathy. Therefore, about 20% of the patients developed retinopathy within ten years of being diagnosed as having diabetes mellitus. This strongly suggests that screening of diabetic patients for the presence of retinopathy should not be delayed until they have suffered from the disease for 10 years, and should commence sooner. We also noticed from the results that the longer the patients had had diabetes, the greater the likelihood of them having advanced grades of diabetic retinopathy, with 75% of patients with severe NPDR and proliferative diabetic retinopathy having had diabetes for more than 30 years and 87.5% of those with proliferative diabetic retinopathy having had diabetes for more than 40 years. There were positive
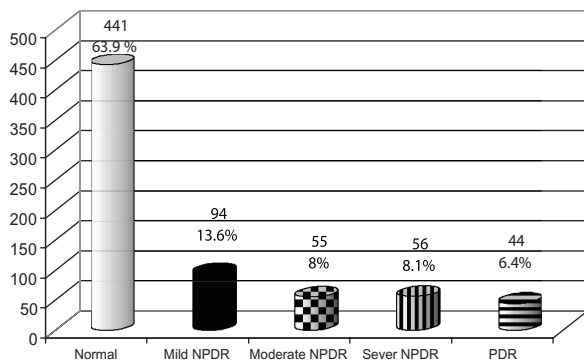

Figure 1 Distribution of diabetic patients according to retinopathy grade. The white cylinder represents diabetic patients with a normal retina, the black cylinder shows mild NPDR, the check board cylinder shows moderate NPDR, the cylinder with vertical lines shows severe NPDR, and the cylinder with horizontal lines shows PDR.
Abbreviations: PDR, proliferative diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy.
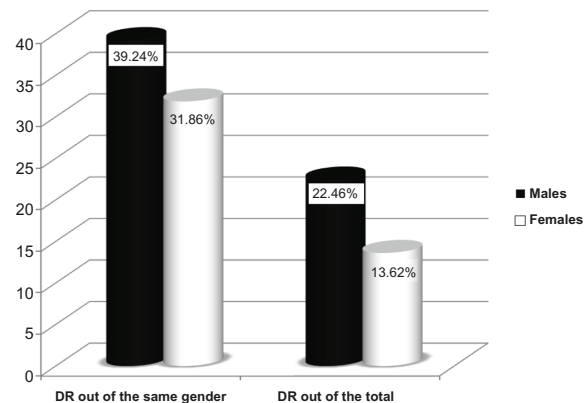

Figure 2 Diabetic retinopathy in all diabetic patients according to gender. The white cylinder represents female diabetic patients and males are represented by the black cylinder.
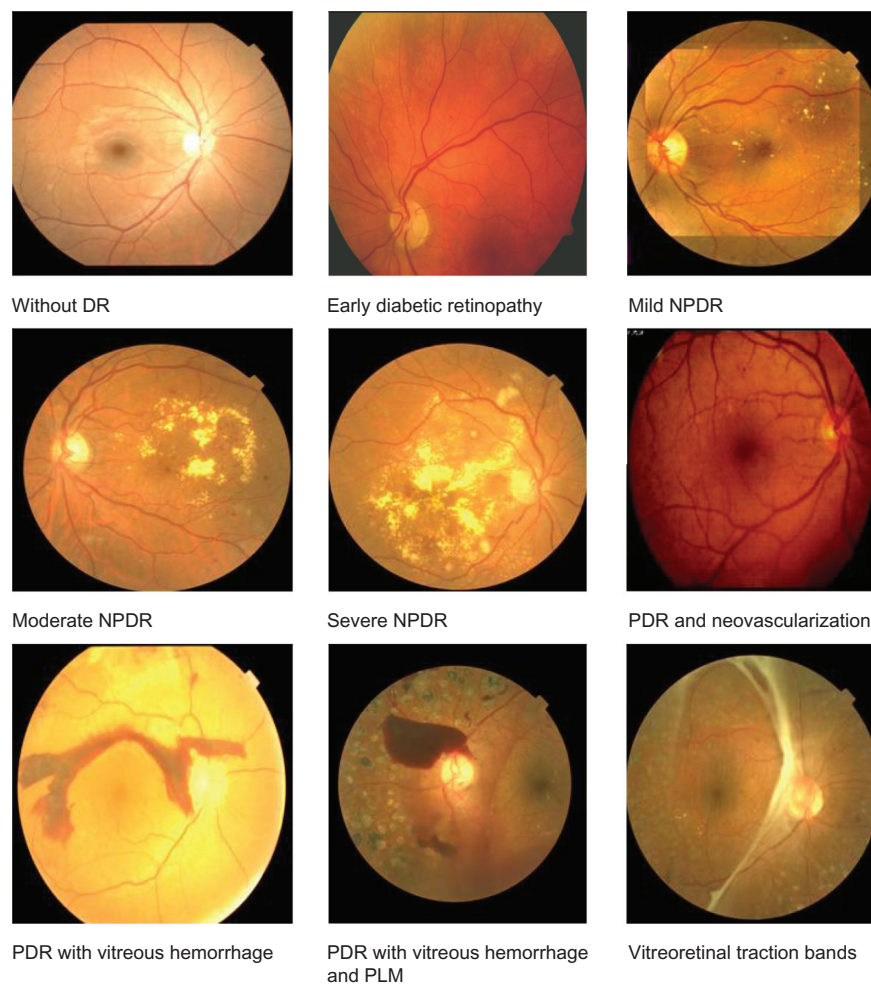**Abbreviation:** DR, diabetic retinopathy.

Without DR	Early diabetic retinopathy	Mild NPDR
Moderate NPDR	Severe NPDR	PDR and neovascularization
PDR with vitreous hemorrhage	PDR with vitreous hemorrhage and PLM	Vitreoretinal traction bands

Figure 3 Fundus images of normal (background retinopathy), mild NPDR, moderate NPDR, severe NPDR, PDR, PDR with new vascularization, and PDR with PLM and with vitreous hemorrhage.
Abbreviations: PDR, proliferative diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PLM, previous laser marks.

significant correlations between the duration of diabetes mellitus, HbA_{1c}, and grades of diabetic retinopathy (R^2 0.835 and 0.796, respectively, Figures 4 and 5).

Discussion

The International Diabetes Federation in 2003 ranked the Kingdom of Saudi Arabia prevalence rates for type 2 diabetes

Table 3 Diabetic retinopathy grade in diabetic patients according to gender

Diabetic retinopathy grades	Males			Females		
	n	% of grade	% of total	n	% of grade	% of total
Normal	240	54.4	34.8	201	45.6	29.2
Mild NPDR	57	60.6	8.3	37	39.4	5.4
Moderate NPDR	30	54.5	4.3	25	45.5	3.6
Severe NPDR	33	58.9	4.8	23	41.1	3.3
PDR	35	79.5	5.1	9	20.5	1.3

Abbreviations: PDR, proliferative diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy.

mellitus and impaired glucose tolerance as the second highest in the world (20% and 26%, respectively)[3] indicating that the disease and its complications, such as retinopathy, might constitute a sizable health care burden to the population. Despite that, little is known about the true impact of diabetes and its complications, including diabetic retinopathy, in the population of the Kingdom of Saudi Arabia.

Retinopathy was present in 34.6% of our study population. It was suggested in 1998 that 20% of diabetics worldwide will develop diabetic retinopathy,[38] which is similar to the rate recorded in Al-Ain, United Arab Emirates (19%), but is clearly lower than that reported in other populations such as the US (40%–45%),[13] Saudi Arabia (31%),[17] the Sultanate of Oman (42%),[39] and Egypt (42%).[40] However, it is substantially higher than the 8% rate reported in a similar study in Kuwait,[41] 11.6% in Saudi Arabia during 2002,[42] and 16.9% in China.[43] Studies in Ethiopia, France, and Japan have demonstrated higher rates.[44–46] The substantial

Table 4 Diabetic retinopathy grades according to duration of diabetes

Diabetes duration (years)	Normal		Mild NPDR		Moderate NPDR		Severe NPDR		PDR		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
<10	208	79.38	51	19.46	3	1.14	0	0	0	0	262	37.97
<20	140	52.83	32	12.07	47	17.73	35	13.20	11	4.15	265	38.41
<30	93	68.88	7	5.18	3	2.22	14	10.37	18	13.33	135	19.56
<40	0	0	3	15	2	10	7	35	8	40	20	2.90
>40	0	0	1	12.5	0	0	0	0	7	87.5	8	1.16
Total	441	63.91	94	13.62	55	7.97	56	8.11	44	6.37	690	100

Abbreviations: PDR, proliferative diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy.

heterogeneity in reported prevalence of retinopathy may be real to some extent. This may be due to differences in the age distribution of different populations, but may also be due to differences in study methodology and population sampling. The large number of late diabetic cases recorded in our study could have led to a relatively high prevalence rate.

As demonstrated elsewhere, our findings clearly show that diabetic retinopathy is a common health problem and may well be among the leading causes of blindness in Saudi adults. It is well established that nearly all patients with type 1 and type 2 diabetes are at increasing high risk for the disease.[2,16]

The fact that the majority of our study population (63%) was not well educated further emphasizes the seriousness and complexity of the diabetes problem in the Kingdom of Saudi Arabia. Therefore, heightened awareness of the importance of a comprehensive annual eye examination with pupil dilation in illiterate patients is necessary. Clinicians treating these patients should also be reminded to follow the treatment guidelines for diabetes closely and refer all diabetics to an ophthalmologist for management and treatment as indicated to preserve vision.

Analysis of our study population shows that diabetic retinopathy increases with patient age and disease duration; this positive association between diabetic retinopathy and duration of diabetes is noted in the literature.[8,9,14,15,18] For example, the reported rate of retinopathy in southern India[46] and in the Sultanate of Oman[47] was 7% in individuals with a short duration of diabetes (less than 10 years), 26% in those with disease of 10–14 years' duration, and 63% in those with a diabetes duration of 15 years, and these observations close match those of our study. Duration of diabetes is known to reflect total glycemic control and risk factor exposure over time.[2,18] While this may suggest avenues for primary prevention, the true prospects for that are currently unknown.

In a longitudinal study, Wang et al[16] showed that nearly all type 1 diabetics and approximately two-thirds of type 2 diabetics develop retinopathy after a disease duration of 20 years, regardless of their diabetic control. However, their analysis revealed that diabetic retinopathy in the study sample was only marginally associated with hypertension, which is widely regarded as a significant risk factor for diabetic retinopathy in most studies.[10,19] Improved monitoring and control of hypertension among diabetic patients in the United Arab Emirates, which has been shown to slow the progression of retinopathy, particularly among those with poorly controlled diabetes, is strongly recommended.[20]
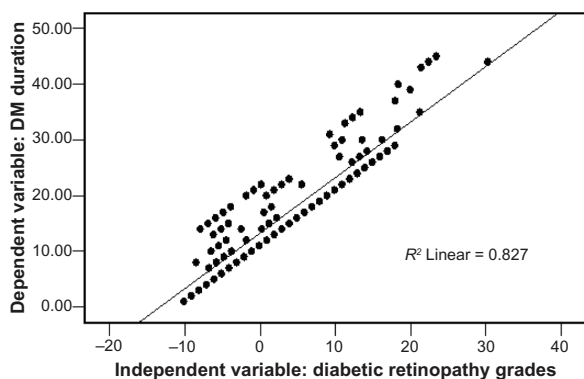

Figure 4 Correlation between diabetic retinopathy grades according to duration of diabetes.
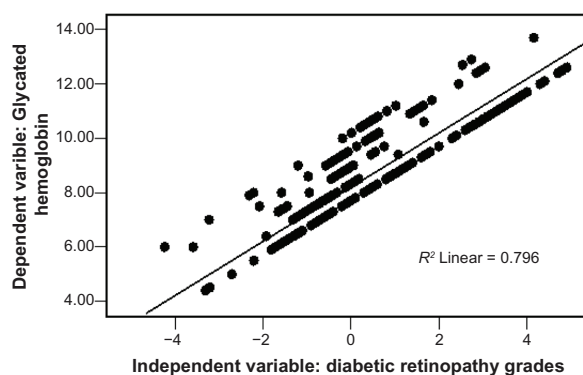**Abbreviation:** DM, diabetes mellitus.

Figure 5 Correlation between diabetic retinopathy grades according to glycated hemoglobin.

Our results showing a significant positive association between HbA_{1C} levels and different grades of diabetic retinopathy are consistent with other reports.[12–16] HbA_{1C} levels in diabetic Saudi patients were more than 8%, and there was a positive correlation between diabetic retinopathy and hyperlipidemia. It is strongly recommended that glycemic and lipidemic control be widely promoted and that HbA_{1C} and lipid profile investigations be carried out routinely.

In Saudi Arabia, women had significantly higher rates of diabetic retinopathy than men, which is in agreement with a study in Sweden where women had higher rates than men[49] and in other studies.[13,19]Two further studies have suggested nonsignificant differences in diabetic retinopathy according to gender.[50,51] However, our results are in contrast with results from Oman.[48] Smoking was associated with an increased likelihood of having diabetic retinopathy, as reported in other studies.[17,18,39–41]

Our study results are consistent with those in neighboring countries, such as the Sultanate of Oman[48] and the United Arab Emirates,[52] where the prevalence of retinopathy was also higher in patients with diabetes and its complications such as coronary artery disease, peripheral neuropathy, and vascular disease,[22,23] such as hypertension.[12,13] Surprisingly, and unlike findings elsewhere,[53] the degree of glycemic control did not show any significant association with diabetic retinopathy in the study sample.

Our study has some limitations. First, the assumption that diabetic patients with blindness and cataract had diabetic retinopathy as the primary cause may have led to some slight overestimation of the prevalence of retinopathy. Second, it is known that diabetes is notoriously underdiagnosed; therefore, while our sample probably reflects diabetic retinopathy among diagnosed diabetic patients adequately, it is likely that this proportion still represents only the tip of the iceberg.

Conclusion

The prevalence of diabetic retinopathy in Al-Madinah Al-Munawarah, Kingdom of Saudi Arabia, was 36.1%. Based on the findings of the current study, it is strongly recommended to perform regular screening for diabetic retinopathy, thereby increasing the chances of preventing a lot of diabetes-related blindness. Long duration since diagnosis of diabetes, hypertension, high HbA_{1C} levels, advancing age, and male gender are associated with advanced stages of diabetic retinopathy.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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