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Incidence and risk factors of severe non-proliferative/proliferative diabetic retinopathy: More than a decade follow up in the Tehran Lipids and Glucose Study

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ABSTRACT

Aims/Introduction: To examine the incidence rate of severe non-proliferative and proliferative diabetic retinopathy (severe-NPDR/PDR) and determine its potential risk factors.

Materials and Methods: The study consisted of 1,169 participants (675 women) with type 2 diabetes mellitus, aged ≥20 years. A trained interviewer collected information about the history of pan-retinal photocoagulation as a result of diabetic retinopathy. Multivariable Cox proportional hazards regression models were applied.

Results: We found 187 cases (126 women) of severe-NPDR/PDR during a median follow-up period of 12.7 years; the corresponding incidence rate was 13.6 per 1,000 person-years. Being overweight (hazard ratio [HR], 95% confidence interval [CI] 0.60, 0.39–0.92) and obese (HR 0.48, 95% CI 0.27–0.83) were associated with lower risk, whereas being smoker (HR 1.75, 95% CI 1.12–2.74), having fasting plasma glucose levels 7.22–10.0 mmol/L (HR 2.81, 95% CI 1.70–4.62), fasting plasma glucose ≥10 mmol/L (HR 5.87, 95% CI 3.67–9.41), taking glucose-lowering medications (HR 2.58, 95% CI 1.87–3.56), prehypertension status (HR 1.65, 95% CI 1.05–2.58) and newly diagnosed hypertension (HR 1.96, 95% CI 1.06–3.65) increased the risk of severe-NPDR/PDR. Among newly diagnosed diabetes patients, being male was associated with a 59% lower risk of severe-NPDR/PDR (HR 0.41, 95% CI 0.21–0.79). Furthermore, patients who had an intermediate level of education (6–12 years) had a higher risk of developing PDR (HR 1.86, 95% CI 1.05–3.30) compared with those who had <6 years of education.

Conclusions: Among Iranians with type 2 diabetes mellitus, 1.36% developed severe-NPDR/PDR annually. Normal bodyweight, being a smoker, out of target fasting plasma glucose level, prehypertension and newly diagnosed hypertension status were independent risk factors of severe-NPDR/PDR. Regarding the sight-threatening entity of advanced diabetic retinopathy, the multicomponent strategy to control diabetes, abstinence of smoking and tight control of blood pressure should be considered.

INTRODUCTION

Over the past few decades, increasing prevalence and incidence rates of type 2 diabetes mellitus have made it the most critical key health priority. Currently, type 2 diabetes mellitus affects 425 million adults worldwide with a prevalence rate of 8.8%, and it is estimated to reach 500 million by the year 2030[1,2]. With increasing diabetes trends globally, devastating diabetes-related complications and morbidities, including diabetic retinopathy (DR), are rising and have emerged as public health concerns[3].

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DR is the most common microvascular complication of diabetes, and is a leading cause of visual impairment and blindness in the working-age population[4,5]. Additionally, DR, especially in the advanced stages, has a strong association with a two- to threefold excess risk of cardiovascular diseases and ischemic stroke[6,7]. Hence, timely diagnosis and management of DR seem vital. The American Diabetes Association and the American Academy of Ophthalmology recommend that after the diagnosis of type 2 diabetes mellitus, patients with type 2 diabetes mellitus should undergo a complete ophthalmic examination at least once a year[8,9].

Several potential risk factors are introduced to initiate or progress DR among patients with type 2 diabetes mellitus, including the duration of diabetes, hypertension, advanced diabetic nephropathy, severe carotid artery occlusive disease and pregnancy[10,11]. Furthermore, Scanlon *et al.* showed that race plays an important role in the progression of DR among various populations[12].

Between 2008 and 2011, the prevalence of type 2 diabetes mellitus among the Tehran population was reported to be >13%; >1% of the Iranian population developed diabetes each year[2]. A previous cross-sectional study in Iran reported a high prevalence of DR among type 2 diabetes mellitus patients; the value reached 27.3% for non-proliferative DR (NPDR) and 9.6% for proliferative DR (PDR)[13].

In the present study, we aimed to determine the incidence and risk factors of severe-NPDR/PDR over 10 years of follow up in the population-based cohort of the Tehran Lipid and Glucose Study (TLGS).

MATERIALS AND METHODS

Study population

The TLGS is a prospective cohort study that was carried out with individuals who lived in district 13 of Tehran. It aimed at determining the prevalence, incidence and other epidemiological aspects of non-communicable diseases. It also looked at counteracting the non-communicable diseases burden by developing a healthier lifestyle. The TLGS enrollment was carried out in two phases, the first of which was from 31 January 1999 to 3 July 2001, the second phase was from 20 October 2001 until 22 September 2005. It is planned that data collection will continue for at least 20 years, with approximately 3-year intervals. Further details of the TLGS have been reported elsewhere[14].

Among a total of 1,375 participants with type 2 diabetes mellitus aged ≥20 years (1,164 individuals from phase I and 211 participants from phase II), we excluded individuals with 42% missing data regarding body mass index (BMI), waist circumference (WC), fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, education level, serum creatinine and physical activity at baseline ($n = 54$, considering overlaps between numbers). After excluding individuals without any follow-up measurements after baseline recruitment ($n = 154$), a total of 1,169 participants (675 women) were followed until 20 March 2016 for the current study analyses. No patients had a history of PRP at baseline.

The ethics committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences approved the study proposal (ethics number: IR.SBMU.ENDOCRINE.REC.1400.006 in May 2021) and written informed consent was obtained from all participants.

Clinical and laboratory measurements

Using a standard questionnaire, a trained interviewer collected information, which included demographic data, history of pan-retinal photocoagulation as a result of DR, medication history, cardiovascular disease, smoking habits and education level. Body measurements (weight and height) were carried out while participants were wearing light clothing with shoes removed. Weight was recorded to the nearest 100 g. Height was recorded in a standing position, using a tape measure, while shoulders were in normal alignment. At the level of the umbilicus, WC was measured with light clothing[14]. Using a standard mercury sphygmomanometer (calibrated by the Iranian Institute of Standards and Industrial Research), after 15 min of rest, blood pressure (BP) was measured twice in a seated position. The mean of these two BP measurements was considered as the BP level. After 12–14 h of overnight fasting, blood samples were taken from all participants. Details for laboratory measurements, including FPG, TG, TC, HDL-C and serum creatinine, are published elsewhere[14]. A standard oral glucose tolerance test was carried out in participants with untreated diabetes.

Definition of terms

General obesity was classified into three groups: (i) BMI <25 kg/m^2 as normal; (ii) 25 ≤ BMI < 30 kg/m^2 as overweight; and (iii) ≥30 kg/m^2 as obese. As recommended by 'The Iranian National Committee of Obesity', and based on multiple cross-sectional and prospective studies, we defined central obesity as WC ≥95 cm for both sexes[15,16]. For age categorization, we classified our study population into three groups: (i) 20–40 years; (ii) 40–60 years; and (iii) ≥60 years. Education was sorted into three groups: (i) formal education lasting <6 years; (ii) 6–12 years; and (iii) >12 years. For smoking status categorization, three groups were defined: (i) current smokers (who smoke cigarettes or pipe water daily or occasionally); (ii) former smokers (those who used to smoke); and (iii) never smokers. For phase I-enrolled participants, we used the Lipid Research Clinic questionnaire to evaluate weekly physical activity levels; low physical activity was defined as being physically active for <3 days per week. For phase II-enrolled participants, we also used the Modifiable Activity Questionnaire and individuals with fewer than 600 MET (metabolic equivalent task)-minutes per week were categorized as being in the low physical activity group[14,17]. Regarding hypertension status, we classified BP levels

into five groups: normotensive individuals were individuals with SBP <120 mmHg and DBP <80 mmHg; prehypertensive individuals were individuals with 120 ≤ SBP < 140 or 80 ≤DBP < 90 not on any antihypertensive drug; newly diagnosed hypertensive patients were those who had SBP ≥140 mmHg or DBP ≥90 mmHg without taking any antihypertensive drug; controlled treated hypertensive individuals with SBP <140 mmHg and DBP <90 mmHg, and uncontrolled treated hypertensive individuals with SBP ≥140 mmHg or DBP ≥90 mmHg. Regarding blood glucose level, patients were categorized into three groups: (i) FPG categories were defined as FPG <7.22 mmol/L; (ii) FPG 7.22 to <10.0 mmol/L; and (iii) FPG ≥10 mmol/L, corresponding to hemoglobin A1c levels of <7, 7–8 and ≥8%, respectively[18]; a similar approach was applied in our previous study[19]. High TC and high TG were defined as TC ≥5.18 mmol/L and TG ≥1.695 mmol/L, respectively. Low HDL-C was defined as HDL-C <1.036 mmol/L for men or <1.295 mmol/L for women.

Glomerular filtration rate (GFR) was estimated using the abbreviated prediction equation, provided by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study as follows[20]:

$$\text{eGFR}\,(\text{mL/min per } 1.73\,\text{m}^2) = 141 \times \text{minimum}\,(\text{SCr}/\kappa, 1)\,\alpha \times$$

$$\text{maximum}\,(\text{SCr}/\kappa, 1) - 1.209 \times 0.993\,\text{Age} \times 1.018[\text{if women}],$$

where $\kappa = 0.7$ for women and 0.9 for men, $\alpha = -0.329$ for women and -0.411 for men.

In this equation, estimated GFR (eGFR) is expressed as mL/min per 1.73 m^2 and serum creatinine as mg/dL. CKD was an eGFR of <60 mL/min per 1.73 m^2 (CKD stage 3–5) occurring at any time during the follow-up period.

Outcome: severe-NPDR/PDR

According to the previously published article on outcomes in the TLGS cohort[21], for each participant, any medical event leading to hospitalization was followed up by a telephone call annually. Individuals were asked about any medical conditions by a trained nurse, and later, a trained physician collected complementary data regarding that event during a home visit and by the acquisition of data from medical files. The collected data were then evaluated by an outcome committee consisting of an internist, endocrinologist, cardiologist, epidemiologist and other experts, if required, to assign a specific outcome for every event. Importantly, the outcome committee is blinded to the status of baseline risk factors. Following the TLGS protocol, severe-NPDR/PDR was defined as the history of the first pan-retinal photocoagulation (PRP), which was carried out in the follow-up period. The recommendation of a trial of PRP for severe NPDR and PDR was addressed in several studies[22,23]. Furthermore, carrying out PRP at the severe NPDR stage is likely to be cost-effective compared with delaying photocoagulation until PDR develops[24].

Statistical analysis

Baseline characteristics of the study population are described as the mean (standard deviation; SD) values for continuous variables, and as frequencies (%) for categorical variables. Comparison of the baseline characteristics between male and female participants, and also respondents (entered in the study) and non-respondent (including those with missing data at the baseline or with no follow-up data) individuals was carried out using the Student's *t*-test for normally distributed continuous variables, the χ^2-test for categorical variables, and the Mann–Whitney *U*-statistic for the skewed and ordered variables. The cumulative incidence rate of retinopathy was calculated by dividing the number of event cases by the total number of participants. The crude incidence rate (95% confidence interval [CI]) of retinopathy was calculated by dividing the number of new cases of retinopathy by person-years at risk for each sex and the whole population.

Cox proportional hazards models were applied to evaluate the association of the potential risk factors with incident retinopathy. Univariable analysis was carried out for each potential retinopathy risk factor including sex (reference: women), age (reference: 20–39 years), BMI (reference: normal), smoking status (reference: never), education levels (reference: <6 years), low physical activity, BP level (reference: normal), low HDL-C, high TC, high TG and FPG level categories (reference: <7.22 mmol/L), as well as for central obesity, prevalent cardiovascular disease, CKD and aspirin medication. Those covariates with a *P*-value <0.2 were entered in the multivariable analysis.

The hazard ratios (HRs) and 95% CIs were reported for adjusted risk factors. The proportionality in the Cox model was evaluated with the Schoenfeld residual test and, generally, all proportionality assumptions were appropriate. The event date was defined as the date of the incident PDR. Those who met the following criteria were considered to be censored: leaving the residential area, loss to follow up or end of follow up. For individuals with incident PDR, survival time was considered as the time between the entered date and the severe-NPDR/PDR date. Additionally, for the censored participants, the survival time was considered as the difference between the entered date and the last available follow-up date.

As a sensitivity analysis, a multivariable analysis was carried out among those who had not been on diabetes medications (newly diagnosed patients with type 2 diabetes mellitus) at enrollment.

As another sensitivity analysis, to minimize selection bias, due to missing data at the baseline, the propensity score was calculated and adjusted in the analysis. The propensity score calculated the estimated probability of non-responders based on individual characteristics at baseline. This measure was computed using maximum likelihood logistic regression analysis[25].

All tests were carried out using Stata version 14 SE (StataCorp LP, College Station, TX, USA), which was considered to be significant with a two-tailed *P*-value of <0.05.

RESULTS

The study population consisted of 494 men and 675 women at baseline with a mean age of 56.93 (SD 12.37) and 54.32 (SD 10.66) years, respectively. We compared baseline characteristics of respondent individuals with non-respondent individuals. As shown in Table S1, compared with non-respondents, respondents were less likely to be obese, had higher TG and lower FPG levels. The baseline characteristics of men and women, and also according to BMI categories of the study population are shown in Table 1 and Table S2. There were significant differences between men and women; women who were younger had higher levels of BMI, WC, FPG, TC and HDL-C, and higher frequencies of hypertension and CKD. They were less educated and less likely to be smokers, whereas men reported higher frequencies of aspirin medications and having a positive history of cardiovascular disease. Just 27.9% of the patients with type 2 diabetes mellitus reported use of glucose-lowering medication at the baseline recruitment. The distribution of the medications is shown in Figure 1. Accordingly, sulfonylurea in combination with other glucose-lowering medications was the most common category.

During the median follow-up period of 12.7 years (interquartile range 7.8–16.1), 187 PDR (126 women) were recorded. The crude and age-standardized incidence rates of incident severe-NPDR/PDR in the whole population were 13.6 (95% CI 11.7–15.6) and 11.0 (95% CI 8.7–13.7) per 1,000 person-years. The sex-specific crude incidence rates were 10.8 (95% CI 8.4–13.9) and 15.5 (95% CI 13.0–18.4) per 1,000 person-years in men and women, respectively. The age-standardized incidence of PDR among men and women was 9.5 (95% CI 6.2–13.8) and 12.0 (95% CI 9.0–15.7) per 1,000 person-years, respectively.

Univariable HRs (95% CI) of potential categorical risk factors of developing severe-NPDR/PDR are shown in Table 2. Table 3 shows multivariable-adjusted hazard ratios and 95% CIs of potential severe-NPDR/PDR risk factors. Being overweight and obese was associated with a 40% (HR 0.60, 95% CI 0.39–0.92, $P = 0.02$) and 52% (HR 0.48, 95% CI 0.27–0.83, $P = 0.01$) lower risk of PDR respectively. Furthermore, being a current smoker was associated with a 75% higher risk of PDR (HR 1.75, 95% CI 1.12–2.74, $P = 0.02$). Furthermore, there were significant positive associations between FPG categories ≥7.22 mmol/L, and diabetes medication with severe-NPDR/PDR. The present results showed that prehypertension and newly diagnosed hypertension were also associated with a higher risk of PDR (HR 1.65, 95% CI 1.05–2.58, $P = 0.03$ and HR 1.96, 95% CI 1.06–3.65, $P = 0.03$, respectively). Furthermore, uncontrolled treated hypertensive patients showed a 42% non-significant higher risk of severe-NPDR/PDR (HR 1.42, 95% CI 0.87–2.31).

As a sensitivity analysis, when we excluded known diabetes cases (on glucose-lowering medications) from our data analysis, being male was associated with a 59% lower risk of severe-NPDR/PDR (HR 0.41, 95% CI 0.21–0.79, $P = 0.01$). We observed that the risk of incident severe-NPDR/PDR was significantly related to higher FPG levels. Patients who had an intermediate level of education (6–12 years) had a higher risk of developing PDR (HR 1.86, 95% CI 1.05–3.30, $P = 0.03$) (Table 4).

Furthermore, after further adjustment for inverse probability weighting (1 / propensity score), the results remained essentially unchanged (Tables S3 and S4).

DISCUSSION

Using data from a decade follow up of Iranian patients with type 2 diabetes mellitus, we assessed the incidence rate and potential risk factors of severe-NPDR/PDR. Accordingly, approximately 1.36% of patients with type 2 diabetes mellitus developed severe-NPDR/PDR each year. The present study showed strong associations of higher FPG levels, glucose-lowering medications, smoking, prehypertension and newly diagnosed hypertension with an incidence of severe-NPDR/PDR. Additionally, we found that having a BMI >25 kg/m^2 was generally associated with a lower risk.

The high prevalence of diabetes leads to an increased rate of severe-NPDR/PDR, which has been identified as one of the most common causes of visual impairment worldwide. In the present study, the incidence rate of severe-NPDR/PDR in individuals with type 2 diabetes mellitus accounted for 13.6 per 1,000 person-years. In a large USA managed-care network, 19.6 cases per 1,000 person-years with type 2 diabetes mellitus received the diagnosis of DR during 3 years' follow up. Over 6 years of follow up, among Indians with type 2 diabetes mellitus who were treated, 42.7% developed an advanced form of DR (excluding PDR) in at least one eye[26]. Population-based studies, such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) from the 1980s, reported a 4-year incidence rate of PDR of 2–7% in patients with type 2 diabetes mellitus[27]. Additionally, in a systematic review carried out in 2018, the annual incidence rate of PDR ranged from 0.03% in the Singapore Indian Eye Study (SINDI) to 0.72% in the Nakuru Study[28,29]. Fang *et al.*[30] showed that despite the improvements in early diagnosis, control, and treatment of diabetes and its complications, the prevalence of DR during the first 2 years of diabetes diagnosis had remained high over the past three decades in the USA (1988–1994 to 1999–2008; 13.2–12.1% respectively, P for trend = 0.86)[30]. Furthermore, they also showed that during a decade of progress from 1999 to early the 2010s, glycemic and BO control declined in adult National Health and Nutrition Examination Survey participants with diabetes, whereas lipid control leveled off; it potentially contributes to the high burden of DR[31]. This discrepancy in the incidence of severe-NPDR/PDR might be associated with a variety in participant age range, ethnicity, follow-up duration, sample size, different methods in retinopathy assessment (i.e., dilated radiography, imaging and using patients' claims) and facility to the acquisition of healthcare[32].

Table 1 | Baseline characteristics of the study participants in men, women and total population: Tehran Lipid and Glucose Study 1999–2016

	Total (n = 1,169)	Men (n = 494)	Women (n = 675)	P-value
Continuous variables				
Age (years)	55.4 (11.5)	56.9 (12.4)	54.3 (10.7)	<0.01
BMI (kg/m^2)	28.8 (4.6)	27.6 (3.7)	29.8 (4.8)	<0.01
WC (cm)	96.6 (10.8)	95.9 (10.3)	97.2 (11.1)	0.06
SBP (mmHg)	134.4 (22.9)	133.2 (23.2)	135.3 (22.7)	0.11
DBP (mmHg)	82.3 (11.6)	81.6 (12.2)	82.9 (11.1)	0.07
FPG (mmol/L)	9.1 (3.4)	8.7 (3.1)	9.3 (3.6)	<0.01
eGFR (mL/min/1.73 m^2)	66.4 (13.4)	68.7 (14.1)	64.8 (12.7)	<0.01
TC (mmol/L)	6.02 (1.3)	5.6 (1.2)	6.3 (1.4)	<0.01
HDL-C (mmol/L)	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)	<0.01
TG (mmol/L)	2.4 (1.6)	2.3 (1.7)	2.4 (1.5)	0.18
Categorical variables				
Age categories (years)				<0.01
-20–39	117 (10.0)	52 (10.5)	65 (9.6)	
-40–59	586 (50.1)	217 (43.9)	369 (54.7)	
-≥60	466 (39.9)	225 (45.5)	241 (35.7)	
Central obesity	676 (57.8)	284 (57.5)	392 (58.1)	0.84
BMI categories (kg/m^2)				<0.01
-<25	222 (19.0)	121 (24.5)	101 (15.0)	
-25–30	519 (44.4)	247 (50.5)	272 (40.3)	
-≥30	428 (36.6)	126 (25.5)	302 (44.7)	
Smoking status				<0.01
-Never	884 (75.6)	271 (54.9)	613 (90.8)	
- Former	135 (11.5)	106 (21.5)	29 (4.3)	
-Current	150 (12.8)	117 (23.7)	33 (4.9)	
Education level (years)				<0.01
-<6	728 (62.3)	233 (47.2)	495 (73.3)	
-6–12	366 (31.3)	199 (40.3)	167 (24.7)	
->12	75 (6.4)	62 (12.6)	13 (1.9)	
Low physical activity (yes)	830 (71.0)	348 (70.4)	482 (71.4)	0.72
Blood pressure categories				<0.01
-Normal	210 (18.0)	99 (14.7)	111 (22.5)	
-Prehypertension	378 (32.3)	212 (31.4)	166 (33.6)	
-Newly diagnosed hypertensive	101 (8.6)	72 (10.7)	29 (5.9)	
-Controlled treated hypertensive	169 (14.5)	123 (18.2)	46 (9.3)	
-Uncontrolled treated hypertensive	311 (26.6)	169 (25.0)	142 (28.7)	
FPG level categories (mmol/L)				0.13
-<7.22	447 (38.2)	201 (40.7)	246 (36.4)	
-7.22–10.0	357 (30.5)	154 (31.2)	203 (30.1)	
-≥10	365 (31.2)	139 (28.1)	226 (33.5)	
Low HDL-C	899 (76.9)	346 (70.0)	553 (81.9)	<0.01
High TC	315 (26.9)	179 (36.2)	136 (20.1)	<0.01
High TG	902 (77.2)	366 (74.1)	536 (79.4)	0.03
CKD (yes)	377 (32.2)	139 (28.1)	238 (35.3)	0.01
Prevalence CVD (yes)	160 (13.7)	82 (16.6)	78 (11.6)	0.01
Aspirin medication (yes)	257 (22.0)	124 (25.1)	133 (19.7)	0.03
Glucose-lowering medications (yes)	450 (38.5)	165 (33.4)	285 (42.2)	<0.01
Incident retinopathy (yes)	187 (16.0)	61 (12.3)	126 (18.7)	<0.01

Values are shown as the mean (standard deviation) and number (%), for continuous and categorical variables, respectively. Triglycerides (TG) had skewed distribution, so it is shown as the median (interquartile range). BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference.

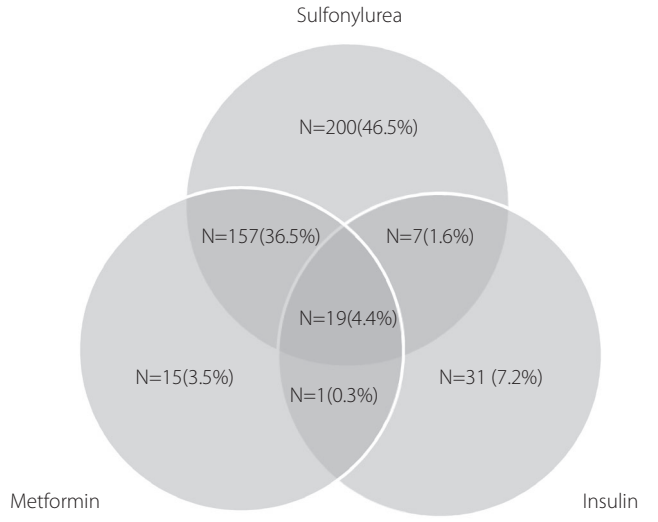

Figure 1 | The number of patients with different types of glucose-lowering medications at baseline or first follow up. The percentage of each group was calculated only among 430 patients with complete information, considering that for 20 patients, types of glucose-lowering medications that they had used were missing.

Table 2 | Hazard ratios and 95% confidence intervals from the univariable analysis of categorical potential risk factors for incident severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy: Tehran Lipid and Glucose Study 1999–2018

	Hazard ratio	95% CI	*P*-value
Sex (male)	0.72	0.53–0.98	0.04
Age categories, years			
-20–39	Reference	Reference	–
-40–59	2.21	1.22–4.01	0.01
-≥60	1.74	0.93–3.25	0.08
Central obesity (yes)	0.80	0.60–1.07	0.15
BMI categories (kg/m^2)			
-<25	Reference	Reference	
-25–30	0.62	0.43–0.89	0.01
-≥30	0.52	0.35–0.77	<0.01
Smoking status			
-Never	Reference	Reference	
-Former	0.86	0.52–1.43	0.57
-Current	1.39	0.92–2.09	0.11
Education level (years)			
-<6	Reference	Reference	
-6–12	0.84	0.61–1.14	0.27
->12	0.49	0.23–1.06	0.07
Low physical activity (yes)	0.91	0.66–1.25	0.57
Blood pressure categories (yes)			
-Normal	Reference	Reference	
-Prehypertension	1.44	0.93–2.22	0.11
-Newly diagnosed hypertensive	1.68	0.94–3.02	0.08
-Controlled treated hypertensive	1.15	0.66–2.00	0.61
-Uncontrolled treated hypertensive	1.21	0.75–1.93	0.44
FPG level categories (mmol/L)			
-<7.22	Reference	Reference	
-7.22–10.0	3.06	1.87–5.00	<0.01
-≥10	8.67	5.53–13.60	<0.01
Low HDL-C (yes)	1.26	0.87–1.81	0.23
High TC (yes)	1.01	0.98–1.05	0.44
High TG (yes)	0.86	0.61–1.22	0.40
CKD (yes)	1.12	0.81–1.54	0.46
Prevalence CVD (yes)	1.01	0.62–1.64	0.98
Glucose-lowering medications (yes)	4.06	3.01–5.47	<0.01
Aspirin medications (yes)	1.22	0.86–1.73	0.26

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Surprisingly, considering BMI, the present results showed that both overweight and obesity status were correlated with the reduced risk of severe-NPDR/PDR; the value reached a significant level only for obese patients. Furthermore, after excluding the patients taking glucose-lowering medications, being overweight and obese were still associated with a lower, but not significant, risk of severe-NPDR/PDR; the issue might be suggestive of the increasing impact of glucose-lowering medication on bodyweight, considering sulfonylurea was the most common medication among the study population. However, we did not find the association between central adiposity and severe-NPDR/PDR, as addressed in some, but not all, studies[33-35]. There is controversy surrounding the effect of a high level of BMI on the incidence of DR. Similar to the present results, Rema *et al.*[36] found the inverse correlation between BMI and DR. They found that a greater level of BMI could decrease the 6-year risk of DR in Indian populations[36]. This lower risk of higher BMI level on DR could be interpreted in several ways. First, patients with higher BMI levels have elevated C-peptide levels, which could reduce the risk of DR[37]. Furthermore, the higher risk of DR among normal weight type 2 diabetes mellitus patients might be attributable to the long duration of disease in these patients, contributing to β-cell failure, insulin deficiency and weight loss[36]. As shown in Table S2, we demonstrated that obese patients with type 2 diabetes mellitus had lower values of FPG and current smoking status compared with normal-weight counterparts, despite having higher levels of hypertension and dyslipidemia, we did not have data regarding the duration. However, among our newly diagnosed cases of type 2 diabetes mellitus, the paradoxical association between BMI and severe-NPDR/PDR was shown, although it did not reach a significant level. In contrast, several studies showed a high BMI level as a significant risk factor for DR[38]. A recent meta-analysis showed that obesity status was not associated with PDR in a significant manner; however, an association was shown for NPDR, with high heterogeneity between included studies[39]. This inconsistent correlation between BMI level and severe-NPDR/PDR

Table 3 | Hazard ratios and 95% confidence intervals from the multivariable analysis of categorical potential risk factors for incident severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy: Tehran Lipid and Glucose Study 1999–2018

	Event/*n*	HR (95% CI)	*P*-value
Sex (male)	61/494	0.79 (0.54–1.16)	0.23
Age (years)	187/1169	1.00 (0.98–1.02)	0.93
Central obesity (yes)	99/676	1.04 (0.70–1.57)	0.84
BMI categories (kg/m^2)			
-<25	44/222	Reference	
-25–30	81/519	0.60 (0.39–0.92)	0.02
-≥30	62/428	0.48 (0.27–0.83)	0.01
Smoking status			
-Never	142/884	Reference	
-Former	17/135	0.88 (0.51–1.51)	0.64
-Current	28/150	1.75 (1.12–2.74)	0.02
Education level, years			
-<6	122/728	Reference	
-6–12	58/366	0.92 (0.63–1.34)	0.66
->12	7/75	0.69 (0.31–1.57)	0.38
Blood pressure categories (yes)			
-Normal	28/210	Reference	
-Prehypertension	71/378	1.65 (1.05–2.58)	0.03
-Newly diagnosed hypertensive	19/101	1.96 (1.06–3.65)	0.03
-Controlled treated hypertensive	23/169	1.14 (0.63–2.08)	0.66
-Uncontrolled treated hypertensive	46/311	1.42 (0.87–2.31)	0.16
FPG level categories (mmol/L)			
-<7.22	23/447	Reference	
-7.22–10.0	52/357	2.81(1.70–4.62)	<0.01
-≥10	112/365	5.87 (3.67–9.41)	<0.01
Glucose-lowering medications (yes)	116/450	2.58 (1.87–3.56)	<0.01

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; FPG, fasting plasma glucose; HR, hazard ratio.

could be explained by variation in ethnicity, socioeconomic status and also obesity paradox issues[33].

The present data showed that regularly smoking could impose deterioration of DR on the proliferative state; this finding had been shown in several studies[40-42]. In comparison with non-smokers, smokers are found to have high levels of carboxyhemoglobin, which induces a decrease in the oxygen-carrying capacity of the blood, with retinal hypoxia leading to the progression of DR[42,43]. Furthermore, nicotine could lead to vasoconstriction, which might aggravate DR[44]. A recent meta-analysis showed that in contrast to patients without type 2 diabetes mellitus, smoking could significantly decrease the risk of DR in patients with type 2 diabetes mellitus. However, as mentioned by the authors, there are several concerns regarding their findings, including that smokers with type 2 diabetes mellitus had lower survival compared with their non-smoker counterparts and had not enough time to develop PDR. Hence, they suggested further population studies in this field[45].

In line with previous studies, we found that use of glucose-lowering medications could be defined as a major predictor for severe-NPDR/PDR. Klein *et al.*[46] declared that the prevalence of DR is 70% in patients with type 2 diabetes mellitus using insulin, compared with just 39% in those not receiving insulin treatment. At the baseline in the present population, just 7% of the patients were treated with insulin. The use of glucose-lowering medications would be an indicator of both the long duration of diabetes and the level of glycemic control that were associated with an increased risk of DR and PDR[47].

One intriguing result reached through the present study was that prehypertension and newly diagnosed hypertensive status could increase the risk of severe-NPDR/PDR by approximately 64 and 96%. Additionally, analysis from the UK Prospective Several studies Diabetes Study (UKPDS) showed that tight control of BP even in prehypertensive cases could lessen the risk of microvascular diabetes complication including progressive retinopathy up to 37%[48]. The present findings regarding the significant association between prehypertension status and PDR might be another reason that justifies the American College of Cardiology/American Heart Association recommendation threshold for initiation of antihypertension medications among patients with type 2 diabetes mellitus who had BP ≥130/80 mmHg[49]. Furthermore, the present result showed that

Table 4 | Hazard ratios and 95% confidence intervals from the multivariable analysis of categorical potential risk factors for incident severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy among those not on glucose-lowering medications: Tehran Lipid and Glucose Study 1999–2018

	Event/*n*	HR (95% CI)	*P*-value
Sex (male)	23/329	0.41 (0.21–0.79)	0.01
Age (years)	71/719	1.01 (0.99–1.04)	0.31
Central obesity (yes)	46/436	1.10 (0.55–2.17)	0.79
BMI categories (kg/m^2)			
-<25	12/117	Reference	
-25–30	23/317	0.52 (0.24–1.15)	0.11
-≥30	36/285	0.79 (0.32–1.95)	0.60
Smoking status			
-Never	51/532	Reference	
-Former	8/88	1.58 (0.67–3.72)	0.29
-Current	12/99	1.87 (0.91–3.86)	0.09
Education level, years			
-<6	39/414	Reference	
-6–12	31/251	1.86 (1.05–3.30)	0.03
->12	1/51	0.36 (0.05–2.85)	0.34
Blood pressure categories (yes)			
-Normal	10/128	Reference	
-Prehypertension	26/245	1.44 (0.68–3.05)	0.34
-Newly diagnosed hypertensive	5/46	1.68 (0.55–5.15)	0.37
-Controlled treated hypertensive	6/85	0.89 (0.30–2.62)	0.84
-Uncontrolled treated hypertensive	24/215	1.75 (0.81–3.76)	0.15
FPG level categories (mmol/L)			
-<7.22	13/363	Reference	
-7.22–10.0	26/223	3.51 (1.79–6.87)	<0.01
-≥10	32/133	8.49 (4.36–16.50)	<0.01

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; FPG, fasting plasma glucose; HR, hazard ratio.

uncontrolled treated hypertension could impose a 42% increase in the risk of development of DR, but in a non-significant manner.

In line with the present results, Nwanyanwu *et al.*[50] found that there is no association between hypertension and progression of DR to PDR. These inconsistencies might reflect the fact that patients with type 2 diabetes mellitus who have BP ≥140/90 mmHg are educated to be more cautious about control of BP by using antihypertension drugs regularly. Increased BP could lead to endothelial dysfunction and inflammation, and vice versa, which have been hypothesized as key mechanisms that contribute to the development of diabetes and its vascular complications, such as DR[51,52]. Additionally, venular dilation and arterial narrowing after prehypertension could impose the progression of DR and the incidence of severe-NPDR/PDR[53-55].

To the best of our knowledge, this is the first long-term study that has reported the various risk factors related to the progression of severe-NPDR/PDR in the Middle East and North Africa region with a high burden of diabetes[56]. Furthermore, the present findings stem from a population-based study rather than data derived from hospitalized surveys, which might confound the results.

The present results should be interpreted in light of some limitations. First, the evidence of pan-retinal photocoagulation as a marker of progression of severe-NPDR/PDR was based on patients' claims data, not an ophthalmic examination or imaging, so data might be slightly underestimated. Second, some physicians carried out PRP in eyes with severe-NPDR in selected patients, and our population might include some of them, hence, we used the term "severe-NPDR/PDR" to avoid results' misinterpretation. Third, we did not have data on two important variables of the duration of diabetes and level of diabetes control as manifested by hemoglobin A1c levels (considering the cost and the absence of a precise method for its measurement); however, to partly address this concern, we reran our data analysis only among newly diagnosed type 2 diabetes patients and we adjusted FPG level as a surrogate of hemoglobin A1c levels[18]. Fourth, the present study was carried out on a sample of the Iranian population, and our results might not be extrapolated to other populations with different ethnicities. Last, but not least, we did not have data regarding the retinal status of patients at the baseline recruitment, hence, some of the individuals might have had some degree of severe-NPDR/PDR in the baseline.

In conclusion, the present study showed that each year approximately 1% of Iranian patients with type 2 diabetes mellitus suffered from severe-NPDR/PDR. Poor control of diabetes, current smoking, prehypertension, newly diagnosed hypertension and normal bodyweight were associated with a higher risk of severe-NPDR/PDR. Regarding the sight-threatening entity of advanced DR, the multicomponent strategy to control diabetes, abstain from smoking and tight control of BP in the prehypertension status should be considered.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of the ethics committee of the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences.

Informed Consent: All informed consent was obtained from the participants.

Approval date of Registry and the Registration No. of the study/trial: 8 May 2021. Approval ethics number: IR.SBMU.ENDOCRINE.REC.1400.006 -.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Baseline characteristics of the respondents (study participants) and non-respondents (including those with missing data at the baseline or with no follow-up data): Tehran Lipid and Glucose Study.

Table S2 | Baseline characteristics of the study participants in different groups of body mass index <25, body mass index 25–30, body mass index ≥30 and total population: Tehran Lipid and Glucose Study 1999–2016.

Table S3 | Hazard ratios and 95% confidence intervals from the multivariable analysis with propensity score of categorical potential risk factors for incident severe non-proliferative and proliferative diabetic retinopathy: Tehran Lipid and Glucose Study (1999–2018).

Table S4 | Hazard ratios and 95% confidence intervals from the multivariable analysis with propensity score of categorical potential risk factors for incident severe non-proliferative and proliferative diabetic retinopathy among those not on glucose-lowering medications: Tehran Lipid and Glucose Study (1999–2018).