

Prevalence and Risk Factors of Diabetic Retinopathy in Xuzhou, China: A Cross-Sectional Study

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Abstract

Background: The prevalence of diabetic retinopathy is not well studied in the Chinese diabetic population. This study investigated the prevalence and risk factors of diabetic retinopathy (DR) among primary care patients with type 2 diabetes mellitus in Xuzhou, China.

Methods: 1578 Chinese patients with type 2 diabetes mellitus who were selected with a multi-stage stratified cluster method, retinal photographs were taken of both eyes. The levels of DR were assessed using fundus photography and the Diabetic Retinopathy Disease Severity Scale. Demographic and physiological characteristics were recorded. Participants completed the Pittsburgh Sleep Quality Index and the Zung Self-Rating Anxiety and Depression Scales. Multiple logistic regression was used to evaluate the factors associated with DR.

Results: The rate of DR was 28.6%; 25.1% of patients (396/1578) had non-proliferative DR and 3.5% of patients (55/1578) had proliferative DR. Logistic regression analyses showed that HbA1c levels, diabetes duration, hypertension, smoking, anxiety, depression, poor sleep quality, and exercise were independently associated with DR.

Conclusions: DR is common in patients with type 2 diabetes mellitus in China. Screening tests for DR should be incorporated into health care settings in China. Patients who have been registered for a long time, or have poor glycemic control, concomitant hypertension, psychological disorders, or sleep disorders, should be considered for early screening of DR.

Keywords: Diabetic retinopathy; Prevalence; Risk factors

Abbreviations: DR: Diabetic Retinopathy; NPDR: Non-Proliferative Retinopathy; PDR: Proliferative Retinopathy; HbA1c: Glycated Hemoglobin; PSQI: Pittsburgh Sleep Quality Index. BMI: Body Mass Index; OR: Odds Ratios; CI: Confidence Interval.

Background

It has been estimated that the number of people with diabetes mellitus worldwide will quadruple by 2035, resulting in approximately 592 million people with this condition [1]. The prevalence of type 2 diabetes mellitus is increasing at a considerable rate in Asia, especially in China. The increased prevalence of type 2 diabetes mellitus in China is probably attributable to rapid economic development, improved living standards, an aging population, and a Westernized lifestyle. Compared with a rate of 0.9% in 1980 [2], the prevalence of diabetes mellitus in China had increased to 11.6% in 2010, according to a national survey [3]. Of these individuals, only 25.8% had been treated, and diabetes was controlled in only 39.7% of those treated [3]. Continuous hyperglycemia or successive poor glycemic control can result in many complications in individuals with diabetes mellitus.

Diabetic retinopathy (DR) is a typical microvascular complication of both type 1 and type 2 diabetes mellitus. It is characterized by retinal

vascular leakage, inflammation, and abnormal neovascularization [4], and is the leading cause of blindness among working-age adults worldwide [4]. The overall prevalence of DR in China is 34.6% (95% CIs: 34.5-34.8) and there are approximately 93 million people with the condition [5]. Previous research and meta-analyses show that longer diabetes duration, poorer glycemic control, and poor BP control are strongly associated with DR [4,5] and are common risk factors of DR in Chinese patients with type 2 diabetes mellitus [6-8]. However, these previous investigations were population-based studies (including cross-sectional and prospective studies). There have been no studies focusing on the prevalence of DR and its relationship with risk factors among Chinese diabetes patients registered with community health service centers. In addition, previous research has not explored the effects of psychological disorders and sleep quality on DR.

Therefore, we aimed to assess the prevalence of DR and its associated differential risk factors, including psychological disorders and sleep quality, in Chinese participants with diabetes registered with community health service centers.

Methods

Study design and recruitment criteria

The Xuzhou urban area includes 32 communities and is a medium-developed area in eastern China. It has a population of 3 million people and the diabetes registry system covers all communities in this area. Each community has a community health service center. Five community health service centers were selected with probability proportional to size based on the number of patients with type 2 diabetes mellitus from all 32 community health service centers in the study area. Patients with type 2 diabetes mellitus who met the inclusion criteria and were registered with community health service centers were selected according to their medical records. At least 1420 people were selected, assuming an estimation prevalence of DR of about 20% in patients with type 2 diabetes mellitus [9], with a 95% power, 5% allowable error, 1.5 design effect, and allowing for a 10% dropout. The study was conducted between August and December 2016. All eligible individuals were invited to visit Xuzhou Third Hospital for a detailed examination. Retinal photographs were taken at Xuzhou Third Hospital and type 2 diabetes mellitus was diagnosed according to the recommendations of the Chinese Type 2 Diabetes Prevention and Control 2013 Guidelines [9]. Participants who were diagnosed with type 2 diabetes mellitus by physicians and were registered with community health service centers were recruited. Exclusion criteria were as follows: (1) Patients with history of glaucoma, dense cataract, uveitis, age-related macular degeneration, and corneal opacities; (2) Patients with mental illness or use of any kind of psychotropic medication; (3) Patients with malignancies, immunologic and infectious inflammatory diseases, patients receiving corticosteroids or cytostatics, and pregnant patients; (4) age <18 years. Written informed consent was obtained from all participants.

The study protocol was approved by Xuzhou Center for Disease Control and Prevention. The procedures followed were in accordance with the standards of the ethics committee of Xuzhou Center for Disease Control and Prevention and with the Declaration of Helsinki (1975, revised 2000). Written informed consent was obtained from all participants.

A total of 1775 patients were sampled, and 103 (5.8%) patients who did not meet the criteria were excluded. 1672 eligible type 2 diabetes mellitus patients aged 27-87 years were invited to participate. Among them, 73 patients declined to take part in the study and 21 patients failed to complete the ophthalmological examination. The response rate was 94.4%. Overall, 1578 patients with type 2 diabetes mellitus participated.

Retinal photography and retinopathy assessment

Ophthalmological evaluation was conducted in the ophthalmology department of Xuzhou Third Hospital following a standardized protocol. Participants underwent vision screening of the naked eye and the corrected visual acuity, non-contact intraocular pressure measurement, ocular anterior segment examination before slit lamp microscope, direct fundus examination with glasses, and fundus color photography was performed by trained technicians after dilation. Two independent ophthalmologists without knowledge of participants' clinical details read together the photographs. DR was defined according to the Diabetic Retinopathy Disease Severity Scale [10]: Grade 0: no abnormalities; Grade 1: mild non-proliferative retinopathy (NPDR) (microaneurysms only); Grade 2: moderate NPDR (more

than just microaneurysms, but less than Grade 3); Grade 3: severe NPDR; Grade 4: proliferative retinopathy (PDR). The level of retinopathy was graded based on the DR level of the worse eye. A sample of 305 retinal photographs (with and without retinopathy) was graded again by one of the two readers to assess internal validity. Overall, there was a high degree of internal and inter-observer reliability for the assessment of retinopathy ($k_1=0.883$ and $k_2=0.871$). Any unresolved disagreements between the two assessors were referred to the group leader for arbitration.

Various associated factors were examined. Data collection was carried out at the ophthalmology department of Xuzhou Third Hospital before conducting fundus photography. Two interviewers administered a standardized questionnaire to collect sociodemographic and anthropometric details: age, gender, physical activities, level of education, cigarette smoking, alcohol consumption, duration of diabetes, sleep quality, anxiety, depression, height, and weight. Cigarette smoking was defined as having smoked at least 100 cigarettes in a lifetime. Information was obtained on the amount and type of alcohol that was consumed during the previous year, and alcohol drinking was defined as the consumption of at least 30 g of alcohol per week for one year or more. Glycated hemoglobin (HbA1c) level was assayed using high-performance liquid chromatography (Bio-Rad Diagnostic Group, CA, USA). We used the level of HbA1c as the index for glycemic control. A HbA1c level of <7.0% (54 mmol/mol) was defined as good glycemic control based on the Chinese Type 2 Diabetes Prevention and Control 2013 Guidelines, whereas a HbA1c level of $\geq 7.0\%$ (54 mmol/mol) was considered poor glycemic control [9].

Serum total cholesterol (TC), triglycerides (TG), HDL-cholesterol (C) and LDL-C levels were measured in the fasting using an automatic biochemical analyzer (AU1000, Olympus, Japan). Standard measures of BP were taken using a sphygmomanometer with the patient in a sitting position. Three measurements were taken at 5-minute intervals for each participant, and the mean of the second and third measurements was used in the analyses. The presence of hypertension was defined as a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or if the individual was prescribed antihypertensive medication.

Body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) in light indoor clothing were measured. BMI (in kg/m^2) was calculated, and categorized as underweight ($<18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5\text{--}23.9 \text{ kg}/\text{m}^2$), and overweight/obese ($\geq 24.0 \text{ kg}/\text{m}^2$) [11]. Regular exercise was defined as participation in at least 30 minutes of moderate-intensity aerobic activity no less than 3 days per week.

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) [12]. The Chinese version of the PSQI used in this study was approved by the original PSQI authors. A global PSQI score >7 had a diagnostic sensitivity of 98.3% and a specificity of 90.2% in distinguishing normal participants from participants with sleep quality problems. The good clinical practice and metrical properties of PSQI suggest its utility both in Chinese psychiatric clinical practice and research activities [13]. Accordingly, we defined a PSQI score <7 as good sleep quality and ≥ 8 as poor sleep quality.

Anxiety and depression were assessed using the Zung Self-Rating Anxiety Scale [14] and the Zung Self-Rating Depression Scale, respectively [15]. These measures are valid and reliable for Chinese participants [16]. Each of these scales includes 20 questions and each question is scored from 1 to 4 as follows: 1, rarely; 2, some of the time; 3, very often/often; 4, almost always. The total score for the 20

questions was multiplied by 1.25, with the integer score as a standard score. A standard score below 50 was considered as indicating no anxiety or depression.

Statistical Analyses

All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, USA). Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as absolute values and percentages. Differences in continuous variables were tested using the F test or the t test, and differences in categorical variables were assessed using the Pearson χ^2 test. The age and gender adjusted prevalence of diabetic retinopathy were calculated using the indirect method according to results of Xu et al. reports [3]. Logistic regression models were used to determine the risk factors for DR. The variables were classified as age (continuous), sex (male or female), educational level (lower than high school, high school, or greater), physical activities (yes or no), cigarette smoking (yes or no), alcohol consumption (yes or no), years since diabetes diagnosis (continuous), BMI (continuous), poor sleep quality (yes or no), anxiety (yes or no), depression (yes or no), HbA1c (continuous), TC (continuous), HDL-C (continuous), LDL-C (continuous), and TG (continuous). ORs and 95% CIs were calculated. The minimum statistical significance level for all analyses was $p < 0.05$.

Results

General characteristics of participants with and without DR

The mean age of the 1578 participants was 59.7 ± 11.7 years, and 57.5% were female. The mean BMI was 23.5 ± 2.6 kg/m², the mean duration of diabetes was 8.9 ± 5.5 years, and the mean HbA1c level was $8.5 \pm 1.9\%$ (69 ± 3 mmol/mol). There were no differences between participants with DR and those without DR in sex, age, or education level. The general characteristics of participants with DR and those without DR are shown in Table 1.

Variables	DR	No DR	P
	(451)	(1127)	
Sex (female)	260 (57.6)	647 (57.4)	0.975
Age	60.3 ± 11.8	59.5 ± 11.5	0.215
Above high school	50(11.1)	127 (11.3)	0.988
Regular exercise	263 (58.3)	808 (71.7)	<0.001
BMI mean (SD)	23.8 ± 2.7	23.3 ± 2.5	0.002
duration of diabetes, mean (SD)	9.5 ± 5.7	8.5 ± 5.1	<0.001
Smokers	99 (22.0)	146 (13.0)	<0.001
Drinking	90 (20.0)	174(15.4)	0.036
Anxiety ≥ 50	271(60.1)	535 (47.5)	<0.001
Depression ≥ 50	217 (48.1)	403(35.8)	<0.001
PSQI ≥ 7	187(41.5)	319(28.3)	<0.001
Hypertension	254(56.3)	402(35.7)	<0.001
HbA1c (%)	8.5 ± 1.9	7.1 ± 1.5	<0.001

TC (mmol/L)	4.6 ± 0.8	4.8 ± 1.0	<0.001
LDL-C (mmol/L)	2.76 ± 0.75	2.8 ± 0.8	0.361
HDL-C (mmol/L)	1.2 ± 0.3	1.18 ± 0.26	0.187
TG (mmol/L)	1.5 ± 0.3	1.6 ± 0.4	<0.0001

Table 1: General characteristics of the participants with and without diabetic retinopathy. BMI: Body mass index; SD: Standard deviation; PSQI: Pittsburgh Sleep Quality Index; HbA1c: glycated hemoglobin; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; All figures are n (%) unless otherwise indicated.

Prevalence and factors associated with DR

The prevalence of any form of DR was 28.6% (451/1578), 28.5% (191/671) for males and 28.7% (260/907) for females. The prevalence of mild, moderate, severe NPDR and PDR were 14.3%(225/1578), 6.2%(98/1578), 4.6%(73/1578) and 3.5%(55/1578), respectively. Patients with DR were further divided into two groups. The first group had NPDR and comprised 25.1% of patients (396/1578); 24.7% (166/671) males and 25.4 (230/907) females. The second group had PDR and comprised 3.5% of patients (55/1578); 3.7% (25/671) males and 3.3% (30/907) females. The age and gender adjusted prevalence of diabetic retinopathy was 30.1%, 29.5% for males and 31.2% (260/907) for females.

Table 2 shows the results of logistic regression analyses for DR in the adult population with diabetes, age, sex, educational level, marriage, physical activity, BMI, diabetes duration, smoking, alcohol consumption, anxiety, depression, sleep quality, presence of hypertension, HbA1c level, serum TC, serum HDL-C, serum LDL-C, and serum TG as covariates. Longer diabetes duration, smoking, anxiety, depression, poor sleep quality, hypertension, higher HbA1c level, and regular exercise were independently associated with DR.

Variable	β	SE	Wald	P	OR	95%CI
Regular exercise	-0.784	0.068	134.311	0	0.456	0.400~0.521
Long disease duration	0.608	0.106	33.028	0	1.837	1.493~2.261
Smoking	0.278	0.097	8.196	0.004	1.321	1.092~1.599
Anxiety	0.435	0.061	50.862	0	1.545	1.3711.741
Depression	0.414	0.042	97.762	0	1.513	1.3941.642
Poor sleep quality	0.535	0.139	14.887	0	1.707	1.3012.241
Hypertension	0.699	0.325	4.626	0.031	2.012	1.064~3.804
HbA1c (%)	0.846	0.102	68.807	0	2.331	1.908~2.847

Table 2: Multivariate logistic regression analysis of risk factors of DR. BMI: Body mass index; SD: Standard deviation; HbA1c: Glycated Hemoglobin; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; OR: Odds ratio; CI: confidence interval. The others covariates were age, sex, educational level, marriage, BMI, alcohol consumption, serum TC, serum HDL-C, serum LDL-C, and serum TG.

Discussion

The prevalence of DR is very common in Chinese participants with type 2 diabetes mellitus, and the DR was mainly categorized as mild retinopathy, we identified different factors associated with DR. Longer diabetes duration, smoking, anxiety, depression, poor sleep quality, hypertension, and higher HbA1c levels were independent risk factors for the development of DR in patients with type 2 diabetes mellitus. In contrast, DR was less associated with regular exercise.

The DR prevalence rate for participants was 28.6%, and the prevalence of PDR was 3.5%, which is inconsistent with previous findings from China. The rate of DR in the present study is lower than that reported in the Beijing Eye Study (37.1%) [6], and higher than that reported in a study in Liaoning province (11.9%) [8]. However, it is consistent with the rate reported by Lu et al. (27.7%) [17], and with rates reported by one meta-analysis of 19 studies in China, which reported a 23% DR prevalence rate among people with diabetes, and a 2.8% PDR prevalence rate [18]. Differences in the reported DR prevalence rates in China might be because of study design, sampling size, region, and the clinical features of the study population, which prevent the direct comparison of study results.

Our results are also inconsistent with the DR prevalence reported for other countries [19,20]. This discrepancy may be because of differences in study design, sampling size, region, and the clinical features of the study population, but could also be a result of ethnic group differences, as many studies have showed that different ethnic groups have different DR prevalence [19].

Many epidemiological studies and clinical trials have demonstrated that poor glycemic control greatly increases the risk of DR [5-8,19,20]. The present findings confirm this, and indicate that a higher HbA1c is independently correlated with an increased risk of DR. Kim and his colleagues reported that for every 1% increase in HbA1c, the risk of DR development increased 1.16-fold (16%) and the risk of progression to PDR increased 1.19-fold (19%) [20]. The United Kingdom Prospective Diabetes Study and the Diabetes Control and Complications Trial showed that a decrease in HbA1c could reduce the risk of DR development and progression in type 2 diabetes mellitus patients [21]. Taken together, these findings suggest that, patient health permitting, blood sugar levels should be maintained at the low end of the normal range.

Many epidemiological studies and clinical trials have demonstrated that hypertension is another important risk factor for DR development [5-8]. Experimental studies have shown that for each 10 mmHg increase in mean arterial BP, the arteriolar-to-venular ratio decreases by 0.02 units [22] and the retinal arteriolar diameters decrease by 4.4 μ m (95% CIs, 3.8-5.0) [23]. Compared with healthy individuals, diabetic patients have thinner arterioles, wider venules, and a smaller arteriolar-to-venular ratio [24]. However, strict BP control can prevent and/or limit the development and progression of DR and visual dysfunction according to the Appropriate Blood Pressure Control in Diabetes study [25]. Therefore, modest and sustained long-term elevations in BP are associated with increased DR in patients with type 2 diabetes mellitus [26].

Many studies have shown that the duration of diabetes is a strong risk factor for development of DR [5-8]. Ancochea et al. demonstrated that the prevalence of any retinopathy was 0.85% at diabetes duration of 5 years; the percentage rose to 5.21% for 5-9 years, to 14.71% for 10-14 years, and surpassed 30% over 15 years [27]. Kim et al. reported that for every 1-year increase, the risk of DR increased 1.13-fold (13%)

[20]. Rema et al. [28] reported that for every 5-year increase in the duration of diabetes, the risk of DR increased 1.89-fold. Longer duration of diabetes is associated with poor glycemic control, which is an important risk factor for DR [29]. An increased diabetes duration is also associated with a decreased arteriolar diameter and arteriolar-to-venular ratio, which can result in DR [28]. Therefore, it is important to emphasize continuous follow-up for DR assessment in diabetic patients [20,27].

The literature on smoking and DR has reported conflicting results. Some studies have found that smoking is associated with a slightly reduced DR risk [30], whereas others have found no association between smoking and DR [27]. The findings of one study are consistent with our results, which show an association between smoking and the prevalence of DR in patients with type 2 diabetes mellitus [31]. This discrepancy may reflect a bias in the reporting of smoking status among study participants. In fact, smokers have a higher HbA1c than never smokers [32] and smoking is associated with decreased retinal blood flow [33]. After adjusting for age, income, and age-related macular degeneration severity, the Beaver Dam Eye Study found that being a current or past smoker was related to a greater change in the numbers of letters lost over a 20-year period [34]. A higher HbA1c, decreased retinal blood flow, and visual impairment are all associated with increased risk of DR. In addition, smoking increases disability, reduces life expectancy, and increases mortality. Therefore, early smoking cessation is important.

The association between BMI and DR has also been extensively studied, but findings are inconclusive. Some studies have found a positive association [35] between BMI and DR, other studies have found a negative association [28,36], and a few studies have found no association [37]. In this study, we found no association between BMI and DR. Chinese people tend to develop type 2 diabetes at a considerably lower BMI compared with European populations [38], and their body weights often decrease during the disease course [36]. Therefore, the association between BMI and DR might not be revealed in a cross-sectional study.

Many studies have reported an association between depressive and anxiety symptoms and DR. A meta-analysis of 27 studies with 5374 subjects showed that depression is consistently associated with increased risk of DR [39]. Sieu et al. confirmed that diabetic patients with comorbid depression have a significantly higher risk of developing DR [40]. Conversely, DR can substantially increase depressive and anxiety symptoms [41,42]. Vision loss also affects DR patients' emotional state [43]. The association between depressive and anxiety symptoms and DR might suggest that comorbid depressive and anxiety disorders are linked to worse glycemic control [44].

To the best of our knowledge, no previous studies have investigated the association between DR and poor sleep quality. These findings are the first to indicate that poor sleep quality is related to DR in patients with type 2 diabetes mellitus. A previous study found a 30% to 50% prevalence rate of poor sleep quality for individuals with type 2 diabetes mellitus [45]. We found a higher rate (41.8%) of poor sleep quality in DR patients compared with a rate of 28.3% of poor sleep quality in patients with no DR. Poor sleep quality is directly related to poor glycemic control [46] and the latter is an independent risk factor for DR development. Therefore, poor sleep quality may aggravate DR in patients with type 2 diabetes mellitus.

A systematic review of 44 studies demonstrated that physical inactivity contributes to the risk of DR [47]. Sedentary persons had a

higher risk of incident visual impairment than persons who were physically active [34]. Physical activity has a protective effect for DR, and this effect persists after adjusting for visual acuity, higher HbA1c levels, and higher BP [48]. Our findings are consistent with these previous results. We suggest that physical activity may benefit vascular endothelial function [49]. In addition, regular physical activity is also associated with lower HbA1c levels [50]. Therefore, regular physical activity has an inverse association with the prevalence of DR.

Other risk factors for the development of DR identified in previous studies are age [8], gender [21], education [6], drinking [30], and lipid profile [7]. These factors showed no correlation with DR in this study. Some of these differences might be a result of sampling or measuring bias.

The strengths of our study include the homogeneity of the random sample, large sample size, and the community-based nature of the sample. However, there are several limitations. First, the cross-sectional design limits the inference of causality and can only demonstrate an association between DR and identified risk factors. Second, we were unable to control for some important risk factors of diabetes; for example, insulin treatment [37], which are causally related to DR. Third, it is possible that some participants were misclassified, as self-report instruments were used to assess anxiety, depression, and poor sleep quality. Fourth, these findings were only derived from a region Chinese patients and need to be carefully replicated in other area, ethnic populations. In the future, the prospective studies should be carry out to examine the associations between DR and anxiety, depression, and poor sleep quality.

Conclusion

In summary, the present findings show that DR is common in patients in China with type 2 diabetes mellitus. We confirmed the association of the development of DR with the traditional, well-known risk factors of poor glycemic control, a longer duration of diabetes, and hypertension. In addition, we found that psychological disorders and sleep disorders are significant risk factors for the development of DR. Our findings suggest that DR screening tests should be incorporated into health care settings in China. Patients who have been registered for a long time or have poor glycemic control, concomitant hypertension, psychological disorders, or sleep disorders should be considered for early screening of DR.

Declarations

Ethics approval and consent to participate

The study protocol was approved by for Disease Control and Prevention. The procedures followed were in accordance with the standards of the ethics committee of for Disease Control and Prevention and with the Declaration of Helsinki (1975, revised 2000). Written informed consent was obtained from all participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and /or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JS participated in writing the title and abstract, reviewed the text, and contributed to writing of the title, abstract, and manuscript. PL conceived the study, participated in the study design, writing the title and abstract, editing the text, data extraction and analysis, and drafting the manuscript. PZ and YS performed literature searches, participated in writing the title and abstract and reviewing the text, and contributed to the manuscript drafts. JW and GC were the lead authors of the original review, contributed to the conception of the study, and contributed to the manuscript drafts. All authors read and approved the final manuscript.

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