·Investigation·

Risk factors for diabetic retinopathy in northern Chinese patients with type 2 diabetes mellitus

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Abstract

• **AIM: To investigate the prevalence and risk factors of diabetic retinopathy (DR) in northern Chinese patients with type 2 diabetes mellitus (T2DM).**

• **METHODS: This retrospective cross-sectional study was performed between May 2011 and April 2012. A total of 1100 patients (male/female, 483/617) were included in this study. DR was defined following the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale. All included patients accepted a comprehensive ophthalmic examination including retinal photographs. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence interval (CI) after adjusting for age and gender.**

• **RESULTS: Retinopathy was present in 307 patients with a prevalence of 27.9%. In univariate logistic analysis, presence of DR was associated with longer duration of diabetes (OR, 5.70; 95% CI, 2.91–12.56), higher concentration of fasting blood glucose (OR, 12.94; 95% CI, 2.40–67.71), higher level of glycosylated hemoglobin HbA1c (OR, 5.50; 95% CI, 3.78–11.97) and insulin treatment (OR, 6.99; 95%CI, 1.39–35.12). The lifestyle of patients with T2DM including smoking, alcohol consumption and regular exercise seemed not associated with the development of DR.**

• **CONCLUSION: Our study suggests that fasting serum glucose concentration, HbA1c level, duration of diabetes and insulin treatment are potential risk factors for DR in northern Chinese patients with T2DM, while the lifestyle of included patients seems not associated with DR.**

• **KEYWORDS:** diabetic retinopathy; type 2 diabetes mellitus; risk factors; lifestyle

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INTRODUCTION

Diabetic retinopathy (DR) is a major cause of visual impairment and blindness among people of working age, seriously affecting the people's health and life quality worldwide [1-2]. According to a report of the World Health Organization, an estimated 20 million Chinese had diabetes in 2000, and the number will increase to 42.3 million by 2030 [3]. Previous studies have shown that more than 77% of patients with diabetes are affected by retinopathy within 15y to 20y after diagnosed with diabetes [3]. Along with the elevated prevalence of diabetes, the burden of DR is increasing in China[4].

Although DR is one of the most prevalent complications of diabetes, the pathological mechanisms that lead to the development of DR are complicated and multi-factorial [5]. Genetic risk factors are thought to play a role in DR especially in proliferative diabetic retinopathy (PDR). Since the pathogenetic mechanisms of DR are very complex, the candidate genes which are implicated in the pathogenesis of DR in patients with type 2 diabetes mellitus (T2DM) are abundant [6]. Several gene variants have been reported to be associated with the development of DR, especially of PDR, such as gene polymorphisms of growth factors, oxidative stress genes, iron metabolism-related genes, cytokines, and so on [6]. Petrovic *et al* [7] demonstrated that rs6060566 polymorphism of the Romo-1 gene (a kind of oxidative stress genes) was an independent risk factor for DR in Caucasians with T2DM. However, several candidate genes for DR did not appear to be consistently associated with DR after replications in a several large, well-powered samples or a systemic Meta-analysis [8-9]. Large cross-sectional studies and well-powered Meta-analyses are still needed to identify more successful gene variants for DR or PDR.

Besides genetic factors, environmental risk factors for the development of DR were also important. It will facilitate to identify the risk of DR through understanding the whole biomarker patterns of diabetic patients. Previous study presented that early proper management and controlling methods such as drugs treating diabetes and blood pressure

control could prevent vision loss and blindness [10]. In addition, several risk factors including glycosylated hemoglobin (HbA1c), duration of diabetes, inadequate control of serum glucose levels, hypertension, hyperlipidemia, body mass index (BMI), genders and insulin treatment have been reported to be involved in the development of DR [11-14]. These factors would affect the development of DR, for example, hyperglycemia could induce metabolic abnormalities including alternation in retinal blood flow, increased oxidative stress and so on, which are implicated in the pathogenesis of DR [15]; smoking could increase the risk of endothelial dysfunction in micro- and macro-vascular complications, especially in patients with diabetes, with manifestation of increasing the risk for DR[16]. Analysis of these risk factors would help us explore the pathogenesis of the development of DR and provide references for prevention of this disease, which is also crucial for optimal clinical management of diabetes. However, many candidate risk factors still contradicted with each other in different studies such as the patients' lifestyle. Therefore, this study was performed to investigate the association between the DR development and patients' lifestyle including smoking, alcohol consumption, physical activity and other potential risk factors among Chinese patients with T2DM.

SUBJECTS AND METHODS

Study Design and Subjects This retrospective cross-sectional study was performed between May 2011 and April 2012 in the Endocrinology Department of the 3rd hospital of Hebei Medical University among patients with T2DM. Some patients were admitted to hospital due to glucose fluctuations, and some were admitted to hospital for regular examination for diabetes. T2DM was diagnosed in patients with one of the following criteria: fasting serum glucose concentration ≥7.0 mmol/L, random blood glucose concentration ≥11.0 mmol/L, or receiving medical treatment for diabetes according to the 1999 World Health Organization (WHO) criteria. If patients had type 1 or other types of DM or other serious primary diseases, they would not be included in the study. The study conforms to the principles of the Helsinki Declaration and was approved by the institutional review board of the 3rd hospital of Hebei Medical University.

Diabetic Retinopathy Assessment Retinal examinations were performed using a Canon CR-DGI non-mydriatic retinal camera and a Canon digital camera EOS 30D (Canon Inc., Tokyo, Japan) after pupil dilation by drops of 0.5% tropicalmide. Retinal photographs including five visual fields-the upper nasal (optic disc included), lower nasal (optic disc included), upper temporal, lower temporal quadrants and the macula (temporal area included)-were taken from both eyes of all participants. DR was defined following the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale [17] and retinopathy was considered present if any characteristic lesions were detected: microaneurysms, hard exudates, cotton wool spots, hemorrhages, new retinal vessels, proliferative vitreoretinopathy (PVR), photocoagulation scars, retinal detachment and vitreous hemorrhages. If photographs of both eyes could not be graded due to inadequate dilation or media opacities, patients would be excluded in this study. The minimum criterion for diagnosis of DR was the presence of at least one definite microaneurysm in any photographed field. Individual classification was performed based on the retinopathy image of worse eye in this study.

Measurement and Definition of Potential Risk Factors Patients included in our study underwent a standardized interview and clinical examination. Demographic and clinical data including gender, age, durations of diabetes, histories of exercises, smoking and drinking were recorded. The duration of diabetes was the period between the year of diagnosis and the year of DR examination, then patients were classified into two classes with duration <10y or ≥10y. Information of physical exercises was collected *via* an interview conducted by a trained physician and participants were then categorized as subjects with routine physical exercise and those without routine physical exercise. In addition, participants were asked which kind of the exercise they spent the most amount of time on average per week. Furthermore, according to the previous description, a person was categorized as non-smoker if he/she had smoked <100 cigarettes in his/her lifetime and as a smoker if ≥100 cigarettes [18]. Based on the participants' alcohol drinking habits, they were classified as non-drinkers (<1 drink/wk) or drinkers (≥1 drink/wk). Participants were also categorized by having accepted insulin treatment or not before the study. Fasting blood samples were collected from participants to detect the plasma glucose concentration using a Beckman glucose analyzer II (Beckman Instruments, Fullerton, California, USA) and the levels of HbA1c, serum total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL). The estimated normal range of HbA1c level is 4.4%-6.4%; <7% was considered as good glycemic control and ≥7% was considered poor[19]. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥90 mm Hg or the use of antihypertensive drugs currently according to the WHO definition of hypertension. Levels of blood cholesterol <5.18 mmol/L, triglycerides <1.7 mmol/L, HDL<1.04 mmol/L and LDH<1.3 mmol/L were considered normal. Hyperlipidmia was diagnosed in patients who presented higher level of cholesterol or serum triglycerides or LDL level than above criteria.

Table 1 Difference of demographic and clinical characteristics between the group of diabetic subjects with DR and the group of diabetic subjects without DR

Variables	With DR (*n*=307)	Without DR (*n*=793)	*P*
Age (a)	53.4 (31-80)	52.4 (30-85)	0.48
Gender			0.39
F	179 (58.3%)	438 (55.2%)	
M	128 (41.7%)	355 (44.8%)	
Duration of diabetes (a)	14.2 (1-25)	8.7 (1-30)	<0.001
Fasting blood glucose concentration (mmol/L)	8.6±6.4	5.1±2.1	0.02
HbA1c	8.0%±1.5%	7.1%±1.4%	<0.001
Hyperlipidmia	73 (23.8%)	203 (25.6%)	0.53
Hypertension	90 (29.3%)	235 (29.6%)	0.38
Smoking status	60 (19.5%)	181 (22.8%)	0.24
Alcohol consumption	75 (24.4%)	203 (25.6%)	0.69
Physical activity	152 (49.5%)	388 (48.9%)	
Walking only	125 (40.7%)	337 (42.5%)	0.82
Other sports	27 (8.8%)	51 (6.4%)	
Insulin treatment	265 (86.3%)	132 (16.6%)	<0.001

DR: Diabetic retinopathy.

Statistical Analysis Statistical analyses were performed using SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA). The results were presented as mean ±standard deviation (SD). Characteristics of the included participants with and without DR were compared using t-test for means and Chi-square test for proportions. Logistic regression models were constructed to determine the odds ratios (OR) and 95% confidence intervals (95% CI) for putative risk factors which were associated with the presence of DR, adjusting for age and gender in all subjects with T2DM. A P value of <0.05 was considered significantly different.

RESULTS

Demographic and Clinical Data of Included Patients A total of 1153 patients diagnosed with T2DM were recruited in the present study, while 53 cases were excluded due to inadequate dilation or media opacities during retinal examinations. Consequently, 1100 patients (male/female, 483/617) participated in the investigation to examine the associations of various risk factors with DR. Among 1100 patients, retinopathy was present in 307 cases (27.9%). The demographic and clinical data of patients with or without DR are shown in Table 1. There were no significant differences between diabetic subjects with DR and without DR in terms of age (P=0.48), gender (P=0.39) as well as the proportion of patients with hyperlipidemia (P=0.53) and hypertension (P=0.38). However, the fasting blood glucose concentration (P=0.02) and HbA1c level (P<0.001) were significantly higher in subjects with DR than those without DR. In addition, subjects with DR showed remarkably longer duration of diabetes and had significantly larger proportion of receiving insulin treatment (P<0.001) than those without DR. Furthermore, the smoking status and drinking habits did not vary significantly between patients with DR and without DR as well.

We also recorded the history of exercise of included patients via an interview conducted by a trained physician. Among 1100 participants, 462 cases (42.0%) chose walking as their only routine exercise and only 78 cases chose other sports as their routine exercise. In order to avoid the effects on statistical power caused by the small sample size of participants treating other sports as routine exercise, we just defined walking as the probable risk factor for DR and the participants were categorized as individuals with routine walking and that without any other exercises. There was no significant difference of proportion of participants with routine walking between diabetic cases with DR and without DR (P=0.82).

Age – and Gender –adjusted Association Between Risk Factors and DR among Patients with Type 2 Diabetes Mellitus Table 2 presented the associations of various demographic and biochemical characteristics with DR among the 1100 patients with T2DM through constructing logistic models. After adjusting for age and gender, factors including longer duration of diabetes (OR, 5.70; 95% CI, 2.91-12.56), higher fast blood glucose concentration (OR, 12.94; 95% CI, 2.40-67.71), higher levels of HbA1c (OR, 5.50; 95%CI, 3.78-11.97) and insulin treatment (OR, 6.99; 95%CI, 1.39-35.12) significantly associated with the presence of DR. While other risk factors including hypertension, hyperlipidemia, smoking, alcohol consumption as well as walking examined in our study were not significantly associated with the presence of DR.

DISCUSSION

The prevalence of DR in patients with T2DM in our study

Table 2 Univariate regression analysis of risk factors associated with DR in type 2 diabetes after adjustment for age and gender

Variables	OR	95% CI	*P*
Gender	0.51	0.08 to 3.34	0.485
Age (a)	0.78	0.15 to 4.0	0.773
Duration of diabetes (a)	5.70	2.91 to 12.56	0.048
Fasting blood glucose concentration	12.94	2.40 to 67.71	0.002
HbA1c	5.50	3.78 to 11.97	0.049
Hypertension	1.33	0.33 to 5.33	0.69
Hyperlipidemia	1.54	0.41 to 4.50	0.88
Smoking	2.79	0.23 to 34.08	0.42
Alcohol consumption	1.40	0.11 to 17.40	0.79
Physical activity (walking)	0.71	0.13 to 3.87	0.69
Insulin treatment	6.99	1.39 to 35.12	0.02

Duration of diabetes was considered binary traits and patients were classified into two classes with duration <10y or ⩾10y. DR: Diabetic retinopathy.

was 27.9%. This figure agreed with the results of several previous studies. A hospital-based study in China including 746 patients with T2DM showed the prevalence of DR was 29.5% and another Beijing Communities Diabetes Study showed the DR prevalence of 24.7% among patients with T2DM [20-21]. In addition, the overall prevalence of DR in another hospital-based investigation on 2131 patients with T2DM in China was 27.3%[22]. The prevalence of DR among patients with T2DM in recent investigations was significantly higher than the results of the previous population-based study conducted in the years 1994 to 1995 which was 9.84%[23]. The increase of the prevalence of DR might be attributed to changes of the patients' lifestyle. Over the past decade, following with the fast economic growth and obvious improvement of the people's life, the prevalence of DM in China has increased from 2.6% to 9.7%, which can increase the risk for the presence of DR [24]. However, the direct association between the development of DR and people's lifestyle still remains elusive. In the present study, we studied the independent association of the development of DR with multiple potential risk factors including the patients' lifestyle through a multivariate logistical regression model.

Following the results in our study, the duration of diabetes was independently associated with the development of DR among Chinese people with T2DM. Consistent with the several previous studies [25-27], duration of diabetes is one of the strongest predictor of the prevalence of DR. Moreover, DR seemed to develop more rapidly among patients with high levels of fasting blood glucose and HbA1c in the present investigation. Numerous previous studies have identified the association between an elevated level of HbA1c and the development of DR[21,28]. The level of HbA1c was significantly higher in patients with DR than in the patients without DR in our study. The association between the elevated level of HbA1c and the development of DR may be caused by the same mechanism underlying the "metabolic memory" phenomenon or the mechanism for the short-term "early worsening" that was attributed to the insufficient time for long-term benefits in patients with fluctuating glycemic control [29]. Previous studies have identified that the progression of DR does not halt when the good control of glucose has been obtained, which is a so-called "metabolic memory" phenomenon [30]. This memory of prior exposure to high glucose would lead to persistence of the harmful effects on the target cells long after achievement of the glycaemic control [30]. The epigenetic modifications have been reported to play a role in the metabolic memory associated with DR. Recently Mishra *et al* [31] have clarified the molecular mechanisms of epigenetic modifications extending the harmful effects of high glucose after reversal of hyperglycemia. In addition, the development of DR seemed associated with treatment of insulin in our study, which was consistent with previous investigation [32]. This findings conforms the view that other factors including differences in the ability of insulin secretion, differences in the ability of insulin secretion or adverse events associated with insulin therapy like hypoglycemia must exist [33]. Additionally, previous study found that vitreous concentrations of insulin-like growth factors are increased in patients with diabetic retinopathy, and the high level of insulin treatment could bind to insulin-like growth factors receptors, leading to an increase of free insulin-like growth factors level[34].

Smoking has been found not associated with the development of DR in patients with T2DM in the present study. The association between smoking and DR was ambiguous. Previous studies[35-36] have shown that smoking is not likely to be an important risk factor for DR, while the inconsistent results have been obtained in several other studies which indicated the strong association between smoking and the development of DR [27,12]. The contradicted results of the association between smoking and DR from different studies may be caused by the different population under investigation. The association between the alcohol consumption and DR has not been established yet. As shown in previous investigation, alcohol consumption is associated with increased risk of deterioration of visual acuity but not with retinopathy in patients with T2DM[37]. We also observed that the drinking habit of patients was not associated with the development of DR in the present study. Previous study [38] suggested that greater level of physical activity with moderate intensity and duration is associated with substantial reduction in risk of T2DM. We also investigated the association of regular exercise (walking) with the complication of T2DM, while walking seemed not helpful for the reduction of DR in patients with T2DM in our study. Following our results, the lifestyle of patients with T2DM in northern China was not related with the development of DR. However, the present study is a cross-sectional and

retrospective research, and the information of patients' lifestyle we obtained only reflect the recent status of patients. A prospective study is still needed to evaluate the relationship between the development of DR and the lifestyle habits in the Chinese population.

In addition, blood pressure and serum lipids were both not directly associated with the development of DR in the present study. Our result of association between hypertension and DR was inconsistent with the previous study, which presented that estimated risk for DR after ten years in patients with hypertension was more than two times than that without hypertension [39]. Different study among different population may explain these contradicted results. Furthermore, there were inconsistent results of the association of serum lipids with DR[40-42]. In the present study, hyperlipidemia seemed not directly related with the prevalence of DR. The negative results of this association in the present study provide further evidence to the inconformity of the association.

Several limitations of this study should be noted. Firstly, the severity of DR was not graded in the present study that would prevent us from achieving more information of this disease. Secondly, DR was diagnosed based on 5 digital images per eye that may have missed some peripheral lesions. Moreover, patients that may have DR have been excluded due to media opacities and inadequate dilatation. Both would lead to underestimation the prevalence of DR, but such underestimation may not be substantial. Thirdly, all patients were consecutively selected from the Endocrinology Department of the Third Hospital of Hebei Medical University but not randomly selected and further multicenter-based study of randomly sampled cases should be conducted. Fourthly, all patients were selected from northern regions of China, and the results may not cover the patients with T2DM in other regions of China.

In conclusion, the presence of DR in patients with T2DM was tightly associated with the fasting serum glucose concentration, HbA1c level, duration of diabetes and insulin treatment in the present study. However, patients' lifestyle including smoking status, alcohol consumption and walking habits seemed not associated with the development of DR. Further multicenter-based investigation of randomly sampled cases should be conducted with more detailed information of participants.

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