·Clinical Research·

Risk factors associated with retinal neovasculari – zation of diabetic retinopathy in type 2 diabetes mellitus

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Abstract

• AIM: To evaluate the risk factors associated with retinal neovascularization of diabetic retinopathy in northern Chinese Han patients with type 2 diabetes mellitus (T2DM).

• METHODS: The clinical characteristics of 200 patients with proliferative diabetic retinopathy (PDR) and 100 age-matched healthy individuals were compared. The univariate and multivariate logistic regression analysis were performed in the patients with PDR.

• RESULTS: Fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), blood urea nitrogen (BUN), uric acid (UA), white blood cell count (WBC), absolute neutrophil count, hematocrit (HCT) and mean platelet volume (MPV) and mean platelet volume (MPV) were all significantly higher in patients with PDR than in the control group (P<0.05). The univariate and multivariate logistic regression analysis showed that risk factors independently associated with retinal neovascularization of DR were duration of diabetes mellitus (OR=1.112; P=0.000), BUN (OR=1.277; P=0.000), smoking (OR=3.967; P=0.000) and MPV (OR=2.472; P=0.000). On the other hand, panretinal photocoagulation was associated with reduced risk of retinal neovascularization (OR=0.983; P=0.000).

• CONCLUSION: Preventing and controlling T2DM in terms of risk factors, including duration of diabetes, BUN, smoking and MPV, might offer novel approaches to prevent or delay the onset of retinal neovascularization in patients with PDR.

• KEYWORDS: diabetic retinopathy; diabetes mellitus, type 2; retinal neovascularization; risk factors

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INTRODUCTION

Diabetic retinopathy (DR) is a common microangiopathy of type 2 diabetes mellitus (T2DM) and is an important cause of visual impairments. The stage of proliferative diabetic retinopathy (PDR) is characterized by retinal neovascularization on the optic disc or elsewhere on the retina. Abnormal retinal neovascularization could lead to many complications including retinal detachment, haemorrhage and glaucoma [1]. Retinopathy is a relatively common complication of T2DM and is associated with genetic and environmental factors. Furthermore, there are substantial differences in the rate of onset and severity of retinal neovascularization among different populations with T2DM. Because some risk factors and protective factors are associated with diabetic microangiopathy, it is likely that the retinal neovascularization of DR may also be related to these factors, warranting studies to determine which risk factors are involved in PDR among the population with T2DM.

Many factors have been reported to be associated with the progression and severity of DR, including the duration of DM, hyperglycemia, hypertension, smoking, genetic factors, abdominal obesity, urine albumin and hyperopic refractive error [2-8]. However, few studies have attempted to identify the risk factors associated with retinal neovascularization of DR among northern Chinese Han patients with T2DM. Therefore, we studied the independent associations between retinal neovascularization of DR and potential risk factors using logistic regression analysis in a cohort of northern Chinese Han patients with T2DM.

MATERIALS AND METHODS

Subjects 200 individuals (88 men and 112 women), randomly selected from 400 northern Chinese Han patients with PDR, participated in the study (age range: 45-74 years old; median: 55.8 years). All patients were recruited from

the Center of Vitreoretinopathy at Tianjin Eye Hospital (Tianjin, China) between September 2006 and May 2009. All participants with PDR underwent a comprehensive dilated fundus examination to detect DR by indirect ophthalmoscopy and were diagnosed by fundus fluorescence angiography. A further 100 healthy individuals (42 men and 58 women) randomly selected from 200 normal persons were enrolled (age range: 45-74 years old; median: 55.0 years) to comprise a control group. All protocols conformed to the guidelines of the Declaration of Helsinki. This study was approved by Ethics Committee of Tianjin Medical University, Ethics Committee of Tianjin Eye Hospital. All subjects agreed to participate in this trial and signed written informed consent.

T2DM was diagnosed according to the World Health Organization Expert Consultation Report [9] and consisted of one of the following: fasting blood glucose(FBG) ≥7.0mmol/L, blood glucose ≥11.1mmol/L 2 hours after an oral glucose tolerance test (OGTT); or a random blood glucose ≥11.1mmol/L. DR was clinically graded in accordance with the International Clinical Diabetic Retinopathy guidelines [10] based on fundus fluorescence angiography. Patients were excluded if they had acute complications of DM; type 1 or other types of DM; serious cardiovascular, hepatic, nephritic or other complications; or other serious primary diseases or mental illness. Individuals screened for the control group were excluded if they had any diseases of any system, as identified from their history and physical examinations.

Methods Clinical characteristics of subjects were recorded: age, sex, duration of diabetes, duration of hypertension, history of heart disease, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, postprandial blood glucose (PBG), blood urea nitrogen (BUN), creatinine (CREA), triglyceride (TG), total cholesterol (TC), urine albumin, uric acid (UA), hematocrit (HCT), hemoglobin (HGB); white blood cell (WBC), red blood cell (RBC), platelet (PLT) neutrophil counts, intermediate cell and lymphocyte counts, mean platelet volume (MPV), prothrombin time, active partial thromboplastin time, and histories of smoking, drinking and panretinal photocoagulation.

Statistical Analysis The baseline characteristics of individuals with PDR were compared with those of the control group using *t*-test for continuous variables and χ^2 test for categorical variables.Two-sided *P*-values <0.05 was considered statistically significant. To determine independent factors associated with retinal neovascularisation of DR, we conducted univariate and multivariate logistic regression analysis. For the univariate analysis, the associations between the severity of DR and the individual study variables were evaluated using non-parametric statistics (Spearman's rank correlation coefficient). Next, we used logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CI) with retinopathy as the outcome and the following predictive factors: duration of diabetes; duration of hypertension; tertiles of SBP, DBP, CREA, FBG, PBG or BUN levels compared with the lowest tertile; smoking versus non-smoking; and panretinal photocoagulation versus no panretinal photocoagulation. The severity of PDR was treated as an ordinal variable (1: new vessels and vitrous haemorrhages, 2: new vessels and fibrovascular proliferation, 3: new vessels and retinal detachment [10]) . Statistical analysis was performed using SPSS for Windows, version 13.0 (SPSS, Chicago, IL, USA).

RESULTS

Clinical Characteristics There were no differences between the two groups in terms of age (t=0.73, P>0.05) or sex (χ^2=0.13, P>0.05). FBG, TG, TC, BUN, UA, WBC, neutrophil counts, HCT and MPV were all significantly higher in the PDR group than in the control group (P< 0.05). On the other hand, there were differences (P>0.05) in CREA, HGB, or RBC, PLT, intermediate cell and lymphocyte counts between the two groups (Table 1).

Univariate Analysis In univariate analysis, the severity of retinal neovascularisation in patients with DR was positively associated with the duration of diabetes (P= 0.004), TC (P =0.015), BUN (P =0.017), smoking (P =0.006), intermediate cell count (P=0.016), prothrombin time (P= 0.020) and MPV (P= 0.015) (Table 1).

Multivariate Logistic Regression The factors were extracted from the original variables by principal component factor analyses and rotation of the factor analysis. Logistic regression analysis revealed that retinal neovascularisation in patients with T2DM was independently associated with the duration of diabetes, BUN, smoking and MPV. In contrast, panretinal photocoagulation was independently associated reduced risk of retinal neovascularisation (Table 2).

Association between age of patients with PDR and duration of DM The proportion of patients aged ≤ 60 years was particularly high among patients with PDR and a duration of diabetes of ≤10 years. In contrast, the proportion of patients aged >61 years was low among patients with PDR and a duration of diabetes of 11-20 years (Table 3).

DISCUSSION

In the present study, we found that the duration of diabetes (OR=1.112; P=0.000) was independently associated with retinal neovascularization of PDR in northern Chinese Han patients with T2DM. It is consistent with the fact that the

Table 1 Clinical characteristics between PDR group and control group

Clinical characteristics	PDR	Control	*t*	*P*
Age, yr (mean±SD range)	55.80±8.00	54.90±10.40	0.73	0.46
FBG, mmol/L (mean±SD range)	6.97±2.06	5.29±0.35	8.04	0.00
TG, mmol/L (mean±SD range)	2.03±1.64	1.17±0.53	4.99	0.00
TC, mmol/L (mean±SD range)	5.22±0.99	4.25±0.80	7.58	0.00
CREA, umol/L(mean±SD range)	78.30±46.30	83.00±17.10	-0.95	0.34
BUN,mmol/L (mean±SD range)	6.67±2.43	4.47±1.14	8.19	0.00
UA,umol/L(mean±SD range)	318.00±76.00	268±823	4.46	0.00
WBC,10^9/L(mean±SD range)	6.60±1.80	5.80±1.30	3.68	0.00
RBC,10^{12}/L(mean±SD range)	4.37±0.51	4.29±0.31	1.39	0.16
Hb,g/l (mean±SD range)	132.00±17.00	133.00±12.00	-0.77	0.44
Blood platelet,10^9/L (mean±SD range)	223.00±97.00	203.00±55.00	1.72	0.09
Neutrophil count,10^9/L(mean±SD range)	4.20±1.60	3.40±1.00	4.01	0.00
Intermediate cell count,10^9/L(mean±SD range)	0.53±0.22	0.48±0.17	1.79	0.08
Lymphocyte count,10^9/L (mean±SD range)	1.88±0.52	1.91±0.51	-0.41	0.69
HCT(mean±SD range)	0.38±0.05	0.14±0.03	6.07	0.00
MPV,fL(mean±SD range)	10.09±0.92	9.46±0.93	4.87	0.00

SD, standard deviation

Table 2 Multivariate logistic regression analysis in the patients with PDR

Parameter	*P*	O R (95% CI)
Duration of diabetes	0.000	1.112(1.088-1.136)
BUN	0.000	1.277(1.205-1.353)
Smoking	0.000	3.967(2.938-5.357)
MPV	0.000	2.472(2.019-2.904)
Panretinal photocoagulation	0.000	0.983 (0.785-0. 997)

Table 3 Association between age of patients with PDR and duration of DM [%(*n*)]

Age (yr)	Duration of DM		
	0-10 yr (*n*=101)	11-20 yr (*n*=97)	21-30 yr (*n*=2)
41-50	34.65 (35)	25.77(25)	0.00 (0)
51-60	48.51 (49)	55.67(54)	0.00 (0)
61-70	14.85 (15)	15.46(15)	0.00 (0)
71-80	1.98 (2)	3.09(3)	100.00(2)

duration of diabetes is one of the most important risk factors for the development of diabetic retinopathy [4,11-14]. In addition, DR seemed to develop more rapidly among younger individuals, and over 80% of those aged ≤60 years with a duration of diabetes ≤10 years developed PDR (Table 3). By contrast, among older patients aged >61 years with a duration of diabetes ≤10 years, DR seemed to develop more slowly (Table 3). Thus, the severity of retinal neovascularization of PDR seemed to be associated with the duration of diabetes, the age of the patient and vascular function under the influence of various factors. Therefore, preventing and controlling T2DM including maintaining tight control of hyperglycemia and hypertension might prevent the onset of retinal microvascularization in patients with T2DM.

A novel finding from this study was that BUN (OR=1.277; P=0.000) was an independent risk factor related to retinal neovascularization of PDR in northern Chinese Han patients with T2DM. Another study reported that urine albumin was an independent risk factor of DR and the albuminuria level may indicate the degree of DR [4]. Therefore, the data revealed that there might be a link between diabetic microvascular complications and the indicators of vascular hyperpermeability, including elevated urine albumin. Similarly, BUN may reflect the severity of renal dysfunction and indicate the presence of microvascular complications in T2DM. Because diabetic nephropathy and DR were both diabetic microangiopathy, we considered that elevated BUN might be a sign of retinal neovascularization of DR and a predictor of PDR.

In this study, an exciting finding was that smoking (OR= 3.967; P =0.000) was strongly associated with retinal neovascularization of PDR in northern Chinese Han patients with T2DM. This is consistent with the study that smoking is related to diabetic complications including nephropathy, neuropathy and retinopathy [15]. Interestingly, because the OR for smoking in the present study was higher than that in another study[2], we consider that this finding was associated with the prevalence of male smokers or female passive smokers among the northern Chinese Han population, which is higher than that in other regions. Nevertheless, the results should be investigated in a larger study population. Besides, other studies demonstrated that smoking is associated with diabetic nephropathy in Chinese patients [16,17]. Accordingly, smoking greatly increases the risk of endothelial dysfunction in micro- and macro-vascular complications [15], particularly

in diabetic patients, manifesting substantially increased risk of complications such as DR. Therefore, we inferred that smoking control might prevent or reduce the risk of diabetic microvascular and/or macrovascular complications, including diabetic neuropathy.

Another finding of the present study was that MPV (OR= 2.472; *P*=0.000) was an important risk factor independently related with retinal neovascularization of PDR in northern Chinese Han patients with T2DM. It is consistent with the fact that increased MPV was associated with the onset of coronary thrombosis and acute myocardial infarction [18, 19]. Accordingly, we considered that increased MPV might be a marker for the hypercoagulation state and tissue ischaemia in patients with PDR. Therefore, we inferred that the indicators related to morphology and function of PLT, including MPV, might provide targets to prevent retinal neovascularisation of DR in patients with T2DM.

A limitation of this study is its relatively small sample size. Nevertheless, the associations observed persisted in multivariate analyses. Besides, it must also be acknowledged that all of the patients of Han nationality were selected from northern regions of China. Thus, the results may not be generalisable to patients in other regions of China or to patients in other countries. Therefore, future studies should investigate the independent associations between retinal neovascularization among other Chinese Han patients with T2DM and a variety of other risk factors. The future findings of such studies might help us to understand the pathogenesis and risk factors for retinal neovascularization in T2DM and establish targets to prevent DR.

In conclusion, this study demonstrates that the duration of diabetes, BUN, smoking and MPV are independent risk factors for retinal neovascularization of PDR in northern Chinese Han patients with T2DM. Furthermore, preventing and controlling T2DM in terms of these risk factors might provide us with novel approaches to prevent or delay the onset of retinal neovascularization in patients with T2DM and DR.

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