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Protective factors for diabetic retinopathy in Type 2 diabetes mellitus patients: Long duration of no less than 10 years

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ABSTRACT

Aim: To study the factors protecting against diabetic retinopathy (DR) in patients with over a decade-long history of type 2 diabetes mellitus.
Methods: A total of 490 patients with type 2 diabetes mellitus lasting for ≥10 years were divided into DR and no diabetic retinopathy (no DR) groups. Their basic information was collected, including age, sex, and duration of diabetes mellitus, as well as pertinent laboratory data. Potential correlations between these factors and DR were evaluated using multivariate analysis.
Results: Overall, 208 patients met the diagnostic criteria for DR. Multivariate logistic regression was used to evaluate factors with $P < 0.10$ after univariate analysis. Age, total bilirubin, and total cholesterol were found to be protective factors against DR. Presence of diabetic kidney disease and diabetic peripheral neuropathy, duration of diabetes mellitus, apolipoprotein B, blood urea nitrogen, and prothrombin time were found to be risk factors for DR.
Conclusions: We conclude that total cholesterol is a protective factor against DR. Specifically, it was confirmed that high levels of total cholesterol reduce the risk of DR. These findings may provide a basis for new diet and lifestyle guidelines for patients with diabetes mellitus.

1. Introduction

Diabetic retinopathy (DR) is one of the most serious complications of type 2 diabetes mellitus (T2DM) and the leading cause of blindness in adults.[1] Many studies have found that duration of T2DM is an important risk factor for DR. However, in clinical practice, some patients with chronic T2DM with poorly-controlled glucose levels either do not have DR or their DR is not severe. Moreover, some patients with short-term T2DM and well-controlled blood glucose levels are diagnosed with serious DR. Thus, it is important to identify factors that prevent the occurrence of DR in T2DM patients. Therefore, the aim of this study was to explore both the protective and risk factors involved in the development of DR.

Many epidemiological studies on DR have evaluated its associated risk factors in order to help prevent or control the disease. Similar research studies have also been conducted in Asia. A prospective Korean cohort study demonstrated that longer diabetes duration is a significant risk factor for the incidence of DR.[7] T2DM is a severe metabolic disease with many complications, such as diabetic kidney disease (DKD) and diabetic peripheral neuropathy (DPN). Studies conducted in China concluded that DKD and DPN are independent risk factors for DR development and progression.[8,9] Apolipoprotein B (Apo B)[10] and prothrombin time (PT)[11] have also been found to be associated with development of DR. A multi-hospital-based cross-sectional study comparing the Western population with diabetes have found similar risk factors for DR in Chinese diabetic patients, such as blood urea nitrogen (BUN).[12]

Declaration of interest: none.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Compliance with Ethical Standards: All human samples were obtained from the Third Affiliated Hospital of Southern Medical University (GuangZhou,China). All patients gave informed consent to use their clinical information for scientific research. The study was approved by the Ethics Committee of the Third Affiliated Hospital of Southern Medical University.

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DR and its risk factors have gained much attention and many abnormal indicators have been confirmed as risk factors, thus potentially facilitating early detection and treatment of the disease. However, protective factors, which may steer doctor focus toward valuable indicators, have gained less attention. More studies and improved awareness of the protective factors are therefore required.

2. Materials and methods

2.1. Study selection and data collection

A total of 490 patients with T2DM underwent binocular color fundus photography using a mydriatic auto fundus camera (TRC 50DX; TOPCON, Tokyo, Japan) in The Third Affiliated Hospital of Southern Medical University between January 1, 2016 and June 29, 2018. The sample pool included 227 males and 263 females with a mean age of 65.5 years (age range: 32–91 years) and a mean T2DM duration of 14.7 years (range: 10–40 years). T2DM diagnosis complied with the new diagnostic and classification criteria for diabetes mellitus published by the WHO in 1999,[2] which indicate that diabetes mellitus can be diagnosed with random plasma glucose level ≥ 11.1 mmol/L, fasting plasma glucose ≥ 7.0 mmol/L, or 2-h plasma glucose ≥ 11.1 mmol/L during an oral glucose tolerance test. Participants whose fundus images were blurred and who were identified as having an unclear optic disk and surrounding vessels were excluded from the research study; as were those who had T2DM with ketoacidosis or hypoglycemia, or exhibited acute or chronic infection, blood disease, malignant tumor, or liver disease. Diagnostic criteria for DR were based on the Diagnostic Criteria for Clinical Diagnosis and Treatment of Diabetic Retinopathy in China.[3] Subjects were divided into the following two groups: a group with DR in at least one eye and a no diabetic retinopathy (no DR) group with no DR in either eye.

Recorded patient demographic characteristics included sex, age, diabetes mellitus duration, body mass index, blood pressure, and presence or absence of hypertension, diabetic foot, DKD, and DPN. DKD is a chronic kidney disease complicated by diabetes mellitus, with glomerular filtration rate (GFR) < 60 ml·min^{-1}·1.73 m^{-2} or urinary albumin/creatinine ratio (ACR) > 30 mg/g lasting >3 months.[4] Patients were clinically diagnosed with DPN if they had a clear diagnosis of diabetes mellitus, neuropathy occurring after the diabetes mellitus diagnosis, clinical signs and symptoms consistent with DPN, or at least one abnormal test result among five tests that included sputum reflex, needle sensation, vibration sensation, pressure sensation, and temperature sensation in patients with clinical symptoms (pain, numbness, and paresthesia).[5] Blood samples from the subjects were collected to determine the red blood cell count (RBC), platelet count (PLT, XT-2000I; Sysmex, Japan), glycosylated hemoglobin (HbA1c, G8; Vastec, Hong Kong), fasting blood glucose (FBG), total bilirubin (TBIL), total cholesterol (TC), triglyceride (TG), high-density-lipoprotein cholesterol (HDL-c), low-density-lipoprotein cholesterol (LDL-c), apolipoprotein A (Apo A), Apo B, serum creatinine (Scr), BUN, blood uric acid (BUA), GFR, PT, activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB, Cobas® 8000 modular analyzer series).

2.2. Statistical analysis

Statistical analysis was performed using the IBM SPSS software version 21. Continuous data were expressed as mean ± standard deviation ($\overline{\chi} \pm s$) and count data were expressed as percentage (n%). Data for the DR and no DR groups were compared using two independent-samples t-tests. Chi-squared test was used to compare rates. Multivariate logistic regression analysis was used to analyze factors with $P < 0.10$ after univariate analysis. Differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. Count data univariate analysis in DR and no DR groups

The morbidity rate for DR was 42.5%. The prevalence rates for hypertension, DKD, and DPN were higher in the DR group than in the no DR group ($P < 0.10$, Table 1).

3.2. Measurement data univariate analysis in DR and no DR groups

The values for T2DM duration, systolic blood pressure, Hb1Ac, TC, LDL-c, Apo B, Scr, BUN, PT, and FIB were higher in the DR group than in the no DR group. The values for age, RBC, TBIL, and GFR were lower in the DR group than in the no DR group ($P < 0.10$, Table 2).

3.3. Logistic regression analysis for risk and protective DR factors

Multivariate logistic regression analysis was performed for variables with $P < 0.10$ after univariate analysis. Significant risk factors for DR in T2DM patients were DKD (OR = 3.176, $P < 0.05$), DPN (OR = 1.864, $P < 0.05$), T2DM duration (OR = 1.066, $P < 0.05$), Apo B (OR = 30.647, $P < 0.05$), BUN (OR = 1.095, $P < 0.05$), and PT (OR = 1.494, $P < 0.05$). Significant protective factors for DR in T2DM were age (OR = 0.953, $P < 0.05$), TBIL (OR = 0.943, $P < 0.05$), and TC (OR = 0.704, $P < 0.05$, Table 3).

4. Discussion

A previous study has shown that initiation and development of DR are related to the duration of T2DM and blood glucose control.[6] However, some patients with long-term diabetes mellitus and poorly-controlled blood glucose do not develop DR or exhibit mild cases of it. Conversely, some patients have severe DR despite a relatively short disease period and good blood glucose control. In this study, data were collected from systemic and ocular examinations of chronic T2DM patients with a disease duration of no <10 years to identify the factors protecting against DR and explore the mechanisms that resist damage caused by DR. It is vital to study the mechanisms of DR development to determine the factors protective against it and to provide reasonable guidelines for patients with T2DM to prevent severe DR.

The results of this study show that T2DM duration, DKD, DPN, and Apo B are risk factors for DR, which is consistent with many earlier studies.[7–10] In addition, BUN and PT are also risk factors for DR. Few reports on the relevance of BUN and PT in DR have been published,[11,12] thus future studies on this subject are warranted.

In this study, it was found that TBIL, age, and TC were protective factors for DR. T2DM patients with long-term hyperglycemia have excessive amounts of reactive oxygen species (ROS) in the body, causing systemic oxidative stress. An increase in intracellular ROS can lead to cytotoxicity and tissue damage, including in retinal vascular endothelial and other related cells. Bilirubin has a strong antioxidant capacity and can effectively reduce oxidative damage, which is consistent with our finding that it is a factor protective against DR.[13,14]

Table 1
Univariate analysis of count data.

Characteristic	no DR (n = 282)	DR (n = 208)	χ^2	P value
Sex				
Male	131(46.45%)	96(46.15%)	0.004	0.948
Female	151(53.55%)	112(53.85%)		
Hypertension	174(61.7%)	150(72.12%)	5.795	0.016
Diabetic foot	14(4.96%)	15(7.21%)	1.085	0.297
DKD	56(19.86%)	109(52.40%)	56.771	<0.001
DPN	113(40.07%)	124(59.62%)	18.31	<0.001

no DR = no diabetic retinopathy; DR = diabetic retinopathy; DKD = diabetic kidney disease; DPN = diabetic peripheral neuropathy.

Table 2
Univariate analysis of measurement data.

Characteristic	no DR group	DR group	*T* value	*P* value
Baseline				
Age (years)	66.79 ± 11.10	63.73 ± 9.83	3.162	0.002
T2DM course (years)	14.25 ± 5.19	15.23 ± 4.76	−2.135	0.033
BMI (kg/m^2)	23.81 ± 3.41	23.70 ± 3.48	0.327	0.744
Systolic blood pressure (mmHg)	139.43 ± 19.43	145.07 ± 24.1	−2.866	0.004
Diastolic blood pressure (mmHg)	74.59 ± 10.61	75.55 ± 12.88	−0.908	0.365
RBC (×10^{12}/L)	4.43 ± 0.86	4.12 ± 0.76	4.084	<0.001
PLT (×10^9/L)	237.64 ± 74.19	246.14 ± 79.67	−1.215	0.225
HbA1c (%)	8.58 ± 2.64	9.03 ± 2.30	−2.000	0.046
FBG (mmol/L)	7.63 ± 3.41	7.81 ± 3.80	−0.544	0.587
Lipid profile				
TBIL (μmol/L)	8.96 ± 4.35	7.58 ± 3.61	3.726	<0.001
TC (mmol/L)	4.55 ± 1.20	4.82 ± 1.24	−2.422	0.016
TG (mmol/L)	1.82 ± 1.55	1.89 ± 1.46	−0.476	0.634
HDL-c (mmol/L)	1.18 ± 0.36	1.18 ± 0.32	0.083	0.934
LDL-c (mmol/L)	2.57 ± 1.05	2.80 ± 1.22	−2.306	0.022
Apo A (g/L)	1.17 ± 0.32	1.17 ± 0.31	0.020	0.984
Apo B (g/L)	0.85 ± 0.22	0.93 ± 0.25	−3.641	<0.001
Liver and renal function tests				
SCRA (mold/L)	87.36 ± 46.05	142.84 ± 201.56	−4.469	<0.001
BUA (μmol/L)	373.82 ± 108.34	381.81 ± 115.69	−0.784	0.433
BUN (μmol/L)	6.21 ± 2.86	8.7 ± 7.35	−5.178	<0.001
GFR (ml/min)	78.98 ± 29.02	67.48 ± 36.18	3.901	<0.001
Coagulation test				
PT (s)	10.98 ± 0.95	11.21 ± 1.57	−1.997	0.046
TT (s)	19.36 ± 6.86	19.01 ± 3.09	0.696	0.487
APTT (s)	25.20 ± 4.17	24.99 ± 4.21	0.532	0.595
FIB (g/L)	3.14 ± 0.93	3.36 ± 1.07	−2.475	0.014

no DR = no diabetic retinopathy; DR = diabetic retinopathy; T2DM = type 2 diabetes mellitus; BMI = body mass index; RBC = red blood cell; PLT = platelet; HbA1c = glycosylated hemoglobin; FBG = fasting blood glucose; TBIL = total bilirubin; TC = total cholesterol; TG = triglyceride; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; Apo A = apolipoprotein A; Apo B = apolipoprotein B; Scr = serum creatinine; BUN = blood urea nitrogen; BUA = blood uric acid; GFR = glomerular filtration rate; PT = prothrombin time; APTT = activated partial thromboplastin time; TT = thrombin time; FIB = fibrinogen.

Other studies have shown that perfusion rate is low in the retina of patients with severe myopia,[15] which is known to protect against the development of DR.[16–18] Among patients of advanced age, central retinal artery hemodynamics change significantly before the occurrence of severe retinopathy, with clear decreases in both peak systolic velocity (V_s) and end diastolic velocity (V_d) of this artery.[19] V_s reflects the intensity of vascular filling and blood supplementation, while V_d describes blood perfusion of the tissue. Decreases in V_s and V_d indicate a serious lack of tissue perfusion. Retinas of middle-aged and elderly patients are already in a state of low perfusion, inhibiting the development of DR. Therefore, age is a protective factor against DR.

Table 3
Multivariate Logistic Regression Analysis for DR.

Characteristic	OR value	*P* value	95% C.I.
DKD	3.176	<0.001	1.974–5.111
DPN	1.864	0.005	1.212–2.867
Age (years)	0.953	<0.001	0.932–0.975
T2DM course (years)	1.066	0.005	1.019–1.115
TBIL (μmol/L)	0.943	0.046	0.89–0.999
TC (mmol/L)	0.704	0.032	0.512–0.97
Apo B (g/L)	30.647	<0.001	5.678–165.418
BUN (μmol/L)	1.095	0.008	1.024–1.172
PT (s)	1.494	<0.001	1.193–1.871

Variables entered on step 1: age, DM duration, systolic blood pressure, hypertension, DKD, DPN, RBC, HbA1c, TBIL, TC, LDL-c, Apo B, Scr, BUN, GFR, PT, FIB.
OR = odds ratio; C.I. = confidence intervals; DKD = diabetic kidney disease; DPN = diabetic peripheral neuropathy; T2DM = type 2 diabetes mellitus; TBIL = total bilirubin; TC = total cholesterol; Apo B = apolipoprotein B; BUN = blood urea nitrogen; PT = prothrombin time.

Our research also shows that moderate to high TC is a factor protective against DR. Previous research has found an association between low cholesterol levels and DR, but the mechanistic details of this phenomenon were not revealed. Other studies have shown that hypercholesterolemia is a risk factor for DR.[20,21] In the Singapore Malay Eye study, a high TC level was found to protect against DR.[22] Considering this data, in order to ensure the quality of measurements in this study, factors related to TC were recalculated. In univariate analysis, when a threshold for the *P*-value was set at 0.05, TC remained a statistically significant parameter and the results did not change. Some studies have shown that Müller glial cells (MGCs) are actively involved in retinal development and promote homeostasis through a variety of intracellular mechanisms. Retinal health certainly depends on MGCs, as they display different responses according to stimulus severity and trigger distinct events throughout the disease course.[23] MGCs are highly sensitive to metabolic alteration of diabetes, such as hyperglycemia along with dyslipidemia, hypoinsulinemia, and hypertension.[24] Overexposure and underexposure to cholesterol activate MGCs and modulate their ability to sense and transduce environmental signals, which conduct a mechanism of retinal defense, thus maintaining an anti- and pro-inflammatory balance.[25] Cholesterol supplementation and depletion have also been reported to have striking effects on the ability of retinal glial cells to sense information from the environment.[26] Therefore, high levels of total cholesterol may reduce the risk of DR by activating MGCs.

In the 2015–2020 Dietary Guidelines for Americans,[27] the upper limit for cholesterol has been eliminated, prompting us to reexamine the status of cholesterol as it pertains to those with diabetes mellitus. In future work, we plan to expand the sample size and design relevant experiments to confirm the role of cholesterol in DR.

In conclusion, data of this study is from the most recent epidemiology data on DR in The Third Affiliated Hospital of Southern Medical University, and assess the protective factors for DR. This study still has some limitations. Considering that this is a cross-sectional study, longitudinal studies should be performed to prove the causal association or protective effect of any systemic factor for DR. Additional limitations include small sample size and hospital-based population. TC is a protective factor for DR. Although this can be explained in many ways, dietary data in relation to cholesterol may have an influence on this effect. Further studies need to be performed in the future. These results may contribute to new guidelines for the diet and lifestyle of patients with T2DM.

References

1. Willis JR, Doan QV, Gleeson M, et al. Vision-related functional burden of diabetic retinopathy across severity levels in the United States. JAMA ophthalmology 2017;135:926-32.
2. Qian RL. New diagnostic criteria and classification for diabetes. Chinese Journal of Diabetes 2000;8:5-6.
3. Chinese Ophthalmological Society. Guidelines for clinical diagnosis and treatment of diabetic retinopathy in China (2014). Chin J Ophthalmol 2014;50:851-65.
4. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA consensus conference. Am J Kidney Dis 2014;64:510-33.
5. Neurology Department of Chinese Medical Association. Consensus diagnosis and treatment of diabetic peripheral neuropathy. Chin J Neurol 2013;46:787-9.
6. Liu Y, Yang J, Tao L, et al. Risk factors of diabetic retinopathy and sight-threatening diabetic retinopathy: a cross-sectional study of 13 473 patients with type 2 diabetes mellitus in mainland China. BMJ Open 2017;7, e016280.
7. Yun JS, Lim TS, Cha SA, et al. Clinical course and risk factors of diabetic retinopathy in patients with type 2 diabetes mellitus in Korea. Diabetes Metab J 2016;40:482-93.
8. Jeng CJ, Hsieh YT, Yang CM, et al. Diabetic retinopathy in patients with diabetic nephropathy: development and progression. PLoS One 2016;11, e0161897.
9. Wei WW, Yang XF, Gu F, et al. Association of diabetic retinopathy with diabetic peripheral neuropathy in type 2 diabetic patients: the Beijing Desheng Diabetic Eye Disease Study. China Journal of Ophthalmology 2017;53:509-13.
10. Ankit BS, Mathur G, Agrawal RP, et al. Stronger relationship of serum apolipoprotein A-1 and B with diabetic retinopathy than traditional lipids. Indian J Endocrinol Metab 2017;21:102-5.
11. Wang HJ, Liu X. Clinical analysis of coagulation function and related risk factors in patients with type 2 diabetic retinopathy. Clinical Laboratory Journal (Electronic Edition) 2017;6:68-70.

12. Zhang G, Chen H, Chen W, et al. Prevalence and risk factors for diabetic retinopathy in China: a multi-hospital-based cross-sectional study. Br J Ophthalmol 2017;101:1591-5.
13. Chen JX, Lin RH. Diagnostic value of serum midkine combined with total bilirubin for diabetic retinopathy. Chin J Diabetes 2017;25:121-4.
14. Zhang D, Liu XY, Liu B. Role of total bilirubin level in early diagnosis of diabetic retinopathy. Chin J Diabetes 2015;23:995-7.
15. Lim LS, Cheung CY, Lin X, et al. Influence of refractive error and axial length on retinal vessel geometric characteristics. Invest Ophthalmol Vis Sci 2011;52:669-78.
16. Bazzazi N, Akbarzadeh S, Yavarikia M, et al. High myopia and diabetic retinopathy: a contralateral eye study in diabetic patients with high myopic anisometropia. Retina 2017;37:1270-6.
17. Quigley M, Cohen S. A new pressure attenuation index to evaluate retinal circulation. A link to protective factors in diabetic retinopathy. Arch Ophthalmol 1999;117:84-9.
18. Guo YN, Zhou XY. The relevance between high myopia and diabetic retinopathy. Int Rev Ophthalmol 2015;39:120-3.
19. Yang JD, Zhang ZD. Hemodynamic detection of central retinal artery in middle-aged and elderly patients with diabetes. Zhejiang Medical Journal 2000;22:304.
20. Weiler DL, Engelke CB, Moore AL, et al. Arteriole tortuosity associated with diabetic retinopathy and cholesterol. Optom Vis Sci 2015;92:384-91.
21. Wong TY, Cheung N, Tay WT, et al. Prevalence and risk factors for diabetic retinopathy: the Singapore Malay Eye Study. Ophthalmology 2008;115:1869-75.
22. Wong TY, Cheung N, Tay WT, et al. Prevalence and risk factors for diabetic retinopathy: the Singapore Malay Eye Study. Ophthalmology 2008;115:1869-75.
23. Subirada PV, Paz MC, Ridano ME, et al. A journey into the retina: Muller glia commanding survival and death. Eur J Neurosci 2018;47:1429-43.
24. Rübsam A, Parikh S, Fort PE. Role of Inflammation in Diabetic Retinopathy. Int J Mol Sci 2018; 19: pii: E942.
25. Lakk M, Yarishkin O, Baumann JM, et al. Cholesterol regulates polymodal sensory transduction in Muller glia. Glia 2017;65:2038-50.
26. Lakk M, Vazquez-Chona F, Yarishkin O, et al. Dyslipidemia modulates Muller glial sensing and transduction of ambient information. Neural Regen Res 2018;13:207-10.
27. Fresán U, Sabaté J, Martínez-Gonzalez MA, et al. Adherence to the 2015 Dietary Guidelines for Americans and mortality risk in a Mediterranean cohort: the SUN project. Prev Med 2018;118:317-24.