https://doi.org/10.31689/rmm.2024.31.2.149

ORIGINAL PAPERS

Assessment of Risk Factors for the Development of Diabetic Retinopathy in T2D

Asadullah JATOI

Abstract

Objective: To estimate the risk factors that contributes to the incidence of diabetic retinopathy (DR) in type 2 diabetes (T2D).

Methodology: We conducted serial fundus photography in individuals at high risk of developing type 2 diabetes, including after the onset of diabetes. The ETDRS (Early Treatment Diabetic Retinopathy Study) grading system was used to evaluate the fundus photographs.

Results: A total of 400 participants with a 3:3.6 male-to-female ratio were included in this study. The T2 DM patients with mean age 48.73±9.24 and 47.53±8.53 years with and without retinopathy respectively were observed, which shows that there is a non-significant difference (p=0.801). The differences in weight and BMI in T2 D participants with and without diabetic retinopathy were also not significant. The study found that the history of pregnancy, history of gestational DM, measures of HOMA-B, HOMA-IR, insulin genic index, oral disposition index, urine albumin to creatinine ratio, and hs-CRP were not associated with the presence of retinopathy. Association of nonglycemic risk factors in T2D. The study found that mean HbA1c during follow-up was significantly associated (P < 0.0001) with the prevalence of retinopathy, The study found that retinopathy was associated with measures of higher blood pressure (systolic blood pressure, diastolic blood pressure, and presence of hypertension) and lipid profile.

Conclusions: The development of DR can occur in the early stages of T2D. Hemoglobin A1c was found to be a significant risk factor for the occurrence of DR across the intact glycemic range in patients with T2D.

Keyword: Assessment, Risk factors, Development, Diabetic retinopathy, T2D

Institute of Ophthalmology, Liaquat University of Medical and Health Sciences, Jamshoro, Sindh, Pakistan.

*Corresponding author:
Asadullah JATOI, Institute of Ophthalmology, Liaquat University of Medical and Health Sciences, Jamshoro, Sindh, Pakistan
E-mail: jatoiasadullah7@gmail.com

INTRODUCTION

Diabetic retinopathy (DR) refers to the characteristic retinal lesions that can occur in either eye as a result of diabetes. These micro vascular lesions are a well-known complication of diabetes and are indicative of progressive retinal disease, which can eventually lead to vision impairment or even blindness[1]. In type 1 diabetes (T1D), there is a strong and well-established link between hyperglycemia and the development of retinopathy. Research has shown that improving glycemic control can significantly decrease the risk of developing retinopathy and slow down its progression. Therefore, it is important for individuals with T1D to maintain better control of their blood glucose concentration to minimize the risk of developing diabetic retinopathy and other complications associated with diabetes[2,3]. Studies have also shown a good association between hyperglycemia and the development of retinopathy in individuals with T2D. DR is actually one of the leading causes of new cases of blindness among adults aged range 30-65 years in the United States[4,5].

Furthermore, research has revealed that African Americans have more risk of developing DR when compared to Caucasians. This highlights the importance of early detection and management of DR in high-risk populations, particularly among individuals with T2D, to prevent vision loss and related complications[6,7]. Numerous studies have previously identified several risk factors accompanying the development of any DR, including longer diabetes duration, hyperglycemia, and hypertension. However, identifying risk factors for progression to more advanced stages of DR is crucial given the significant risk of vision loss in these subjects[2,7,8].

Interestingly, results suggest that the risk factors for advanced stages of DR may differ somewhat from those for any diabetic retinopathy[9]. As an example, the Diabetes Prevention Program (DPP) study found that 12.6% of participants who had progressed to diabetes, as determined by an oral glucose tolerance test (OGTT), had lesions consistent with DR based on initial results. Among a subgroup of subjects who had not yet progressed to diabetes, the prevalence of such lesions was 7.9%[10-12]. To investigate the potential factors that contribute to the occurrence DR, we conducted a study using fundus photography to assess the prevalence and severity of DR in individuals with diabetes over the course of 1 year. Our aim was to identify the risk factors associated with the development of diabetic retinopathy.

METHODOLOGY

We conducted a case-control study at a university that involved 400 participants diagnosed with T2D, with and without retinopathy. To be included in the study, subjects were required to meet the American Diabetes Association criteria for diabetes, which was confirmed using a 2-hour oral glucose tolerance test (OGTT), a fasting glucose measurement taken 6-months between OGTTs, or an HbA1c measurement of 6.5% or higher confirmed with glucose-based testing. The study excluded individuals who did not have diabetes. This study was conducted after receiving approval from the ethical review committee. Glycemia testing was performed routinely, allowing for precise determination of diabetes onset within a six-month period. All available and consenting participants underwent fundus photography to diagnose the presence of DR, which was identified by the presence of typical DR lesions such as exudates, micro aneurysms, or hemorrhages in either eye (indicated by an ETDRS score of ≥20 in one or both eyes).

We considered various potential risk factors, including demographic variables, and average values over time for weight, BMI, fasting glucose, HbA1c, systolic & diastolic blood pressure up to and including the time points at which the stereoscopic fundus photographs were taken.

We also assessed the lipid profile of the participants, including measurements of total cholesterol, HDL, LDL, as well as triglycerides. In addition, we determined the urinary albumin to creatinine ratio and assessed the GFR based on serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation. Hypertension and dyslipidemia were well-defined according to the current criteria, which included a BP ≥140/90 or the use of antihypertensive medications, and an LDL level ≥130 mg/dL, HDL level ≤40 mg/dL, a triglyceride level ≥200 mg/dL, or the use of lipid-lowering medications. We also obtained information on the participants' pregnancy history, including any history of gestational DM. To assess insulin sensitivity and insulin secretion, we measured fasting insulin and used the homeostatic model assessment of insulin resistance (HOMA-IR) and homeostatic model assessment of beta cell function (HOMA-B) methods. We

also calculated the insulinogenic index, which measures the ratio of the change in insulin to the change in glucose during an oral glucose tolerance test (OGTT), and the oral disposition index, which is a measure of insulin secretion relative to insulin sensitivity (calculated as 1 / fasting insulin × [ΔIns120 – Ins0] / [Gluu120 – Glu0]).

RESULTS

Total of 400 participants with a male (n=220) to female (n=180) ratio of 3:3.6 were included in this study. Males still tended to be less likely than females to develop DR (P=0.08). The T2 DM patients' age between 43 to 60 years of age with mean age 48.73±9.24 and 47.53±8.53 years with and without retinopathy respectively were observed, which shows that there is a non-significant difference (p=0.801). The differences in weight and BMI in T2 DM participants with and without diabetic retinopathy were also not significant **[Table 1]**.

Table 1: Characteristics of subjects with and without DR in T2D

Characteristics	**T2D (*n* = 1,546)**		P value
	With retinopathy	**Without retinopathy**	
Age (years)	48.73±9.24 Y	47.53±8.53	0.801
Weight (kg)	89.63±15.24	91.37±9.73	0.139
BMI (kg/m2)	34.58± 5.72	33.52±6.18	0.2811

The study found that the history of pregnancy, history of gestational DM, measures of HOMA-B, HOMA-IR, insulinogenic index, oral disposition index, urine albumin to creatinine ratio, and hs-CRP were not associated with the presence of retinopathy, indicating that these factors may not be independent risk factors for diabetic retinopathy **[Table 2]**.

The study found that there was a significant association between mean HbA1c during follow-up and the prevalence of retinopathy, indicating that higher levels of HbA1c and plasma glucose were associated with an increased risk of retinopathy. Additionally, the study found that the risk of retinopathy began to increase when fasting plasma glucose levels reached the threshold considered diagnostic of diabetes, suggesting that

Table 2: Association of nonglycemic risk factors in T2DM

Characteristics	**T2D (*n* = 1,546)**		P value
	With retinopathy	**Without retinopathy**	
Gestational diabetes mellitus (female participants only)	27	23	0.776
pregnant (female participants only)	58	67	0.9664
HOMA-B*	211.49	207.52	0.245
HOMA-IR	6.39	6.84	0.641
Insulinogenic index (mU/mg)	102.89	97.59	0.512
Oral disposition index	2375	2495	0.836
Albumin-to-creatinine ratio (mg/g)	6.28	4.93	0.006
hs-CRP (mg/dL)	0.53	0.34	0.01

increasing plasma glucose levels were associated with a progressively increasing risk of retinopathy **[Table 3]**.

The study found that retinopathy was associated with measures of higher blood pressure (systolic and diastolic BP, and the presence of hypertension). The relationship between retinopathy risk and average blood pressure levels during follow-up was further analyzed, and it was observed that the risk of retinopathy increased with higher average diastolic blood pressure levels. However, the risk of retinopathy peaked around an average systolic blood pressure of 145 mmHg, indicating that the association between retinopathy risk

Table 3: Glycemic risk factors for the presence of DR

Characteristics	**T2D (*n* = 1,546)**		P value
	With retinopathy	**Without retinopathy**	
HbA1c (%)	6.61±1.39	6.11±1.27	<0.0001
Fasting glucose (mg/dL)	129.6±19.49	118.8±14.73	<0.0001
120-min glucose (mg/dL)	180.3±30.21	175.7±26.89	0.009

and average systolic blood pressure may not continue to increase beyond this threshold (Figure 1).

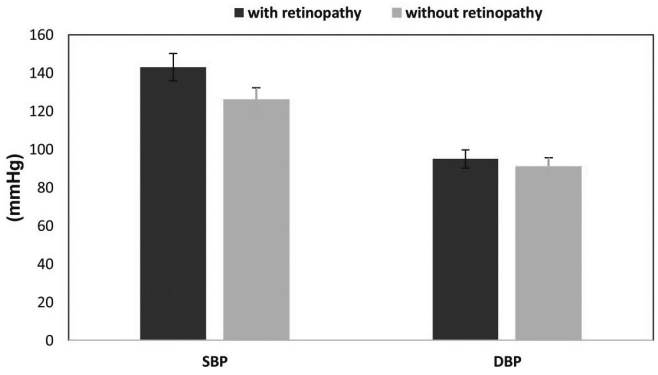

Figure 1: Association of blood pressure with and without retinopathy in T2DM

It was observed that there is a positive association between dyslipidemia and DR as shown in (Figure 2).

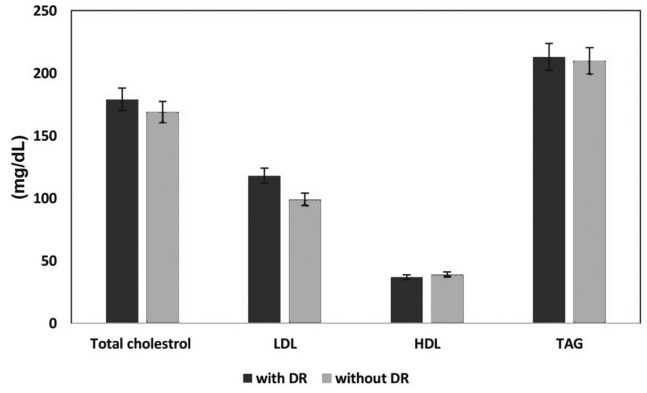

Figure 2: Association of lipid profile with and without DR

DISCUSSION

The study showed a significant association between the presence of DR and type 2 diabetes as well as hypertension. However, it should be observed that Hemoglobin A1c levels were based on a single measurement taken at the time of fundus photography, and therefore, the average levels over a longer diabetes duration were not available. The results also support previous research that has found an association between higher BP and DR, regardless of ethnicity or diabetes type[13-15]. Several prospective RCT in subjects with T2D have also demonstrated the beneficial effects of blood pressure control on the progression of retinopathy[10,11]. Previous trials examining the effect of BP control on progression of retinopathy in patients with T2D have mainly involved Caucasian populations. However, a study conducted on African Americans with T1D found that, in addition to glycemic control and renal disease, elevated BP was also associated with DR[14]. Although previous studies have reported associations between these factors and DR in other populations, in our current study with individuals having type 2 diabetes, we found age, sex, BMI, serum lipid levels, and blood pressure to be independently associated with DR[16]. Despite some studies reporting associations between age, sex, BMI, serum lipid profile, and blood pressure with DR in other populations, these factors have not been consistently found to impact the occurrence of DR. On the other hand, RCT in subjects with T2D has consistently demonstrated the importance of glycemic control in reducing the risk of DR progression[7,10]. In our study, although worse glycemic control, as measured by a more Hemoglobin A1c concentration, was linked with DR, it was non-significant. Similar findings were observed in a DR study conducted in a Latino population[17]. One possible reason for the weakened association between HbA1c and DR in advanced stages of retinopathy is that the diagnosis of DR can prompt patients to improve their blood sugar control. Therefore, the HbA1c levels after the DR diagnosis may not accurately reflect the glycemic control for the majority of the patient's diabetic history. In addition, there is conflicting evidence regarding whether DR can develop at lower HbA1c levels. This phenomenon has been revealed in a similar study of DR in a Latino population[14,16,17].

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

Conflicts of interest

There are no conflicts of interest regarding this article.

References

1. Yoshida, Y., et al., Risk factors for the development of diabetic retinopathy in Japanese type 2 diabetic patients. Diabetes research and clinical practice, 2001. 51(3): p. 195-203.
2. Al-Rubeaan, K., et al., Diabetic retinopathy and its risk factors in a society with a type 2 diabetes epidemic: a S audi N ational D iabetes R egistry-based study. Acta ophthalmologica, 2015. 93(2): p. e140-e147.

3. GARG, P. and M. KHAN. Awareness of Diabetic Retinopathy among Adult Population Attending Rural Health Care Center, Uttar Pardesh. Medicina Moderna - Modern Medicine. 2022; 29(1). 53-57. https://doi.org/10.31689/rmm.2021.29.1.53.
4. Rani, P., et al., Risk factors for diabetic retinopathy in self-reported rural population with diabetes. Journal of postgraduate medicine, 2009. 55(2): p. 92-96.
5. Liu, L., et al., Incidence density and risk factors of diabetic retinopathy within type 2 diabetes: a five-year cohort study in China (Report 1). International journal of environmental research and public health, 2015. 12(7): p. 7899-7909.
6. Wang, S.Y., et al., Incidence and risk factors for developing diabetic retinopathy among youths with type 1 or type 2 diabetes throughout the United States. Ophthalmology, 2017. 124(4): p. 424-430.
7. Kostev, K. and W. Rathmann, Diabetic retinopathy at diagnosis of type 2 diabetes in the UK: a database analysis. Diabetologia, 2013. 56: p. 109-111.
8. Vujosevic, S., et al., Screening for diabetic retinopathy: new perspectives and challenges. The Lancet Diabetes & Endocrinology, 2020. 8(4): p. 337-347.
9. MHARCHI, S. and A. MAAMRI, Diet, Physical Activity, and Their Impact on Chronic Diseases (Hypertension and T2DM) among North-Eastern Morocco's Population. Medicina Moderna - Modern Medicine. 2024. 31(1). 37-48. https://doi.org/10.31689/rmm.2024.31.1.37.
10. Tsao, H.-Y., P.-Y. Chan, and E.C.-Y. Su, Predicting diabetic retinopathy and identifying interpretable biomedical features using machine learning algorithms. BMC bioinformatics, 2018. 19: p. 111-121.
11. Thomas, R.L., et al., Incidence of diabetic retinopathy in people with type 2 diabetes mellitus attending the Diabetic Retinopathy Screening Service for Wales: retrospective analysis. Bmj, 2012. 344.
12. Raman, R., et al., Prevalence and risk factors for diabetic microvascular complications in newly diagnosed type II diabetes mellitus. Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS, report 27). Journal of Diabetes and its Complications, 2012. 26(2): p. 123-128.
13. Xu, J., et al., Prevalence and risk factors for diabetic retinopathy: the Beijing Communities Diabetes Study 6. Retina, 2012. 32(2): p. 322-329.
14. Martinell, M., et al., Prevalence and risk factors for diabetic retinopathy at diagnosis (DRAD) in patients recently diagnosed with type 2 diabetes (T2D) or latent autoimmune diabetes in the adult (LADA). Journal of diabetes and its complications, 2016. 30(8): p. 1456-1461.
15. BOBIRCA, F.T., et al., Surgical Implications in the Pathology of Diabetes Mellitus–Review of the Literature. Medicina Moderna - Modern Medicine. 2023. 30(1). 17-22. https://doi.org/10.31689/rmm.2023.30.1.17
16. Buraczynska, M., et al., Association of the VEGF gene polymorphism with diabetic retinopathy in type 2 diabetes patients. Nephrology dialysis transplantation, 2007. 22(3): p. 827-832.
17. White, N.H., et al., Risk factors for the development of retinopathy in prediabetes and type 2 diabetes: the diabetes prevention program experience. Diabetes care, 2022. 45(11): p. 2653-2661.