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REVIEW ARTICLE

Unveiling the link between lifestyle risk factors and diabetic retinopathy

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Abstract

Introduction Diabetic retinopathy (DR) is recognized as a significant complication of diabetes and continues to be a prominent contributor to global blindness. Epidemiological investigations have pinpointed various lifestyle risk factors accountable for the onset and progression of DR. However, pinpointing the most influential factors is challenging due to variability in ethnic background, study design, and sample size in previous research.

Methodology In the present study, a systematic and comprehensive review was conducted to identify significant factors contributing to DR development. Following the PRISMA guidelines, 322 articles were screened, and six articles discussing various lifestyle factors were included.

Result Elevated blood sugar levels (hyperglycemia), abnormal lipid profiles (dyslipidemia), high blood pressure (hypertension), and the duration of diabetes have been identified as the predominant lifestyle risk factors associated with the development and progression of DR. Furthermore, male gender was also linked to the occurrence of DR.

Conclusion While gender is beyond control, the other identified factors associated with DR can be managed through improved eating habits and regular exercise. Future investigations should prioritize exploring the collective influence of these factors on the development and progression of DR.

Keywords Diabetic retinopathy · Hyperglycemia · Hypertension · Duration of diabetes · Dyslipidemia

Introduction

Diabetes is a chronic systemic metabolic disorder that emerges when there is inadequate insulin secretion or when the cells are unable to effectively utilize insulin for the metabolism of sugar [1]. The global prevalence of diabetes mellitus (DM) was approximated to be 537 million among individuals aged 20–79 years in 2021, and it is anticipated to rise to 783 million by the year 2045 (IDF 2021) [2]. China, India, and Pakistan with 140.9, 74.2, and 33 million people having diabetes, respectively, making Asia home to a diabetic population globally [3]. Being one of the prominent microvascular complications associated with diabetes, diabetic retinopathy (DR) stands as the primary cause of visual impairment and blindness among the working-age population worldwide [4]. DR evolves gradually, manifesting progressive alterations in the retinal microcirculation, ultimately resulting in heightened vascular permeability, vascular proliferation, and retinal hypoperfusion [5]. Approximately 100 million individuals are estimated to have DR as of today, and 1 in 3 of them are at risk of becoming blind [6, 7]. DR pathogenesis is complex, which involves a cumulative effect of both genetic and lifestyle factors. The lifestyle risk factors such as smoking, body mass index (BMI), diet, and central obesity (i.e., waist-height ratio, WHR) are influenced by factors such as ethnicity, geography, religion, and cultural beliefs. The duration of diabetes, gender, hypertension, glycosylated hemoglobin (HbA1C), and family history of diabetes are some of the potential risk factors associated with the initiation or advancement of DR. However, results among different populations are inconsistent due to differences in

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the research protocols, ethnicity, and geographical regions included in the studies. The aim of this paper is to analyze lifestyle risk factors among different populations with various ethnic backgrounds and to identify potential factors that could aid in the prevention of DR.

Methods

Search strategy

A comprehensive literature review was conducted by searching PubMed database to identify all published papers in English language which were focused on lifestyle risk factors associated with DR. Our literature search adhered to the guidelines outlined in the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement.

Criteria for study selection

Inclusion criteria

To conduct a comprehensive literature review, we established inclusion criteria encompassing: (a) case-control studies, cross-sectional studies, or observational studies and (b) inclusion of T2D patients with DR as the case group and T2D patients without DR as the control group. Our screening process includes articles published in English language between January 2012 and August 2022. The keywords used were "T2D retinopathy hypertension," "T2D retinopathy duration of diabetes," "T2D retinopathy hyperglycaemia," "T2D retinopathy dyslipidemia," "T2D retinopathy physical inactivity," "T2D retinopathy obesity," and "T2D retinopathy gender."

Exclusion criteria

Our analysis excluded articles that fulfilled any of the subsequent exclusion criteria: (a) involved non-observational research; (b) did not provide information on the relevant risk factors; (c) constituted an individual case study, review, or non-research article; (d) animal model-based studies; (e) only DR prevalence related studies; and (f) studies showing protocols and guidelines.

Data screening

After article selection, we obtained the full texts, and reviewers PU and RS extracted relevant variables. Each study contributed data on (1) searched lifestyle risk factor, (2) the countries of sample origin, (3) *p* value obtained, and (4) odds ratio or hazard ratio obtained. All recorded data was systematically documented in a Microsoft Excel spreadsheet. To uphold accuracy, a third reviewer (HG) meticulously reviewed and validated the extracted data from the initial two reviewers for all included publications. Any disparities identified in the extracted information were promptly addressed. The reviewers worked collaboratively to achieve a consensus, resolving discrepancies in the data through mutual agreement.

Results

During the preliminary screening on PubMed, we acquired a total of 322 articles. Out of these, 44 articles were excluded after applying the following filters (a) books and documents; (b) clinical trial; (c) meta-analysis; (d) randomized controlled trial review; and (e) systematic review. A total of 278 articles were screened by two authors (PU and RS), out of which 115 duplicate articles were removed. Further narrowing down the selection, 163 articles sought for retrieval out of which 147 articles were removed based on title and abstracts. Finally, 16 articles were assessed for eligibility, out of which 10 articles were excluded based on exclusion criteria. Ultimately, we have included six articles in this review as shown in Fig. 1.

In the six included studies, the authors have focused on different lifestyle risk factors, including HbA1c, gender, systolic and diastolic blood pressure, and the duration of diabetes. The summary of these six studies have been given in Supplementary Table 1.

Discussion

Hyperglycemia

The UKPDS Group documented levels of HbA1c as one of the main risk factors towards the development of DR among T2D patients [8]. Hyperglycemia in T2D causes insulin resistance and insulin deficiency which further causes upregulation of polyol pathway. This activation further causes increased formation of AGEs, activation of PKC and NF-κB resulting in the disruption of endothelial function, ultimately contributing to complications associated with diabetes [9, 10]. During the early stage of DR, a notable rise in pericyte apoptosis has been documented [11]. Nevertheless, in vitro studies have indicated that a sudden fluctuation in glucose levels can trigger apoptosis in retinal pericytes [12]. Furthermore, studies have reported that plasma glucose, independent of glycosylated hemoglobin (HbA1c), was associated with pulsatile ocular blood flow resulting into damage in retinal pericyte and hypoxia [13]. Fort et al. has proposed

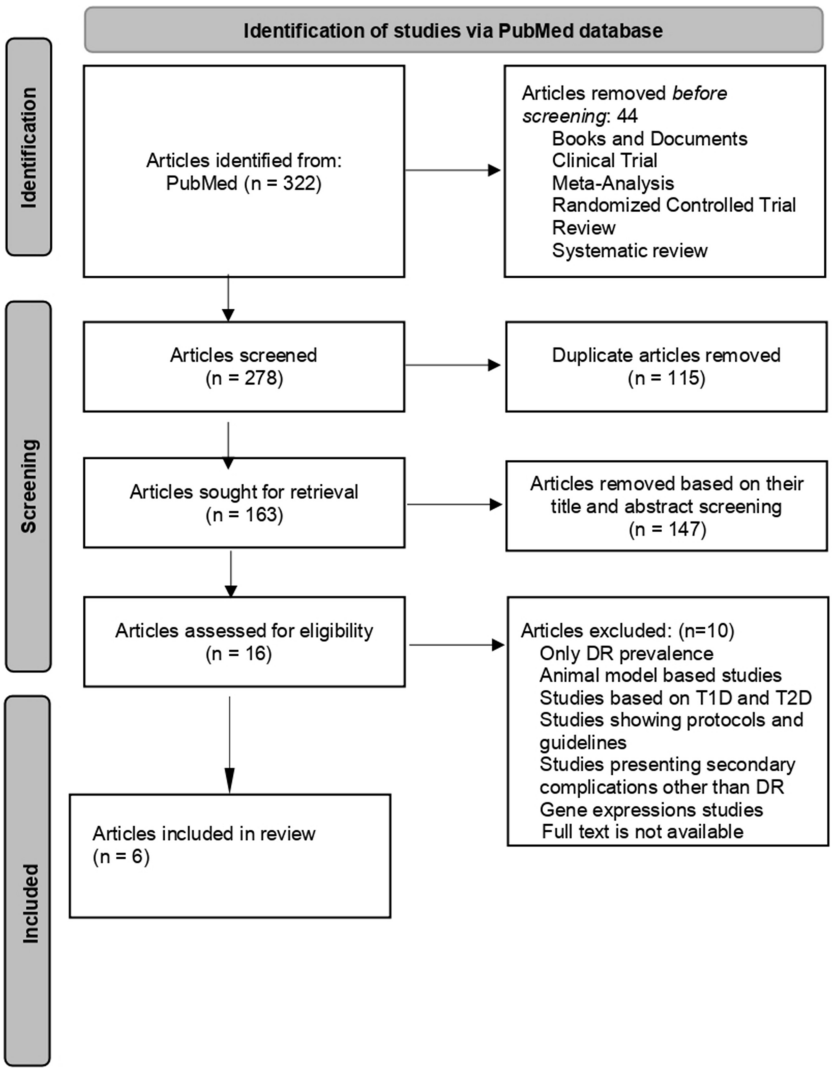

Fig. 1 Flow diagram of literature search showing study selection process implemented for this article

that elevated blood glucose levels lead to resistance against the action of growth factors in the retina, potentially contributing to the normalization of diabetes-induced retinal damage and vision loss [14].

In a 15-year follow-up study conducted in the population of Bangladesh, the risk of developing DR among individuals with T2D was estimated to be 50.6% (95% CI 47.5–53.8%) [15]. A higher value of HbA1c was noticed in individuals with T2D plus DR compared to the ones with T2D but without DR, with a hazard ratio (HR) of 0.59 (95% CI 0.48–0.74). In the Singaporean population, the DR was reported in 172 patients among 398 T2D cases [16]. The study has reported HbA1c as an important risk factor for DR among known diabetics after adjusting from other risk factors ($p < 0.001$,OR = 1.70 (95% CI 1.29–2.25)). However, no significant association of HbA1C was observed with the onset of DR ($p = 0.064$,OR = 1.138 (95% CI 0.992–1.304)) in another Singaporean cohort [17]. In the Chinese population, the influence of an early onset age on the risk of DR was identified as most pronounced in T2D patients with HbA1c level of ≥9% (OR = 3.889, 95% CI 1.852–8.167) [18, 19]. Documented HbA1c as a key risk factor associated with the onset of DR in the Chinese population (HR = 1.77, 95% CI 1.57–2.36). In the South Indian Genetics of Diabetic Retinopathy (SIGNATR) Study, a higher mean HbA1c was observed among proliferative diabetic retinopathy (PDR) cases, with a 1.13-fold increased risk compared to non-proliferative diabetic retinopathy (NPDR) cases ($p < 0.001$,OR = 1.13, 95% CI 1.07–1.20) [20]. These findings indicate that elevated HbA1c levels are associated with the onset of DR and may contribute to retinal damage and vision loss.

Duration of diabetes

DR is present in over 77% of patients with a diabetes duration exceeding 20 years [21] and is identified as one of the crucial factors associated with the severity of DR [19, 22]. According to UKPDS group, DR occurs in nearly 84.5% of

patients after 15 years of diabetes [8]. In the South-Indian cohort, the duration of diabetes as the strongest predictor for the presence and severity of DR [19]. This aligns with the outcomes of the Chennai Urban Rural Epidemiology Study (CURES), revealing that with each 5-year rise in the duration of diabetes, the risk of DR increased by 1.89-fold. Similarly, in the Asian population from Singapore, a higher duration of diabetes was recorded among DR patients as compared to non-DR diabetic cases [16]. In another cohort from Singapore, a ~1.5-fold increased risk for DR was observed when the duration of T2D was >10 years [17]. A 5-fold elevated risk was reported for the onset of DR with a T2D duration of >15years among Chinese population [18]. Similarly, in another Chinese cohort, ~2-fold increased risk was reported towards DR development with a T2D duration >10 years [23]. In SIGNATR study, T2D duration is reported to be responsible for the progression to PDR from NPDR [$p < 0.01$,OR = 1.10 (95% CI 1.08–1.12)] [20]. These results suggest that the duration of diabetes plays a significant role in influencing the development of DR.

Gender

In a Bangladeshi study, similar DR incidence was found in both genders [15], aligning with findings in Chinese [18], Japanese [24], Whites [25], Mexican Americans [26], Pima Indians [27], and South Indian (Tamil Nadu) population studies [28]. However, we reported ~1.8-fold more risk towards DR development among males [$p = 0.003$,OR = 1.86 (1.22–2.81)] in the North Indian population [29]. Similarly, increased percentage of males was reported to develop DR in Chinese population [$p < 0.01$,OR = 1.79 (95% CI 1.31–2.32)] [23] and other Asian population [$p = 0.011$,OR = 1.26 (95% CI 0.83–1.91)] [17]. In the SIGNATR study, male gender has been reported as a key factor for the progression towards PDR from NPDR [$p < 0.001$,OR = 1.91 (1.47–2.49)] [20]. Remarkably, the Early Treatment of Diabetic Retinopathy Study (ETDRS, [30] and study conducted on a Spanish population [HR = 1.12 (95% CI, 0.84–1.49)] [31] observed an increased risk for women towards the progression of DR. These results indicate that gender indeed plays a crucial role in the development of DR. However, more studies are warranted to overcome the conflicting results in different populations.

Hypertension

Hypertension, often known as high or increased blood pressure (SBP/DBP ≥ 140/90 mmHg), is a medical condition characterized by the sustained elevation of pressure within the blood vessels [32]. Multiple studies have indicated that meticulous control of hypertension could potentially reduce the advancement of DR [33, 34]. In independent studies on the Asian population from Singapore, SBP was reported as a primary risk factor linked to DR [16, 17]. In Chinese population, ~1.4-fold HR was observed for the development of DR with hypertension [$p < 00.01$,HR = 1.39 (1.01–1.62)] [23]. In the SIGNATR study from North Indian population, hypertension provided ~1.7-fold risk towards DR [$p < 0.001$; OR = 1.73 (95% CI 1.31–2.270)] [20]. In the same line, history of hypertension provided ~13-fold risk to DR,this was observed in a North Indian population [$p < 0.001$; OR = 13.64 (95% CI 9.15–20.34)] [29]. Similarly, a 15-year follow-up study in the Bangladeshi population revealed elevated values of SBP and DBP among DR cases. On the contrary, Ahmed et al. did not discover any correlation between hypertension and DR [15]. Similarly, no association between DR and hypertension was observed in the Chinese population [18].

Dyslipidemia

Dyslipidemia induces endothelial cell dysfunction and diminishes the bioavailability of nitric oxide, a critical factor in the formation of retinal exudates in DR [35]. Additional factors, such as hyperglycemia, activation of the protein kinase C pathway, and the generation of advanced glycation end products, bring about physiological alterations in the retina in T2D. The collective impact of these factors results in the differential synthesis of extracellular matrix (ECM) proteins, remodeling of the ECM, heightened release of angiogenic factors, ultimately leading to capillary occlusion and alterations in retinal blood flow [36]. No substantial involvement of dyslipidemia in the onset of DR was noted in the Bangladeshi population [15] and among the Asian population [16, 17]. Susarla et al. identified an association between low-density lipoprotein and high-density lipoprotein with the progression from NPDR to PDR [20], however, there was no significant association observed with triglycerides, as reported in the SIGNATR study [2, 10].

Conclusion

This review highlights the crucial impact of lifestyle factors on the development and progression of DR, emphasizing the importance of understanding and addressing lifestyle influences. Key factors, such as poor blood sugar control, diabetes duration, hypertension, and dyslipidemia, can be managed through improved eating habits and regular exercise. While gender is beyond control, exploring the cumulative impact of these factors on DR should be a focus of future research.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-024-01332-6.

Data availability No data was used for the research described in the article.

Declarations

Ethical approval Not applicable.

Competing interests The authors declare no competing interests.

References

1. Kumar A, Gangwar R, Ahmad Zargar A, Kumar R, Sharma A. Prevalence of diabetes in India: a review of IDF Diabetes Atlas 10th edition. Curr Diabetes Rev. 2023.
2. International Diabetes Federation. Diabetes facts and figures. Available online: https://idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html. Accessed 9 Dec 2021.
3. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Magliano DJ. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
4. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas. Diabetes Res Clin Pract, 2019;157, 107843.
5. Mrugacz M, Bryl A, Zorena K. Retinal vascular endothelial cell dysfunction and neuroretinal degeneration in diabetic patients. J Clin Med. 2021;10:458.
6. Ting DSW, Cheung GCM, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. Clin Exp Ophthalmol. 2016;44:260–77.
7. Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35:556–64.
8. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. Bri Med J. 1998;317:703–13.
9. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414(6865):813–20.
10. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615–25.
11. Kowluru RA, Abbas SN. Diabetes-induced mitochondrial dysfunction in the retina. Invest Ophthalmol Vis Sci. 2003;44(12):5327–34.
12. Li W, Liu X, Yanoff M, Cohen S, Ye X. Cultured retinal capillary pericytes die by apoptosis after an abrupt fluctuation from high to low glucose levels: a comparative study with retinal capillary endothelial cells. Diabetologia. 1996;39:537–47.
13. Perrott RL, North RV, Drasdo N, Ahmed KA, Owens DR. The influence of plasma glucose upon pulsatile ocular blood flow in subjects with type II diabetes mellitus. Diabetologia. 2001;44:700–5.
14. Fort PE, Losiewicz MK, Reiter CE, Singh RS, Nakamura M, Abcouwer SF, Barber AJ, Gardner TW. Differential roles of hyperglycemia and hypoinsulinemia in diabetes induced retinal cell death: evidence for retinal insulin resistance. PloS one. 2011;6(10):e26498.
15. Ahmed KR, Karim MN, Bhowmik B, Habib SH, Bukht MS, Ali L, Hussain A. Incidence of diabetic retinopathy in Bangladesh: a 15-year follow-up study. J Diabetes. 2012;4(4):386–91.
16. Foo V, Quah J, Cheung G, Tan NC, Ma Zar KL, Chan CM, Lamoureux E, Tien Yin W, Tan G, Sabanayagam C. HbA1c, systolic blood pressure variability and diabetic retinopathy in Asian type 2 diabetics. J Diabetes. 2017;9(2):200–7.
17. Moh A, Neelam K, Zhang X, Sum CF, Tavintharan S, Ang K, Lee SBM, Tang WE, Lim SC. Excess visceral adiposity is associated with diabetic retinopathy in a multiethnic Asian cohort with longstanding type 2 diabetes. Endocr Res. 2018;43(3):186–94.
18. Yuan J, Zhang L, Jia P, Xin Z, Yang JK. Early onset age increased the risk of diabetic retinopathy in type 2 diabetes patients with duration of 10–20 years and HbA1C ≥7%: a hospital-based case-control study. Int J Endocrinol. 2021;10(2021):5539654.
19. Rani PK, Raman R, Chandrakantan A, Pal SS, Perumal GM, Sharma T. Risk factors for diabetic retinopathy in self-reported rural population with diabetes. J Postgrad Med. 2009;55(2):92.
20. Susarla G, Rizza AN, Li A, Han S, Khan R, Chan W, Sobrin L. Younger age and albuminuria are associated with proliferative diabetic retinopathy and diabetic macular edema in the South Indian GeNetics of DiAbeTic Retinopathy (SIGNATR) Study. Curr Eye Res. 2022;47(10):1416–23.
21. Wild S, Roglic G, Green A, Sicree R, King H. Lobal prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27:1047–53.
22. Bamashmus MA, Gunaid AA, Khandekar RB. Diabetic retinopathy, visual impairment and ocular status among patients with diabetes mellitus in Yemen: a hospital-based study. Indian J Ophthalmol. 2009;57(4):293–8.
23. Liu L, Wu J, Yue S, Geng J, Lian J, Teng W, Huang D, Chen L. Incidence density and risk factors of diabetic retinopathy within type 2 diabetes: a five-year cohort study in China (report 1). Int J Environ Res Public Health. 2015;12(7):7899–909.
24. Yoshida Y, Hagura R, Hara Y, Sugasawa G, Akanuma Y. Risk factors for the development of diabetic retinopathy in Japanese type 2 diabetic patients. Diabetes Res Clin Pract. 2001;51:195–203.
25. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The wisconsin epidemiologic study of diabetic retinopathy: XIV. Ten-year incidence and progression of diabetic retinopathy. Arch Ophthalmol. 1994;112(9):1217–28.
26. Haffner SM, Fong D, Stern MP, Pugh JA, Hazuda HP, Patterson JK, Klein R. Diabetic retinopathy in Mexican Americans and non-Hispanic whites. Diabetes. 1988;37(7):878–84.
27. Nelson RG, Wolfe JA, Horton MB, Pettitt DJ, Bennett PH, Knowler WC. Proliferative retinopathy in NIDDM: incidence and risk factors in Pima Indians. Diabetes. 1989;38(4):435–40.
28. Namperumalsamy P, Kim R, Vignesh TP, Nithya N, Royes J, Gijo T, Vijayakumar V. Prevalence and risk factors for diabetic retinopathy: a population-based assessment from Theni District, south India. Postgrad Med J. 2009;85(1010):643–8.
29. Sikka R, Raina P, Soni R, Gupta H, Bhanwer AJS. Genomic profile of diabetic retinopathy in a north Indian cohort. Mol Biol Rep. 2023;50:1–10.
30. Davis MD, Fisher MR, Gangnon RE, Barton F, Aiello LM, Chew EY, Ferris FL, Knatterud GL. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report# 18. Invest Ophthalmol Visual Sci. 1998;39:233–52.
31. Salinero-Fort MA, San Andres-Rebollo FJ, de Burgos-Lunar C, Arrieta-Blanco FJ, Gomez-Campelo P, MADIABETES Group. Four-year incidence of diabetic retinopathy in a Spanish cohort: the MADIABETES study. PLoS One, 2013;8(10), e76417
32. WHO. Hypertension. 2023. https://www.who.int/news-room/fact-sheets/detail/hypertension.

33. Snow V, Weiss KB, Mottur-Pilson C. Clinical Efficacy Assessment Subcommittee of the American College of Physicians*. The evidence base for tight blood pressure control in the management of type 2 diabetes mellitus. Annals Internal Med, 2003;138(7), 587-592.
34. United Kingdom Prospective Diabetes Study Group.UK Prospective Diabetes Study 30: diabetic retinopathy at diagnosis of type 2 diabetes and associated risk factors. Arch Ophthalmol 1998; 116:297–303.
35. Landmesser ULF, Hornig B, Drexler H. Endothelial dysfunction in hypercholesterolemia: mechanisms, pathophysiological importance, and therapeutic interventions. In Semin Thromb Hemost. 2000;26:529–38.
36. Huang Q, Yuan Y. Interaction of PKC and NOS in signal transduction of microvascular hyperpermeability. Am J Physiol-Heart Circ Physiol. 1997;273:H2442-51.