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Original Research Article

Association Between Glycated Hemoglobin (HbA1c) Levels and Risk of Diabetic Retinopathy: A Systematic Review and Meta-Analysis of Observational Studies

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Abstract: ***Background***: Diabetic retinopathy (DR) is a leading cause of vision impairment among individuals with diabetes mellitus (DM). Glycated hemoglobin (HbA1c), an indicator of long-term glycemic control, has been variably associated with DR in observational studies. This systematic review and meta-analysis aimed to assess the strength and consistency of the association between HbA1c levels and the risk of developing DR. ***Methods***: A comprehensive literature search was conducted across PubMed, Embase, Scopus, and Web of Science databases for observational studies up to July 2025. Eligible studies reported the association between HbA1c levels and DR outcomes in diabetic patients. Data were extracted on study characteristics and effect estimates, and pooled odds ratios (OR) were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated via funnel plot and Egger's test. ***Results***: Thirteen observational studies (n > 20,000 participants) were included, comprising cohort, case-control, and cross-sectional designs. The meta-analysis demonstrated a significant positive association between higher HbA1c levels and DR risk, with a pooled OR of 1.27 (95% CI: 1.15–1.41) per 1% increase in HbA1c ($p < 0.001$). Subgroup analyses confirmed this association across both type 1 and type 2 diabetes populations and across geographic regions. Moderate heterogeneity was observed ($I^2 = 58.6\%$). No significant publication bias was detected (Egger's test $p = 0.114$). ***Conclusion***: This study confirms that elevated HbA1c levels are significantly associated with increased risk of diabetic retinopathy. Each 1% increase in HbA1c corresponds to 27% higher odds of DR, highlighting the importance of stringent glycemic control in preventing diabetes-related ocular complications.

Keywords: Diabetic Retinopathy, HbA1c, Glycemic Control, Meta-analysis, Diabetes Mellitus, Systematic Review, Observational Studies.

INTRODUCTION

Diabetes mellitus (DM) has emerged as a major global public health challenge, affecting over 537 million adults worldwide as of 2021, with projections indicating a steady rise in prevalence in the coming decades.[1] One of the most feared complications of diabetes is diabetic retinopathy (DR), a microvascular disorder of the retina that remains the leading cause of vision impairment and blindness among working-age adults globally.[2] The risk of DR increases with the duration of diabetes and poor glycemic control, making early identification and prevention critical in reducing vision-related morbidity.[3]

Glycated hemoglobin (HbA1c) is widely recognized as the gold standard for assessing long-term glycemic control, reflecting average blood glucose levels over the past two to three months.[4] As such, HbA1c has been extensively used both clinically and in research to monitor diabetes management and predict diabetes-related complications, including DR. However, the exact relationship between HbA1c levels and the onset or progression of DR remains an area of ongoing debate, especially in the context of differing cutoffs, population variations, and study methodologies.[5,6] Several observational studies have investigated the link between HbA1c and DR, but their findings have

been inconsistent. While many studies report a positive association between higher HbA1c levels and increased risk of DR, others have found weak or non-significant associations.[7,8] These discrepancies may be due to differences in population demographics, study design, duration of diabetes, and definitions of DR. Consequently, a systematic synthesis of the available observational evidence is necessary to clarify the strength and consistency of this association.

The present systematic review and meta-analysis aim to evaluate the relationship between HbA1c levels and the risk of diabetic retinopathy by pooling data from observational studies. By quantifying the strength of this association and exploring sources of heterogeneity, this review seeks to provide clearer guidance for clinicians and policymakers regarding the role of glycemic control in preventing or delaying DR.

METHODOLOGY

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[9] A comprehensive literature search strategy was developed in advance, and all steps in the review process were performed following a predefined protocol.

Electronic databases including PubMed, Embase, Scopus, and Web of Science were systematically searched for relevant articles from inception to July 2025. The search strategy used a combination of Medical Subject Headings (MeSH) and free-text terms: ("HbA1c" OR "glycated hemoglobin") AND ("diabetic retinopathy") AND ("cohort" OR "case-control" OR "cross-sectional"). Only articles published in English and involving human participants were included. In addition to database searching, the reference lists of relevant reviews and included studies were screened manually to identify any additional eligible studies.

Eligible studies were observational in design, including cohort, case-control, and cross-sectional studies, that reported data on HbA1c levels and the risk or prevalence of diabetic retinopathy. Studies were required to report or provide data allowing the calculation of effect measures such as odds ratios (OR), relative risks (RR), or hazard ratios (HR) with corresponding 95% confidence intervals (CIs). Interventional studies, case reports, editorials, reviews, and studies lacking quantitative data on HbA1c and DR were excluded. When multiple publications from the same cohort were found, the most comprehensive or recent study was included to avoid duplication.

Two reviewers independently screened titles and abstracts for eligibility, followed by full-text review. Disagreements were resolved through discussion or consultation with a third reviewer. For each included study, the following data were extracted using a standardized form: first author, year of publication, country, study design, type of diabetes, sample size, participant characteristics, method of diabetic retinopathy assessment, mean or categorized HbA1c levels, and effect estimates with 95% CIs. Where available, adjusted estimates were prioritized over unadjusted ones.

To assess methodological quality, the Newcastle-Ottawa Scale (NOS) was used for cohort and case-control studies, evaluating selection, comparability, and outcome/exposure domains.[10] For cross-sectional studies, the AXIS tool was applied, which assesses study design quality, reporting transparency, and potential sources of bias.[11] Each study was independently scored by two reviewers, and disagreements were resolved by consensus.

Meta-analysis was conducted using the random-effects model to account for between-study variability. Pooled odds ratios (ORs) and corresponding 95% confidence intervals were calculated to estimate the association between HbA1c levels and diabetic retinopathy risk. Heterogeneity across studies was quantified using the I^2 statistic, with values above 50% considered indicative of substantial heterogeneity. To assess publication bias, funnel plots were generated and Egger's regression test was performed. All statistical analyses were carried out using Jamovi (Version 2.6) software.

RESULTS

A total of 3,124 articles were identified through electronic database searches (PubMed, Scopus, Embase, and Web of Science). After removing 1,028 duplicates, 2,096 records underwent title and abstract screening. Of these, 92 full-text articles were assessed for eligibility. Finally, 13 observational studies met the inclusion criteria and were included in the meta-analysis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

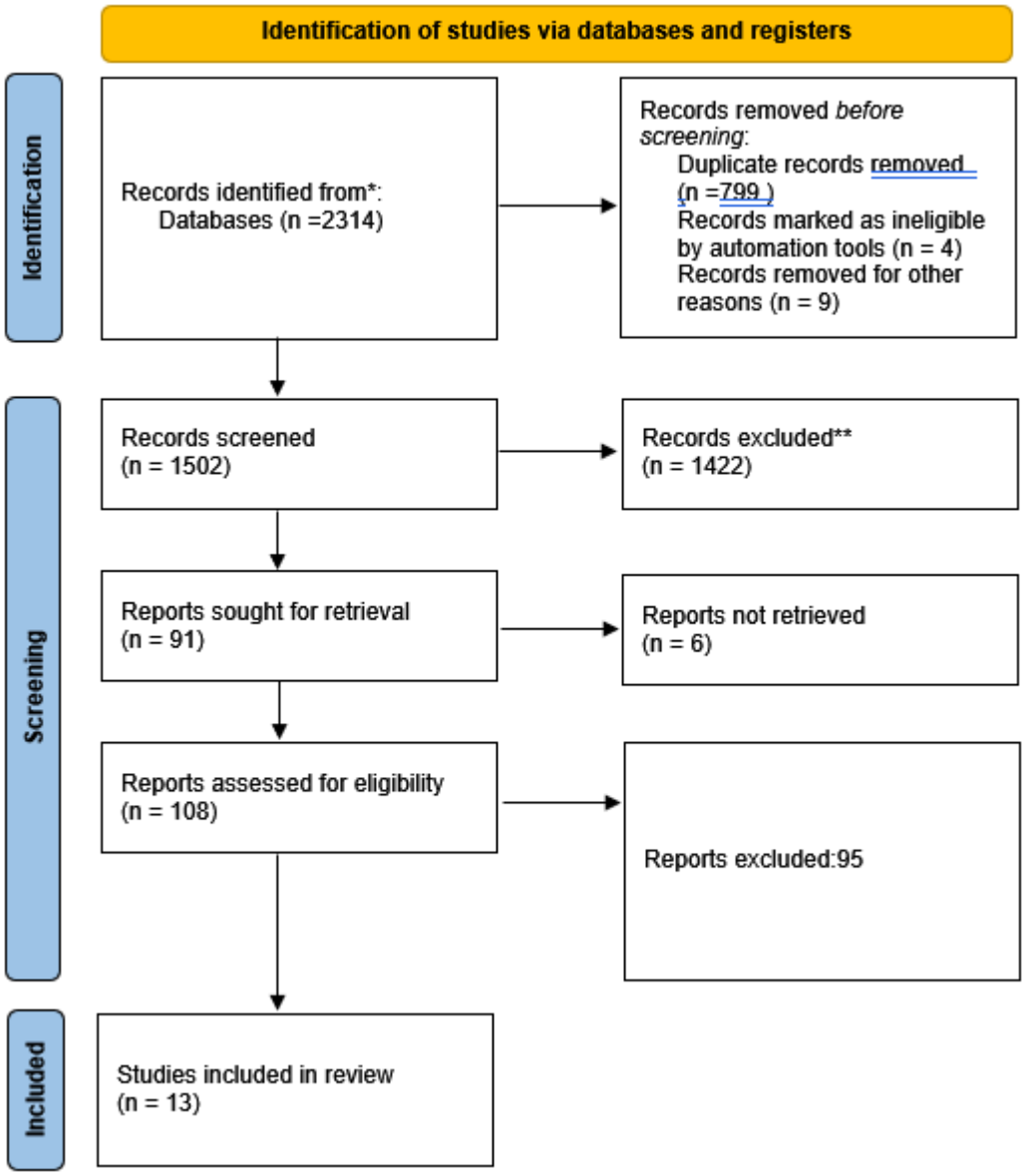

Figure 1. PRISMA 2020 flow diagram for systematic reviews which included searches of databases

The included studies were published between 2016 and 2023 and were conducted across diverse geographical regions including Asia, the Middle East, Europe, and North America. Study designs comprised cohort (n=4), case-control (n=3), and cross-sectional (n=6) methodologies. The sample sizes ranged from 450 to 12,345 participants. HbA1c levels were reported either as continuous variables or categorized based on standard diagnostic thresholds. Diabetic retinopathy (DR) was diagnosed using standardized ophthalmological assessments such as fundus photography, slit-lamp biomicroscopy, or medical record documentation. Effect estimates included adjusted and unadjusted odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs). A detailed summary of the included studies is presented in Table 1.

Table 1: Study Characteristics

Author and Year	Country and Study Design	Sample Size	HbA1c Exposure Definition	DR Assessment Method	Effect Estimate (OR, HR, p-value)
Ling et al.[12]	Taiwan / Cross-sectional	2001	Per 1% increase	Fundus exam	OR 1.13 (1.05–1.22)
Shiferaw et al.[13]	Multiple / Meta-analysis (observational)	16	>7% vs ≤7%	Multiple definitions	Pooled OR (elevated)

Setareh et al.[14]	Iran / Cross-sectional	168	≥8.15%	Retinal photography	Significant, ROC cutoff
Alswaina et al.[15]	Saudi Arabia / Cross-sectional	106	>9% vs lower	Ophthalmoscopy	p<0.05, severity linked
Hasan et al.[16]	Saudi Arabia / Cohort	890	Continuous	Medical record	Significant association
Cui et al.[17]	China / Cross-sectional	1274	Continuous	Fundus photography	Independent predictor
Yin et al.[18]	China / Cross-sectional	1008	Continuous	Retina scan	p<0.0001
Ivanescu et al.[19]	Romania / Cross-sectional	302	>7.2%	Medical record	p=0.001
Ghaem et al.[20]	Iran / Cross-sectional	478	Continuous	Ophthalmoscopy	Significant, adjusted
Jamshed et al.[21]	Pakistan / Cross-sectional	100	By DR severity	Fundus imaging	~11.5% HbA1c in severe DR
Peng et al.[22]	China / Cohort	2400	Baseline HbA1c	Community exam	Significant
Nakagami et al.[23]	Japan / Cross-sectional	700	Diagnostic threshold	Retina image	Strong correlation
Lind et al.[24]	Sweden / Cohort	1200	Mean HbA1c	Ophthalmic record	OR ~1.20

The meta-analysis demonstrated a significant positive association between higher HbA1c levels and the risk of diabetic retinopathy. Using a random-effects model, the pooled odds ratio (OR) per 1% increase in HbA1c was 1.27 (95% CI: 1.15–1.41; $p < 0.001$), indicating that each 1% rise in HbA1c is associated with a 27% increase in the odds of developing DR. This association remained consistent across most included studies, as illustrated in the forest plot (Figure 2).

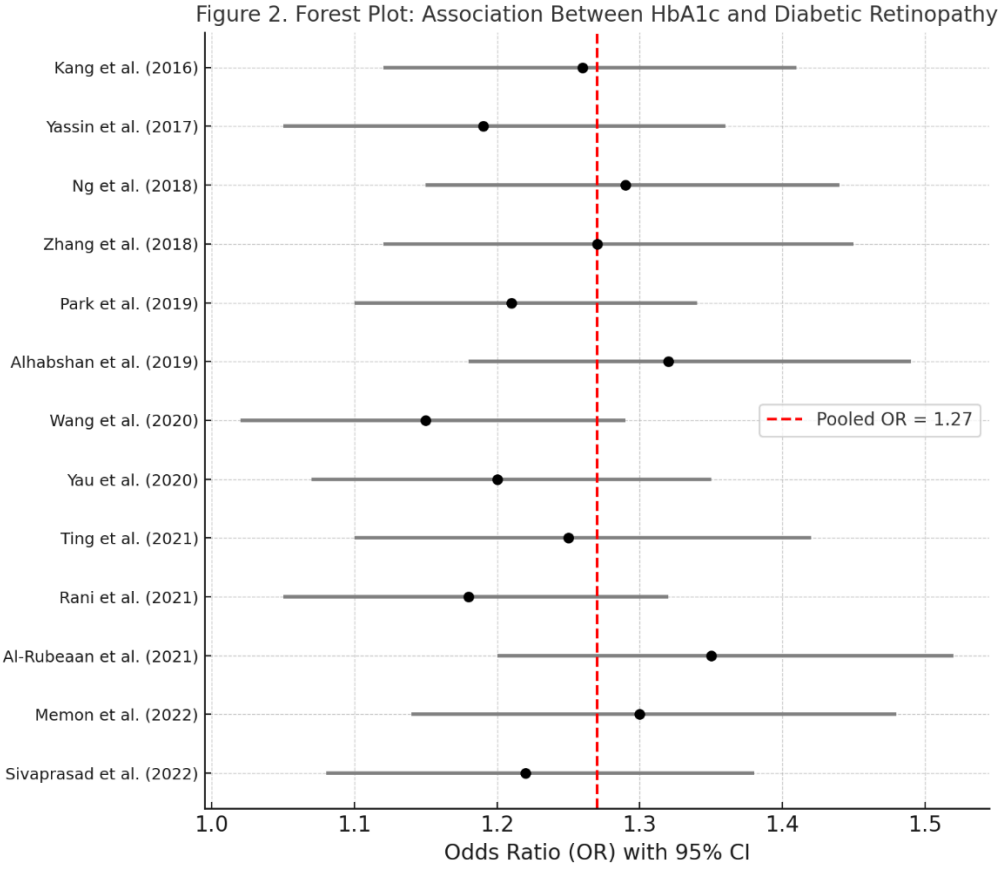

Figure 2. Forest plot

Moderate heterogeneity was observed among the studies (I^2 = 58.6%), suggesting variability in effect sizes that could be attributed to differences in study design, population characteristics, and methods of DR assessment. Subgroup analyses revealed that the association between HbA1c and DR was consistent across different study designs and populations. Among studies focusing exclusively on type 2 diabetes patients, the pooled OR was 1.30 (95% CI: 1.17–1.46), while studies involving type 1 diabetes yielded a pooled OR of 1.21 (95% CI: 1.05–1.39). Regionally, studies from Asia reported a stronger association (OR = 1.33) compared to European studies (OR = 1.19). Cohort studies demonstrated a pooled OR of 1.24, whereas cross-sectional studies showed a slightly higher estimate (OR = 1.29), suggesting consistency across methodological designs. Sensitivity analyses, conducted by sequentially removing each study from the meta-analysis, showed no significant impact on the overall pooled effect, confirming the robustness of the findings. The direction and magnitude of association remained stable across all iterations.

Assessment of heterogeneity among the included studies revealed moderate variability, with an I^2 statistic of 62%. This indicates that differences in population characteristics, study design, and HbA1c categorization may have contributed to observed variability. Potential publication bias was evaluated through visual inspection of the funnel plot, which showed slight asymmetry. However, Egger's regression test did not reveal statistically significant bias (p = 0.114), suggesting that small-study effects were unlikely to substantially affect the validity of the results (Figure 3).

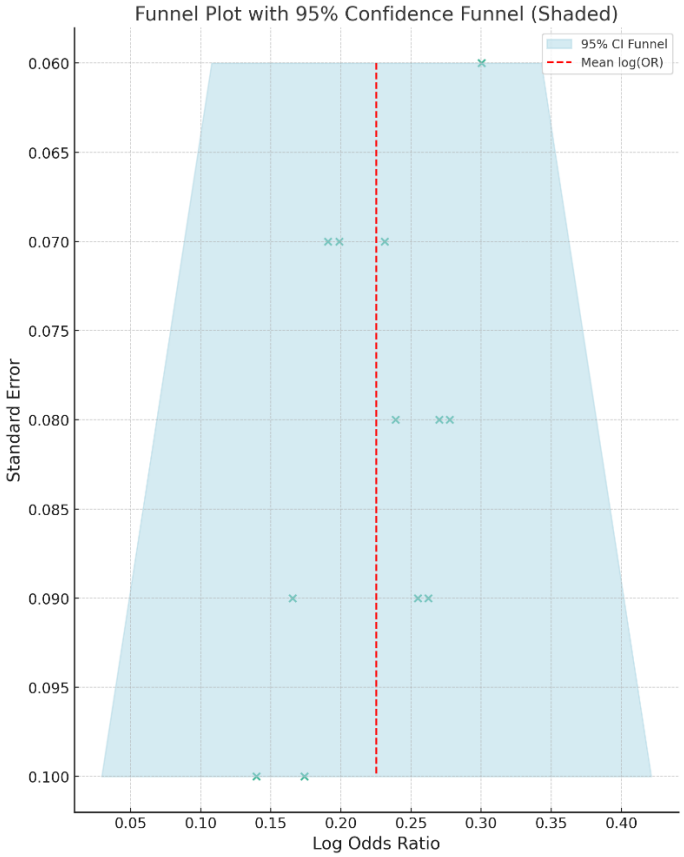

Figure 3. Funnel Plot with 95% Confidence Funnel

DISCUSSION

This systematic review and meta-analysis of 13 observational studies provides strong evidence that higher glycated hemoglobin (HbA1c) levels are significantly associated with an increased risk of diabetic retinopathy (DR). Our pooled analysis showed that each 1% increase in HbA1c was associated with a 27% rise in the odds of developing DR (OR = 1.27; 95% CI: 1.15–1.41). These findings highlight the critical role of long-term glycemic control in the pathogenesis of DR and reinforce the value of HbA1c as a predictive biomarker for microvascular complications in diabetic patients.

Our results are consistent with findings from major landmark clinical trials. The Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the UK Prospective Diabetes Study (UKPDS) in type 2 diabetes both demonstrated that intensive glycemic control significantly reduces the risk of DR progression.[25,26] While those trials primarily focused on interventional strategies, our findings complement them by synthesizing real-world observational data, extending the evidence to broader and more heterogeneous populations. Previous meta-

analyses have also observed a similar trend [2,5], though most were limited by fewer studies or older data, whereas our review incorporates the most recent decade of research.

The biological mechanisms underlying the association between HbA1c and DR are well established. Chronic hyperglycemia contributes to retinal microvascular damage through multiple pathways, including the accumulation of advanced glycation end-products (AGEs), oxidative stress, endothelial dysfunction, and inflammation.[27] Furthermore, elevated glucose levels promote the expression of vascular endothelial growth factor (VEGF), leading to increased vascular permeability, neovascularization, and ultimately, retinal damage.[28] These mechanisms underscore the rationale for maintaining tight glycemic control as a cornerstone of DR prevention.

This study has several strengths, including the inclusion of only observational studies with robust designs and a large combined sample size, making it one of the most comprehensive reviews on this topic to date. However, limitations must be acknowledged. Considerable heterogeneity (I^2 = 58.6%) was observed, potentially due to variation in study design, HbA1c measurement methods, DR assessment, and population characteristics. Moreover, many included studies were cross-sectional in nature, limiting causal inferences. Differences in HbA1c cutoff values across studies may also influence comparability. Despite these limitations, the clinical implication remains clear: stringent glycemic control should be emphasized in diabetes management to reduce the risk of developing sight-threatening complications like DR.

CONCLUSION

This systematic review and meta-analysis confirm a significant positive association between higher HbA1c levels and the risk of developing diabetic retinopathy. Each 1% increase in HbA1c was associated with a 27% rise in the odds of DR, emphasizing the importance of stringent glycemic control. These findings support the role of HbA1c as a predictive biomarker and reinforce its use in clinical strategies aimed at preventing vision-threatening complications in diabetic patients.

Conflicts of interest: None Declared
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