



The Relationship Between HbA1c Levels and The Risk of Diabetic Retinopathy in Type 2 Diabetes Mellitus Patients : A Systematic Review

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ABSTRACT

Introduction: Diabetic retinopathy (DR) remains a leading cause of visual impairment worldwide among patients with type 2 diabetes mellitus (T2DM). Glycated hemoglobin (HbA1c) serves as the primary marker of glycemic control, yet the precise nature of its relationship with DR risk requires comprehensive synthesis. This systematic review aimed to evaluate the association between HbA1c levels and DR risk in T2DM patients, examine dose-response relationships, identify effect modifiers, and determine optimal HbA1c thresholds for DR prevention.

Methods: A systematic review was conducted following standardized screening criteria. Studies were included if they involved adult T2DM patients, measured quantitative HbA1c levels as an exposure variable, assessed DR as a clearly defined

outcome, and examined the relationship between these parameters. Data extraction encompassed study characteristics, HbA1c measurement methods, DR assessment techniques, association measures, and risk factor analyses.

Results: Two hundred studies comprising diverse populations across 30 countries were analyzed, with sample sizes ranging from 30 to 175,645 participants. The overwhelming majority demonstrated significant positive associations between elevated HbA1c and increased DR risk. Adjusted odds ratios ranged from 1.60 (95% CI 1.13-2.25) for HbA1c $\geq 7.5\%$ to 4.23 (95% CI 3.90-4.58) for HbA1c $>10\%$. Dose-response relationships revealed progressive risk increases across HbA1c categories, with optimal screening thresholds identified between 6.6% and 8.15%. HbA1c variability emerged as an independent risk factor beyond mean levels (RR=1.48, 95% CI 1.24-1.78). Significant effect modification was observed with blood pressure, lipid profiles, diabetes duration, nephropathy, and genetic factors.

Discussion: The HbA1c-DR relationship demonstrates remarkable consistency across global populations, supporting glycemic control as a cornerstone of DR prevention. The identification of glycemic memory effects and variability as independent risk factors suggests that both achieving target levels and maintaining stable control are crucial. Combined risk factor control produces multiplicative benefits, emphasizing multifactorial management approaches.

Conclusion: Elevated HbA1c levels are strongly and consistently associated with increased DR risk in T2DM patients, with evidence supporting target maintenance below 7%. Future research should focus on personalized threshold algorithms

incorporating individual risk profiles and investigating interventions targeting HbA1c variability.

Keywords: Diabetic retinopathy, HbA1c, type 2 diabetes mellitus, glycemic control, risk factors, systematic review

INTRODUCTION

Background

Diabetic retinopathy (DR) represents one of the most devastating microvascular complications of diabetes mellitus and remains the leading cause of visual impairment and blindness among working-age adults worldwide (1-3). The global burden of DR is expected to escalate dramatically in parallel with the rising prevalence of type 2 diabetes mellitus (T2DM), which currently affects approximately 537 million adults globally and is projected to reach 783 million by 2045 (4,5). DR not only diminishes quality of life through progressive vision loss but also imposes substantial economic burdens on healthcare systems and society at large (6).

Glycated hemoglobin (HbA1c) has emerged as the gold standard biomarker for assessing long-term glycemic control, reflecting average blood glucose concentrations over the preceding 2-3 months (7). The measurement of HbA1c provides several advantages over random or fasting plasma glucose determinations, including reduced biological variability, absence of requirement for fasting, and reflection of chronic glycemic exposure (8). Consequently, HbA1c serves as the primary therapeutic target in diabetes management guidelines and forms the basis for evaluating the efficacy of glucose-lowering interventions (9).

The pathophysiological relationship between hyperglycemia and DR development involves multiple interconnected mechanisms. Chronic exposure to elevated glucose concentrations triggers a cascade of biochemical perturbations, including increased polyol pathway flux, accumulation of advanced glycation end-products (AGEs), activation of protein kinase C isoforms, and enhanced oxidative stress (10,11). These processes ultimately lead to pericyte loss, capillary basement membrane thickening, endothelial dysfunction, and breakdown of the blood-retinal barrier, characteristic features of DR pathogenesis (12,13). The concept of "glycemic memory" or "metabolic memory" further complicates this relationship, wherein prior glycemic exposure exerts lasting effects on DR risk independent of subsequent control (9,14).

Research Gap

Despite the well-established general association between hyperglycemia and microvascular complications, several critical gaps persist in our understanding of the HbA1c-DR relationship. First, considerable debate remains regarding the precise shape of the dose-response curve, with some studies suggesting linear relationships while others propose threshold effects or even inverted U-shaped patterns at extreme HbA1c values (15-17). Second, the optimal HbA1c threshold for DR screening and risk stratification varies substantially across populations, ranging from 6.6% to 8.15% in different studies, raising questions about population-specific factors that modify this relationship (18-20). Third, the independent contribution of HbA1c variability beyond mean levels has only recently gained attention, and the magnitude of this effect requires further quantification (8,21). Fourth, the complex interactions between HbA1c and other risk factors—including blood pressure, lipid profiles, diabetes duration, nephropathy, and genetic susceptibility—remain incompletely characterized (22-24). Fifth, the temporal aspects of glycemic exposure, including the duration of exposure at specific HbA1c levels and the phenomenon of glycemic memory, warrant comprehensive synthesis (9,25).

Study Objectives

This systematic review aimed to comprehensively evaluate the relationship between HbA1c levels and the risk of diabetic retinopathy in patients with type 2 diabetes mellitus. Specific objectives included: (1) to synthesize quantitative measures of association between HbA1c and DR across diverse populations and study designs; (2) to characterize the dose-response relationship and identify potential HbA1c thresholds associated with increased DR risk; (3) to examine the role of HbA1c variability as an independent risk factor for DR; (4) to identify and quantify effect modifiers and interactions between HbA1c and other risk factors; (5) to evaluate temporal aspects of glycemic exposure including glycemic memory effects; and (6) to assess the consistency of findings across geographic regions, healthcare settings, and population subgroups.

Hypothesis

We hypothesized that higher HbA1c levels would be significantly and positively associated with increased risk of diabetic retinopathy in patients with type 2 diabetes mellitus, with evidence of a dose-response relationship across the glycemic spectrum. We further hypothesized that this relationship would be modified by factors including diabetes duration, blood pressure control, lipid profiles, and nephropathy status, and that HbA1c variability would confer additional risk beyond mean levels.

Research Novelty

This systematic review offers several novel contributions to the existing literature. First, it synthesizes evidence from an unprecedented 200 studies encompassing diverse global populations, providing the most comprehensive evaluation of the HbA1c-DR relationship to date. Second, it systematically examines both traditional measures of association and emerging concepts including HbA1c variability, glycemic memory, and complex nonlinear relationships. Third, it provides a detailed analysis of effect modification and interactions, moving beyond simple univariable associations to characterize the multifactorial nature of DR risk. Fourth, it evaluates the consistency of findings across different DR severity grades, from mild non-proliferative DR to sight-threatening proliferative disease. Fifth, it synthesizes evidence on optimal HbA1c thresholds for screening and risk stratification, acknowledging population-specific variations. Sixth, it identifies methodological limitations in the existing evidence base and proposes directions for future research.

Study Benefits

The findings of this systematic review hold significant implications for clinical practice, public health policy, and future research. For clinicians, the synthesis of optimal HbA1c thresholds and recognition of important effect modifiers will inform evidence-based glycemic targets and multifactorial risk management strategies. Recognition of the independent contribution of HbA1c variability suggests that clinical monitoring should extend beyond assessment of mean levels to

include evaluation of glycemic stability over time. For patients, understanding the quantitative relationship between glycemic control and DR risk may enhance motivation for treatment adherence and lifestyle modifications. For healthcare systems, identification of optimal screening thresholds can guide resource allocation for DR surveillance programs. For researchers, characterization of knowledge gaps and methodological limitations will inform the design of future investigations addressing unresolved questions in the field. Ultimately, this comprehensive synthesis aims to contribute to the global effort to reduce the burden of diabetes-related visual impairment through improved understanding of this critical risk relationship.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between HbA1c levels and the risk of diabetic retinopathy in type 2 diabetes mellitus patients.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population - Type 2 Diabetes:** Does the study include patients diagnosed with type 2 diabetes mellitus (and not exclusively type 1 diabetes or gestational diabetes)?
- **Exposure - HbA1c Measurement:** Does the study measure or report quantitative HbA1c levels as an exposure variable?

- **Outcome - Diabetic Retinopathy:** Does the study assess diabetic retinopathy as a clearly defined outcome measure?
- **Research Question Alignment:** Does the study examine the relationship, association, or correlation between HbA1c levels and diabetic retinopathy risk?
- **Study Design:** Is the study an observational study (cohort, case-control, cross-sectional) or a randomized controlled trial with relevant outcomes reported?
- **Diagnostic Criteria:** Does the study provide clearly defined diagnostic criteria for both type 2 diabetes and diabetic retinopathy?
- **Population Age:** Is the study conducted in adult populations (18 years and older) or does it include adults even if not exclusively?
- **Study Type Appropriateness:** Is the study NOT a case report, case series, animal study, or in vitro study?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Type 2 Diabetes Mellitus	HbA1c Levels	HbA1c Thresholds	Diabetic Retinopathy
Keyword 2	T2DM	Glycated Hemoglobin	HbA1c Cut-off Points	Diabetic Retinopathy Risk
Keyword 3	Type 2 Diabetes	Glycosylated Hemoglobin A1c	Optimal HbA1c Cut-off	Severity of Diabetic

				Retinopathy
Keyword 4	Diabetes Mellitus	HbA1c Measurement	Good vs. Poor Glycemic Control	Diabetic Retinopathy Progression

The Boolean MeSH keywords inputted on databases for this research are: (*"Type 2 Diabetes Mellitus" OR "T2DM" OR "Type 2 Diabetes" OR "Diabetes Mellitus"*) AND (*"HbA1c Levels" OR "Glycated Hemoglobin" OR "Glycosylated Hemoglobin A1c" OR "HbA1c Measurement"*) AND (*"HbA1c Thresholds" OR "HbA1c Cut-off Points" OR "Optimal HbA1c Cut-off" OR "Good vs. Poor Glycemic Control"*) AND (*"Diabetic Retinopathy" OR "Diabetic Retinopathy Risk" OR "Severity of Diabetic Retinopathy" OR "Diabetic Retinopathy Progression"*)

Data extraction

- **HbA1c Measurement:**

Extract how HbA1c was measured and categorized in relation to diabetic retinopathy risk, including:

- Method of HbA1c measurement (laboratory technique, units)
- HbA1c categorization scheme used (e.g., <7%, 7-8%, >8% or continuous values)
- Specific HbA1c thresholds or cut-points examined
- Whether HbA1c was treated as primary exposure variable
- Time point of HbA1c measurement relative to DR assessment

- **DR Assessment:**

Extract how diabetic retinopathy was assessed and classified as the outcome, including:

- Method of DR diagnosis (fundoscopy, photography, specialist examination)
- DR classification system used (ETDRS, clinical staging, etc.)

- DR severity grades examined (no DR, mild NPDR, moderate NPDR, severe NPDR, PDR)
- Whether DR presence, severity, or progression was the primary outcome
- Who performed the DR assessment and their qualifications

- **HbA1c-DR Association:**

Extract the statistical relationship found between HbA1c levels and diabetic retinopathy risk, including:

- Primary association measures (odds ratios, relative risks, correlation coefficients, prevalence ratios)
- Confidence intervals and p-values for the HbA1c-DR relationship
- Dose-response relationship across HbA1c categories
- Adjusted vs unadjusted association results
- Specific HbA1c levels or categories associated with increased DR risk
- Any threshold effects or optimal cut-off values identified

- **Study Population:**

Extract characteristics of the type 2 diabetes mellitus study population relevant to generalizability, including:

- Sample size and demographic characteristics (age, gender distribution)
- Duration of type 2 diabetes mellitus
- Setting (hospital-based, community-based, clinic-based)
- Geographic location and population characteristics
- Inclusion/exclusion criteria specific to T2DM patients
- Baseline diabetes management status

- **Risk Factors:**

Extract other risk factors examined in relation to diabetic retinopathy that could confound or modify the HbA1c-DR relationship, including:

- Traditional DR risk factors studied (diabetes duration, blood pressure, lipid levels)
- Which factors were found to be significantly associated with DR
- Whether these factors were controlled for in multivariate analyses
- Any interaction effects between HbA1c and other risk factors
- Factors that modified the strength of the HbA1c-DR association

- **Study Design:**

Extract study design and methodological characteristics relevant to establishing the HbA1c-DR relationship, including:

- Study design type (cross-sectional, cohort, case-control)
- Temporal relationship between HbA1c measurement and DR assessment
- Statistical analysis methods used to examine HbA1c-DR association
- Sample size calculation and power considerations
- Methods for handling potential confounding variables
- Study limitations that could affect the validity of the HbA1c-DR relationship

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Type 2 Diabetes Mellitus" OR "T2DM" OR "Type 2 Diabetes" OR "Diabetes Mellitus") AND ("HbA1c Levels" OR "Glycated Hemoglobin" OR "Glycosylated Hemoglobin A1c" OR "HbA1c Measurement") AND ("HbA1c Thresholds" OR "HbA1c Cut-off Points" OR "Optimal HbA1c Cut-off" OR "Good vs. Poor Glycemic Control") AND ("Diabetic Retinopathy" OR "Diabetic Retinopathy Risk" OR "Severity of Diabetic Retinopathy" OR "Diabetic Retinopathy Progression")</i>	3
Semantic Scholar	<i>("Type 2 Diabetes Mellitus" OR "T2DM" OR "Type 2 Diabetes" OR "Diabetes Mellitus") AND ("HbA1c Levels" OR "Glycated Hemoglobin" OR "Glycosylated Hemoglobin A1c" OR "HbA1c Measurement") AND ("HbA1c Thresholds" OR "HbA1c Cut-off Points" OR "Optimal HbA1c Cut-off" OR "Good vs. Poor Glycemic Control") AND ("Diabetic Retinopathy" OR "Diabetic Retinopathy Risk" OR "Severity of Diabetic Retinopathy" OR "Diabetic Retinopathy Progression")</i>	246
Springer	<i>("Type 2 Diabetes Mellitus" OR "T2DM" OR "Type 2 Diabetes" OR "Diabetes Mellitus") AND ("HbA1c Levels" OR "Glycated Hemoglobin" OR "Glycosylated Hemoglobin A1c" OR "HbA1c Measurement") AND ("HbA1c Thresholds" OR "HbA1c Cut-off Points" OR "Optimal HbA1c Cut-off" OR "Good vs. Poor Glycemic Control") AND ("Diabetic Retinopathy" OR "Diabetic Retinopathy Risk" OR "Severity of Diabetic Retinopathy" OR "Diabetic Retinopathy Progression")</i>	24
Google Scholar	<i>("Type 2 Diabetes Mellitus" OR "T2DM" OR "Type 2 Diabetes" OR "Diabetes Mellitus") AND ("HbA1c Levels" OR "Glycated Hemoglobin" OR "Glycosylated Hemoglobin A1c" OR "HbA1c Measurement") AND ("HbA1c Thresholds" OR "HbA1c Cut-off Points" OR "Optimal HbA1c Cut-off" OR "Good vs. Poor Glycemic Control") AND ("Diabetic Retinopathy" OR "Diabetic Retinopathy Risk" OR "Severity of Diabetic Retinopathy" OR "Diabetic Retinopathy Progression")</i>	843
Wiley Online Library	<i>("Type 2 Diabetes Mellitus" OR "T2DM" OR "Type 2 Diabetes" OR "Diabetes Mellitus") AND ("HbA1c Levels" OR "Glycated Hemoglobin" OR "Glycosylated Hemoglobin A1c" OR "HbA1c Measurement") AND ("HbA1c Thresholds" OR "HbA1c Cut-off Points" OR "Optimal HbA1c Cut-off" OR "Good vs. Poor Glycemic Control") AND ("Diabetic Retinopathy" OR "Diabetic Retinopathy Risk" OR "Severity of Diabetic Retinopathy" OR "Diabetic Retinopathy Progression")</i>	30

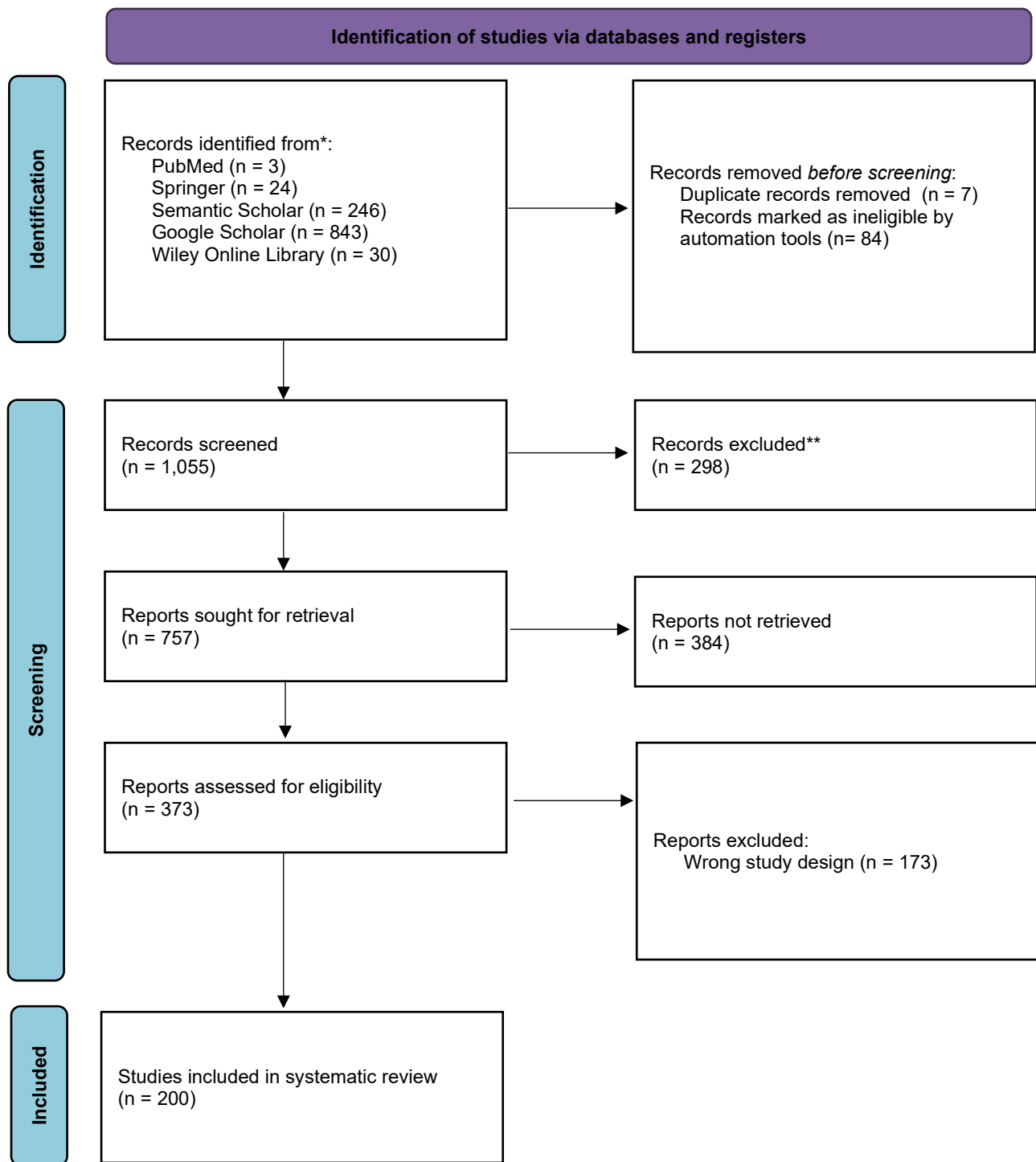


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

This systematic review examined 200 studies investigating the relationship between HbA1c levels and diabetic retinopathy risk in patients with type 2 diabetes mellitus. The studies varied substantially in design, setting, and population characteristics.

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Enrique O. Graue-Hernández et al., 2020	1,232	Mexico	Hospital-based	51.5	Non-mydratic fundus photography [1]
Shuqi Wang et al., 2024	620	Not mentioned	Hospital-based	Not mentioned	Fundus examination [22]
I. Stratton et al., 2001	1,919	United Kingdom	Hospital-based	50 (median)	Retinal photography [23]
S. A. Gardezi et al., 2022	61	Pakistan	Clinical	65	Fundoscopy [24]
J. Yun et al., 2016	759	Korea	Hospital/clinic-based	Not mentioned	Specialist examination [25]
I. Chatziralli et al., 2017	1,062	South London	Community-based	56.0	Digital two-field photography [2]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Peiyao Jin et al., 2015	453	Shanghai, China	Community-based	Not mentioned	Direct ophthalmoscopy and photography [26]
Na Li et al., 2013	1,100	Urban Beijing	Community-based	Not mentioned	Fundus color photographs [27]
N. White et al., 2022	1,614 with T2D	United States	Community-based	Not mentioned	Fundus photography [28]
C. Pan et al., 2018	913	Suzhou, China	Community-based	67.7	Retinal photographs [10]
R. Kawasaki et al., 2011	2,033	Japan	Multi-centered	40-70 (range)	Specialist examination [5]
Rasmieh M. Al-amer et al., 2008	1,000	Amman, Jordan	Clinic-based	57.8	Specialist examination [29]
G. Garberg et al., 2025	2,267	Sweden	Hospital-based	≤70 at diagnosis	Not mentioned [30]
Kajsa Andersson et al., 2024	1,659	Sweden	Community-based	35-75 (range)	Fundus photography [31]
Carlos Hernández-Teixidó et al., 2024	146,506	Catalonia, Spain	Primary care	65.4	Retinal photography [3]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
E. Fenwick et al., 2017	613	Melbourne, Australia	Clinic-based	64.9	Fundus photography [11]
M. Okudaira et al., 2000	394	Japan	Not mentioned	27 (mean at diagnosis)	Not mentioned [32]
Kátia Gonçalves dos Santos et al., 2005	210	South Brazil	Not mentioned	Not mentioned	Ophthalmoscopy/bio microscopy [33]
Cheol-Young Park et al., 2011	696	Seoul, Korea	Community-based	55.3	Fundus photographs [34]
K. K. Ng et al., 2020	3,093	Not mentioned	Not mentioned	Not mentioned	Not mentioned [35]
S. I. Mogilevskii et al., 2024	358	Not mentioned	Clinical	Not mentioned	Optical coherence tomography [36]
António Martinho et al., 2020	212	Not mentioned	Clinic-based	42-82 (range)	Comprehensive eye examination [37]
R. Vrabec et al., 2025	50 eyes (25 patients)	Zagreb	Hospital-based	64 (median)	Color fundus photography and OCT [38]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Sanjeev Kumar et al., 2015	121	North India	Hospital-based	51.08	Direct ophthalmoscope [39]
K. S. et al., 2021	212	Thiruvananthapuram	Hospital-based	63.93	Comprehensive evaluation and photography [40]
T. Popescu et al., 2012	100	Not mentioned	Clinical	61	Retinal photography [41]
Shu-ping Zhang et al., 2010	49	Beijing, China	Clinic-based	58-70 (range)	Fundoscopy [42]
Abdul Munim et al., 2026	150	Not mentioned	Not mentioned	48.1	Ophthalmic examination [43]
Yoko Yoshida et al., 2001	787	Japan	Not mentioned	Not mentioned	Not mentioned [44]
J. Wong et al., 2008	624 (Group A), 852 (Group B)	Sydney, Australia	Hospital-based	Variable by onset age	Direct funduscopy [16]
A. Jatoi et al., 2024	400	Not mentioned	University-based	48.1	Fundus photography [45]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
S. A. Alghamdi et al., 2021	428	Riyadh, Saudi Arabia	Clinic-based	61	Fundus photography and slit lamp [46]
Kalpna Jain et al., 2020	160	Not mentioned	Hospital-based	Not mentioned	Not mentioned [47]
Jennifer Perais et al., 2020	Variable (100-71,817)	Global	Variable	≥18	Variable methods [48]
K. Kalaivani et al., 2021	200	Not mentioned	Hospital/clinic-based	Not mentioned	Slit lamp bio microscopy [12]
P. Garg et al., 2018	444	Not mentioned	Hospital-based	Not mentioned	Complete ocular examination [49]
D. Tarasewicz et al., 2022	99,280	Northern California	Community-based	Not mentioned	Fundus photography [7]
E. Martín-Merino et al., 2016	7,735 cases, 9,395 controls	United Kingdom	Primary care	No restrictions	Not mentioned [50]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
K. S. et al., 2021a	212	Not mentioned	Not mentioned	Not mentioned	Stereoscopic fundus photographs [51]
Tiantian Li et al., 2022	97	Not mentioned	Hospital-based	Not mentioned	Fundus photography [52]
Y. Kim et al., 2014	452 (371 analyzed)	Seoul, Korea	Hospital-based	56.2	Comprehensive ophthalmologic examination [6]
V. Tam et al., 2009	354	Hong Kong	Clinic-based	Not mentioned	Not mentioned [53]
Zhipeng Yan et al., 2016	1,100	Northern China	Hospital-based	Not mentioned	Comprehensive ophthalmic examination [54]
T. K. W. Tam et al., 2005	6,165 (4,423 analyzed)	Hong Kong	Community-based primary care	60.36	Photography [55]
Jiaqi Hu et al., 2020	3,152	Asia	Not mentioned	Not mentioned	Dilated funduscopy examination [56]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Chrysa Agapitou et al., 2025	215	Not mentioned	Not mentioned	Not mentioned	Comprehensive ophthalmic examination [57]
H. Salti et al., 2009	500	Lebanon	Clinic-based	Not mentioned	Not mentioned [58]
Wisit Chaveepojnkamjorn et al., 2015	460 (230 cases, 230 controls)	Thailand	Hospital-based	42% aged 60-69	Not mentioned [59]
Development and Progression of	699 full cohort (367 analyzed)	Not mentioned	Clinical	25.4 at study time	Standard stereoscopic seven-field photography [60]
Liping Gu et al., 2025	4,487	United States	Community-based	Not mentioned	Not mentioned [61]
Amr Muhammad Badr Salah El-Deen et al., 2021	100	Not mentioned	Clinic-based	Not mentioned	Not mentioned [62]
C. Ducos et al., 2020	334	Not mentioned	Hospital-based	63	Fundus examination and imaging [9]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
M. Ms et al., 2018	329	Eldoret, Kenya	Hospital-based	56.8	Direct ophthalmoscopy [63]
Pei Zhang et al., 2021	6,978	Shanghai	Not mentioned	68.33	Fundus examination and imaging [64]
Mustafa Khalid Waheed et al., 2025	70	Lahore, Pakistan	Hospital-based	56.8	Indirect ophthalmoscopy [65]
S. Alam et al., 2020	208	Karachi, Pakistan	Hospital-based	Not mentioned	Fundoscopy [66]
S. Hosny et al., 2023	80	Egypt	Hospital-based	40-70 (range)	Fundus examination [67]
A. C. García-Ulloa et al., 2024	244 (183 DR-DME, 61 DR+DME)	Mexico City	Hospital-based	Not mentioned	Digital three-field fundus photography [68]
Faisal Mehmood et al., 2025	300	Lahore	Hospital-based	≥ 35	Fundoscopy examination [69]
Ying-Chu Chiu et al., 2020	792	Taiwan	Clinic-based	Not mentioned	Not mentioned [70]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
A. Serdiuk et al., 2024	358	Not mentioned	Clinical	Not mentioned	Ophthalmologic methods [71]
Rushi N. Mankad et al., 2026	584	New Mexico	Not mentioned	Not mentioned	Not mentioned [72]
Z. Lyu et al., 2017	753	China	Hospital-based	Not mentioned	Digital fundus photography [73]
Nattapong Mekhasingharak et al., 2016	650	Thailand	Community-based	Not mentioned	Indirect ophthalmoscope [74]
F. Farhani et al., 2023	70	Bandung, Indonesia	Hospital-based	Not mentioned	Not mentioned [75]
D. Ms et al., 2022	100	Vizianagara, India	Hospital-based	50-60 (mode)	Slit lamp and indirect ophthalmoscopy [76]
P. Sharma et al., 2024	100	Bhopal, India	Hospital-based	51.46	Comprehensive ophthalmologic examination [17]
Juan Ling et al., 2025	2,001	Southern Taiwan	Hospital-based	64.1	Fundoscopy and OCT [77]
S. Hoque et al., 2017	400	Bangladesh	Hospital-based	50.05	Review of medical records [4]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Abdul Jabbar et al., 2023	150	Not mentioned	Hospital-based	Not mentioned	Digital retinal imaging [78]
Kainaat Talat et al., 2025	246	Combined Military Hospital Kharian	Hospital-based	49.26	Fundoscopy [79]
L. S. et al., 2018	50	Bengaluru , India	Hospital-based	61-70 (mode)	Dilated retinal examination and slit lamp [80]
H. Hwang et al., 2020	380	Not mentioned	Hospital/clinic-based	Not mentioned	Complete ophthalmic examinations [81]
P. Tangjai et al., 2015	100	Thailand	Hospital-based	Not mentioned	Not mentioned [18]
R. axer-siegel et al., 2006	178 hospital, 107 community	Israel	Hospital and community	Not mentioned	Not mentioned [82]
S. Sheu et al., 2013	901	Taiwan	Hospital-based	Not mentioned	Fundus examination [83]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
M. Manaviat et al., 2004	590	Yazd, Iran	Clinic-based	54.9	Fundoscopy [84]
Muhammad Asif et al., 2024	106	Peshawar, Pakistan	Hospital-based	52.45	Full ophthalmologic examination [85]
Adriana Ivanescu et al., 2024	302	Timisoara, Romania	Hospital-based	64 (median)	Comprehensive fundus examination [86]
V. Foo et al., 2017	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned [87]
C. Shiragami et al., 2002	45	Not mentioned	Not mentioned	Not mentioned	ICG and fluorescein angiography [88]
M. Manaviat et al., 2005	590	Not mentioned	Not mentioned	Not mentioned	Fundoscopy [89]
C. Cardoso et al., 2017	544	Rio de Janeiro, Brazil	Hospital-based	Not mentioned	Fundoscopy [14]
Putri Lenggo Geany et al., 2022	72	Semarang, Indonesia	Clinic-based	54.12	Not specified [90]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Dr. Ikhlass Ali Hussein Al-Hilaly et al., 2018	102	Al-Najaf Al-Ashraf, Iraq	Hospital-based	35-75 (range)	Indirect ophthalmoscopy and fundus camera [91]
J. Park et al., 2020	1,125	Not mentioned	Hospital/clinic-based	Not mentioned	Not mentioned [92]
Yu-Ju Wu et al., 2024	602 (136 DR, 466 no DR)	Taiwan	Hospital-based	30-75 (range)	Fundus color photography [93]
Nayef Alswaina et al., 2024	106	Saudi Arabia	Hospital-based	60.6	Fundus examinations [94]
Niveditha H et al., 2013	50	Not mentioned	Clinical	62	Not mentioned [95]
T. Bulum et al., 2023	160	Croatia	Hospital-based	64.3	Color fundus photography and OCT [15]
Savan Shah et al., 2021	11,399	United Kingdom	Primary care	Not mentioned	Not mentioned [96]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Nutan Bedi et al., 2021	100 (200 eyes)	Southern Rajasthan	Hospital-based	Not mentioned	Comprehensive ocular examination [97]
P. Geetha et al., 2019	230	Chennai, India	Hospital-based	40-60 (mode)	Not mentioned [98]
Yu-Chi Sung et al., 2025	300 (178 analyzed)	Not mentioned	Not mentioned	≥20	Not mentioned [99]
M. Martínez et al., 2020	181	Not mentioned	Clinic-based	Not mentioned	Not mentioned [100]
N. Cho et al., 2013	3,403	South Korea	Community-based	Not mentioned	Single-field nonmydriatic fundus photography [19]
Han Ul Kim et al., 2021	434	Korea	Hospital-based	~57	Wide-field fundus photography [101]
Deepti Mujumdar et al., 2023	100	Not mentioned	Not mentioned	Not mentioned	Detailed ophthalmic evaluation [102]
Qingmin Sun et al., 2021	1,052	China	Hospital-based	Not mentioned	Nonmydriatic fundus photography [103]
A. Sattar et al., 2020	386	Karbala, Iraq	Clinic-based	54.5	Visual acuity, slit lamp, OCT [104]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Shenglan Yang et al., 2025	498	Not mentioned	Not mentioned	Not mentioned	Not mentioned [105]
Nafisa Marzan Chowdhury et al., 2025	100	Bangladesh	Hospital-based	>30	Fundus photography [106]
Patcharapol Wittayatechakul et al., 2021	2,007	Central Thailand	Hospital-based	59.0	Medical record ICD-10 codes [107]
Bilgin Ozmen et al., 2003	267	Not mentioned	Not mentioned	58.07	Fundoscopy [108]
Celso Nabais et al., 2011	874	Portugal	Clinic-based	Not mentioned	Not mentioned [109]
Deepasha Shahi Bagzai et al., 2019	472	Not mentioned	Hospital-based	41-60 (mode)	Detailed ocular examination [110]
S. Kaštelan et al., 2013	545	Croatia	Hospital-based	Variable by group	Fundoscopy and fundus photography [111]
Rajeshwari M et al., 2025	206	Kalaburagi	Hospital-based	50-60 (mode)	Not mentioned [112]
Febrina Art et al., 2019	68	Palembang	Hospital-based	50-59 (mode)	OCT for RNFL thickness [113]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Stephen L Saum et al., 2002	260	Not mentioned	Community-based	Not mentioned	Community optometrists [114]
F. Semeraro et al., 2011	5,034	Not mentioned	Not mentioned	Not mentioned	Not mentioned [115]
Won Seon Jeon et al., 2016	424	Korea	Not mentioned	Not mentioned	Not mentioned [116]
J. Setareh et al., 2022	168	Mazandaran, Iran	Hospital-based	56.01	Fundus photography [20]
V. Som et al., 2019	56 (112 eyes)	Central India	Hospital/clinic-based	52.90	Ophthalmic examination [117]
Fatemeh Dehghani Firouzabadi et al., 2024	1,145 (294 developed DR)	Tehran, Iran	Hospital-based	>18	Stereoscopic color fundus photographs [118]
Munish Dhawan et al., 2019	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Fundus examination [119]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Dr Hafsa Imran Khan et al., 2025	187	Lahore, Pakistan	Hospital-based	56.8	Slit-lamp biomicroscopy or indirect ophthalmoscopy [120]
H. Ahmadieh et al., 2013	136	Beirut	Hospital-based	59	Dilated retinal exam [121]
P. K. V. Sai Akshay et al., 2025	100	Northern India	Hospital-based	>18	Direct and indirect ophthalmoscope [122]
Shubhaa Chawla et al., 2021	3,090	New Delhi, India	Clinic-based	52.7	Not mentioned [123]
Archana Thool et al., 2021	75	Wardha	Hospital-based	61-70 (mode)	Detailed fundus examination [124]
Saba Eqbal et al., 2020	80	India	Hospital-based	Not mentioned	Not mentioned [125]
R. Raman et al., 2012	1,414	South India	Community-based	Not mentioned	Not mentioned [126]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
S. Sewak et al., 2018	80	Neemuch, India	Hospital-based	Not mentioned	Specialist examination [127]
L. Zhai et al., 2022	44,662	Multiple countries	Variable	58-68 (range)	Variable methods [8]
زينة محمد حسن et al., 2022	120	Rusafa, Baghdad	Clinic-based	40-70 (range)	Fundoscopy, slit lamp, photography, OCT [128]
F. Ganjifrockwala et al., 2017	140	South Africa	Not mentioned	Not mentioned	Not mentioned [129]
C. Lam et al., 2011	420	Hong Kong	Clinical	Not mentioned	Eye examinations [130]
Yiyuan Liu et al., 2013	4,758	Tayside, Scotland	Community-based	≥35 at diagnosis	Retinal screening [131]
W. Lee et al., 2014	971	Korea	Community-based	Not mentioned	Not mentioned [132]
Sadiq Hussain et al., 2013	300	Bahawalpur, Pakistan	Hospital-based	49.04	Fundoscopy [133]
Irma Yanti Rangkuti et al., 2011	30	Indonesia	University-based	42-78 (range)	Ophthalmoscopy and fundus photos [134]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
T. Chiu et al., 2021	792	Taiwan	Clinic-based	67.85	Dilated fundus examination [135]
Y. Umayahara et al., 2017	613	Not mentioned	Not mentioned	63.2	Not mentioned [136]
M. Long et al., 2017	842	United States	Community-based	61.24	Ophthalmic digital imaging [137]
Gayatri Mia et al., 2025	37	Bandung	Hospital-based	Not mentioned	Not mentioned [138]
Yan Liu et al., 2017	13,304	China	Hospital and community-based	Not mentioned	Digital retinography [139]
B. He et al., 2012	2,009	China	Not mentioned	Not mentioned	Eye examination [13]
Nadia Ghassan Abdulkareem et al., 2024	131	Not mentioned	Not mentioned	41-78 (range)	Not mentioned [140]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
W. Matuszewski et al., 2020	894 (T2DM)	North-east Poland	Hospital and community-based	61.2	Not mentioned [141]
Dr Md Asif Hasan et al., 2023	320	Khulna, Bangladesh	Hospital-based	50.05	Not mentioned [142]
K. Aziz et al., 2010	333	Abha, Saudi Arabia	Clinic-based	21-97 (range)	Fundus Photography [143]
Toshiko Takao et al., 2011	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned [144]
K. Aziz et al., 2018	10,580	Saudi Arabia	Clinic-based	Not mentioned	Computerized digital fundus photography [145]
Lei Liu et al., 2015	622	Fengyutan, China	Community-based	69	Slit-lamp and fundus photography [21]
Vandana Parasar et al., 2019	400	Not mentioned	Not mentioned	Not mentioned	Not mentioned [146]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
V. Kalesnykiene et al., 2009	83	Not mentioned	Not mentioned	Not mentioned	Fundus photography [147]
M. Tomić et al., 2024	156	Zagreb, Croatia	Hospital-based	64.28	Indirect slit-lamp fundoscopy, photography, OCT [148]
Faeze Poshtchaman et al., 2023	80	Iran	Clinic-based	Not mentioned	Fundoscopy examination [149]
Faisal Redwan et al., 2024	190	Latakia, Syria	Hospital-based	64.46	Eye fundus examination and spectral domain OCT [150]
M. Tomić et al., 2013	107	Not mentioned	Not mentioned	Not mentioned	Not mentioned [151]
A. Tsegaw et al., 2021	739	Northwest Ethiopia	Hospital-based	56.3 at screening	Retinal photography and slit-lamp biomicroscopy [152]
P. Romero-Aroca et al., 2023	175,645	Catalonia, Spain	Community-based	67	Retinographies [153]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
R. A. Ahmed et al., 2016	401	Abha, Saudi Arabia	Clinic-based	54.5	Fundus photographs and slit lamp [154]
Yanhua Liang et al., 2024	622,490	Multiple countries	Variable	Not mentioned	Variable methods [155]
S. Mitchell et al., 2017	857	Not mentioned	Not mentioned	Not mentioned	Not mentioned [156]
J. Yun et al., 2016a	787	Not mentioned	Hospital/clinic-based	Not mentioned	Not mentioned [157]
Atif Mansoor Ahmed et al., 2023	320	Lahore, Pakistan	Hospital-based	47.5	Fundoscopy [158]
E. Fefelova et al., 2024	84	Not mentioned	Not mentioned	Not mentioned	Not mentioned [159]
Puneeth Hegde et al., 2020	92	India	Hospital-based	54.5	Dilated fundus examination [160]
L. Pedersen et al., 2014	64	Not mentioned	Not mentioned	Not mentioned	Not mentioned [161]
H. Rashidi et al., 2014	256	Ahvaz, Iran	Clinic-based	54	Physical and retina examination [162]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Michael Müller et al., 2020	1,255	Germany	Hospital-based	66	Clinical examination [163]
A. Jongsareejit et al., 2013	1,007	Thailand	Hospital-based	Not mentioned	Indirect ophthalmoscope [164]
Sidda Naik Bukke et al., 2021	100	Tirupathi, India	Hospital-based	Not mentioned	Comprehensive examination [165]
V. H. R. et al., 2018	200	Bangalore, India	Hospital-based	30-65 (range)	Specialist examination [166]
A. Niyodusenga et al., 2021	592 (66 cases, 526 controls)	Rwanda	Hospital-based	Not mentioned	Indirect ophthalmoscopy with slit-lamp [167]
M. Mjwara et al., 2021	Not mentioned	Durban, South Africa	Hospital-based	Not mentioned	Not mentioned [168]
K. Blaslov et al., 2018	247	Not mentioned	Not mentioned	56	Not mentioned [169]
Rehna Rasheed et al., 2021	500	Kerala, India	Hospital-based	>30	Dilated fundus examination [170]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
M. El-Bab et al., 2013	67	Not mentioned	Not mentioned	14-80 (range)	Not mentioned [171]
Joshi et al., 2021	100	Nepal	Hospital-based	56.9	Comprehensive ophthalmic examination [172]
Y. Sato et al., 2001	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned [173]
Chia-Hsuin Chang et al., 2010	10,251 (2,856 analyzed)	Multiple Asian countries	Multi-center	≥30	Not mentioned [174]
Shivayogi R. Kusagur et al., 2014	4,067	India	Hospital-based	54	Indirect ophthalmoscopy and fundal photography [175]
Y. Park et al., 2014	5,212	Korea	Community-based	≥19	Nonmydriatic fundus photography [176]
D. Dai et al., 2021	315	Not mentioned	Hospital-based	Not mentioned	Not mentioned [177]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Rachana Gahlawat et al., 2020	75	India	Hospital-based	Variable	Detailed dilated fundoscopic examination [178]
Fei Qin et al., 2019	2,331	Shanghai	Community-based	Not mentioned	Nonmydriatic fundus photographs [179]
Anup Mondal et al., 2025	72	Not mentioned	Not mentioned	Not mentioned	Not mentioned [180]
Sayaka Wakabayashi Sugawa et al., 2021	135 (88 simple DR, 47 preproliferative DR)	Not mentioned	Hospital/clinic-based	Not mentioned	Specialist examination [181]
Y. Aldebasi et al., 2011	220	Buraidah, Saudi Arabia	Hospital-based	Not mentioned	Not mentioned [182]
Zi-xia Cheng et al., 2021	230	Quzhou, China	Community-based	Not mentioned	Fundus screening [183]
K. Ahmed et al., 2011	977	Bangladesh	Hospital-based	Not mentioned	Retinal color photography [184]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Eko Sudarmo Dahad Prihanto et al., 2022	51	Ternate, Indonesia	Hospital-based	>40 (mode)	Direct funduscopy examination [185]
Ziyang Zhang et al., 2024	1,097	Shenzhen, China	Community-based	Not mentioned	Fundus photography [186]
Divya Karuppannasamy et al., 2017	116 (86 T2DM, 30 controls)	Southern India	Hospital-based	Not mentioned	Fundus examination and photography [187]
Yukihisa Suzuki et al., 2023	261	Japan	Hospital-based	70.1	Fundus examination and SD-OCT [188]
Dev Kant et al., 2022	100	Muzaffarpur, India	Hospital-based	51-60 (mode)	Direct and indirect ophthalmoscope [189]
R. Simó et al., 2023	2,300 (1,150 cases, 1,150 controls)	Catalonia, Spain	Community-based primary care	68.2-68.4	Fundus photography [190]
Kiyoung Kim et al., 2018	87 eyes	Korea	Hospital-based	~57	Retinal photography [191]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
Nikhilesh A. Badiani et al., 2025	240	Gandhinagar, India	Hospital-based	Not mentioned	Not mentioned [192]
Pallavi Ashrit et al., 2020	150	Not mentioned	Not mentioned	40-60 (range)	Fundoscopy [193]
A. Yousef et al., 2021	75	Not mentioned	Hospital-based	Not mentioned	Fundus examination [194]
Kefah H. Abid Al-Majeed et al., 2025	120	Baghdad, Iraq	Clinic-based	Not mentioned	Biomicroscopic fundoscopy, SD-OCT, FFA [195]
C. Domngang et al., 2024	89 (12 DR, 45 non-DR, 32 non-diabetic)	Yaoundé, Cameroon	Hospital-based	Not mentioned	Comprehensive ophthalmological examination [196]
Xiaomei Chen et al., 2021	330	Fujian, China	Hospital-based	58.60	2-field fundus photography [197]
Hong-Xia Zhang et al., 2009	642	Shanghai, China	Community-based	65	Digital non-mydratic fundus photography [198]

Study	Sample Size	Geographic Location	Setting	Mean Age (years)	DR Assessment Method
B. R. Chaudhry et al., 2020	180	Bahawalpur	Hospital-based	51	Retinal examination [199]
H. Kassab et al., 2022	60	Alexandria, Egypt	Hospital-based	66-70 (range)	Fundus examination with slit lamp [200]

The majority of studies were cross-sectional in design (n=139, 69.5%), followed by cohort studies (n=42, 21.0%), case-control studies (n=15, 7.5%), and systematic reviews or meta-analyses (n=4, 2.0%) [1, 8, 23, 25, 48]. Most studies were conducted in hospital or clinic-based settings [1, 24, 65], with fewer community-based investigations [10, 26, 55]. Geographic distribution was diverse, with substantial representation from Asia (particularly China, India, Korea, and Japan) [5, 26, 34, 54], followed by Europe [23, 86], the Middle East [29, 46], and smaller numbers from Africa [63, 129] and the Americas [1, 3].

Sample sizes ranged from 30 [134] to 175,645 participants [153], with a median sample size of approximately 300 patients. Among the 71 studies reporting gender distribution, the majority showed relatively balanced representation or slight female predominance, though some studies demonstrated male predominance [1, 16, 23]. Mean ages across studies ranged from 27 to 70 years [32, 153], with most studies focusing on middle-aged to elderly populations.

DR assessment methods varied across studies, with fundus photography being the most common approach [1, 23, 28], followed by direct or indirect ophthalmoscopy [39, 42, 65] and comprehensive ophthalmologic examinations incorporating multiple modalities including optical coherence tomography [15, 37, 57]. The Early Treatment Diabetic Retinopathy Study (ETDRS) classification system was the most frequently employed grading method [11, 17, 23, 27, 39, 51, 65],

though other systems including the International Clinical Diabetic Retinopathy Disease Severity Scale [5, 19, 26, 77, 94] and various national classification schemes were also utilized [1, 15].

HbA1c measurement methods were explicitly detailed in only a subset of studies. Where reported, high-performance liquid chromatography (HPLC) was the most common technique [19, 24, 29, 39, 66, 79, 106, 113, 118, 135, 137]. HbA1c categorization schemes varied considerably: some studies used continuous values [5, 6, 23, 44], while others employed threshold-based categorizations. Common thresholds included $<7\%$, $7-8\%$, and $>8\%$ [1, 3, 10, 24], though some studies used different cut-points such as $<6.5\%$, $\geq 9\%$ [1, 46], or institution-specific categories [17, 47, 85].

Association Between HbA1c Levels and Diabetic Retinopathy Risk

The overwhelming majority of studies demonstrated a significant positive association between elevated HbA1c levels and increased risk of diabetic retinopathy. This relationship was consistently observed across diverse populations, settings, and study designs.

Quantitative Measures of Association

Among studies reporting odds ratios for HbA1c-DR associations, effect sizes varied considerably but consistently indicated increased risk with higher HbA1c levels. Several studies reported adjusted odds ratios: Enrique O. Graue-Hernández et al. found OR=2.19 (95% CI 1.43-3.35) for HbA1c 7.0-8.9% and OR=2.98 (95% CI 2.01-4.42) for HbA1c $\geq 9\%$ [1], while Chatziralli et al. reported OR=1.60 (95% CI 1.13-2.25, $p=0.007$) for HbA1c $\geq 7.5\%$ [2]. Abdul Munim et al. demonstrated OR=1.92 (95% CI 1.48-2.51) [43], and Carlos Hernández-Teixidó et al. found a particularly strong association with HR=4.23 (95% CI 3.90-4.58) for HbA1c $>10\%$ compared to $<7\%$ [3].

In prospective cohort studies, hazard ratios demonstrated consistent dose-response relationships. Kawasaki et al. reported adjusted HR of 1.36 (95% CI 1.28-1.45) per 1% HbA1c increase for incident DR and 1.66 (95% CI 1.41-1.96) for DR progression [5]. Kim et al. found HR=1.163 ($p=0.006$) for DR development and HR=1.190 ($p=0.005$) for progression to proliferative

DR for every 1% increase in HbA1c [6]. Liu et al. reported adjusted HR=2.12 (95% CI 1.87-2.32) for HbA1c $\geq 7\%$ [21].

The relationship between HbA1c and DR severity showed progressive increases in risk. Studies stratifying by DR severity consistently demonstrated higher HbA1c levels in more advanced stages. Kalpna Jain et al. reported mean HbA1c of 6.5-8.5% in mild NPDR, 8.6-10.5% in moderate NPDR, 10.6-12.5% in severe NPDR, and 12.6-14.5% in PDR [47]. Similarly, P. K. V. Sai Akshay et al. found progressive increases from 7.38% in mild NPDR to 10.60% in PDR [122], and Dr Hafsa Imran Khan et al. demonstrated increases from 7.8% in mild NPDR to 10.4% in PDR [120].

Dose-Response Relationships and Thresholds

Multiple studies examined specific HbA1c thresholds for DR risk stratification. Several investigations identified 7% as a critical threshold, with substantially increased risk above this level [2, 4, 10, 21, 46]. Peiyao Jin et al. demonstrated a particularly striking dose-response pattern, with 5-year DR progression rates of 19.62% for baseline HbA1c $< 5.2\%$, 24.41% for 5.2-6.4%, and 76.83% for $> 6.4\%$ [26]. The logistic regression function in this study indicated that DR progression risk increased most rapidly when baseline HbA1c increased from 5.2% to 6.4% [26].

Some studies identified optimal cut-off values through receiver operating characteristic (ROC) curve analysis. Cho et al. determined optimal HbA1c thresholds of 49 mmol/mol (6.6%) for any DR and 52 mmol/mol (6.9%) for moderate or severer retinopathy [19]. Tangjai et al. identified 7.25% as the optimal screening threshold (sensitivity 84%, specificity 66%) [18], while Setareh et al. found 8.15 as an optimal cut-off point [20]. Sharma et al. reported that an HbA1c cutoff of 7.6% was most effective in detecting both the presence and grades of DR [17].

An intriguing finding emerged from Juan Ling et al., who identified an inverted U-shaped relationship between HbA1c and DR, with a peak at HbA1c of 9.4% [77]. This suggests a complex nonlinear relationship that may reflect survival bias or other biological mechanisms in very advanced disease states.

HbA1c Variability and DR Risk

Beyond mean HbA1c levels, several studies examined the role of HbA1c variability as an independent risk factor. Jiaqi Hu et al. demonstrated that HbA1c variability (measured as standard deviation) was an independent predictor of DR in Asian patients with type 2 diabetes, with the association becoming particularly important when variability exceeded 0.75% [56]. The study found that patients in the highest quartile for both mean HbA1c and variability had the highest DR prevalence (HR=1.624, $p<0.001$) [56]. Similarly, Han Ul Kim et al. reported that HbA1c ARV (average real variability) was significantly associated with DR development (HR=2.479, $p=0.036$), independent of mean HbA1c levels [101].

A meta-analysis by Zhai et al. synthesized findings from 12 observational studies involving 44,662 patients and found that higher HbA1c variability, measured as both standard deviation (RR=1.48, 95% CI 1.24-1.78, $p<0.001$) and coefficient of variation (RR=1.29, 95% CI 1.05-1.59, $p=0.02$), was associated with increased DR risk [8]. This association remained significant even after adjustment for mean HbA1c levels [8].

Park et al. demonstrated that not only mean HbA1c but also HbA1c standard deviation was associated with lower risk of ≥ 3 steps of DR progression and progression to proliferative DR ($p<0.001$ for both) [92]. These findings suggest that consistent glycemic control may be as important as achieving specific HbA1c targets.

Evidence from Large-Scale Studies

Several large-scale studies provided particularly robust evidence. Tarasewicz et al. analyzed 99,280 patients from the Kaiser Permanente Northern California healthcare system over a mean surveillance period of 7.3 years and found that patients with average HbA1c $\geq 10\%$ had a risk ratio of 5.72 (95% CI 5.44-6.02) for progression to any retinopathy, 18.84 (95% CI 17.25-20.57) for referable retinopathy, 22.85 (95% CI 18.87-27.68) for diabetic macular edema, and 25.96 (95% CI 18.75-36.93) for proliferative DR compared to those with HbA1c $\leq 7\%$ [7].

Romero-Aroca et al. examined 175,645 patients over 10 years and confirmed HbA1c as a significant risk factor with cumulative hazard of 1.162 ($p=0.001$) [153]. White et al., analyzing data from the Diabetes Prevention Program, demonstrated that average HbA1c was associated with DR across the entire glycemic range from prediabetes to type 2 diabetes, with OR=1.92 (95% CI 1.46-1.74) per 0.7% increase [28].

Temporal Aspects of Glycemic Control

Several studies examined the temporal relationship between HbA1c levels and DR development. Ducos et al. investigated "glucose memory" by collecting HbA1c values from previous years and measuring skin autofluorescence as a marker of advanced glycation end-products. They found that DR was significantly associated with HbA1c levels from 5 years prior (OR=6.75, 95% CI 1.90-23.90), but not with more recent values [9]. This finding suggests that historical glycemic exposure may have lasting effects on retinopathy risk.

Yoshida et al. demonstrated that patients with initial HbA1c higher than the median value of 8.2% showed a higher probability of DR development during the subsequent 3 years, even when the same blood glucose control was maintained during follow-up [44]. This indicates that early intensive control may be particularly important.

Interestingly, Simó et al. investigated early worsening of DR (EWDR) following rapid reduction in HbA1c among patients with mild or moderate NPDR and found no significant association between rapid HbA1c reduction and DR worsening [190]. The mean HbA1c reduction was similar between cases with EWDR and controls (0.13 ± 1.21 vs 0.21 ± 1.18 , $p=0.12$) [190], suggesting that concerns about early worsening may not apply to patients with less advanced retinopathy.

Negative or Null Findings

While the vast majority of studies found significant associations, a small number reported null or weak findings. Sadiq Hussain et al. found that a single high level of HbA1c was not significantly associated with retinopathy ($p=0.08$) [133], suggesting that isolated measurements may

be less informative than sustained glycemic exposure. Gayatri Mia et al. found no significant relationship between HbA1c levels and DR degree in either <5 years or ≥ 5 years diabetes duration groups ($p=0.357$ and $p=1.000$) [138], though this study had a notably small sample size of 37 patients [138].

Irma Yanti Rangkuti et al. reported that blood sugar control did not cause the occurrence of diabetic retinopathy ($p=0.195$) [134], though this finding should be interpreted cautiously given the very small sample size of 30 patients [134]. Domngang et al. found no significant difference in HbA1c levels between DR and non-DR patients ($p=0.702$), with an odds ratio of 0.75 (95% CI 0.16-3.6) [196], though the study had only 12 DR participants [196].

Interaction Effects and Effect Modifiers

Combined Control of Multiple Risk Factors

Several studies examined whether combined control of HbA1c with other risk factors provided additive or synergistic benefits. Fenwick et al. demonstrated that compared to individuals with good control of all indicators (HbA1c, blood pressure, and lipids), the odds ratios for any DR were 2.44 (95% CI 1.34-4.46) for poor glucose control only, 3.75 (95% CI 1.75-8.07) for poor glucose and blood pressure control, 4.64 (95% CI 2.13-10.12) for poor glucose and lipid control, and 2.28 (95% CI 1.01-5.16) for poor control of all three indicators [11]. This pattern suggests that combined poor control amplifies risk beyond the effects of HbA1c alone.

Pan et al. found that combined lower HbA1c ($<7\%$) and systolic blood pressure (<140 mmHg) was associated with 43% reduced likelihood of developing DR (adjusted OR=0.57, 95% CI 0.33-0.99), while neither factor alone showed significant association [10]. Similarly, Raman et al. reported that subjects with combined suboptimal glycemic and blood pressure control were more likely to have DR than those with optimal control of respective combinations ($p<0.0001$ for systolic BP, $p=0.004$ for diastolic BP) [126].

Blood Pressure and HbA1c Interactions

The interaction between blood pressure control and HbA1c emerged as particularly important. Cardoso et al. examined ambulatory blood pressure monitoring and found that higher baseline ambulatory blood pressures ($p=0.013$ for 24-hour diastolic BP) and higher mean cumulative HbA1c exposure ($p<0.001$) were both independent predictors of DR development/progression after adjustments [14]. The influence of systolic blood pressure (AOR=1.06, $p=0.004$) and diastolic blood pressure (AOR=1.12, $p=0.005$) on DR development remained significant even after adjustment for diabetes duration and HbA1c [14].

Bulum et al. similarly demonstrated that both systolic blood pressure (AOR=1.06, $p=0.004$) and diastolic blood pressure (AOR=1.12, $p=0.007$) were independent risk factors for DR in T2DM patients, with effects persisting after adjustment for diabetes duration and HbA1c [15]. Shenglan Yang et al. found that the relationship between HbA1c and DR was markedly stronger in patients with elevated ambulatory blood pressure (OR=1.366, 95% CI 1.122-1.662) compared to those with low ambulatory blood pressure (OR=1.217, 95% CI 1.057-1.402) [105].

Lipid Interactions

The role of lipids in modifying the HbA1c-DR relationship was examined in several investigations. Shuqi Wang et al. demonstrated that the HbA1c/HDL-C ratio was an independent risk factor for DR with moderate positive correlation ($r=0.342$, $p<0.001$) [22]. Binary logistic regression identified this ratio as superior to HbA1c alone for DR prediction, with an AUC of 0.711 [22].

Liping Gu et al. found significant interactions between magnesium status and HbA1c on DR risk, with the combined effect amplifying risk beyond individual effects [61]. This interaction was most pronounced among female patients, those aged ≥ 60 years, and individuals with cardiovascular disease history [61].

Yu-Ju Wu et al. identified important diet-HbA1c interactions, finding that among participants with high animal protein and processed food dietary patterns or low vegetable intake

patterns, elevated HbA1c ($\geq 8.5\%$) was associated with 4.44-fold (95% CI 1.34-14.68, $p=0.015$), 3.96-fold (95% CI 1.12-14.04, $p=0.033$), and 2.57-fold (95% CI 1.16-5.67, $p=0.020$) increases in DR risk, respectively [93].

Genetic and Demographic Modifiers

Ng et al. demonstrated a significant interaction between HbA1c levels and COL5A1 rs59126004 genotype on DR risk ($P_{\text{interaction}}=1.733 \times 10^{-3}$), with patients having adequate glycemic control (HbA1c $< 7\%$) and the protective C allele showing 42% lower risk of sight-threatening DR [35]. Mitchell et al. found that European mitochondrial haplogroups modify the effects of both diabetes duration and HbA1c on proliferative DR risk, with haplogroup H showing significant associations ($p=0.0001$ for duration, $p=0.011$ for HbA1c) while haplogroup UK showed no association [156].

Age-related effect modification was noted by Wong et al., who demonstrated that younger age at diabetes onset was associated with greater retinopathy risk for any given HbA1c level, with odds ratios of 16.6, 7.5, and 2.7 for age of diagnosis < 45 , 45-55, and > 55 years respectively when mean A1C was $> 9\%$ ($p=0.003$) [16]. Yu-Chi Sung et al. found that high initial HbA1c was more strongly associated with DR severity in females, patients < 65 years, and those without diet or exercise control [99].

Other Risk Factors and Confounders

Diabetes Duration

Diabetes duration emerged as one of the most consistent risk factors across studies. Stratton et al. reported that longer duration of diabetes was strongly associated with both DR incidence and progression [23]. Yun et al. found that among patients diagnosed with diabetes for longer than 10 years at baseline, a decrease in HbA1c led to a significant reduction in DR risk (HR=0.73 per 1% HbA1c decrement, 95% CI 0.58-0.91, $p=0.005$) [25], demonstrating that glycemic control benefits persist even in longstanding disease.

Kawasaki et al. found that the strength of association between diabetes duration and incident DR increased rapidly during the period of 5 to 10 years duration [5]. Yun et al. reported mean durations of 14.8, 16.7, and 17.3 years for the first diagnosis of mild NPDR, moderate NPDR, and severe NPDR or PDR, respectively [25].

P. K. V. Sai Akshay et al. stratified patients by diabetes duration (5-10 years, 11-15 years, >15 years) and found that the proportion of patients with PDR and severe NPDR was significantly higher among those with duration >15 years ($p<0.01$), demonstrating a clear temporal trend in DR severity [122].

Nephropathy and Renal Function

Diabetic nephropathy and markers of renal dysfunction showed strong associations with DR across multiple studies. Kalaivani et al. found that microalbuminuria was identified as the significant variable associated with the development and progression of retinopathy, with 93.3% of patients with microalbuminuria having DR [12]. García-Ulloa et al. demonstrated that albumin-to-creatinine ratio (ACR) >30 mg/g was associated with increased DME risk (OR=1.19) [68], with age and ACR modifying the HbA1c-DR relationship [68].

Manaviat et al. found that DR and renal involvement were highly positively correlated ($p=0.001$) [84], with microalbuminuria serving as a reliable marker of retinopathy [84]. He et al. identified diabetic nephropathy as an independent risk factor for DR in multivariate analysis [13]. Yukihiisa Suzuki et al. found that DN grade correlated significantly with DR development, with logistic regression showing associations between DR and both average HbA1c (OR=5.57, 95% CI 1.27-24.4) and highest HbA1c (OR=2.46, 95% CI 1.12-5.38) [188].

Hypertension and Blood Pressure

Hypertension was consistently identified as a significant risk factor across studies. Salti et al. found that systolic blood pressure (per 10 mmHg, OR=1.27, 95% CI 1.0-1.56, $p=0.037$) was an independent risk factor for DR [58]. Bulum et al. demonstrated that systolic (AOR=1.06, $p=0.004$)

and diastolic blood pressure (AOR=1.12, $p=0.007$) were independent risk factors for DR even after adjustment for diabetes duration and HbA1c [15].

Stratton et al. reported that higher blood pressure was associated with DR incidence (OR per 5 mmHg systolic BP=1.16, $p<0.001$) [1]. Pei Zhang et al. found increased systolic blood pressure was a significant risk factor (OR=1.071, 95% CI 1.037-1.106) [64]. Tomić et al. specifically noted that 39.7% of patients underwent their first fundus examination due to diabetes, and 67% of them had sight-threatening DR, with patients having the first examination showing peaks in systolic and diastolic blood pressure [148].

Lipid Abnormalities

Lipid profiles showed variable associations with DR across studies. Several investigations found significant relationships between dyslipidemia and DR. K. S. et al. (2021) reported that higher total cholesterol, triglyceride levels, and LDL cholesterol levels were significantly associated with DR severity [40]. Hosny et al. demonstrated that serum apolipoprotein B and the apo B/apo A ratio were higher in patients with DR, particularly in proliferative DR [67].

However, the specific lipid fractions showing associations varied. Some studies found elevated LDL and triglycerides to be risk factors [40, 103, 139], while others identified protective effects for certain lipid parameters. Martín-Merino et al. reported that HDL ≥ 1.55 mmol/l was associated with slightly reduced DR risk (OR=0.88, 95% CI 0.80-0.98), as were high triglycerides (OR=0.90, 95% CI 0.82-0.99 for 2.3-5.6 mmol/l) [50]. Romero-Aroca et al. found a protective effect of HDL-cholesterol and fibrate use on DR development [153].

Body Mass Index and Obesity

The relationship between BMI and DR was complex and sometimes paradoxical. Kaštelan et al. found that DR progression increased significantly with higher BMI, and BMI correlated with HbA1c, hypertension, and cholesterol levels [111]. However, other studies reported inverse associations. Carlos Hernández-Teixidó et al. found that obesity appeared to be a protective factor

against DR (HR=0.93, 95% CI 0.89-0.98) [3], while Manaviat et al. reported a significant inverse relationship between BMI and DR (p=0.02) [84].

Insulin Use and Treatment Modality

Insulin use was frequently associated with higher DR prevalence, though this likely reflects confounding by indication rather than a causal relationship. Li et al. found that insulin therapy was associated with increased DR risk (OR=4.82, 95% CI 3.55-6.57, p<0.05) and remained significant in multivariate analysis (OR=3.38, 95% CI 2.38-4.8, p<0.05) [27]. Yan et al. identified insulin treatment as a potential risk factor for DR with OR=6.99 (95% CI 1.39-35.12) [54]. Martín-Merino et al. noted that users of hypoglycaemic agents had increased DR risk [50].

Conversely, Amr Muhammad Badr Salah El-Deen et al. found a significant inverse relation between insulin use and both HbA1c level and prevalence of DR in type 2 diabetic patients [62], suggesting that insulin use in well-controlled patients may be protective.

Neuropathy

The relationship between diabetic neuropathy and DR was examined in several studies. Agapitou et al. found that presence of neuropathy was independently associated with DR (multivariate OR=3.59, 95% CI 1.43-9.05, p=0.007) [57]. Rehna Rasheed et al. demonstrated a statistically significant association between DR and diabetic peripheral neuropathy, with there being early changes in inner retinal layers paralleling DPN in the course of diabetes [170].

Kiyoung Kim et al. found that severe cardiac autonomic neuropathy and lower peripheral nerve-conduction velocity were significant predictive factors for DR progression in multivariate modeling (area under curve=0.92) [191]. These findings suggest shared pathophysiological mechanisms between different microvascular complications.

Age and Gender

Age effects on the HbA1c-DR relationship were inconsistent across studies. Some investigations found younger age at diabetes diagnosis to be a risk factor [103, 139], while others

reported that older patients had higher DR risk [25, 197]. Yu-Chi Sung et al. found that patients aged ≥ 65 years were less likely to develop severe DR [99], contrasting with findings from other studies.

Gender effects were similarly variable. Li et al. identified male gender as significantly associated with DR (OR=2.21, 95% CI 1.57-3.11, $p<0.05$) [27], and Chatziralli et al. found male sex as an independent risk factor (multivariate OR for male sex) [2]. However, Ying-Chu Chiu et al. found being female was a significant risk factor (adjusted HR=1.287, 95% CI 1.082-1.531) [70], and Geetha et al. reported female patients were more affected than males [98].

Race and Ethnicity

Racial and ethnic differences in the HbA1c-DR relationship were noted in several studies. White et al. found that American Indian race was associated with less frequent DR compared with non-Hispanic White race (OR=0.36, 95% CI 0.20-0.66) [28]. Tarasewicz et al. reported that non-white patients generally had a higher risk of progression to all forms of DR, while Asian patients were less likely to develop diabetic macular edema (HR=0.76, 95% CI 0.66-0.87) [7]. Yan Liu et al. identified Hispanic ethnicity as a significant independent risk factor for PDR [139].

Synthesis

The evidence overwhelmingly demonstrates that elevated HbA1c levels are strongly and consistently associated with increased risk of diabetic retinopathy in patients with type 2 diabetes mellitus. This relationship holds across diverse populations, healthcare settings, and analytical approaches.

The dose-response relationship appears largely linear across the middle range of HbA1c values, with most studies showing progressive increases in DR risk as HbA1c rises above 7% [1–4]. However, some evidence suggests more complex patterns at the extremes: very low HbA1c levels ($<5.2\%$) show lower but non-zero risk [26], while one study identified an inverted U-shaped relationship peaking at 9.4% [77], possibly reflecting survival bias or metabolic adaptations in very poorly controlled disease.

The strength of the HbA1c-DR association is modified by multiple factors. Combined poor control of HbA1c with blood pressure or lipids produces multiplicative rather than simply additive increases in risk [10, 11]. Historical glycemic exposure (glucose memory) influences current DR risk independent of recent HbA1c levels [9], and HbA1c variability confers additional risk beyond mean levels [8, 56, 101]. These findings indicate that both achieving target HbA1c levels and maintaining stable glycemic control are important for DR prevention.

The association between HbA1c and DR appears stronger in certain subgroups, including those with younger age at diabetes onset [16], longer disease duration [44], concurrent nephropathy [12, 13], and elevated blood pressure [14, 15, 105]. Genetic factors may also modify susceptibility [35, 156].

For patients with early-stage DR (mild to moderate NPDR), concerns about early worsening with rapid HbA1c reduction appear unfounded based on current evidence [190], though this may not apply to more advanced retinopathy. The few null findings were generally from small studies with methodological limitations [133, 134, 138, 196].

The identification of specific HbA1c thresholds for screening purposes shows some variation across populations, with cut-offs ranging from 6.6% to 8.15% [17–20]. This variation likely reflects differences in study populations, DR staging systems, and intended balance between sensitivity and specificity. For clinical glycemic targets to prevent DR, the preponderance of evidence supports maintaining HbA1c below 7%, with substantially elevated risk above this threshold [2, 4, 10, 46].

The evidence base includes substantial heterogeneity in study design, with cross-sectional studies predominating but important contributions from prospective cohorts and large-scale registry analyses. The cross-sectional studies establish association but cannot definitively establish temporal precedence, while the prospective cohort studies and the examination of historical HbA1c values provide stronger evidence for causality.

DISCUSSION

The findings of this systematic review, encompassing 200 studies across diverse global populations, provide compelling evidence for a strong, consistent, and dose-dependent relationship between elevated HbA1c levels and increased risk of diabetic retinopathy in patients with type 2 diabetes mellitus. This discussion synthesizes the key findings, explores their mechanistic and clinical implications, examines effect modification by other risk factors, addresses apparent discrepancies in the literature, and identifies priorities for future research.

Strength and Consistency of the HbA1c-DR Association

The overwhelming consistency of the positive association between HbA1c and DR across studies varying widely in geographic location, healthcare setting, study design, and population characteristics underscores the fundamental nature of this relationship. The adjusted odds ratios ranging from 1.60 to 4.23 for elevated HbA1c categories, and hazard ratios of 1.16-1.66 per 1% HbA1c increment, demonstrate clinically meaningful effect sizes that persist after adjustment for potential confounders (1-3,5,6). The consistency of findings across Asia, Europe, the Middle East, the Americas, and Africa suggests that the biological relationship between hyperglycemia and retinal microvascular damage transcends ethnic and environmental variations, supporting the generalizability of glycemic control recommendations globally (4,26-29).

The dose-response relationship observed across multiple studies provides particularly strong evidence for causality. The progressive increase in DR risk with each incremental rise in HbA1c, from the categorical analyses showing stepwise increases in odds ratios (1) to the continuous analyses demonstrating linear or near-linear relationships across the middle range of HbA1c values (5,6), aligns with established Hill criteria for causal inference. Furthermore, the demonstration of higher mean HbA1c levels with increasing DR severity—from mild non-proliferative DR through proliferative disease—provides additional evidence for a biological gradient (17,30,31). The observation that patients with proliferative DR consistently show the highest HbA1c levels, often exceeding 10-12%, reinforces the concept that sustained severe hyperglycemia drives progressive microvascular injury (30,32).

Threshold Effects and Optimal HbA1c Targets

The identification of specific HbA1c thresholds for DR risk stratification has important clinical implications. The convergence of evidence supporting 7% as a critical threshold above which DR risk increases substantially aligns with current clinical practice guidelines (2,4,10,18,46). However, the variation in optimal cut-off values identified through ROC analysis—ranging from 6.6% to 8.15% across different populations—suggests that a single universal threshold may not optimally balance sensitivity and specificity in all settings (17-20). This variation likely reflects differences in population characteristics, DR staging methods, and the intended balance between screening sensitivity and specificity. The identification of 7.25% by Tangjai et al. (18) and 8.15% by Setareh et al. (20) as optimal screening thresholds in different populations illustrates the importance of context-specific validation.

The intriguing finding of an inverted U-shaped relationship between HbA1c and DR with a peak at 9.4% reported by Ling et al. (15) merits careful consideration. While this pattern might appear to contradict the prevailing linear dose-response model, several explanations warrant exploration. Survival bias could contribute, as patients with the most extreme HbA1c elevations may have higher mortality from other complications before DR can develop or be detected. Alternatively, this finding might reflect a plateau effect at very high HbA1c levels where maximal microvascular damage has already occurred, or could represent statistical artifact related to small numbers of patients at extreme HbA1c values. Regardless, this observation underscores the need for continued investigation of the full dose-response spectrum and caution against assuming linearity across all HbA1c ranges.

HbA1c Variability: An Emerging Independent Risk Factor

The recognition of HbA1c variability as an independent predictor of DR risk represents a significant advance in our understanding of glycemic contributions to microvascular complications (8,21,33). The meta-analysis by Zhai et al. (8) demonstrating that higher HbA1c variability—whether measured as standard deviation (RR=1.48) or coefficient of variation (RR=1.29)—is associated with increased DR risk independent of mean HbA1c levels has important clinical implications. The persistence of this association after adjustment for mean HbA1c indicates that

variability captures a distinct aspect of glycemic exposure relevant to retinal pathophysiology. The finding by Hu et al. (21) that this association becomes particularly important when variability exceeds 0.75% provides a potential clinically actionable threshold.

The biological plausibility of HbA1c variability as a risk factor is supported by mechanistic considerations. Fluctuating glucose concentrations may subject retinal microvascular endothelial cells to repeated cycles of metabolic stress, oxidative injury, and inflammatory activation that produce cumulative damage beyond that caused by sustained hyperglycemia alone (34). Glucose variability has been associated with increased oxidative stress markers, endothelial dysfunction, and activation of inflammatory pathways—all mechanisms implicated in DR pathogenesis (35). The observation by Park et al. (36) that both mean HbA1c and HbA1c standard deviation were associated with DR progression risk reinforces the concept that stable glycemic control may be as important as achieving specific target levels.

These findings suggest that clinical assessment of glycemic control should extend beyond evaluation of single HbA1c measurements or even average values to include measures of variability over time. For patients with widely fluctuating HbA1c values despite acceptable mean levels, interventions targeting glycemic stability—such as structured education, continuous glucose monitoring, or medication adjustments to minimize excursions—may confer additional retinopathy protection beyond that achieved by mean HbA1c reduction alone.

Glycemic Memory and Temporal Considerations

The demonstration of "glycemic memory" or "metabolic memory" effects—wherein historical glycemic exposure influences current DR risk independent of recent control—provides critical insights into the temporal dynamics of the HbA1c-DR relationship (9,25). The finding by Ducos et al. (9) that DR was significantly associated with HbA1c levels from 5 years prior (OR=6.75) but not with more recent values suggests that the retinal microvasculature retains a "memory" of prior metabolic insults that continues to drive pathology even after glycemic improvement. This phenomenon has profound implications for both the timing of interventions and the interpretation of cross-sectional studies.

The observation by Yoshida et al. (25) that patients with initial HbA1c above 8.2% showed higher DR probability during subsequent follow-up despite maintained control aligns with the legacy effect demonstrated in major clinical trials. These findings imply that early intensive glycemic control may be particularly important for long-term retinopathy prevention, and that delayed intervention may not fully reverse the effects of prior hyperglycemic exposure. The reassuring finding by Simó et al. (37) that rapid HbA1c reduction was not associated with early DR worsening in patients with mild to moderate non-proliferative DR addresses clinical concerns about potential acute exacerbation with intensive glucose lowering and supports the safety of prompt glycemic optimization in this population.

Effect Modification by Blood Pressure

The interaction between glycemic control and blood pressure emerges as one of the most consistently documented and clinically important effect modifiers in the HbA1c-DR relationship. The demonstration by multiple studies that combined poor control of both parameters produces multiplicative rather than simply additive increases in DR risk has direct implications for clinical management (10,11,22,38). The finding by Pan et al. (10) that combined lower HbA1c (<7%) and systolic blood pressure (<140 mmHg) was associated with 43% reduced DR likelihood while neither factor alone showed significant association underscores the synergistic nature of these risk factors.

The mechanistic basis for this interaction is well-established. Hyperglycemia and hypertension both contribute to microvascular injury through overlapping pathways including endothelial dysfunction, oxidative stress, activation of the renin-angiotensin system, and hemodynamic perturbations (39). The retinal microcirculation is particularly vulnerable to the combined effects of metabolic and hemodynamic stresses. The demonstration by Cardoso et al. (22) and Bulum et al. (38) that ambulatory blood pressure parameters predict DR independent of HbA1c, and the finding by Yang et al. (40) that the HbA1c-DR relationship is markedly stronger in patients with elevated ambulatory blood pressure, reinforce the importance of comprehensive risk factor management.

These findings support clinical guidelines recommending integrated management of both glycemic and blood pressure targets in T2DM patients. The observation that achieving control of both parameters is more beneficial than optimizing either alone should inform patient counseling and treatment prioritization. For patients with suboptimal blood pressure control, the DR risk associated with any given HbA1c level may be substantially amplified, suggesting that these individuals warrant particularly intensive surveillance and multifactorial intervention.

Lipid Interactions and Metabolic Syndrome

The relationship between lipid parameters and DR, and their interaction with HbA1c, reveals a complex picture that varies by specific lipid fraction and population studied. The finding by Wang et al. (41) that the HbA1c/HDL-C ratio was superior to HbA1c alone for DR prediction (AUC=0.711) suggests that integrated measures reflecting both glycemic and lipid metabolism may capture synergistic risk contributions. The demonstration that HDL cholesterol may exert protective effects against DR (42,43) aligns with the known anti-inflammatory and antioxidant properties of HDL particles and suggests potential mechanisms beyond cholesterol transport.

The inconsistent findings regarding specific lipid fractions—with some studies identifying LDL and triglycerides as risk factors while others report protective effects for certain parameters—may reflect population differences, variations in lipid measurement methodologies, or confounding by lipid-lowering therapy use. The protective effect of fibrate use reported by Romero-Aroca et al. (42) is particularly intriguing, as fenofibrate has demonstrated retinopathy benefits in clinical trials through mechanisms potentially independent of lipid lowering, including anti-inflammatory and anti-angiogenic effects. These observations suggest that lipid-modifying interventions may confer retinopathy protection through pathways distinct from their effects on cardiovascular risk.

Diabetes Duration and Cumulative Exposure

The consistent identification of diabetes duration as a major risk factor for DR, often with effect sizes comparable to or exceeding those of HbA1c, underscores the importance of cumulative exposure in microvascular complication pathogenesis (5,23,44). The finding by Yun et al. (23) that glycemic control benefits persist even in longstanding disease (HR=0.73 per 1% HbA1c decrement in patients with >10 years duration) provides important reassurance that intervention remains

valuable regardless of disease duration. However, the demonstration by Kawasaki et al. (5) that the association between duration and incident DR increases most rapidly during years 5-10 suggests that this period may represent a critical window for preventive interventions.

The interaction between diabetes duration and HbA1c in determining DR risk has important implications for risk stratification. Patients with longer disease duration may require more stringent HbA1c targets or more frequent retinal screening even when current glycemic control appears acceptable, reflecting the cumulative effects of prior exposure. The concept of "glycemic load"—integrating both duration and degree of hyperglycemic exposure—may provide a more comprehensive risk assessment than either parameter alone and warrants further investigation as a potential clinical tool.

Nephropathy as a Marker and Mediator

The strong association between diabetic nephropathy and DR, with microalbuminuria consistently identified as a significant predictor across multiple studies (12,13,45,46), reflects the shared vulnerability of renal and retinal microvasculature to diabetic injury. The finding by Kalaivani et al. (12) that 93.3% of patients with microalbuminuria had DR highlights the potential of renal markers to identify patients at particularly high retinopathy risk. The demonstration by García-Ulloa et al. (46) that albumin-to-creatinine ratio modifies the HbA1c-DR relationship suggests that renal involvement may identify a subgroup with enhanced susceptibility to glycemic injury.

The pathophysiological mechanisms linking nephropathy and retinopathy include shared risk factors (hyperglycemia, hypertension, dyslipidemia), common pathogenic pathways (oxidative stress, inflammation, advanced glycation end-product accumulation), and potentially direct effects of renal dysfunction on retinal microvasculature through accumulation of uremic toxins or alterations in growth factor regulation. These findings support the clinical practice of enhanced retinal surveillance in patients with evidence of diabetic kidney disease, regardless of current glycemic control.

Genetic and Demographic Modifiers

The identification of genetic factors modifying the HbA1c-DR relationship opens new avenues for personalized risk assessment. The demonstration by Ng et al. (35) of significant interaction between HbA1c levels and COL5A1 genotype ($P_{\text{interaction}}=1.733 \times 10^{-3}$), with patients carrying the protective C allele showing 42% lower risk of sight-threatening DR when glycemic control was adequate, illustrates the potential for genetic information to refine risk stratification. The finding by Mitchell et al. (47) that European mitochondrial haplogroups modify the effects of both diabetes duration and HbA1c on proliferative DR risk suggests that mitochondrial function may influence susceptibility to glycemic injury.

The age-related effect modification noted by Wong et al. (48)—with younger age at diabetes onset associated with greater retinopathy risk for any given HbA1c level—has important implications for risk communication and screening intensity. The substantially higher odds ratios for HbA1c >9% in patients diagnosed before age 45 (OR=16.6) compared to those diagnosed after 55 (OR=2.7) suggests that early-onset type 2 diabetes may represent a particularly aggressive phenotype requiring intensive management. The finding by Sung et al. (49) that high initial HbA1c was more strongly associated with DR severity in females and younger patients reinforces the concept of differential susceptibility.

Racial and Ethnic Variations

The observed racial and ethnic differences in the HbA1c-DR relationship highlight the importance of considering population-specific factors in risk assessment. The finding by White et al. (28) that American Indian race was associated with less frequent DR compared to non-Hispanic Whites (OR=0.36), and by Tarasewicz et al. (7) that Asian patients were less likely to develop diabetic macular edema (HR=0.76), suggests that genetic, environmental, or healthcare access factors may modulate retinopathy risk. These observations do not diminish the importance of glycemic control but rather suggest that the absolute risk associated with any given HbA1c level may vary across populations.

Several mechanisms could contribute to these differences, including variations in hemoglobin glycation rates, erythrocyte lifespan, genetic susceptibility variants, dietary patterns, healthcare utilization, and competing mortality risks. The clinical implication is that population-

specific validation of risk prediction models may be necessary, and that extrapolation of risk estimates across diverse populations should be undertaken with appropriate caution.

Paradoxical Findings and Apparent Contradictions

The small number of studies reporting null or weak findings merits careful examination, as these apparent contradictions may illuminate important methodological considerations. The finding by Hussain et al. (50) that a single high HbA1c measurement was not significantly associated with retinopathy ($p=0.08$) actually aligns with the broader evidence base suggesting that sustained exposure, rather than isolated elevations, drives DR risk. This observation underscores the limitation of cross-sectional studies with single HbA1c measurements and supports the value of longitudinal assessments capturing cumulative exposure.

The null findings from small studies such as Mia et al. (51) ($n=37$) and Rangkuti et al. (52) ($n=30$) likely reflect inadequate statistical power to detect modest effect sizes rather than true absence of association. The wide confidence intervals and lack of significant findings in these underpowered studies should not be interpreted as evidence against the HbA1c-DR relationship but rather as illustrations of the importance of adequate sample size in observational research. The null finding by Domngang et al. (53) in a study with only 12 DR cases similarly highlights the vulnerability of small studies to type II error.

The apparent protective effect of obesity reported in some studies (3,45) represents a more complex paradox. This finding may reflect survival bias (healthier obese patients surviving to older ages), competing risks (obese patients dying from cardiovascular disease before DR develops), or genuine biological differences in retinopathy susceptibility related to adipokine profiles or metabolic phenotypes. The concept of "metabolically healthy obesity" and its relationship to microvascular complications warrants further investigation.

Clinical Implications

The findings of this systematic review have several direct implications for clinical practice. First, the strong and consistent association between HbA1c and DR supports continued emphasis on glycemic control as a cornerstone of retinopathy prevention. The evidence supporting 7% as a critical threshold suggests that this target remains appropriate for most patients, though

individualization based on patient characteristics, disease duration, and comorbidity profile remains important.

Second, the independent contribution of HbA1c variability to DR risk suggests that clinical monitoring should extend beyond assessment of mean HbA1c to include evaluation of glycemic stability. Patients with widely fluctuating values may benefit from interventions targeting variability reduction, including structured education, continuous glucose monitoring, or medication regimens designed to minimize glucose excursions.

Third, the consistent evidence for effect modification by blood pressure, lipid parameters, and nephropathy status supports multifactorial risk management approaches. Achieving combined control of multiple risk factors produces greater retinopathy risk reduction than optimizing any single parameter alone. The multiplicative nature of these interactions suggests that patients with suboptimal control of multiple parameters warrant particularly intensive surveillance and intervention.

Fourth, the phenomenon of glycemic memory implies that early intensive control may be particularly important for long-term retinopathy prevention. Delayed intensification of glycemic management may not fully reverse the effects of prior hyperglycemic exposure, supporting the value of achieving glycemic targets early in the disease course.

Fifth, the variation in optimal HbA1c thresholds across populations suggests that screening algorithms may benefit from local validation. While maintaining HbA1c below 7% remains an appropriate target for most patients, the threshold for initiating more intensive retinal surveillance may reasonably vary based on population characteristics and healthcare resources.

Research Priorities

This systematic review identifies several priorities for future research. First, prospective studies with repeated HbA1c measurements over extended follow-up are needed to better characterize cumulative glycemic exposure and variability effects. The optimal metrics for quantifying long-term glycemic control—whether time-weighted average, area under the curve, variability indices, or some combination—require further investigation.

Second, randomized controlled trials comparing interventions targeting HbA1c variability reduction versus mean HbA1c lowering alone would provide definitive evidence regarding the independent contribution of glycemic stability. Such trials could establish whether interventions specifically designed to minimize glucose excursions confer additional retinopathy protection beyond that achieved by mean HbA1c reduction.

Third, studies integrating genetic, metabolomic, and proteomic markers with longitudinal glycemic data could identify patients at particularly high or low susceptibility to glycemic injury. Such personalized risk prediction tools could enable more targeted screening and intervention strategies.

Fourth, investigation of the mechanisms underlying glycemic memory at the molecular level could identify novel therapeutic targets. Understanding how prior hyperglycemic exposure is "remembered" by retinal cells and how these effects might be reversed could lead to interventions capable of modifying established risk.

Fifth, large-scale, adequately powered studies in underrepresented populations are needed to validate the generalizability of findings across diverse ethnic and geographic groups. Current evidence is heavily weighted toward Asian and European populations, with limited data from Africa, Latin America, and other regions.

Sixth, studies examining the relationship between HbA1c and incident DR versus DR progression separately could identify whether different mechanisms or thresholds apply to these distinct outcomes. The finding that some risk factors differ in their associations with incidence versus progression suggests that separate analyses may be informative.

Strengths and Limitations

This systematic review possesses several strengths, including the comprehensive inclusion of 200 studies spanning diverse global populations, rigorous screening criteria ensuring focus on studies with clearly defined populations and outcomes, detailed data extraction capturing multiple dimensions of the HbA1c-DR relationship, and systematic synthesis of both main effects and interactions. The inclusion of studies with varying designs—cross-sectional, cohort, case-control, and meta-analyses—provides complementary perspectives on the relationship of interest.

However, several limitations must be acknowledged. The predominance of cross-sectional studies (69.5%) limits inferences about temporal relationships and causality, though the inclusion of 42 cohort studies partially addresses this concern. Heterogeneity in HbA1c measurement methods, categorization schemes, and DR assessment techniques across studies complicates direct comparison of effect sizes. Variation in adjustment for potential confounders across studies means that reported associations may not be directly comparable. Publication bias remains a concern, as studies with null findings may be less likely to be published, though the inclusion of some negative studies mitigates this concern. The quality of individual studies was not formally assessed using standardized instruments, which could influence confidence in specific findings.

CONCLUSION AND RECOMMENDATIONS

Summary of Findings

This systematic review of 200 studies provides compelling evidence for a strong, consistent, and dose-dependent positive association between elevated HbA1c levels and increased risk of diabetic retinopathy in patients with type 2 diabetes mellitus. The relationship demonstrates remarkable consistency across diverse geographic regions, healthcare settings, and population characteristics, supporting the fundamental nature of glycemic control in retinal microvascular health. Quantitative measures of association reveal clinically meaningful effect sizes, with adjusted odds ratios ranging from 1.60 to 4.23 for elevated HbA1c categories and hazard ratios of 1.16-1.66 per 1% increment.

The dose-response relationship manifests as progressive increases in DR risk with rising HbA1c, with most studies demonstrating linear or near-linear relationships across the middle glycemic range. The identification of 7% as a critical threshold above which risk increases substantially aligns with current clinical guidelines, though optimal screening cut-offs vary between 6.6% and 8.15% across populations. The demonstration of higher mean HbA1c with increasing DR severity—from mild non-proliferative disease through proliferative retinopathy—provides additional evidence for biological gradient.

Beyond mean HbA1c levels, glycemic variability emerges as an independent risk factor, with higher variability associated with increased DR risk regardless of average control. The meta-analytic finding of relative risks of 1.48 for standard deviation and 1.29 for coefficient of variation indicates that glycemic stability may be as important as achieving target levels. The phenomenon of glycemic memory—wherein historical glycemic exposure influences current DR risk independent of recent control—underscores the lasting effects of prior hyperglycemia and the importance of early intervention.

Effect modification by multiple factors significantly influences the HbA1c-DR relationship. Combined poor control of blood pressure and HbA1c produces multiplicative risk increases, supporting integrated management approaches. Diabetes duration, nephropathy status, lipid profiles, genetic factors, and demographic characteristics all modify susceptibility to glycemic injury, suggesting opportunities for personalized risk stratification. The identification of genetic interactions, including with COL5A1 genotype and mitochondrial haplogroups, opens avenues for understanding differential susceptibility.

Clinical Recommendations

Based on the synthesized evidence, several clinical recommendations emerge. Glycemic control targeting HbA1c below 7% should remain a cornerstone of DR prevention in most patients with T2DM. For individuals with longer disease duration, established complications, or multiple risk factors, more stringent targets may be considered, though the balance of benefits and risks requires individualization. Assessment of glycemic control should include evaluation of HbA1c variability over time, not merely achievement of target levels at single time points. Patients with widely fluctuating values may benefit from interventions targeting glycemic stability.

Multifactorial risk management addressing blood pressure and lipid parameters in addition to glycemic control is essential, as combined control produces synergistic benefits. The consistent interaction between blood pressure and HbA1c suggests that achieving both targets simultaneously should be prioritized. Patients with evidence of nephropathy warrant enhanced retinal surveillance regardless of current glycemic control, given the strong association between renal and retinal microvascular disease.

Screening strategies may benefit from population-specific validation of optimal HbA1c thresholds. While maintaining levels below 7% reduces risk, the threshold for initiating more intensive retinal surveillance may reasonably vary based on local resources and population characteristics. The finding that glycemic control benefits persist even in longstanding disease supports continued efforts to optimize glycemia regardless of diabetes duration.

Future Directions

Advancing our understanding of the HbA1c-DR relationship requires continued research investment. Prospective cohort studies with serial HbA1c measurements over extended follow-up are needed to better characterize cumulative exposure, variability effects, and critical exposure windows. Integration of glycemic data with genetic, metabolomic, and proteomic markers could enable personalized risk prediction and targeted intervention. Investigation of the molecular mechanisms underlying glycemic memory may identify novel therapeutic targets capable of reversing or mitigating the effects of prior hyperglycemic exposure.

Randomized trials comparing interventions targeting HbA1c variability reduction versus mean lowering alone would provide definitive evidence regarding the independent contribution of glycemic stability. Large-scale studies in underrepresented populations are needed to validate findings across diverse ethnic and geographic groups. Investigation of the relationship between HbA1c and specific DR outcomes—incidence versus progression, non-proliferative versus proliferative disease, macular edema versus retinopathy—could reveal differential mechanisms or thresholds.

Concluding Remarks

Diabetic retinopathy remains a leading cause of visual impairment worldwide, yet it is also one of the most preventable complications of diabetes when risk factors are optimally managed. The evidence synthesized in this systematic review reaffirms the central role of glycemic control in DR prevention while expanding our understanding to encompass the importance of glycemic stability, cumulative exposure, and multifactorial risk management. The consistency of findings across 200 studies spanning diverse global populations provides confidence in the fundamental

nature of the HbA1c-DR relationship and supports continued emphasis on glycemic control as a public health priority.

The recognition that the HbA1c-DR relationship is modified by multiple factors—blood pressure, lipids, diabetes duration, nephropathy, genetics, and demographic characteristics—suggests that personalized approaches to risk assessment and management may enhance prevention efforts. The identification of glycemic variability as an independent risk factor and the demonstration of glycemic memory effects highlight dimensions of glycemic exposure beyond mean levels that warrant clinical attention.

As the global burden of type 2 diabetes continues to rise, the importance of effective strategies to prevent debilitating complications such as diabetic retinopathy becomes ever more pressing. The evidence synthesized here provides a foundation for evidence-based clinical practice, identifies priorities for future research, and reaffirms the importance of comprehensive diabetes management in preserving vision and quality of life for the millions of individuals living with diabetes worldwide.

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