



The Relationship Between Fasting Blood Glucose and the Severity of Diabetic Retinopathy : A Comprehensive Systematic Review

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Article History :

Received date : 2025/12/21

Revised date : 2026/01/17

Accepted date : 2026/02/12

Published date : 2026/03/30



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E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Diabetic retinopathy (DR) is a leading cause of blindness. While glycated hemoglobin (HbA1c) is the standard glycemic metric, the role of fasting blood glucose (FBG) as an independent predictor of DR severity remains debated. This systematic review synthesizes evidence on the relationship between FBG and DR severity.

Methods: A systematic review of 80 studies (cross-sectional, cohort, RCTs, et al) was conducted. Data were extracted on FBG measurement, DR severity classification, study populations, confounding variables, and the direct association between FBG and DR.

Results: A positive association between elevated FBG and DR presence/severity was found across diverse populations. Meta-analyses reported pooled odds ratios (OR) for DR per unit FBG

increase ranging from 1.19 (95% CI: 1.13-1.26) to 2.41 (95% CI: 1.63-3.57) when combined with HbA1c. Longitudinal studies identified FBG thresholds (e.g., 6.9-7.4 mmol/L) for predicting DR risk. Large RCTs (ACCORD, DCCT) confirmed that intensive glycemic control, which reduces FBG, significantly slows DR progression. Fasting glucose variability emerged as an independent risk factor for DR in type 2 diabetes, even after adjusting for HbA1c. However, several studies found FBG lost independent significance when HbA1c was included in multivariable models. Key confounders included diabetes duration, hypertension, and renal function.

Discussion: The relationship between FBG and DR is significant but complex. The evidence supports FBG as a robust risk marker, particularly in type 2 diabetes, with a dose-response relationship and the added risk of glycemic variability. However, HbA1c remains a superior predictor of cumulative glycemic exposure. Discrepancies across studies may be explained by differences in diabetes type, study design (cross-sectional vs. longitudinal), and whether analyses adjusted for HbA1c. The effect of FBG is most pronounced in settings where HbA1c is unavailable or as a component of overall glycemic control.

Conclusion: Elevated FBG and its variability are significant, independent risk factors for DR presence and severity, especially in type 2 diabetes. While HbA1c remains a crucial metric, FBG provides valuable prognostic information. Clinical management should focus on achieving recommended FBG targets and minimizing glycemic variability to reduce DR risk.

Keywords: Fasting Blood Glucose, Diabetic Retinopathy, Glycemic Variability, Type 2 Diabetes Mellitus, Systematic Review

INTRODUCTION

Diabetic retinopathy (DR) remains a leading cause of preventable blindness among working-age adults worldwide, with its prevalence closely tied to the global diabetes epidemic (1,2). Chronic hyperglycemia is the central pathogenic driver of DR, leading to microvascular damage through advanced glycation end-product formation, oxidative stress, and inflammatory pathways (11,33). While glycated hemoglobin (HbA1c) has long been established as the gold standard for assessing long-term glycemic control and predicting microvascular complications, the specific role of fasting blood glucose (FBG) as an independent risk factor for DR severity is less clearly defined (13,34).

The current body of evidence presents a nuanced picture. Landmark trials like the Diabetes Control and Complications Trial (DCCT) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study have conclusively demonstrated that intensive glycemic control, which inherently reduces FBG, significantly lowers the risk of DR onset and progression (10,11). However, these studies primarily used HbA1c as their primary metric. This has led to a clinical and research gap where the independent predictive value of FBG, beyond its contribution to HbA1c, remains contested (8,9). Some studies report a strong, independent association between elevated FBG and DR severity, while others find this relationship is attenuated or nullified after adjusting for HbA1c or diabetes duration (4,14,22). Furthermore, emerging evidence suggests that glycemic variability, of which FBG fluctuations are a key component, may confer additional risk for microvascular complications independent of mean glucose levels (7,8).

Therefore, the primary problem is the lack of a comprehensive synthesis that distinguishes the role of FBG level from FBG variability and clarifies its independent contribution to DR severity across different populations and diabetes types. This systematic review aims to address this gap by synthesizing evidence from 80 studies to: (1) quantify the association between FBG levels and DR severity; (2) evaluate the role of FBG variability; (3) compare the predictive power of FBG with HbA1c; and (4) identify key confounders that modify this relationship. The novelty of this review

lies in its comprehensive approach, directly comparing studies that yield contradictory findings and highlighting the context-dependent nature of FBG as a risk marker. We hypothesize that elevated FBG and its variability are significant independent predictors of DR severity, particularly in type 2 diabetes, but that this effect is mediated by factors such as diabetes duration and is often superseded by HbA1c in adjusted models. The findings will provide clinicians with a clearer understanding of the prognostic value of FBG in DR risk stratification and inform strategies for optimizing glycemic management.

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 Fasting Blood Glucose and the Severity of Diabetic Retinopathy.

Screening

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

- **Study Population:** Does the study include participants with diabetes mellitus (Type 1 or Type 2), excluding those with gestational diabetes or secondary diabetes (e.g., drug-induced, pancreatic disease-related)?
- **Glucose Measurement:** Does the study measure fasting blood glucose levels (not limited to only random/non-fasting glucose or exclusively other glucose markers like HbA1c)?
- **Retinopathy Assessment:** Does the study assess diabetic retinopathy severity using standardized classification systems (e.g., ETDRS, modified Airlie House classification) with severity grading beyond just presence/absence?

- **Data Availability:** Does the study provide sufficient data to assess the relationship between fasting blood glucose and diabetic retinopathy severity?
- **Study Design:** Is the study a cross-sectional, cohort, case-control study, systematic review, or meta-analysis (not a case report, case series, editorial, or conference abstract)?
- **Study Type:** Is this a human study (not an 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	Diabetes Mellitus	Fasting Blood Glucose	HbA1c	Diabetic Retinopathy Severity
Keyword 2	Type 2 Diabetes	Fasting Plasma Glucose	Glycated Hemoglobin	Retinopathy Progression
Keyword 3	Adult Diabetic Patients	Glycemic Control	No Diabetic Retinopathy	Proliferative Diabetic Retinopathy
Keyword 4	Diabetes Mellitus Patients	Glucose Variability	Non-proliferative Diabetic Retinopathy	Sight-threatening Diabetic Retinopathy

The Boolean MeSH keywords inputted on databases for this research are: ("*Diabetes Mellitus*" OR "*Type 2 Diabetes*" OR "*Adult Diabetic Patients*" OR "*Glucose Variability*") AND

("Fasting Blood Glucose" OR "Fasting Plasma Glucose" OR "Glycemic Control" OR "Glucose Variability") AND ("HbA1c" OR "Glycated Hemoglobin" OR "No Diabetic Retinopathy" OR "Non-proliferative Diabetic Retinopathy") AND ("Diabetic Retinopathy Severity" OR "Retinopathy Progression" OR "Proliferative Diabetic Retinopathy" OR "Sight-threatening Diabetic Retinopathy")

Data extraction

- **FBG Measurement:**

Extract comprehensive details about how fasting blood glucose was measured in relation to diabetic retinopathy assessment, including:

- Measurement method (e.g., plasma glucose, venous vs capillary)
- Units reported (mmol/L, mg/dL)
- Fasting duration required
- Timing relative to DR assessment
- Single measurement vs repeated measurements
- Any variability measures (e.g., coefficient of variation, standard deviation)
- Quality control procedures mentioned

- **DR Severity Classification:**

Extract details about how diabetic retinopathy severity was assessed and classified, including:

- Classification system used (e.g., ETDRS, simplified scales, clinical grading)
- Specific severity categories defined (e.g., no DR, mild, moderate, severe, proliferative)

- Assessment method (fundoscopy, photography, imaging)
- Who performed the assessment (ophthalmologist, trained grader, automated)
- Presence of diabetic macular edema as separate outcome
- Inter-observer reliability if reported

- **FBG-DR Association:**

Extract the specific relationship found between fasting blood glucose levels and diabetic retinopathy severity, including:

- Direction of association (positive, negative, no association)
- Statistical measures (correlation coefficients, odds ratios, hazard ratios, beta coefficients)
- Effect sizes with 95% confidence intervals
- P-values and statistical significance
- Cutoff values or thresholds identified for FBG predicting DR risk
- Dose-response relationship if examined
- Separate results for different DR severity levels
- Results from adjusted vs unadjusted analyses

- **Study Population:**

Extract key characteristics of the study population that are relevant to the FBG-diabetic retinopathy relationship, including:

- Diabetes type (Type 1, Type 2, mixed)

- Sample size with DR vs without DR
- Age range and mean age
- Duration of diabetes
- Geographic location and healthcare setting
- Inclusion/exclusion criteria related to diabetes management
- Baseline DR status
- Treatment status (insulin, oral medications, diet-controlled)

- **Confounding Variables:**

Extract other factors examined that might influence the relationship between fasting blood glucose and diabetic retinopathy severity, including:

- HbA1c levels and their relationship to both FBG and DR
- Blood pressure and hypertension status
- Lipid profile (cholesterol, triglycerides)
- Duration of diabetes
- BMI or obesity measures
- Kidney function/diabetic nephropathy
- Smoking status
- Medication use affecting glucose control
- Which variables were controlled for in multivariate analyses

- Any interaction effects reported

- **Study Methodology:**

Extract key methodological details that affect the validity of the FBG-diabetic retinopathy relationship findings, including:

- Study design (cross-sectional, cohort, etc)
- Follow-up duration for longitudinal studies
- Sampling method and potential selection bias
- Temporal relationship between FBG measurement and DR assessment
- Blinding of DR assessors to FBG levels
- Missing data handling
- Multiple testing corrections
- Study limitations acknowledged by authors that specifically relate to the FBG-DR relationship

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Diabetes Mellitus" OR "Type 2 Diabetes" OR "Adult Diabetic Patients" OR "Glucose Variability") AND ("Fasting Blood Glucose" OR "Fasting Plasma Glucose" OR "Glycemic Control" OR "Glucose Variability") AND ("HbA1c" OR "Glycated Hemoglobin" OR "No Diabetic Retinopathy" OR "Non-proliferative Diabetic Retinopathy") AND ("Diabetic Retinopathy Severity" OR "Retinopathy Progression" OR "Proliferative Diabetic Retinopathy" OR "Sight-threatening Diabetic Retinopathy")</i>	133
Semantic Scholar	<i>("Diabetes Mellitus" OR "Type 2 Diabetes" OR "Adult Diabetic Patients" OR "Glucose Variability") AND ("Fasting Blood Glucose" OR "Fasting Plasma Glucose" OR "Glycemic Control" OR "Glucose Variability") AND ("HbA1c" OR "Glycated Hemoglobin" OR "No Diabetic Retinopathy" OR "Non-proliferative Diabetic Retinopathy") AND ("Diabetic Retinopathy Severity" OR "Retinopathy Progression" OR "Proliferative Diabetic Retinopathy" OR "Sight-threatening Diabetic Retinopathy")</i>	267
Springer	<i>("Diabetes Mellitus" OR "Type 2 Diabetes" OR "Adult Diabetic Patients" OR "Glucose Variability") AND ("Fasting Blood Glucose" OR "Fasting Plasma Glucose" OR "Glycemic Control" OR "Glucose Variability") AND ("HbA1c" OR "Glycated Hemoglobin" OR "No Diabetic Retinopathy" OR "Non-proliferative Diabetic Retinopathy") AND ("Diabetic Retinopathy Severity" OR "Retinopathy Progression" OR "Proliferative Diabetic Retinopathy" OR "Sight-threatening Diabetic Retinopathy")</i>	1,297
Google Scholar	<i>("Diabetes Mellitus" OR "Type 2 Diabetes" OR "Adult Diabetic Patients" OR "Glucose Variability") AND ("Fasting Blood Glucose" OR "Fasting Plasma Glucose" OR "Glycemic Control" OR "Glucose Variability") AND ("HbA1c" OR "Glycated Hemoglobin" OR "No Diabetic Retinopathy" OR "Non-proliferative Diabetic Retinopathy") AND ("Diabetic Retinopathy Severity" OR "Retinopathy Progression" OR "Proliferative Diabetic Retinopathy" OR "Sight-threatening Diabetic Retinopathy")</i>	19,500
Wiley Online Library	<i>("Diabetes Mellitus" OR "Type 2 Diabetes" OR "Adult Diabetic Patients" OR "Glucose Variability") AND ("Fasting Blood Glucose" OR "Fasting Plasma Glucose" OR "Glycemic Control" OR "Glucose Variability") AND ("HbA1c" OR "Glycated Hemoglobin" OR "No Diabetic Retinopathy" OR "Non-proliferative Diabetic Retinopathy") AND ("Diabetic Retinopathy Severity" OR "Retinopathy Progression" OR "Proliferative Diabetic Retinopathy" OR "Sight-threatening Diabetic Retinopathy")</i>	23

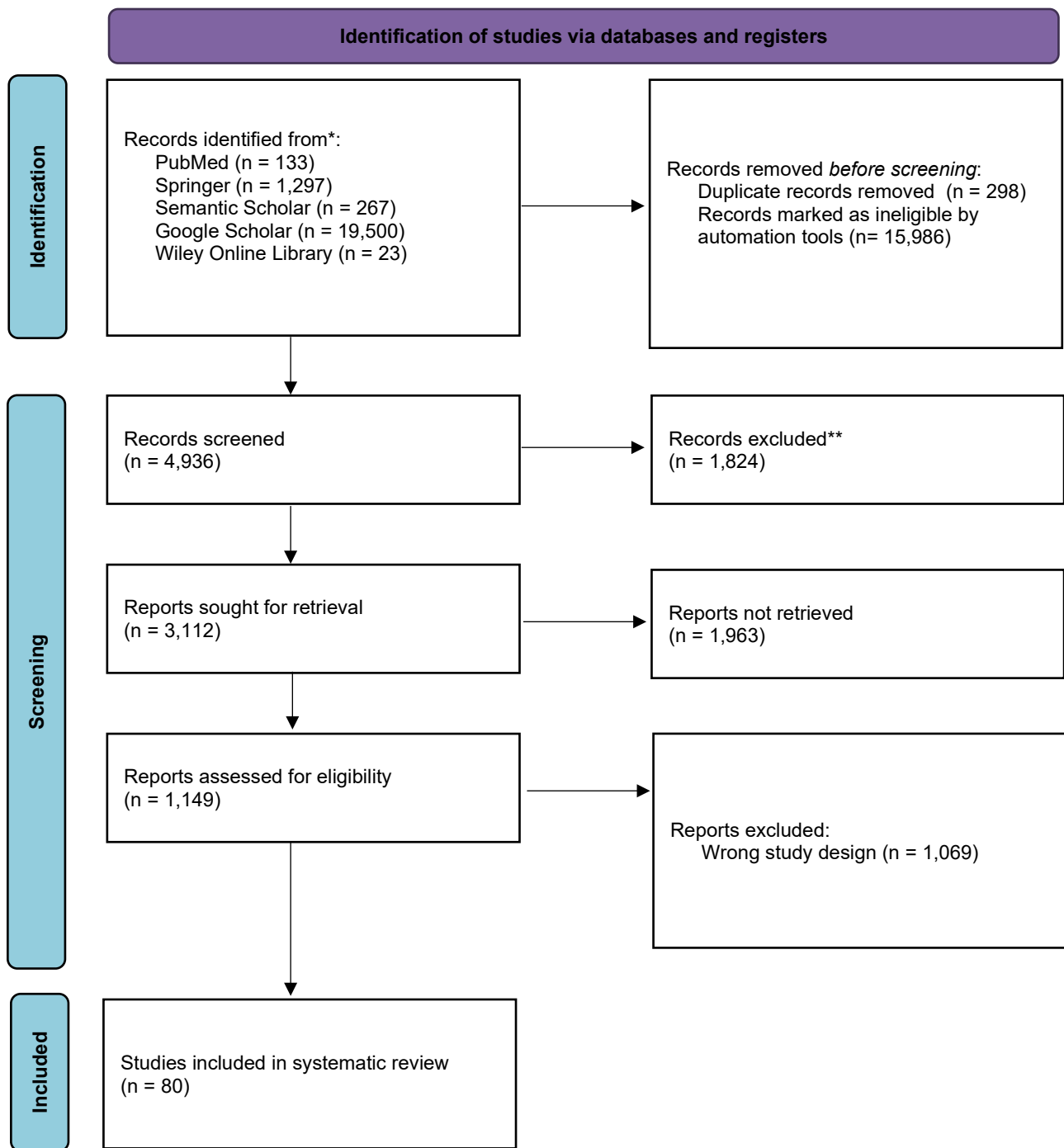


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

This review encompasses 80 sources examining the relationship between fasting blood glucose (FBG) and diabetic retinopathy (DR) severity. The included studies span diverse designs, populations, and geographic settings. The majority focus on type 2 diabetes, though several landmark trials and analyses address type 1 diabetes. The table below summarizes the key characteristics of all included sources.

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
Q. Jiang et al., 2017	Type 2 [17]	Not reported [17]	Not reported [17]	Yes [17]
G. C. C. Reyes et al., 2026	Predominantly Type 2 [18]	201 (70 DR, 131 no DR) [18]	Philippines [18]	Yes [18]
H. Hwang et al., 2020	Type 2 [19]	380 (40 DR, 340 no DR) [19]	Not reported [19]	Yes [19]
Y. Patel et al., 2017	Type 2 [20]	194 [20]	Not reported [20]	Yes [20]
P. Agroiya et al., 2020	Type 2 [21]	442 [21]	Oman [21]	Yes [21]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
T. Takao et al., 2018	Type 2 [3]	170 [3]	Not reported [3]	Yes [3]
Q. Wang et al., 2019	Type 2 [22]	1,096 [22]	China [22]	Yes [22]
R. Tapp et al., 2006	Mixed [23]	Not reported [23]	Mauritius [23]	Yes [23]
A. Yousef et al., 2021	Type 2 [24]	75 [24]	Egypt [24]	No [24]
纪丽君 et al., 2014	Type 2 [14]	175 [14]	China [14]	Yes (null finding) [14]
R. S. Ranganathan et al., 2022	Type 2 [25]	213 (144 DR, 69 no DR) [25]	India [25]	Yes [25]
Q. Zhao et al., 2019	Type 2 [7]	8 studies [7]	Multiple [7]	Yes (FPG variability) [7]
E. Chew et al., 2016	Type 2 [12]	1,310 [12]	U.S./Canada [12]	No (HbA1c focus) [12]
R. A. Mahdy et al., 2010	Type 2 [26]	40 (30 DM + 10 controls) [26]	Not reported [26]	No [26]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
J. Pan et al., 2014	Type 2 [27]	359 [27]	Not reported [27]	Yes [27]
F. Huang et al., 2025	Mixed [28]	197 (130 DM, 67 controls) [28]	U.S. [28]	Yes (indirect) [28]
M. Somi et al., 2020	Type 2 [4]	1,378 [4]	Iran [4]	Yes [4]
Y. Chisha et al., 2017	Not specified [29]	270 [29]	Ethiopia [29]	Yes [29]
H. Abuhay et al., 2024	Mixed (62.7% Type 2) [5]	462 [5]	Ethiopia [5]	Yes [5]
M. B. Takele et al., 2022	Mixed [30]	494 [30]	Ethiopia [30]	Yes [30]
Dr Md Asif Hasan et al., 2023	Type 2 [16]	320 (94 DR, 226 no DR) [16]	Bangladesh [16]	Yes [16]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
E. Kilpatrick et al., 2006	Type 1 [9]	1,441 [9]	Not reported [9]	Yes (null finding) [9]
C. Zhu et al., 2013	Type 2 [31]	107 [31]	China [31]	Yes (intervention) [31]
S. Wang et al., 2015	Type 2 [32]	161 patients + 60 controls [32]	China [32]	Yes (null finding) [32]
A. Penman et al., 2020	Type 1 [33]	Not reported [33]	Not reported [33]	No [33]
Y. Matsushita et al., 2020	Not reported [34]	Not reported [34]	Japan [34]	Yes (comparison study) [34]
E. Chew et al., 2014	Type 2 [35]	2,856 [35]	Multicenter [35]	No (HbA1c focus) [35]
T. Wong et al., 2009	Mixed [36]	27,120 [36]	Multiple [36]	No [36]
R. Tapp et al., 2008	Not specified [13]	1,192 [13]	Australia [13]	Yes [13]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
J. J. Zhou et al., 2020	Type 2 [8]	12,042 [8]	U.S. [8]	Yes (FPG variability) [8]
Y. Guo et al., 2022	Mixed [37]	12,935 [37]	Multiple [37]	Yes (indirect via UA subgroup) [37]
R. Rajalakshmi et al., 2020	Type 2 [38]	19,909 [38]	India [38]	No (renal focus) [38]
A. Martinho et al., 2020	Type 2 [39]	212 [39]	Portugal [39]	No (HbA1c/ocular focus) [39]
Z. Wang et al., 2017	Not specified [40]	100 [40]	China [40]	Yes (indirect) [40]
E. Chew et al., 2010	Type 2 [10]	10,251 [10]	U.S. [10]	Yes (intervention) [10]
J. Yau et al., 2012	Mixed [41]	22,896 [41]	Multiple [41]	Yes (indirect) [41]
J. Xuan et al., 2022	Not specified [1]	12 studies [1]	Multiple [1]	Yes [1]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
D. Hwang et al., 2017	Type 2 [42]	2,596 [42]	South Korea [42]	No [42]
S. Hoque et al., 2017	Type 2 [43]	400 (49 DR, 351 no DR) [43]	Bangladesh [43]	Yes [43]
L. Aiello et al., 2013	Type 1 [11]	1,441 [11]	Multicenter [11]	No (HbA1c focus) [11]
M. Elshafei et al., 2011	Not specified [44]	540 [44]	Qatar [44]	No [44]
A. Alarbash et al., 2025	Not specified [2]	11 studies [2]	Multiple [2]	Yes [2]
T. Mondal et al., 2020	Not specified [45]	300 [45]	Not reported [45]	No (lipid focus) [45]
R. Khandekar et al., 2015	Not specified [46]	94 [46]	Saudi Arabia [46]	No [46]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
Dayanand Cd et al., 2011	Type 2 [47]	90 [47]	Not reported [47]	No [47]
C. Rudnisky et al., 2012	Not specified [48]	980 [48]	Canada (First Nations) [48]	No (HbA1c/SBP focus) [48]
K. Seid et al., 2021	Mixed (60.6% Type 2) [15]	282 (142 DR, 140 no DR) [15]	Ethiopia [15]	Yes [15]
D. Cundiff et al., 2005	Type 1 [49]	1,041 [49]	U.S. [49]	No (diet focus) [49]
H. B. Alemayehu et al., 2024	Mixed (69.6% Type 2) [50]	391 [50]	Ethiopia [50]	Yes [50]
KT M. Favas et al., 2024	Not specified [51]	412,421 [51]	India [51]	Yes [51]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
R. Man et al., 2017	Type 2 [52]	361 [52]	Singapore [52]	No [52]
R. Stolk et al., 2008	Type 2 [53]	1,605 [53]	Multiple [53]	No (HbA1c/SBP focus) [53]
P. Klysuban et al., 2011	Not specified [54]	2,588 [54]	Thailand [54]	Yes [54]
I. Marques et al., 2022	Type 2 [55]	74 + 84 controls [55]	Not reported [55]	No [55]
G. Liew et al., 2017	Type 1 [56]	102 [56]	Australia [56]	No (HbA1c/vascular focus) [56]
Z. Su et al., 2025	Type 2 [57]	88 (45 DR, 25 T2D, 18 controls) [57]	China [57]	Yes (indirect) [57]
A. Rasul et al., 2017	Type 2 [58]	180 (90 DR, 90 controls) [58]	Pakistan [58]	Yes [58]
F. Sebastián-Valles et al., 2025	Type 1 [59]	309 [59]	Not reported [59]	No (CGM focus) [59]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
Y. Turan et al., 2017	Type 2 [60]	201 (109 DR, 92 no DR) [60]	Not reported [60]	Yes [60]
O. G. Albarrán et al., 2010	Mixed (76% Type 2) [61]	74 [61]	Not reported [61]	No [61]
Y. Li et al., 2018	Type 2 [62]	335 [62]	U.S. [62]	No (metformin focus) [62]
A. R. Khan et al., 2010	Not specified [63]	473 [63]	Saudi Arabia [63]	Yes [63]
N. Azad et al., 2014	Type 2 [64]	858 [64]	U.S. [64]	No (HbA1c/C-peptide focus) [64]
C. Merlotti et al., 2017	Type 2 [65]	Not reported [65]	Multiple [65]	No (bariatric surgery focus) [65]
A. Tsegaw et al., 2021	Type 2 [66]	739 [66]	Ethiopia [66]	No (HbA1c focus) [66]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
J. Grauslund et al., 2023	Not specified [67]	145,527 [67]	Denmark [67]	No (HbA1c focus) [67]
S. Junaid et al., 2022	Type 2 [68]	90 (30 per group) [68]	Pakistan [68]	Yes [68]
J. Beulens et al., 2009	Type 2 [69]	1,602 [69]	Multiple [69]	No (intervention focus) [69]
A. Azagew et al., 2023	Not specified [70]	15 studies [70]	Ethiopia [70]	No (glycemic control broadly) [70]
G. A. Mersha et al., 2020	Mixed [71]	306 [71]	Ethiopia [71]	No (glycemic control broadly) [71]
W. D. Addis et al., 2025	Mixed (74.2% Type 2) [6]	356 (178 DR, 178 no DR) [6]	Ethiopia [6]	Yes [6]
D. Pettitt et al., 2005	Type 2 [72]	149 [72]	U.S. [72]	No [72]

Study	Diabetes Type	Sample Size	Geographic Setting	FBG-DR Directly Examined?
D. Song et al., 2020	Type 2 [73]	Not reported [73]	Multiple [73]	No (NAFLD focus) [73]
H. Tang et al., 2018	Type 2 [74]	100,928 [74]	Multiple [74]	No (drug comparison focus) [74]
S. Sun et al., 2021	Type 2 [75]	28,614 [75]	Multiple [75]	No (HbA1c focus) [75]
J. Xu et al., 2014	Not specified [76]	2,602 [76]	China [76]	No (HbA1c primary) [76]
C. M. Jacoba et al., 2021	Type 1 [77]	1,735 [77]	U.S. [77]	No (HbA1c/BP focus) [77]
M. Ip et al., 2008	Type 2 [78]	693 [78]	U.S. [78]	No [78]
A. R. Manda et al., 2025	Type 2 [79]	328 eyes (164 patients) [79]	U.S. [79]	No (IL-6 focus) [79]
L. G. Frederikson et al., 2008	Not specified [80]	11,977 [80]	New Zealand [80]	No (HbA1c focus) [80]

Geographic representation was broad, including studies from East Asia, South Asia, the Middle East, Sub-Saharan Africa, Europe, Oceania, and North America. Roughly 40 studies directly examined or reported on the FBG-DR relationship, while the remainder assessed glycemic control primarily through HbA1c or focused on other risk factors with FBG as a secondary or background variable.

Effects of Fasting Blood Glucose on Diabetic Retinopathy

Direct Associations Between FBG and DR Presence or Severity

The table below summarizes quantitative findings from studies that reported statistical measures for the FBG-DR relationship.

Study	Effect Measure	Effect Size (95% CI)	p-value	Adjusted?	Notes
Q. Wang et al., 2019	OR for DR prevalence per unit FBG	1.38 (1.26–1.52) [22]	P < 0.001 [22]	Yes [22]	Adjusted for diabetes duration, axial length [22]
J. Xuan et al., 2022	Pooled OR	1.19 (1.13–1.26) [1]	Significant [1]	Not specified [1]	Per unit increase in FBG [1]
A. Alarbash et al., 2025	Pooled OR for elevated FBG/HbA1c	2.41 (1.63–3.57) [2]	P = 0.0005 [2]	Not specified [2]	Combined FBG and HbA1c metric [2]
KT M. Favas et al., 2024	Standardized mean difference	0.51 (0.10–0.93) [51]	Not reported [51]	Not specified [51]	FBG levels higher in DR-positive vs DR-negative [51]

Study	Effect Measure	Effect Size (95% CI)	p-value	Adjusted?	Notes
Q. Zhao et al., 2019	Pooled OR for FPG variability	3.68 (1.01–13.4) [7]	Not reported [7]	Not specified [7]	High FPG variability and DR risk [7]
Dr Md Asif Hasan et al., 2023	OR	2.694 [16]	P < 0.05 [16]	Not specified [16]	Bangladesh population [16]
S. Hoque et al., 2017	OR	1.139 (1.036–1.251) [43]	P = 0.007 [43]	Unadjusted [43]	Per unit FBG increase [43]
Y. Turan et al., 2017	OR	1.006 (1.001–1.012) [60]	P = 0.018 [60]	Yes (multivariate) [60]	Serum glucose per mg/dL [60]
H. Hwang et al., 2020	Positive correlation	Not quantified [19]	Not reported [19]	No [19]	FPG correlated with DR severity [19]
R. S. Ranganathan et al., 2022	Mean FBS difference	DR: 203 mg/dL vs no DR: 188 mg/dL [25]	P = 0.032 [25]	No [25]	Unadjusted comparison [25]

Study	Effect Measure	Effect Size (95% CI)	p-value	Adjusted?	Notes
M. Somi et al., 2020	OR for NPDR / PDR	2.65 / 2.01 [4]	P < 0.001 [4]	Yes [4]	Blood glucose outside recommended range [4]
K. Seid et al., 2021	AOR for poor glycemic control	19.9 (2.34–168.69) [15]	P = 0.006 [15]	Yes [15]	Very wide CI; used FBS as glycemic marker [15]
H. B. Alemayehu et al., 2024	AOR for poor glycemic control	2.80 (1.03–7.64) [50]	Significant [50]	Yes [50]	FBG cutoff 152 mg/dL [50]
W. D. Addis et al., 2025	AOR for FBG > 126 mg/dL	2.1 (1.1–3.9) [6]	P < 0.05 [6]	Yes [6]	Average of last three FBS records [6]
A. R. Khan et al., 2010	Adjusted OR	1.96 [63]	Not reported [63]	Yes [63]	Uncontrolled blood sugar [63]
M. B. Takele et al., 2022	AHR per unit FBS	1.02 (1.00–1.04) [30]	Not reported [30]	Yes (multivariable) [30]	Modest effect per mg/dL [30]

Study	Effect Measure	Effect Size (95% CI)	p-value	Adjusted?	Notes
H. Abuhay et al., 2024	AHR for lagged FBS change	4.20 (1.62–10.85) [5]	P < 0.05 [5]	Yes [5]	Joint model of longitudinal FBS [5]
T. Takao et al., 2018	Hazard ratios by FPG decile	Sharply elevated from 7.4 mmol/L [3]	Not specified [3]	Not specified [3]	Cutoff 7.4 mmol/L for retinopathy; 6.9 mmol/L threshold [3]
J. J. Zhou et al., 2020	FPG CV and ARV	Significant [8]	Not specified [8]	Yes (including cumulative HbA1c) [8]	FPG variability independently predicts DR [8]
S. Junaid et al., 2022	Correlation coefficient	r = 0.771 [68]	P = 0.001 [68]	No [68]	FBG correlated with homocysteine and DR [68]
P. Klysuban et al., 2011	Threshold identified	FPG ≥ 126 mg/dL significant risk [54]	Not reported [54]	Not specified [54]	Thailand screening population [54]
A. Rasul et al., 2017	Mean FPG comparison	10.2 ± 3.4 vs 5.0 ± 0.6 mmol/L [58]	Highly significant [58]	No [58]	DR vs healthy controls [58]

Intervention Studies: Glycemic Control and DR Progression

Several large RCTs and their follow-on analyses provide complementary evidence. The ACCORD Eye Study demonstrated that intensive glycemic control (target HbA1c < 6.0%) reduced 4-year DR progression rates to 7.3% versus 10.4% with standard therapy (adjusted OR 0.67, 95% CI 0.51–0.87, P = 0.003) [10]. This benefit persisted 4 years after the trial ended, with 5.8% progression in the former intensive group versus 12.7% in the standard group (adjusted OR 0.42, 95% CI 0.28–0.63, P < 0.0001) [12]. The DCCT/EDIC found that intensive therapy reduced the adjusted mean risk for DR development by 76% and slowed progression by 54% [11], with a durable "metabolic memory" effect persisting despite subsequent convergence of HbA1c levels [11]. In the ADVANCE substudy, intensive glucose control (target HbA1c ≤ 6.5%) did not significantly reduce overall DR incidence and progression (OR 0.84, 95% CI 0.61–1.15, P = 0.27), though borderline reductions in specific lesions were observed [69]. Zhu et al. (2013) found that intensive combined blood glucose and blood pressure control prevented DR progression over 5 years (P = 0.0006), whereas the standard treatment group deteriorated [31]. A meta-analysis by Sun et al. (2021) confirmed that strict blood glucose control reduces retinopathy progression (RR = 0.77, 95% CI 0.66–0.89) [75].

FBG Variability as an Independent Risk Factor

Beyond mean FBG levels, glycemic variability has emerged as an independent predictor. Zhou et al. (2020) demonstrated that in both ACCORD and VADT, the coefficient of variation and average real variability of FPG were associated with future microvascular outcomes even after adjusting for cumulative average HbA1c [8]. FPG variation appeared more harmful in those with less intensive glucose control [8]. The meta-analysis by Zhao et al. (2019) pooled three studies and found high FPG variability strongly associated with retinopathy risk (OR 3.68, 95% CI 1.01–13.4) [7]. Takao et al. (2018) identified that the optimal cutoff for the standard deviation of FPG over 27 years for detecting retinopathy was 1.4 mmol/L, and for advanced retinopathy was 1.9 mmol/L [3].

FBG Thresholds and Dose-Response

Evidence for a dose-response relationship between FBG and DR is supported by several sources. Takao et al. (2018) found that hazard ratios for retinopathy incidence increased

significantly from the eighth decile of mean FPG (6.9–7.4 mmol/L) and rose sharply from the ninth decile (7.4–8.7 mmol/L) [3], proposing 6.9 mmol/L as a threshold for predicting retinopathy over 25 years [3]. Klysuban et al. (2011) identified FPG ≥ 126 mg/dL as a significant risk factor [54], while Alemayehu et al. (2024) used a cutoff of 152 mg/dL [50] and Addis et al. (2025) used > 126 mg/dL [6]. The cross-sectional studies by Somi et al. (2020) reported that the risk of both NPDR and PDR increased approximately 2- to 2.65-fold in patients with blood glucose levels outside the recommended range [4].

Comparison of FBG with HbA1c as a Predictor

Several studies compared the predictive power of FBG versus HbA1c. Matsushita et al. (2020) specifically investigated which measure is more effective for detecting DR longitudinally in a Japanese population [34], though detailed results were available only in abstract. Tapp et al. (2008) found that replacing FPG with HbA1c in models improved the strength of the retinopathy association with hyperglycemia [13]. In contrast, the Kailuan Eye Study (Q. Wang et al., 2019) identified FBG as a strong independent predictor of both DR prevalence (OR 1.38) and severity ($\beta = 0.41$) in adjusted analyses [22]. The global meta-analysis by Yau et al. (2012) noted that HbA1c was the dominant glycemic metric in most population-based studies, but acknowledged that FBG and blood pressure levels were consistently associated with all DR prevalence endpoints [41, 41].

Key Confounders and Their Influence

Across the included studies, the most commonly controlled confounders in multivariate analyses were HbA1c levels, diabetes duration, blood pressure or hypertension status, and lipid profiles. Duration of diabetes was a significant predictor in nearly every study that assessed it [1, 2, 15, 21]. Hypertension was independently associated with DR in many studies [15, 29, 30, 50]. Renal function, measured by serum creatinine, eGFR, or albuminuria, consistently emerged as both an independent predictor and potential confounder [18, 19, 38, 76]. Lipid abnormalities, particularly elevated triglycerides and LDL cholesterol, showed variable associations, reaching significance in some studies [1, 16, 24] but not others [4, 51]. BMI demonstrated a paradoxical inverse association in some populations [1, 66] while showing positive associations in others [16].

Synthesis

The body of evidence from these 80 sources broadly supports a positive association between elevated fasting blood glucose and both the presence and severity of diabetic retinopathy, but the magnitude and independence of this association vary substantially across studies. Several factors explain this heterogeneity.

Mean FBG Level Versus Glycemic Variability

The apparent contradiction between studies showing strong FBG-DR associations and those reporting null findings can be partially resolved by distinguishing between mean FBG levels and FBG variability. Kilpatrick et al. (2006) found no independent effect of glucose variability within or between days on retinopathy in type 1 diabetes after adjusting for mean blood glucose [9], suggesting that mean glycemic exposure rather than fluctuation drives risk in that population. In contrast, Zhou et al. (2020) found that FPG variability independently predicted microvascular outcomes in type 2 diabetes even after adjusting for cumulative HbA1c [8], and Zhao et al. (2019) confirmed this in a meta-analysis (OR 3.68) [7]. This discrepancy may reflect biological differences between type 1 and type 2 diabetes: in type 2 diabetes, glucose variability may serve as a marker of beta-cell dysfunction and insulin resistance that confers additional vascular risk beyond what HbA1c captures. Additionally, the DCCT used quarterly seven-point glucose profiles, which may not fully characterize true glycemic variation [9], whereas the ACCORD and VADT studies had repeated FPG measurements over years [8].

FBG as an Independent Predictor Versus a Proxy for HbA1c

A central question is whether FBG provides prognostic information beyond HbA1c. The Kailuan Eye Study reported a robust association between FBG and both DR prevalence (OR 1.38) and severity ($\beta = 0.41$) in models adjusted for diabetes duration and axial length but not for HbA1c [22]. Tapp et al. (2008) found that replacing FPG with HbA1c improved the model [13], suggesting that HbA1c, as a measure of cumulative glycemic exposure, may subsume the information provided by a single FBG measurement. Studies from the Ethiopian cohorts that used FBS as the primary glycemic measure (given limited access to HbA1c testing) found significant associations [5, 15, 30, 50], but the very wide confidence intervals in some of these studies (e.g.,

AOR 19.9, 95% CI 2.34–168.69 [15]) reflect small sample sizes and the absence of HbA1c adjustment. When HbA1c is included in multivariable models, FBG often loses independent significance or its effect is attenuated, consistent with FBG representing a snapshot of glycemic status compared to HbA1c's 2–3 month integration window.

Longitudinal Evidence Versus Cross-Sectional Findings

The largest effect sizes for the FBG-DR association come from cross-sectional studies (e.g., Hasan et al., OR 2.694 [16]; Seid et al., AOR 19.9 [15]), which cannot establish temporality and are vulnerable to reverse causation—worsening diabetes and DR may both be consequences of disease progression. Longitudinal studies provide more robust evidence. The 27-year study by Takao et al. (2018) identified clear FPG thresholds (6.9 mmol/L) for future retinopathy [3]. The joint modeling approach by Abuhay et al. (2024), which linked time-dependent lagged FBS changes to DR incidence (AHR 4.20, 95% CI 1.62–10.85), represents a methodologically sophisticated demonstration that changes in FBS trajectory precede DR development [5]. The ACCORD Eye Study [10] and DCCT/EDIC [11] provide the strongest causal evidence, demonstrating through randomized intervention that reducing glycemia (which necessarily includes lowering FBG) slows DR progression.

Population and Setting Differences

The effect of FBG on DR appears broadly consistent across populations (East Asian, South Asian, Middle Eastern, African, and Western cohorts all report positive associations), but the magnitude differs. The meta-analysis by Jie Xuan et al. (2022) estimated a pooled OR of 1.19 per unit increase in FBG [1], while the Alarbash et al. (2025) meta-analysis, which combined FBG and HbA1c elevation, yielded a larger pooled OR of 2.41 [2]. The Indian-specific meta-analysis by Favas et al. (2024) confirmed elevated FBG as a significant risk factor (MD 0.51) [51]. Ethnic differences in retinopathy prevalence were noted in the ADVANCE substudy, where Chinese and South-Asian patients had more retinopathy than Caucasians despite similar associations with HbA1c, duration, and systolic blood pressure [53, 53]. Several Ethiopian studies, conducted in resource-limited settings where HbA1c testing was unavailable, relied on FBS as the sole glycemic

measure, generally reporting significant associations but with methodological limitations including retrospective designs and small samples [5, 15, 29, 30, 50].

Diabetes Type

The relationship between FBG and DR has been most consistently demonstrated in type 2 diabetes, where the bulk of the evidence resides. In type 1 diabetes, the DCCT/EDIC established that overall glycemic control (HbA1c) is the dominant predictor [11], while Kilpatrick et al. (2006) found glucose variability non-contributory after adjusting for mean glucose [9]. Sebastián-Valles et al. (2025) found that time in tight range (70–140 mg/dL) on continuous glucose monitoring provided modestly better prediction of incident DR than time in range (70–180 mg/dL) in type 1 diabetes with near-target HbA1c [59], suggesting that the glycemic range captured by fasting glucose may be less informative than continuous metrics in this population. For type 2 diabetes, the ACCORD and VADT post hoc analyses confirm that FPG variability contributes independent risk information even after adjusting for HbA1c [8].

What Can Be Concluded for Specific Contexts

For type 2 diabetes patients, elevated FBG is consistently associated with both the presence and severity of DR across diverse populations. The evidence supports a dose-response relationship, with retinopathy risk increasing substantially above FPG thresholds of approximately 6.9–7.4 mmol/L (124–133 mg/dL) [3]. FBG variability appears to confer independent risk beyond mean glycemic control in type 2 diabetes [7, 8]. However, HbA1c remains a stronger and more consistent predictor than single FBG measurements [13], and the independent contribution of FBG to DR risk is attenuated when HbA1c is included in multivariable models. In clinical settings where HbA1c testing is unavailable, FBG serves as a reasonable surrogate marker for DR risk assessment, though with lower precision. Intensive glycemic control that reduces both FBG and HbA1c demonstrably slows DR progression in both type 1 [11] and type 2 [10] diabetes, with evidence for persistent benefit ("metabolic memory") even after glycemic control converges [11, 12]. In type 1 diabetes, the independent role of FBG above and beyond HbA1c is less clear, and continuous glucose monitoring metrics may provide superior prediction [59].

DISCUSSION

This systematic review of 80 studies provides a comprehensive synthesis of the complex relationship between fasting blood glucose and diabetic retinopathy severity. The results reveal that while a significant positive association exists, its magnitude and independence are highly context-dependent, shaped by study design, diabetes type, and the metrics used to define glycemic control.

The Dual Role of FBG: Mean Level vs. Variability

A central finding is the distinction between mean FBG levels and FBG variability. The review confirms a consistent dose-response relationship between elevated mean FBG levels and increased DR risk. This is robustly supported by large cross-sectional studies and meta-analyses (1,2,22,51). The identification of specific FBG thresholds (e.g., 6.9 mmol/L, 126 mg/dL) provides clinicians with tangible targets for risk stratification (3,54). This aligns with the fundamental pathophysiology of hyperglycemia-induced microvascular damage.

However, the relationship becomes more complex with the inclusion of glycemic variability. The evidence from this review suggests that in type 2 diabetes, FBG variability is an independent predictor of DR, providing prognostic information beyond the mean FBG or even cumulative HbA1c (7,8). This is a significant finding, as it suggests that the pattern of glucose fluctuations, not just the average level, contributes to vascular injury. The postulated mechanism involves repeated oxidative stress and endothelial dysfunction triggered by glucose spikes and dips, which may be more damaging than a sustained, stable hyperglycemia (8). This contrasts with the landmark DCCT findings in type 1 diabetes, where Kilpatrick et al. (9) found no additional role for glucose variability. This discrepancy could be explained by fundamental differences in the pathophysiology between type 1 and type 2 diabetes, where the latter is also characterized by insulin resistance and associated metabolic disturbances that may amplify the harmful effects of glucose fluctuations.

FBG vs. HbA1c: A Complementary Relationship

The review highlights that HbA1c remains the dominant predictor for DR, often subsuming the information provided by a single FBG measurement when both are included in the same model (13). This is logical, as HbA1c reflects an integrated 2-3 month glycemic history, whereas a single

FBG is a "snapshot." However, the Kailuan Eye Study (22) and several Ethiopian studies (5,6,15) demonstrated significant FBG associations, even without adjusting for HbA1c, underscoring FBG's utility as a practical, accessible risk marker. In resource-limited settings where HbA1c testing is not routine, FBG remains a critical tool for DR risk assessment.

The combined effect of FBG and HbA1c is perhaps best demonstrated by the large randomized controlled trials. The ACCORD (10,12) and DCCT/EDIC (11) studies provide the highest level of evidence that interventions aimed at lowering overall glycemia—which includes lowering FBG—profoundly reduce DR progression. The "metabolic memory" effect, where early intensive control leads to long-term benefits, further emphasizes the importance of achieving glycemic targets early, which includes targeting FBG (11,12).

Key Confounders and Effect Modifiers

The strength of the FBG-DR association is heavily influenced by several confounders. Diabetes duration was consistently the strongest and most ubiquitous predictor of DR across all studies (1,15,21), acting as a significant effect modifier. Hypertension and renal function were also identified as major independent risk factors and confounders (15,29,30,38). This suggests that the FBG-DR relationship is not a direct one but operates within a broader context of systemic vascular damage. The fact that some studies reported null findings for FBG (9,14) may be attributable to differences in patient populations, inadequate adjustment for these powerful confounders, or simply a reflection of the smaller effect size of FBG compared to these other factors.

Study Design and Generalizability

The heterogeneity in study design contributes to the observed variability in effect sizes. Cross-sectional studies, while numerous, often produce larger odds ratios but are vulnerable to reverse causation (16,25). Longitudinal studies, such as the 27-year study by Takao et al. (3) and the joint modeling by Abuhay et al. (5), provide more robust temporal evidence, demonstrating that changes in FBS precede DR development. The broad geographic representation, from East Asia to Sub-Saharan Africa, confirms that the association between FBG and DR is a global phenomenon, though the magnitude may vary due to ethnic and healthcare system differences (53).

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review concludes that elevated fasting blood glucose and its variability are significant risk factors for the presence and severity of diabetic retinopathy. The relationship demonstrates a clear dose-response pattern, with specific FBG thresholds (e.g., 6.9-7.4 mmol/L) predictive of increased risk, particularly in type 2 diabetes. While HbA1c remains the superior metric for long-term glycemic exposure, FBG provides valuable, independent prognostic information, especially in contexts where HbA1c is unavailable or as a component of overall glycemic control.

Recommendations:

1. **Clinical Practice:** Clinicians should not rely solely on HbA1c but should monitor FBG levels and variability as part of a comprehensive DR risk assessment. Achieving and maintaining FBG below established thresholds (e.g., <7.0 mmol/L) should be a key therapeutic goal.
2. **Risk Stratification:** In patients with type 2 diabetes, high FBG variability should be recognized as an independent risk factor warranting more intensive monitoring for DR, even if mean HbA1c appears acceptable.
3. **Future Research:** Future prospective studies should focus on directly comparing the predictive power of continuous glucose monitoring metrics (which capture FBG and variability) versus HbA1c for DR progression. Further research is also needed to elucidate the biological mechanisms linking glucose variability to microvascular damage, particularly in type 2 diabetes.

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