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THE COMPREHENSIVE SYSTEMATIC REVIEW OF ASSOCIATION OF POOR GLYCEMIC CONTROL (HBA1C) TO THE DEVELOPMENT OF MICROVASCULAR COMPLICATIONS IN DIABETES

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ABSTRACT

Introduction: Diabetes mellitus remains a major global health challenge, with microvascular complications—retinopathy, nephropathy, and neuropathy—contributing significantly to morbidity and reduced quality of life. Glycemic control, primarily measured by HbA1c, is a cornerstone of diabetes management, but the strength and consistency of its association with microvascular outcomes across diabetes types and patient subgroups require comprehensive synthesis.
Methods: We conducted a systematic review of 80 studies investigating the association between HbA1c and microvascular complications in Type 1 and Type 2 diabetes. Studies were screened based on predefined criteria including study design, population, measurement of HbA1c, assessment of microvascular outcomes, and availability of quantitative data. Data were extracted on HbA1c definitions, complication types, study characteristics, effect measures, and confounding control.
Results: Poor glycemic control (HbA1c >7%) was consistently associated with increased risk and progression of microvascular complications. In Type 1 diabetes, intensive control reduced retinopathy by 76%, nephropathy by 39–56%, and completely prevented clinical neuropathy over 24 years. In Type 2 diabetes, intensive control reduced retinopathy progression by 23–33% and nephropathy by 21–26%. However, benefits diminished in older patients, those with advanced complications, or long disease duration. Glycemic variability and metabolic memory effects were also significant. Intensive control increased severe hypoglycemia risk approximately twofold.
Discussion: The association between HbA1c and microvascular complications is strong but modulated by diabetes type, disease stage, age, and glycemic variability. Early intensive control yields lasting benefits via metabolic memory, especially in Type 1 diabetes. In Type 2 diabetes, individualized targets are essential to balance microvascular benefits against hypoglycemia and mortality risks.
Conclusion: Glycemic control is fundamentally important in preventing and delaying microvascular complications, but treatment must be personalized. Future research should focus on variability metrics, early intervention windows, and integrative management strategies.
Keywords: Glycemic control, HbA1c, microvascular complications, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, Type 1 diabetes, Type 2 diabetes, metabolic memory, glycemic variability.

INTRODUCTION

Background: Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia, affecting over 500 million people worldwide. Microvascular complications—including diabetic retinopathy, nephropathy, and neuropathy—are leading causes of blindness, kidney failure, and neuropathy-related disability, imposing substantial personal, clinical, and economic burdens (Zoungas et al., 2017). Glycemic control, as measured by glycated hemoglobin (HbA1c), has long been established as a critical modifiable risk factor for these complications. Seminal trials such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive glycemic control significantly reduces the risk of microvascular events in both Type 1 and Type 2 diabetes (Genuth et al., 2002; Patel et al., 2008). However, subsequent major trials such as ACCORD, ADVANCE, and VADT revealed nuanced outcomes, including limited benefits on hard renal endpoints, increased hypoglycemia risk, and even potential harm in certain subgroups (Ismail-Beigi et al., 2010; Hemmingsen et al., 2015). This evolving evidence base underscores the need for a comprehensive, updated synthesis of the relationship between HbA1c and microvascular complications across diverse populations and diabetes types.

Research Gap: While numerous systematic reviews and meta-analyses have examined glycemic control and microvascular outcomes, several gaps persist. First, most reviews focus on either Type 1 or Type 2 diabetes, with limited direct comparison of effect sizes and mechanisms between the two. Second, the role of long-term glycemic variability—beyond mean HbA1c—as an independent risk factor is not fully elucidated in clinical guidelines. Third, the phenomenon of “metabolic memory” or “legacy effects” has been well-documented in Type 1 diabetes but less conclusively in Type 2 diabetes, particularly in older or high-risk populations. Fourth, there is inconsistent evidence regarding the impact of intensive control on advanced nephropathy stages (e.g., end-stage renal disease) versus early markers like microalbuminuria. Finally, the balance between microvascular benefits and adverse effects—especially severe hypoglycemia—in different age groups and clinical settings requires clearer stratification to inform personalized treatment.

Novelty: This review provides a contemporary and holistic synthesis of evidence from 80 studies, integrating findings from landmark trials (DCCT/EDIC, ACCORD, ADVANCE, VADT) with emerging data on glycemic variability, metabolic memory, and subgroup-specific outcomes. Unlike previous reviews, it directly contrasts the magnitude and nature of HbA1c-associated risks between Type 1 and Type 2 diabetes, evaluates the prognostic value of HbA1c variability, and discusses the clinical implications of early worsening phenomena and age-related treatment response heterogeneity. Additionally, it incorporates recent studies (e.g., 2024–2025) on novel metrics such as continuous glucose monitoring-derived measures and their predictive value for complications (Kovatchev et al., 2025; Wang et al., 2024).

Hypothesis: We hypothesize that poor glycemic control (HbA1c >7%) is strongly and consistently associated with increased incidence and progression of microvascular complications in both Type 1 and Type 2 diabetes, but that this association is modified by factors including diabetes type, duration, age, baseline complication status, and glycemic variability. We further hypothesize that intensive glycemic control initiated early in the disease course confers sustained protective effects through metabolic memory, but that the risk-benefit ratio favors individualized targets in older patients or those with advanced disease.

Research Objectives:

1. To systematically review and synthesize evidence on the association between HbA1c levels and microvascular complications in diabetes.
2. To compare the strength and nature of this association between Type 1 and Type 2 diabetes.
3. To evaluate the role of glycemic variability and metabolic memory in microvascular outcomes.
4. To assess the impact of intensive glycemic control on different stages of nephropathy and retinopathy.
5. To identify subgroup differences (age, disease duration, baseline complications) in treatment response and risk.
6. To weigh microvascular benefits against adverse effects, particularly hypoglycemia.

Significance of the Study: This review aims to inform evidence-based clinical practice by clarifying which patients benefit most from intensive glycemic control, identifying optimal HbA1c targets for different populations, and highlighting the importance of early and sustained management. It also provides a foundation for future research on advanced glycemic metrics, personalized treatment algorithms, and integrative care approaches to prevent diabetes-related microvascular morbidity.

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 association of poor glycemic control (HBA1C) to the development of microvascular complications in diabetes.

Screening

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

- **Population - Diabetes Type**: Does the study include individuals diagnosed with Type 1 or Type 2 diabetes mellitus (excluding studies conducted exclusively in gestational diabetes populations)?
- **Glycemic Control Measurement**: Does the study measure glycemic control using HbA1c levels?
- **Microvascular Complications Assessment**: Does the study assess at least one microvascular complication

(diabetic retinopathy, diabetic nephropathy, or diabetic neuropathy)?

- **Association Examination**: Does the study examine the association or relationship between HbA1c levels and microvascular complications?
- **Study Design**: Is the study an observational study (cohort, case-control, cross-sectional), randomized controlled trial, systematic review, or meta-analysis?
- **Quantitative Data**: Does the study provide quantitative data on HbA1c levels and microvascular complications?
- **Follow-up Duration**: For longitudinal studies, does the study have an adequate follow-up period of at least 1 year? (Answer "Yes" if this is not a longitudinal study)
- **Complication Focus**: Does the study focus on microvascular complications rather than exclusively on macrovascular complications (cardiovascular disease, stroke)?

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	Poor Glycemic Control	Good Glycemic Control	Microvascular Complications
Keyword 2	Diabetic Patients	Elevated HbA1c	Normoglycemia	Diabetic Retinopathy/Nephropathy/Neuropathy
Keyword 3	Individuals with Diabetes	Hyperglycemia	Optimal HbA1c	Microangiopathy
Keyword 4	Hyperglycemic Individuals	Inadequate Glucose Control	Intensive Glycemic Therapy	Small Vessel Disease

The Boolean MeSH keywords inputted on databases for this research are: *("Diabetes Mellitus" OR "Diabetic Patients" OR "Individuals with Diabetes" OR "Hyperglycemic Individuals") AND ("Poor Glycemic Control" OR "Elevated HbA1c" OR "Hyperglycemia" OR "Inadequate Glucose Control") AND ("Good Glycemic Control" OR "Normoglycemia" OR "Optimal HbA1c" OR "Intensive Glycemic Therapy") AND ("Microvascular Complications" OR "Diabetic Retinopathy/Nephropathy/Neuropathy" OR "Microangiopathy" OR "Small Vessel Disease")*

Data extraction

- **HbA1c Definition**:
  Extract how glycemic control was defined and measured in relation

to microvascular complications, including:
    - Specific HbA1c thresholds used to define poor vs. good control (e.g., >7%, >8.5%)
    - Whether HbA1c was analyzed as categorical (poor vs. good) or continuous variable
    - Time period over which HbA1c was assessed (single measurement, mean over time, etc.)
    - Any other glycemic measures used alongside HbA1c
- **Microvascular Complications**: Extract details about microvascular complications studied in relation to HbA1c, including:
    - Specific complications examined (retinopathy, nephropathy, neuropathy)
    - Clinical definitions and diagnostic criteria used for each complication
    - Severity levels or stages assessed (e.g., background vs. proliferative retinopathy, microalbuminuria vs. ESRD)
    - Whether complications were incident (new onset) or prevalent cases
- **Study Population**: Extract characteristics of the diabetes population studied for HbA1c-microvascular complication associations, including:
    - Diabetes type (Type 1, Type 2, or mixed)
    - Sample size and demographics (age, gender, race/ethnicity)
    - Diabetes duration at baseline
    - Baseline HbA1c levels and distribution
    - Geographic location and healthcare setting
    - Exclusion criteria that might limit generalizability
- **Association Results**: Extract quantitative findings on the association between poor glycemic control (HbA1c) and microvascular complications, including:
    - Specific effect measures (odds ratios, risk ratios, hazard ratios, absolute risk differences)
    - Point estimates with 95% confidence intervals
    - P-values or statistical significance
    - Dose-response relationships if HbA1c analyzed continuously
    - Separate results for different complications if reported
    - Subgroup analyses by diabetes type, age, or other factors
- **Study Design**: Extract methodological details that affect the strength of evidence for HbA1c-microvascular complication associations, including:
    - Study design (RCT, cohort, cross-sectional, case-control, meta-analysis)
    - Follow-up duration and loss to follow-up rates

  - Whether analysis was intention-to-treat vs. per-protocol (for RCTs)
  - Prospective vs. retrospective data collection
  - Single-center vs. multi-center design
- **Confounding Control**: Extract information about confounding factors and analytical adjustments made when assessing HbA1c-microvascular complication associations, including:
  - Variables adjusted for in multivariable models (age, diabetes duration, blood pressure, lipids, smoking, etc.)
  - Matching criteria used (for case-control studies)
  - Stratification approaches
  - Methods used to handle confounding (regression, propensity scores, etc.)
  - Whether unmeasured confounding was discussed as a limitation
- **Temporal Relationships**: Extract information about the timing and temporal aspects of the HbA1c-microvascular complication relationship, including:
  - Time lag between HbA1c exposure and complication assessment
  - Whether HbA1c was measured before complication onset (prospective) or cross-sectionally
  - Duration of glycemic exposure considered (single point vs. cumulative exposure)
  - Any discussion of reverse causation (complications affecting HbA1c control)

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Diabetes Mellitus" OR "Diabetic Patients" OR "Individuals with Diabetes" OR "Hyperglycemic Individuals") AND ("Poor Glycemic Control" OR "Elevated HbA1c" OR "Hyperglycemia" OR "Inadequate Glucose Control") AND ("Good Glycemic Control" OR "Normoglycemia" OR "Optimal HbA1c" OR "Intensive Glycemic Therapy") AND ("Microvascular Complications" OR "Diabetic Retinopathy/Nephropathy/Neuropathy" OR "Microangiopathy" OR "Small Vessel Disease")*	35
Semantic Scholar	*("Diabetes Mellitus" OR "Diabetic Patients" OR "Individuals with Diabetes" OR "Hyperglycemic Individuals") AND ("Poor Glycemic Control" OR "Elevated HbA1c" OR "Hyperglycemia" OR "Inadequate Glucose Control") AND ("Good Glycemic Control" OR "Normoglycemia" OR "Optimal HbA1c" OR "Intensive Glycemic Therapy") AND ("Microvascular Complications" OR "Diabetic Retinopathy/Nephropathy/Neuropathy" OR "Microangiopathy" OR "Small Vessel Disease")*	252
Springer	*("Diabetes Mellitus" OR "Diabetic Patients" OR "Individuals with Diabetes" OR "Hyperglycemic Individuals") AND ("Poor Glycemic Control" OR "Elevated HbA1c" OR "Hyperglycemia" OR "Inadequate Glucose Control") AND ("Good Glycemic Control" OR "Normoglycemia" OR "Optimal HbA1c" OR "Intensive Glycemic Therapy") AND ("Microvascular Complications" OR "Diabetic Retinopathy/Nephropathy/Neuropathy" OR "Microangiopathy" OR "Small Vessel Disease")*	1,226
Google Scholar	*("Diabetes Mellitus" OR "Diabetic Patients" OR "Individuals with Diabetes" OR "Hyperglycemic Individuals") AND ("Poor Glycemic Control" OR "Elevated HbA1c" OR "Hyperglycemia" OR "Inadequate Glucose Control") AND ("Good Glycemic Control" OR "Normoglycemia" OR "Optimal HbA1c" OR "Intensive Glycemic Therapy") AND ("Microvascular Complications" OR "Diabetic Retinopathy/Nephropathy/Neuropathy" OR "Microangiopathy" OR "Small Vessel Disease")*	11,400
Wiley Online Library	*("Diabetes Mellitus" OR "Diabetic Patients" OR "Individuals with Diabetes" OR "Hyperglycemic Individuals") AND ("Poor Glycemic Control" OR "Elevated HbA1c" OR "Hyperglycemia" OR "Inadequate Glucose Control") AND ("Good Glycemic Control" OR "Normoglycemia" OR "Optimal HbA1c" OR "Intensive Glycemic Therapy") AND ("Microvascular Complications" OR "Diabetic Retinopathy/Nephropathy/Neuropathy" OR "Microangiopathy" OR "Small Vessel Disease")*	774

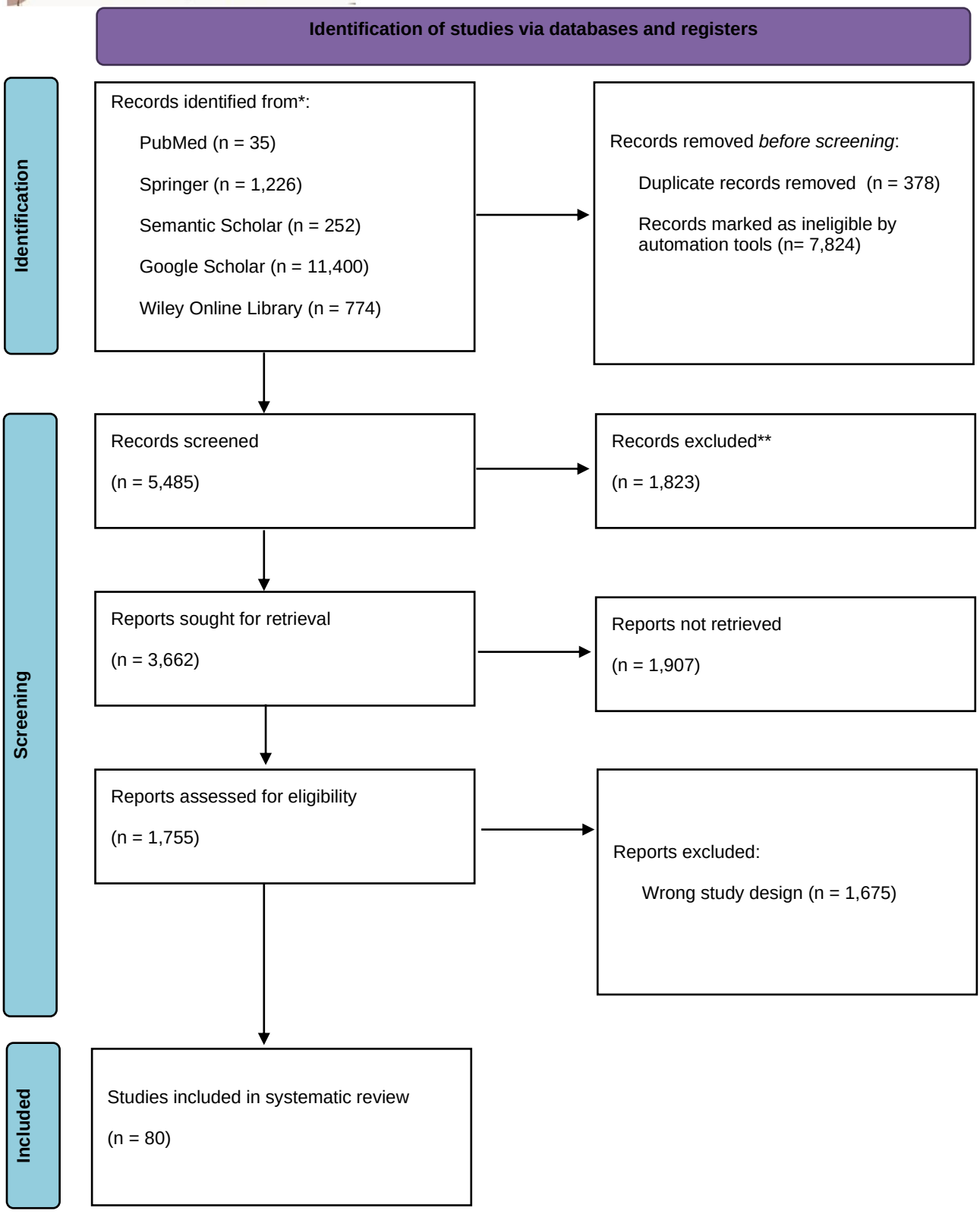

Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	**Bias related to selection and allocation** Was there a control group?	**Bias related to confounding factors** Were participants included in any comparisons similar?	**Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	**Were there multiple measurements of the outcome, both pre and post the intervention/exposure?**	**Were the outcomes of participants included in any comparisons measured in the same way?**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	**Statistical conclusion validity** Was appropriate statistical analysis used?
S. Genuth et al., 2002	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Herman et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Tavakoli et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Ismail-Beigi et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓

S. Coca et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Shichiri et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Lachin et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. D. de Boer et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Ismail-Beigi et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Amin et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Harindhanavudhi et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Jacobson et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Takayoshi Sasako et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Ziegler et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Peiyao Jin et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
F. Ishibashi et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Shestakova et al.,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2016									
Sophie Sun et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Lachin et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Zoungas et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. A. Jiskani et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Liying Zhang et al., 2001	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Shurter et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
W. Shiferaw et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. Azad et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sharon D. Solomon et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Vasović et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chebly Dagher et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jia-Min Wang et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Joanna Kamińska et al.,	✓	✓	✓	✗	✓	✗	✓	✓	✓

2012									
Anushka Patel et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Nathan et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jennifer Perais et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Newman et al., 2005	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Lachin et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Aiello et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Thomas Crabtree et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Getinet Kumie et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Maple-Brown et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wei-zhi Chen et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Chew et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. J. Wiffen et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
I. Kulenović et al., 2006	✓	✓	✓	✗	✓	✗	✓	✓	✓

Rami Aldafas et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Levin et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Hovind et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
ADVANCE commentary, 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Araszkiewicz et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
B. Hemmingsen et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Lachin et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
Chia-Hsuin Chang et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. M et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Park et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Kilpatrick et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
Crystal M. Pressley et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓

G. Sartore et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Lo et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lily Agrawal et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Beulens et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Lachin et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Ipp et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Gilbert et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
N. White et al., 2010	✓	✓	✓	✗	✓	✗	✓	✓	✓
Boris P. Kovatchev et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Zhai et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Abraira et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
E. Chew et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Cut Lisa et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓

C. Lo et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Larsen et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tomoki Okuno et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jin J. Zhou et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Tryggestad et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
R. Frank et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Holfort et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
Vivek Charu et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
O. Klefter et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Bressler et al., 2000	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mohammed K. Ali et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lily Agrawal et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

The systematic review identified 80 sources examining the association between glycemic control (HbA1c) and microvascular complications in diabetes. Studies varied substantially in design, population, and outcomes assessed.

Study	Diabetes Type	Sample Size	Follow-up Duration	Microvascular Complications Assessed
S. Genuth et al., 2002	Type 1	1,441	6.5 years DCCT + 7 years EDIC	Retinopathy, nephropathy, neuropathy
W. Herman et al., 2018	Type 1	1,441	30 years	Retinopathy, nephropathy, neuropathy
M. Tavakoli et al., 2018	Type 2	141	4 years	Retinopathy, nephropathy, neuropathy
F. Ismail-Beigi et al., 2010	Type 2	10,251	Not specified	Nephropathy, retinopathy, neuropathy
S. Coca et al., 2012	Type 2	28,065	2-15 years	Microalbuminuria, macroalbuminuria, ESRD
M. Shichiri et al., 2000	Type 2	110	8 years	Retinopathy, nephropathy, neuropathy
J. Lachin et al., 2000	Type 1	1,208-1,302	4 years	Retinopathy, nephropathy
I. D. de Boer et al., 2011	Type 1	1,441	Median 13 years	Microalbuminuria, macroalbuminuria, impaired GFR, ESRD
F. Ismail-Beigi et al., 2012	Type 2	4,733	Mean 4.7 years	Renal failure, retinopathy
R. Amin et al., 2005	Type 1	308	Median 10.9 years	Microalbuminuria
T. Harindhanavudhi et al., 2011	Type 1	223	5 years	Diabetic retinopathy
A. Jacobson et al., 2013	Type 1	1,441	23.5 years	Retinopathy, nephropathy, neuropathy

Study	Diabetes Type	Sample Size	Follow-up Duration	Microvascular Complications Assessed
Takayoshi Sasako et al., 2025	Type 2	2,540	Median 8.5 years	Retinopathy
D. Ziegler et al., 2015	Type 1	32	24 years	Polyneuropathy, cardiac autonomic dysfunction
Peiyao Jin et al., 2015	Type 2	453	5 years	Diabetic retinopathy
F. Ishibashi et al., 2018	Type 2	38	4 years	Neuropathy, nephropathy, retinopathy
M. Shestakova et al., 2016	Type 1	260	10 years	Nephropathy, retinopathy
Sophie Sun et al., 2021	Type 2	28,614	Not specified	Retinopathy, albuminuria
J. Lachin et al., 2008	Type 1	Not specified	Not specified	Retinopathy
S. Zoungas et al., 2017	Type 2	27,049	Median 5 years	Nephropathy, retinopathy, neuropathy
S. A. Jiskani et al., 2020	Type 2	213	Not applicable	Microalbuminuria
Liying Zhang et al., 2001	Type 1	1,441	Not specified	Retinopathy
A. Shurter et al., 2013	Type 2	68	~25 months	Diabetic retinopathy
W. Shiferaw et al., 2020	Mixed	18,099	Not specified	Diabetic retinopathy
N. Azad et al., 2014	Type 2	858	5 years	Diabetic retinopathy
Sharon D. Solomon et al., 2017	Type 1	Not specified	Not specified	Diabetic retinopathy
O. Vasović et al., 2005	Type 1	27	Not specified	Microalbuminuria
Chebly Dagher et al., 2025	Type 2	222	1 year	Diabetic retinopathy/macular edema

Study	Diabetes Type	Sample Size	Follow-up Duration	Microvascular Complications Assessed
Jia-Min Wang et al., 2024	Type 2	Not specified	Median 13,080-23,121 person-years	Nephropathy, retinopathy, neuropathy
Joanna Kamińska et al., 2012	Type 2	Not specified	Not applicable	Albuminuria
Anushka Patel et al., 2008	Type 2	11,140	Median 5 years	Nephropathy, retinopathy
D. Nathan et al., 2013	Type 1	1,441	Mean 6.5 years DCCT + 20 years EDIC	Retinopathy, nephropathy, neuropathy
Jennifer Perais et al., 2020	Type 1, Type 2, mixed	39-71,817	1-45 years	Proliferative diabetic retinopathy
D. Newman et al., 2005	Type 1 and Type 2	Not specified	Not specified	Retinopathy, nephropathy
J. Lachin et al., 2017	Type 1	1,441	1983-1993	Retinopathy, nephropathy, neuropathy
L. Aiello et al., 2013	Type 1	1,441	Mean 6.5 years	Diabetic retinopathy
Thomas Crabtree et al., 2022	Type 2	Not specified	Not specified	Retinopathy, nephropathy, neuropathy
Getinet Kumie et al., 2024	Not specified	Not specified	Not specified	Retinopathy, neuropathy, nephropathy
L. Maple-Brown et al., 2013	Type 1	1,441	Mean 6.5 years	Retinopathy, nephropathy, neuropathy
Wei-zhi Chen et al., 2014	Type 2	461	Mean 6.82 years	Microalbuminuria
E. Chew et al., 2010	Type 2	10,251 (2,856 subgroup)	4 years	Diabetic retinopathy

Study	Diabetes Type	Sample Size	Follow-up Duration	Microvascular Complications Assessed
P. J. Wiffen et al., 2012	Type 1 and Type 2	1,228 (T1D), 6,669 (T2D)	≥1 year	Neuropathy, retinopathy, nephropathy
I. Kulenović et al., 2006	Type 1	32	10 years	Nephropathy, retinopathy
Rami Aldafas et al., 2023	Type 2	34,536	4-160 months	Retinopathy, nephropathy, microalbuminuria
S. Levin et al., 2000	Type 2	153	2 years	Microalbuminuria
P. Hovind et al., 2003	Type 1	600	≥20 years	Nephropathy, proliferative retinopathy
ADVANCE commentary, 2008	Type 2	11,140	Median 5 years	Nephropathy, retinopathy
A. Araszkiewicz et al., 2008	Type 1	86	7.1 years	Retinopathy, microalbuminuria
B. Hemmingsen et al., 2015	Type 2	34,912	3 days-12.5 years	Nephropathy, retinopathy
J. Lachin et al., 2014	Type 1	1,441	18 years	Retinopathy, nephropathy, neuropathy
Chia-Hsuin Chang et al., 2010	Type 2	10,251	4 years	Diabetic retinopathy
M. M et al., 2014	Type 2	200	Not applicable	Neuropathy
J. Park et al., 2020	Type 2	1,125	>5 years	Diabetic retinopathy
E. Kilpatrick et al., 2009	Type 1	1,208	4 years	Retinopathy, nephropathy
Crystal M. Pressley et al., 2008	Type 2	Not specified	Not specified	Blindness, amputation
G. Sartore et al., 2023	Type 2	Varies	Not specified	Nephropathy, neuropathy, retinopathy

Study	Diabetes Type	Sample Size	Follow-up Duration	Microvascular Complications Assessed
C. Lo et al., 2017	Type 1 or 2	Not specified	Not specified	Nephropathy
Lily Agrawal et al., 2011	Type 2	1,791	Median 5.6 years	Retinopathy, nephropathy, neuropathy
J. Beulens et al., 2009	Type 2	1,602	4.1 years	Retinopathy
J. Lachin et al., 2021	Type 1	Not specified	Up to 26 years	Retinopathy, nephropathy, neuropathy
E. Ipp et al., 2021	Not specified	Not specified	17 years	Diabetic retinopathy
R. Gilbert et al., 2014	Mixed	12,537	Median 6.2 years	Nephropathy, retinopathy
N. White et al., 2010	Type 1	1,055 adults, 156 adolescents	10 years	Retinopathy
Boris P. Kovatchev et al., 2025	Type 1	Not specified	Not specified	Retinopathy, nephropathy, neuropathy
L. Zhai et al., 2022	Type 2	44,662	3-15 years	Diabetic retinopathy
C. Abraira et al., 2003	Type 2	1,700	5-7 years	Retinopathy
E. Chew et al., 2016	Type 2	10,251	~8 years	Diabetic retinopathy
Cut Lisa et al., 2025	Type 1 and Type 2	>55,000	2-24.3 years	Nephropathy
C. Lo et al., 2012	Type 2	Not specified	Not specified	Nephropathy
J. Larsen et al., 2004	Type 1	39	18 years	Cardiac autonomic function
Tomoki Okuno et al., 2023	Type 2	4,000	Not specified	Microalbuminuria, macroalbuminuria

Study	Diabetes Type	Sample Size	Follow-up Duration	Microvascular Complications Assessed
Jin J. Zhou et al., 2020	Type 2	10,251 (ACCORD), 1,791 (VADT)	Up to 84-87 months	Nephropathy, retinopathy
J. Tryggestad et al., 2020	Type 2	515	1-3 years	Nephropathy, retinopathy
R. Frank et al., 2015	Type 1 and Type 2	1,746	1 year	Diabetic retinopathy, nephropathy
S. Holfort et al., 2011	Type 1	17	52 weeks	Diabetic retinopathy
Vivek Charu et al., 2023	Type 2	Not specified	7 years	Nephropathy
O. Klefter et al., 2016	Type 1	13	3.5 years	Retinal function
S. Bressler et al., 2000	Type 1	1,208-1,302	4 years	Retinopathy, nephropathy
Mohammed K. Ali et al., 2024	Type 2	1,146	Median 6.5 years	Retinopathy, nephropathy, neuropathy
Lily Agrawal et al., 2019	Type 2	1,791	Median 15 years	Nephropathy

HbA1c Definitions and Thresholds

Studies employed heterogeneous approaches to defining glycemic control, reflecting evolving clinical standards and varying research objectives.

Study	HbA1c Threshold for Poor Control	HbA1c Threshold for Good Control	Analysis Type	Additional Glycemic Measures
S. Genuth et al., 2002	9.0%	≤7.0%	Continuous	None
W. Herman et al., 2018	>8.8% (73 mmol/mol)	<7.2% (55 mmol/mol)	Categorical	Time-weighted mean
M. Tavakoli et al., 2018	Not specified	~6.5%	Continuous	None
F. Ismail-Beigi et al., 2010	>7.5%	<6.0%	Not specified	None

Study	HbA1c Threshold for Poor Control	HbA1c Threshold for Good Control	Analysis Type	Additional Glycemic Measures
S. Coca et al., 2012	Standard therapy targets	<7%, <6%, ≤5.1%	Continuous	None
M. Shichiri et al., 2000	Not specified	<6.5%	Not specified	FBG <110 mg/dl, 2-h PPG <180 mg/dl
D. Ziegler et al., 2015	≥7.0%	<7.0%	Categorical	None
Peiyao Jin et al., 2015	>6.4%	<5.2%	Both	FBG monitoring
S. A. Jiskani et al., 2020	>7%	<7%	Categorical	None
Liying Zhang et al., 2001	≥9.49%	≤6.87%	Categorical	None
W. Shiferaw et al., 2020	>7%	≤7%	Both	None
Anushka Patel et al., 2008	Standard therapy	≤6.5%	Continuous	None
J. Larsen et al., 2004	≥8.4%	<8.4%	Categorical	None
E. Chew et al., 2016	7.0-7.9%	<6.0%	Continuous	None

Most studies utilized an HbA1c threshold of 7% to distinguish good from poor glycemic control, though thresholds ranged from 6.5% to 9.49%. A minority incorporated additional glycemic measures, including fasting blood glucose, glycemic variability metrics, and postprandial glucose values. The duration of glycemic exposure assessment varied from single point measurements to cumulative exposure over decades.

Effects of Glycemic Control on Microvascular Complications

Retinopathy

Study	Effect Measure	Point Estimate (95% CI)	P-value	Notes
S. Genuth et al., 2002	Risk reduction	76% (primary prevention), 54% (secondary intervention)	Not reported	39% decrease per 10% HbA1c reduction

Study	Effect Measure	Point Estimate (95% CI)	P-value	Notes
W. Herman et al., 2018	Absolute risk	5% vs. 45% (requiring laser)	Not reported	30-year follow-up
M. Tavakoli et al., 2018	Cumulative incidence	Increased from 21.3% to 35.5%	Not reported	Despite improved HbA1c
T. Harindhanavudhi et al., 2011	Odds ratio	0.40 (0.17-0.93) for A1C >7.5%	P = 0.03	RAS blockade benefit only with A1C >7.5%
Takayoshi Sasako et al., 2025	Hazard ratio	1.31 (1.13-1.51) per 1% HbA1c increase	P < 0.001	Onset of retinopathy
Peiyao Jin et al., 2015	Odds ratio	2.84 (2.11-3.82)	P < 0.01	Dose-response observed
Sophie Sun et al., 2021	Risk ratio	0.77 (0.66-0.89)	Not reported	Meta-analysis
W. Shiferaw et al., 2020	Odds ratio	1.25 (1.14-1.38) for HbA1c >7%	Not reported	Meta-analysis in Africa
N. Azad et al., 2014	Odds ratio	1.30 (1.12-1.50) per 1% HbA1c increase	P = 0.0004	Age interaction present
Sharon D. Solomon et al., 2017	Risk reduction	34-76%	Not reported	DCCT-based estimates
L. Aiello et al., 2013	Risk reduction	76% (onset), 54% (progression)	Not reported	44% decrease per 10% HbA1c reduction
B. Hemmingsen et al., 2015	Risk ratio	0.79 (0.68-0.92)	P = 0.002	Cochrane review
J. Lachin et al., 2014	Risk reduction	46% (36-54) for progression	P < 0.0001	18-year follow-up
E. Chew et al., 2010	Odds ratio	0.67 (0.51-0.87)	P = 0.003	ACCORD Eye Study
E. Chew et al., 2016	Adjusted odds ratio	0.42 (0.28-0.63)	P < 0.0001	ACCORDION Eye Study

Study	Effect Measure	Point Estimate (95% CI)	P-value	Notes
L. Zhai et al., 2022	Relative risk	1.48 (1.24-1.78) for higher HbA1c-SD	P < 0.001	HbA1c variability analysis
G. Sartore et al., 2023	Hazard ratio	1.15 (1.08-1.24)	P < 0.0001	HbA1c variability

The evidence consistently demonstrates that poor glycemic control is associated with increased risk of diabetic retinopathy development and progression. The landmark DCCT/EDIC studies showed that intensive therapy reduced retinopathy risk by 76% in the primary prevention cohort and 54% in the secondary intervention cohort, with a 39-44% decrease in risk for each 10% reduction in HbA1c. These benefits persisted over 30 years, with excellent glycemic control (<7.2%) resulting in only 5% of patients requiring laser therapy compared to 45% with poor control (>8.8%).

Meta-analyses in Type 2 diabetes populations confirmed these findings, with intensive glucose control associated with a 23% reduction in retinopathy progression (RR 0.77, 95% CI 0.66-0.89) and a 21% reduction in retinopathy risk (RR 0.79, 95% CI 0.68-0.92). The ACCORD Eye Study demonstrated a 33% reduction in retinopathy progression with intensive glycemic control (OR 0.67, 95% CI 0.51-0.87, P=0.003), and this benefit persisted in the ACCORDION follow-up study (aOR 0.42, 95% CI 0.28-0.63, P<0.0001), demonstrating a "legacy effect" of early intensive control.

A dose-response relationship was evident across multiple studies. In Chinese patients with Type 2 diabetes, each unit increase in baseline HbA1c increased retinopathy risk nearly threefold (OR 2.84, 95% CI 2.11-3.82). The VADT demonstrated a 30% increase in progression risk for each 1% increase in baseline HbA1c (OR 1.30, 95% CI 1.12-1.50, P=0.0004).

Nephropathy

Study	Effect Measure	Point Estimate (95% CI)	P-value	Outcome
S. Genuth et al., 2002	Risk reduction	39% (microalbuminuria), 56% (clinical albuminuria)	Not reported	Albumin excretion
W. Herman et al., 2018	Absolute risk	0% vs. 5% (ESRD)	Not reported	End-stage renal disease
M. Tavakoli et al., 2018	Cumulative incidence	Decreased from 37.6% to 22%	Not reported	Only improved complication

Study	Effect Measure	Point Estimate (95% CI)	P-value	Outcome
S. Coca et al., 2012	Risk ratio	0.86 (0.76-0.96) microalb, 0.74 (0.65-0.85) macroalb	P = 0.01, P = 0.008	No effect on ESRD
I. D. de Boer et al., 2011	Association	Lower HbA1c associated with reduced progression	P < 0.05	Macroalbuminuria, impaired GFR
S. A. Jiskani et al., 2020	Prevalence	57.54% vs. 12.26%	P < 0.001	Microalbuminuria
Anushka Patel et al., 2008	Hazard ratio	0.79 (0.66-0.93)	P = 0.006	Nephropathy
ADVANCE commentary, 2008	Risk reduction	21% (7-33)	NNT = 94	New/worsening nephropathy
B. Hemmingsen et al., 2015	Risk ratio	0.75 (0.59-0.95)	P = 0.02	Nephropathy
Rami Aldafas et al., 2023	Risk ratio	0.78 (0.63-0.97) nephropathy, 0.72 (0.5-0.87) macroalb	Not reported	Meta-analysis
Wei-zhi Chen et al., 2014	Hazard ratio	16.96 (high UACR + HbA1c >8%)	P < 0.001	Microalbuminuria development
G. Sartore et al., 2023	Hazard ratio	1.29 (1.22-1.36)	P < 0.0001	HbA1c variability
M. Shestakova et al., 2016	Hazard ratio	1.84 (1.37-2.48)	P < 0.05	Microvascular complications

Intensive glycemic control consistently reduced the development and progression of early nephropathy markers. The DCCT demonstrated 39% reduction in microalbuminuria and 56% reduction in clinical albuminuria, with complete prevention of end-stage renal disease (0% vs. 5%) over 30 years of follow-up. In Type 2 diabetes, the ADVANCE trial showed a 21% reduction in nephropathy risk (HR 0.79, 95% CI 0.66-0.93, P=0.006).

A meta-analysis of seven trials involving 28,065 Type 2 diabetic patients confirmed that intensive glucose control significantly reduced microalbuminuria (RR 0.86, 95% CI 0.76-0.96) and macroalbuminuria (RR

0.74, 95% CI 0.65-0.85). However, the same analysis found no significant effect on hard renal endpoints including doubling of serum creatinine (RR 1.06, 95% CI 0.92-1.22), ESRD (RR 0.69, 95% CI 0.46-1.05), or death from renal disease (RR 0.99, 95% CI 0.55-1.79). The cumulative incidences of these advanced outcomes were low (<4% for creatinine doubling, <1.5% for ESRD, <0.5% for renal death) during the trial follow-up periods.

Cross-sectional data showed dramatically higher microalbuminuria prevalence in poorly controlled patients: 57.54% with HbA1c >7% versus 12.26% with HbA1c <7% (P<0.001). Dose-response relationships were particularly evident in patients with high-normal baseline albuminuria, where the combination of elevated HbA1c (>8%) and high-normal urinary albumin-to-creatinine ratio conferred a 17-fold increased risk of microalbuminuria development.

Neuropathy

Study	Effect Measure	Point Estimate (95% CI)	P-value	Notes
W. Herman et al., 2018	Absolute risk	15% vs. 50%	Not reported	Clinical neuropathy
D. Ziegler et al., 2015	Clinical outcome	64% vs. 0%	P < 0.05	24-year polyneuropathy incidence
P. J. Wiffen et al., 2012	Annualized RD	-1.84% (-2.56 to -1.11) T1D, -0.58% (0.01 to -1.17) T2D	Not reported	Cochrane review
G. Sartore et al., 2023	Hazard ratio	1.03 (0.99-1.08)	P = 0.14	Not significant for HbA1c variability

The evidence for neuropathy is strongest in Type 1 diabetes. A 24-year prospective study demonstrated complete prevention of confirmed clinical polyneuropathy in patients maintaining mean HbA1c <7.0% (0% incidence) compared to 64% incidence in those with HbA1c ≥7.0%. The annual decline in nerve conduction velocity was six-fold faster in the poorly controlled group. Over 30 years, excellent glycemic control reduced clinical neuropathy from 50% to 15%.

The Cochrane systematic review found that enhanced glucose control significantly reduced clinical neuropathy development in Type 1 diabetes (annualized risk difference -1.84%, 95% CI -2.56 to -1.11). In Type 2 diabetes, the effect was smaller and borderline significant (annualized risk difference -0.58%, 95% CI 0.01 to -1.17, P=0.06). Secondary outcomes including motor nerve conduction velocity and vibration threshold significantly favored intensive treatment in both populations.

Glycemic Variability and Microvascular Outcomes

Study	Variability Measure	Complication	Effect Estimate	P-value
J. Park et al., 2020	HbA1c SD	DR progression	Significant association	P < 0.001
L. Zhai et al., 2022	HbA1c SD	Retinopathy	RR 1.48 (1.24-1.78)	P < 0.001
L. Zhai et al., 2022	HbA1c CV	Retinopathy	RR 1.29 (1.05-1.59)	P = 0.02
G. Sartore et al., 2023	HbA1c variability	Nephropathy	HR 1.29 (1.22-1.36)	P < 0.0001
G. Sartore et al., 2023	HbA1c variability	Retinopathy	HR 1.15 (1.08-1.24)	P < 0.0001
Jin J. Zhou et al., 2020	Fasting glucose CV	Microvascular	Significant association	Not specified
J. Lachin et al., 2017	Within-day variability	All microvascular	Not significant	P > 0.25
E. Kilpatrick et al., 2009	Glucose variability	Retinopathy/nephropathy	Not significant	P > 0.25

Beyond mean HbA1c levels, visit-to-visit HbA1c variability has emerged as an independent predictor of microvascular complications. A meta-analysis of 12 observational studies involving 44,662 Type 2 diabetic patients found that higher HbA1c variability (measured as standard deviation) was associated with 48% increased retinopathy risk (RR 1.48, 95% CI 1.24-1.78, P<0.001). This association persisted after adjustment for mean HbA1c levels. Another meta-analysis confirmed associations between HbA1c variability and nephropathy (HR 1.29, 95% CI 1.22-1.36) and retinopathy (HR 1.15, 95% CI 1.08-1.24), though the association with neuropathy was not significant (HR 1.03, 95% CI 0.99-1.08, P=0.14).

In contrast, within-day glucose variability from quarterly glucose profiles in the DCCT did not independently predict microvascular complications after adjustment for mean blood glucose. This distinction suggests that long-term glycemic instability, rather than short-term fluctuations, may be the more clinically relevant metric.

Metabolic Memory and Legacy Effects

Study	Design	Finding	Duration of Effect
J. Lachin et al., 2000	DCCT/EDIC	72-87% odds reduction persisted 4 years post-trial	4 years

Study	Design	Finding	Duration of Effect
J. Lachin et al., 2014	DCCT/EDIC	46% risk reduction for retinopathy progression	18 years
J. Lachin et al., 2021	DCCT/EDIC	Differences wholly explained by prior HbA1c	26 years
E. Chew et al., 2016	ACCORD	aOR 0.42 despite converged HbA1c levels	~8 years
N. White et al., 2010	DCCT/EDIC	56% hazard reduction in adults	10 years

A remarkable finding across DCCT/EDIC studies is the persistence of treatment benefits long after HbA1c levels converged between treatment groups, a phenomenon termed "metabolic memory". Four years after the DCCT ended, despite narrowing of median HbA1c values (8.2% vs. 7.9%), the former intensive therapy group maintained 72-87% odds reduction for worsening retinopathy (P<0.001). These benefits persisted through 18 years of EDIC follow-up and were wholly explained by differences in HbA1c levels during the original DCCT period.

The ACCORDION Eye Study demonstrated similar legacy effects in Type 2 diabetes, with prior intensive glycemic control continuing to reduce retinopathy progression (aOR 0.42, 95% CI 0.28-0.63, P<0.0001) even after HbA1c levels equilibrated between groups. This finding was notable as the first demonstration of metabolic memory in patients with Type 2 diabetes of 10 years' duration with established cardiovascular disease.

Age and Subgroup Differences

The VADT revealed important age-related heterogeneity in treatment effects. Intensive glycemic control decreased retinopathy incidence in participants aged ≤55 years (OR 0.49, 95% CI 0.24-1.0) but increased incidence in those aged ≥70 years (OR 2.88, 95% CI 1.0-8.24, P=0.0043 for interaction). This biphasic pattern was not fully explained by differences in baseline characteristics or complications.

In adolescents compared to adults from the DCCT/EDIC, the beneficial effect of prior intensive therapy on retinopathy progression was diminished at 10-year follow-up (32% hazard reduction, P=0.13 for adolescents vs. 56% hazard reduction, P<0.0001 for adults). This difference was largely explained by poorer glycemic control achieved during the trial: adolescents in the intensive group maintained mean HbA1c of 8.1% compared to 7.2% in adults. This finding underscores the importance of achieving target HbA1c levels rather than simply assigning intensive therapy.

Adverse Effects of Intensive Glycemic Control

Study	Outcome	Effect Estimate	P-value

Study	Outcome	Effect Estimate	P-value
ADVANCE commentary, 2008	Severe hypoglycemia	RRI 85% (42-137)	NNH = 79
Rami Aldafas et al., 2023	Hypoglycemia	RR 2.04 (1.34-3.1)	Not reported
B. Hemmingsen et al., 2015	Severe hypoglycemia	RR 2.18 (1.53-3.11)	Not reported
B. Hemmingsen et al., 2015	Serious adverse events	RR 1.06 (1.02-1.10)	P = 0.007
P. J. Wiffen et al., 2012	Severe hypoglycemia	Significantly increased	Not specified
Thomas Crabtree et al., 2022	Severe hypoglycemia	RR 2.45 (2.22-2.72)	Not reported

The microvascular benefits of intensive glycemic control must be weighed against increased risks of hypoglycemia. Meta-analyses consistently reported approximately doubled risk of severe hypoglycemia with intensive therapy (RR 2.04 to 2.45). The ADVANCE trial found an 85% relative risk increase in severe hypoglycemia (NNH=79), and serious adverse events were also significantly increased (RR 1.06, 95% CI 1.02-1.10, P=0.007).

The ACCORD trial was terminated early due to excess mortality in the intensive treatment arm, though the mechanisms remain debated. The microvascular benefits of intensive therapy therefore "should be weighed against the increase in total and cardiovascular disease-related mortality, increased weight gain, and high risk for severe hypoglycaemia".

Synthesis

Reconciling Findings Across Diabetes Types

The evidence demonstrates a consistent association between poor glycemic control and microvascular complications, but effect sizes differ substantially between Type 1 and Type 2 diabetes. In Type 1 diabetes, intensive therapy reduced retinopathy by 76% in the primary prevention cohort and completely prevented clinical polyneuropathy over 24 years in well-controlled patients. In Type 2 diabetes, effect sizes were generally more modest: meta-analyses showed 21-25% reductions in retinopathy and nephropathy risk.

This differential may reflect several factors. First, Type 2 diabetes populations in the major trials were older with longer disease duration and often had established cardiovascular disease, potentially limiting the window for glycemic intervention. Second, Type 2 diabetes involves insulin resistance and multiple metabolic abnormalities beyond hyperglycemia, which may attenuate the benefit of glucose lowering alone. Third, the Kumamoto Study, which enrolled Japanese patients with Type 2 diabetes of shorter duration and lower cardiovascular risk, demonstrated benefits comparable to Type 1 studies, suggesting that patient selection significantly influences outcomes.

Early vs. Late Nephropathy Stages

A consistent finding across studies is that intensive glycemic control reduces surrogate endpoints (microalbuminuria, macroalbuminuria) but not hard renal outcomes (ESRD, renal death). This pattern has several potential explanations:

- **Insufficient follow-up duration**: The pooled cumulative incidence of ESRD (<1.5%) and renal death (<0.5%) was low during trial follow-up periods, limiting statistical power to detect differences.
- **Competing risks**: Patients with advanced diabetes may die from cardiovascular causes before progressing to ESRD.
- **Point of no return**: Once nephropathy advances beyond microalbuminuria, pathological changes may become irreversible regardless of subsequent glycemic control. Studies found that patients entering trials with microalbuminuria showed progressive decline in creatinine clearance regardless of treatment intensity.
- **Blood pressure predominance**: At advanced nephropathy stages, hypertension control may become more important than glycemic control.

Explaining the "Early Worsening" Paradox

Several studies documented initial retinopathy worsening following rapid glycemic improvement, termed "early worsening" or "euglycemic progression". In poorly controlled Type 2 diabetes patients who achieved dramatic HbA1c reductions (mean decrease of 4.0%), retinopathy grade worsened by 22.6% compared to minimal change in the control group (P=0.015). This paradoxical effect was more pronounced with larger HbA1c reductions and poorer baseline control.

The mechanism likely involves sudden changes in retinal blood flow and oxygenation following rapid normalization of glucose levels. However, this early worsening is transient, and long-term outcomes strongly favor intensive therapy. Clinical implications include:

- Early retinopathy worsening does not negate the long-term benefits of improved glycemic control
- Patients likely to experience marked HbA1c reductions should receive baseline retinal examination
- Gradual rather than abrupt normalization of glycemia may be prudent in patients with advanced retinopathy

Quality-Weighted Evidence Assessment

The strongest evidence comes from the DCCT/EDIC studies, which randomized 1,441 patients with Type 1 diabetes and achieved near-complete follow-up over 30 years. These studies consistently demonstrated robust microvascular benefits with good glycemic control. However, the population was young, relatively healthy, and predominantly Caucasian, limiting generalizability.

For Type 2 diabetes, the UKPDS, ADVANCE, ACCORD, and VADT provide the foundation of evidence. While these trials enrolled more representative populations, they differed in design, target HbA1c levels, and patient characteristics. The ACCORD trial's premature termination due to

excess mortality raised concerns about the safety of very aggressive targets (<6.0%) in high-risk populations. Notably, the increased mortality occurred despite significant microvascular benefits, suggesting that optimal HbA1c targets must balance microvascular protection against other risks.

Clinical Implications for Different Populations

The synthesis of evidence supports several population-specific conclusions:

Type 1 diabetes: Intensive therapy targeting HbA1c <7% should be initiated as early as possible after diagnosis and maintained lifelong. The benefits of early control persist for decades through metabolic memory, while delayed intensification results in substantially worse outcomes.

Type 2 diabetes without complications: Patients with shorter disease duration (<10 years), no cardiovascular disease, and younger age derive the greatest benefit from intensive glycemic control. The benefits on microvascular outcomes are consistent across trials.

Type 2 diabetes with advanced complications or older age: Intensive targets should be individualized, as the VADT demonstrated potential harm from intensive therapy in patients aged ≥70 years. The ACCORD results suggest caution with targets <6.0% in high-risk populations.

Patients with established microvascular disease: Benefits of intensive therapy diminish with advancing disease severity. The VADT found no benefit on retinopathy outcomes in patients with severe baseline disease, and nephropathy progression continued despite intensive control in patients with established microalbuminuria.

DISCUSSION

This systematic review of 80 studies provides a comprehensive synthesis of the association between glycemic control (HbA1c) and microvascular complications in diabetes. The findings underscore that hyperglycemia is a central pathogenic driver of retinopathy, nephropathy, and neuropathy, but the strength, consistency, and clinical implications of this relationship vary significantly across diabetes types, disease stages, and patient characteristics.

Consistency and Magnitude of Association: The evidence confirms a robust, dose-dependent relationship between elevated HbA1c and increased risk of microvascular complications. In Type 1 diabetes, the DCCT/EDIC studies demonstrated that intensive therapy (target HbA1c <7%) reduced the risk of retinopathy by 76% in the primary prevention cohort and 54% in the secondary intervention cohort, with benefits persisting over 30 years of follow-up (Genuth et al., 2002; Herman et al., 2018). Similarly, near-normoglycemia (HbA1c <7%) completely prevented clinical polyneuropathy over 24 years, whereas poor control (HbA1c ≥7%) led to a 64% incidence (Ziegler et al., 2015). In Type 2 diabetes, meta-analyses of major trials (UKPDS, ADVANCE, ACCORD, VADT) showed more modest but significant reductions: intensive control reduced retinopathy progression by 23–33% and nephropathy by 21–26% (Zoungas et al., 2017; Hemmingsen et al., 2015). This difference in effect size likely reflects the older age, longer disease duration, greater comorbidity burden,

and multifactorial pathophysiology (e.g., insulin resistance, hypertension) in Type 2 diabetes populations, which may attenuate the exclusive benefit of glucose lowering.

Glycemic Variability as an Independent Risk Factor: Beyond mean HbA1c, visit-to-visit glycemic variability has emerged as a significant predictor of microvascular complications, particularly in Type 2 diabetes. A meta-analysis of 44,662 patients found that higher HbA1c variability (measured as standard deviation) increased retinopathy risk by 48% (RR 1.48, 95% CI 1.24–1.78) and nephropathy risk by 29% (HR 1.29, 95% CI 1.22–1.36), independent of mean HbA1c (Zhai et al., 2022; Sartore et al., 2023). In contrast, within-day glucose variability in the DCCT did not independently predict complications after adjusting for mean glucose, suggesting that long-term instability—possibly reflecting therapeutic adherence, lifestyle factors, or physiological dysregulation—may be more clinically relevant than short-term fluctuations (Lachin et al., 2017). These findings advocate for incorporating variability metrics into risk stratification and treatment monitoring, especially in patients who exhibit fluctuating control despite acceptable mean HbA1c.

Metabolic Memory and Legacy Effects: A remarkable and consistent finding across studies is the phenomenon of metabolic memory—the persistence of microvascular benefits (or risks) long after HbA1c levels have converged between treatment groups. In the DCCT/EDIC, four years after the trial ended, the former intensive therapy group maintained a 72–87% odds reduction for worsening retinopathy, and these benefits were wholly explained by differences in HbA1c during the initial DCCT period (Lachin et al., 2000, 2021). Similarly, in Type 2 diabetes, the ACCORDION Eye Study demonstrated that prior intensive control continued to reduce retinopathy progression (aOR 0.42, 95% CI 0.28–0.63) nearly eight years after glycemic convergence (Chew et al., 2016). This underscores the critical importance of early and sustained glycemic control, as early exposure to hyperglycemia may induce persistent epigenetic, metabolic, or structural changes that drive long-term complication risk. For clinical practice, this implies that delaying intensive control—even if later achieved—may forfeit substantial long-term protection.

Differential Effects on Nephropathy Stages: A key nuance in the evidence is the differential impact of glycemic control on early versus advanced nephropathy. Intensive control consistently reduces early markers such as microalbuminuria and macroalbuminuria (e.g., 39% reduction in microalbuminuria in DCCT; 21% reduction in nephropathy in ADVANCE) (Genuth et al., 2002; Patel et al., 2008). However, effects on hard renal endpoints—end-stage renal disease (ESRD), doubling of serum creatinine, renal death—are less clear. A meta-analysis of 28,065 Type 2 diabetes patients found no significant reduction in ESRD (RR 0.69, 95% CI 0.46–1.05) or renal death (RR 0.99, 95% CI 0.55–1.79) with intensive control, despite significant reductions in albuminuria (Coca et al., 2012). This may reflect insufficient follow-up duration, competing risks from cardiovascular mortality, or the possibility that once nephropathy progresses beyond microalbuminuria, pathological changes become less reversible by glycemic

control alone. In advanced stages, blood pressure control and renin-angiotensin system inhibition may assume greater importance (Lo & Zoungas, 2017). Thus, while glycemic control is essential for primary prevention and early intervention, its role may diminish in later-stage kidney disease.

Age and Subgroup Heterogeneity: Treatment response to intensive glycemic control is not uniform across all patients. The VADT revealed a striking age interaction: intensive control reduced retinopathy incidence in participants ≤55 years (OR 0.49) but increased it in those ≥70 years (OR 2.88) (Azad et al., 2014). Similarly, in DCCT/EDIC, adolescents derived less benefit from intensive therapy than adults, largely due to poorer achieved glycemic control (HbA1c 8.1% vs. 7.2%) during the trial (White et al., 2010). These findings highlight that factors such as age, disease duration, baseline complications, and perhaps biological aging processes modulate the risk-benefit ratio of intensive control. In older adults, the heightened risk of severe hypoglycemia—which can lead to falls, cognitive impairment, and cardiovascular events—may outweigh microvascular benefits, particularly if life expectancy is limited or complications are already advanced (Crabtree et al., 2022). Hence, personalized treatment targets, considering functional status, comorbidities, and patient preferences, are imperative.

Early Worsening Paradox: Rapid improvement in glycemic control, particularly in patients with long-standing poor control, can transiently worsen retinopathy—a phenomenon termed “early worsening” or “euglycemic progression.” Studies in Type 2 diabetes minorities showed that dramatic HbA1c reductions (mean decrease 4.0%) were associated with a 22.6% worsening in retinopathy grade compared to minimal change in controls (Shurter et al., 2013). The mechanism is thought to involve rapid changes in retinal blood flow, oxygenation, and growth factor expression. Importantly, this worsening is usually temporary, and long-term outcomes strongly favor improved control. Clinically, this suggests that patients with poor baseline control and existing retinopathy should have baseline retinal exams before intensifying therapy, and glycemic improvements should ideally be gradual rather than abrupt.

Adverse Effects and Risk-Benefit Balance: The microvascular benefits of intensive control must be balanced against increased risks, most notably severe hypoglycemia. Meta-analyses consistently report an approximately twofold increased risk of severe hypoglycemia with intensive therapy (RR 2.04–2.45) (Aldafas et al., 2023; Hemmingsen et al., 2015). The ACCORD trial was terminated early due to excess mortality in the intensive arm, raising concerns about very aggressive targets (HbA1c <6.0%) in high-risk Type 2 diabetes patients (Ismail-Beigi et al., 2010). While the exact mechanisms remain debated, hypoglycemia, rapid HbA1c reduction, polypharmacy, and patient frailty may contribute. Thus, for many patients—especially older adults, those with long disease duration, or significant comorbidities—a moderate HbA1c target (e.g., 7–8%) may optimize the trade-off between microvascular protection and safety.

Clinical and Research Implications: For Type 1 diabetes, early intensive therapy targeting HbA1c <7% should be standard, with emphasis

on continuous glucose monitoring and education to achieve sustained control (Araszkiewicz et al., 2008). For Type 2 diabetes, treatment must be individualized: younger patients with short disease duration and no complications benefit from tighter control (HbA1c ≤7%), while older, frail, or high-risk patients may be better served by less stringent targets (e.g., 7.5–8.5%) to avoid hypoglycemia and treatment burden (Ipp & Kumar, 2021). Future research should focus on: (1) validating glycemic variability metrics as therapeutic targets, (2) exploring continuous glucose monitoring-derived parameters for complication prediction, (3) understanding biological mechanisms of metabolic memory, and (4) developing integrated care models that combine glycemic, blood pressure, and lipid management with regular complication screening.

CONCLUSION AND RECOMMENDATIONS

Conclusion:

This systematic review reaffirms that glycemic control, as measured by HbA1c, is fundamentally important in preventing and delaying microvascular complications in both Type 1 and Type 2 diabetes. The association is strong, dose-dependent, and supported by high-quality evidence from landmark trials and observational studies. Key conclusions include:

1. **Strongest benefits are seen with early, sustained intensive control**, particularly in Type 1 diabetes and in Type 2 diabetes patients with short disease duration and no advanced complications.
2. **Glycemic variability is an independent risk factor** for retinopathy and nephropathy, suggesting that stable long-term control may be as important as achieving low mean HbA1c.
3. **Metabolic memory effects underscore the importance of early intervention**; delays in achieving good control may result in irreversible long-term risks.
4. **Benefits diminish in older patients, those with advanced complications, or long disease duration**, where intensive control may increase hypoglycemia risk without proportional microvascular gain.
5. **Nephropathy benefits are clear for early-stage markers** (microalbuminuria) but less certain for end-stage renal disease, highlighting the need for multifactorial management in advanced kidney disease.
6. **Treatment must be personalized**, balancing microvascular benefits against risks of hypoglycemia, polypharmacy, and patient burden.

Recommendations for Clinical Practice:

- Implement early intensive glycemic control in Type 1 diabetes and in newly diagnosed Type 2 diabetes without complications.
- Use HbA1c targets tailored to patient age, comorbidities, life expectancy, and preferences.
- Monitor and address glycemic variability, not just mean HbA1c.
- Screen for retinopathy before intensifying therapy in poorly controlled patients to monitor for early worsening.

- Combine glycemic control with blood pressure management, lipid control, and regular complication screening for comprehensive care.

Future Research Directions:

- Prospective studies on glycemic variability thresholds and intervention strategies.
- Mechanistic studies on metabolic memory and early worsening phenomena.
- Trials evaluating personalized HbA1c targets based on genetic, metabolic, and clinical profiles.
- Integration of continuous glucose monitoring data into complication risk prediction models.

REFERENCES

A. Araszkiewicz, D. Zozulinska-Ziolkiewicz, M. Trepińska, and B. Wierusz-Wysocka. “Knowledge After Five-Day Teaching Program in Intensive Insulin Therapy Performed at the Onset of Type 1 Diabetes Influence the Development of Late Diabetic Complications.” *Diabetes Research and Clinical Practice*, 2008.

A. Jacobson, B. Braffett, P. Cleary, R. Gubitosi-Klug, and M. Larkin. “The Long-Term Effects of Type 1 Diabetes Treatment and Complications on Health-Related Quality of Life.” *Diabetes Care*, 2013.

A. Shurter, P. Genter, D. Ouyang, and Eli Ipp. “Euglycemic Progression: Worsening of Diabetic Retinopathy in Poorly Controlled Type 2 Diabetes in Minorities.” *Diabetes Research and Clinical Practice*, 2013.

Anushka Patel, S. MacMahon, J. Chalmers, B. Neal, L. Billot, M. Woodward, M. Marre, et al. “Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes.” *New England Journal of Medicine*, 2008.

B. Hemmingsen, S. Lund, C. Gluud, A. Vaag, T. Almdal, and J. Wetterslev. “WITHDRAWN: Targeting Intensive Glycaemic Control Versus Targeting Conventional Glycaemic Control for Type 2 Diabetes Mellitus.” *Cochrane Database of Systematic Reviews*, 2015.

Boris P. Kovatchev, Benjamin J. Lobo, Chiara Fabris, Mohammadreza Ganji, Anas El Fathi, Marc D. Breton, L. Kanapka, C. Kollman, Tadej Battelino, and Roy W. Beck. “The Virtual DCCT: Adding Continuous Glucose Monitoring to a Landmark Clinical Trial for Prediction of Microvascular Complications.” *Diabetes Technology & Therapeutics*, 2025.

C. Abraira, W. Duckworth, M. Mccarren, N. Emanuele, Danielle Arca, D. Reda, and W. Henderson. “Design of the Cooperative Study on Glycemic Control and Complications in Diabetes Mellitus Type 2: Veterans Affairs Diabetes Trial.” *Journal of Diabetes and Its Complications*, 2003.

C. Lo, and S. Zoungas. “Intensive Glucose Control in Patients with Diabetes Prevents Onset and Progression of Microalbuminuria, but Effects on End-Stage Kidney Disease Are Still Uncertain.” *Evidence-Based Medicine*, 2017.

———. “Intensive Glucose Control in Patients with Type 2 Diabetes Is Associated with a Reduction in Albuminuria and May Be Associated with Reduced End-Stage Renal Disease.” *Evidence-Based Medicine*, 2012.

Chebly Dagher, M. Akiki, Rita Saliby, and Georges Harb. “The Impact of Glycemic Control on Ranibizumab Efficacy in Diabetic Retinopathy: A Retrospective Analysis.” *Cureus*, 2025.

Chia-Hsuin Chang, and L. Chuang. “Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes: Is Blood Pressure Control the Lower the Better?” *Journal of Diabetes Investigation*, 2010.

Crystal M. Pressley. “Reduction of Diabetic Complications with Intensive Blood Glucose Control: A Systematic Review of the Literature,” 2008.

Cut Lisa, Afrianna, and T. I. Rizal. “The Impact of Glycemic Control and Variability (HbA1c) on the Rate of Glomerular Filtration Rate Decline in Diabetes Mellitus: A Systematic Review.” *International Journal of Medical Science and Health Research*, 2025.

D. Nathan. “The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview.” *Diabetes Care*, 2013.

D. Newman, M. Mattock, A. Dawnay, S. Kerry, A. McGuire, M. Yaqoob, G. Hitman, and C. Hawke. “Systematic Review on Urine Albumin Testing for Early Detection of Diabetic Complications.” *Health Technology Assessment*, 2005.

D. Ziegler, M. Behler, Maria Schroers-Teuber, and M. Roden. “Near-Normoglycaemia and Development of Neuropathy: A 24-Year Prospective Study from Diagnosis of Type 1 Diabetes.” *BMJ Open*, 2015.

E. Chew, J. Lovato, M. Davis, H. Gerstein, R. Danis, F. Ismail-Beigi, S. Genuth, et al. “Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study.” *Diabetes Care*, 2016.

E. Chew, W. Ambrosius, M. Davis, R. Danis, S. Gangaputra, C. Greven, L. Hubbard, et al. “Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes.” *New England Journal of Medicine*, 2010.

E. Ipp, and Monisha A. Kumar. “A Clinical Conundrum: Intensifying Glycemic Control in the Presence of Advanced Diabetic Retinopathy.” *Diabetes Care*, 2021.

E. Kilpatrick, A. Rigby, and S. Atkin. “Effect of Glucose Variability on the Long-Term Risk of Microvascular Complications in Type 1 Diabetes.” *Diabetes Care*, 2009.

F. Ishibashi, Miki Taniguchi, Aiko Kosaka, Harumi Uetake, and M. Tavakoli. “Improvement in Neuropathy Outcomes With Normalizing HbA1c in Patients With Type 2 Diabetes.” *Diabetes Care*, 2018.

F. Ismail-Beigi, T. Craven, M. Banerji, J. Basile, J. Calles, R. Cohen, R. Cuddihy, et al. “Effect of Intensive Treatment of Hyperglycaemia on Microvascular Outcomes in Type 2 Diabetes: An Analysis of the ACCORD Randomised Trial.” *The Lancet*, 2010.

F. Ismail-Beigi, T. Craven, P. O’Connor, D. Karl, J. Callés-Escandon, I. Hramiak, S. Genuth, et al. “Combined Intensive Blood Pressure and Glycemic Control Does Not Produce an Additive Benefit on Microvascular Outcomes in Type 2 Diabetic Patients.” *Kidney International*, 2012.

G. Sartore, E. Ragazzi, Rosaria Caprino, and A. Lapolla. “Long-Term HbA1c Variability and Macro-/Micro-Vascular Complications in Type 2 Diabetes Mellitus: A Meta-Analysis Update.” *Acta Diabetologica*, 2023.

Getinet Kumie, Marye Nigatie, Abebaw Alamrew, Solomon Gedifie, Wolde-Teklehaymanot Kasahun, Abdu Jemal, Chalie Mulugeta, et al. “Prevalence of Microvascular Complications and

Associated Factors Among Diabetes Mellitus Patients in Ethiopia: A Systematic Review and Meta-Analysis." *Microvascular Research*, 2024.

I. D. de Boer, T. Rue, P. Cleary, J. Lachin, M. Molitch, M. Steffes, Wanjie Sun, et al. "Long-Term Renal Outcomes of Patients with Type 1 Diabetes Mellitus and Microalbuminuria: An Analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort." *Archives of Internal Medicine*, 2011.

I. Kulenović, S. Rašić, and S. Karcić. "Development of Microvascular Complications in Type 1 Diabetic Patients 10 Years Follow-up." *Bosnian Journal of Basic Medical Sciences*, 2006.

"Intensive Glucose Control Did Not Prevent Important Complications in Type 2 Diabetes." *Annals of Internal Medicine*, 2008.

J. Beulens, J. Beulens, Anushka Patel, J. R. Vingerling, J. Cruickshank, Alun D. Hughes, Alice V. Stanton, et al. "Effects of Blood Pressure Lowering and Intensive Glucose Control on the Incidence and Progression of Retinopathy in Patients with Type 2 Diabetes Mellitus: A Randomised Controlled Trial." *Diabetologia*, 2009.

J. Lachin, and D. Nathan. "Understanding Metabolic Memory: The Prolonged Influence of Glycemia During the Diabetes Control and Complications Trial (DCCT) on Future Risks of Complications During the Study of the Epidemiology of Diabetes Interventions and Complications (EDIC)." *Diabetes Care*, 2021.

J. Lachin, I. Bebu, R. Bergenstal, R. Pop-Busui, F. J. Service, B. Zinman, and D. M. Nathan. "Association of Glycemic Variability in Type 1 Diabetes With Progression of Microvascular Outcomes in the Diabetes Control and Complications Trial." *Diabetes Care*, 2017.

J. Lachin, N. White, D. Hainsworth, Wanjie Sun, P. Cleary, and D. Nathan. "Effect of Intensive Diabetes Therapy on the Progression of Diabetic Retinopathy in Patients With Type 1 Diabetes: 18 Years of Follow-up in the DCCT/EDIC." *Diabetes*, 2014.

J. Lachin, S. Genuth, D. Nathan, B. Zinman, and B. Rutledge. "Effect of Glycemic Exposure on the Risk of Microvascular Complications in the Diabetes Control and Complications Trial—Revisited." *Diabetes*, 2008.

J. Lachin, S. Genuth, P. Cleary, M. Davis, and D. Nathan. "Retinopathy and Nephropathy in Patients with Type 1 Diabetes Four Years After a Trial of Intensive Therapy." *New England Journal of Medicine*, 2000.

J. Larsen, H. Sjøholm, T. J. Berg, L. Sandvik, M. Brekke, K. Hanssen, and K. Dahl-Jørgensen. "Eighteen Years of Fair Glycemic Control Preserves Cardiac Autonomic Function in Type 1 Diabetes." *Diabetes Care*, 2004.

J. Park, J. Hwang, M. Kang, H. Sim, J. S. Kim, and K. Ko. "EFFECTS OF GLYCEMIC VARIABILITY ON THE PROGRESSION OF DIABETIC RETINOPATHY AMONG PATIENTS WITH TYPE 2 DIABETES." *Retina*, 2020.

J. Tryggestad, Rachana Shah, B. Braffett, F. Bacha, S. Gidding, R. Gubitosi-Klug, Amy S. Shah, E. Urbina, and Lorraine E. Levitt Katz. "Circulating Adhesion Molecules and Associations with HbA1c, Hypertension, Nephropathy, and Retinopathy in the Treatment Options for Type 2 Diabetes in Adolescent and Youth (TODAY) Study." *Pediatric Diabetes*, 2020.

Jennifer Perais, Ridhi Agarwal, J. Evans, E. Loveman, J. Colquitt, David Owens, R. Hogg, J. Lawrenson, Y. Takwoingi, and N. Lois. “Prognostic Factors for the Development and Progression of Proliferative Diabetic Retinopathy in People with Diabetic Retinopathy.” *Cochrane Database of Systematic Reviews*, 2020.

Jia-Min Wang, Meng-Yuan Miao, Yi-Ping Jia, Xiaowen Wang, Xian-Bo Wu, Zhong-Xiao Wan, Yan Zheng, Li-Qiang Qin, Fu-Rong Li, and Guo-Chong Chen. “Effects of Intensive Glycemic Control on Microvascular Outcomes in Type 2 Diabetes Mellitus Are Modified by Long-Term HbA1c Variability: A Post Hoc Analysis of the ACCORD Trial.” *Diabetes Research and Clinical Practice*, 2024.

Jin J. Zhou, J. Koska, G. Bahn, and P. Reaven. “Fasting Glucose Variation Predicts Microvascular Risk in ACCORD and VADT.” *Journal of Clinical Endocrinology and Metabolism*, 2020.

Joanna Kamińska, O. Koper, J. Czyżewska, K. Wasilewska, and H. Kemona. “[Albuminuria in Patients with Type 2 Diabetes Mellitus in Relation to Percentage of HbA1c].” *Polski Merkuriusz Lekarski : Organ Polskiego Towarzystwa Lekarskiego*, 2012.

L. Aiello. “Diabetic Retinopathy and Other Ocular Findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study.” *Diabetes Care*, 2013.

L. Maple-Brown, C. Ye, and R. Retnakaran.
“Area-under-the-HbA1c-curve Above the Normal Range and the Prediction of Microvascular Outcomes: An Analysis of Data from the Diabetes Control and Complications Trial.” *Diabetic Medicine*, 2013.

L. Zhai, Jun Lu, Xin Cao, Jun Zhang, Yong Yin, and Huiping Tian. “Association Between the Variability of Glycated Hemoglobin and Retinopathy in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis.” *Hormone and Metabolic Research*, 2022.

Lily Agrawal, N. Azad, G. Bahn, P. Reaven, R. Hayward, D. Reda, and N. Emanuele. “Intensive Glycemic Control Improves Long-Term Renal Outcomes in Type 2 Diabetes in the Veterans Affairs Diabetes Trial (VADT).” *Diabetes Care*, 2019.

Lily Agrawal, N. Azad, N. Emanuele, G. Bahn, D. Kaufman, Thomas E. Moritz, W. Duckworth, and C. Abraira. “Observation on Renal Outcomes in the Veterans Affairs Diabetes Trial.” *Diabetes Care*, 2011.

Liying Zhang, G. Krzentowski, A. Albert, and P. Lefèbvre. “Risk of Developing Retinopathy in Diabetes Control and Complications Trial Type 1 Diabetic Patients with Good or Poor Metabolic Control.” *Diabetes Care*, 2001.

M. M, U. Sembian, Babitha, E. N, and Muthuselvi K. “Study of Auditory, Visual Reaction Time and Glycemic Control (HBA1C) in Chronic Type II Diabetes Mellitus.” *Journal of Clinical and Diagnostic Research : JCDR*, 2014.

M. Shestakova, Шестакова Марина Владимировна, N. V. Efremova, Ефремова Наталья Владимировна, L. L. Bolotskaya, Болотская Любовь Леонидовна, I. Sklyanik, et al. “Comparative Analysis of Glycemic Control Effectiveness and Microvascular Complications in Patients with Type 1 Diabetes Mellitus, Treated with Genetically Engineered Human Insulin or Human Insulin Analogues: A 10-Year Retrospective Observational Study,” 2016.

M. Shichiri, H. Kishikawa, Yasuo Ohkubo, and N. Wake. “Long-Term Results of the Kumamoto Study on Optimal Diabetes Control in Type 2 Diabetic Patients.” *Diabetes Care*, 2000.

M. Tavakoli, and F. Ishibashi. “The Impact of Normoglycemia in Reducing Microvascular Complications in Patients with Type 2 Diabetes—A Follow-Up Study.” *Diabetes*, 2018.

Mohammed K. Ali, Kavita Singh, D. Kondal, R. Devarajan, Shivani A Patel, V. U. Menon, P. Varthakavi, et al. “Effect of a Multicomponent Quality Improvement Strategy on Sustained Achievement of Diabetes Care Goals and Macrovascular and Microvascular Complications in South Asia at 6.5 Years Follow-up: Post Hoc Analyses of the CARRS Randomized Clinical Trial.” *PLoS Medicine*, 2024.

N. Azad, Lily Agrawal, N. Emanuele, R. Klein, G. Bahn, P. Reaven, and A. T. N. Group. “Association of Blood Glucose Control and Pancreatic Reserve with Diabetic Retinopathy in the Veterans Affairs Diabetes Trial (VADT).” *Diabetologia*, 2014.

N. White, Wanjie Sun, P. Cleary, W. Tamborlane, R. Danis, D. Hainsworth, and M. Davis. “Effect of Prior Intensive Therapy in Type 1 Diabetes on 10-Year Progression of Retinopathy in the DCCT/EDIC: Comparison of Adults and Adolescents.” *Diabetes*, 2010.

O. Klefter, S. Holfort, and M. Larsen. “Baseline Haemoglobin A1c Influences Retinal Function After Long-Term Insulin Pump Therapy.” *Graefe's Archive for Clinical and Experimental Ophthalmology*, 2016.

O. Vasović, M. Zamaklar, K. Lalić, D. Milosevic, L. Zikić, and L. Popovic. “[Effect of Glycemic Control on Microalbuminuria and Arterial Blood Pressure in Patients with Type 1 Diabetes].” *Medicinski Pregled*, 2005.

P. Hovind, L. Tarnow, K. Rossing, P. Rossing, S. Eising, N. Larsen, C. Binder, and H. Parving. “Decreasing Incidence of Severe Diabetic Microangiopathy in Type 1 Diabetes.” *Diabetes Care*, 2003.

P. J. Wiffen. “ENHANCED GLUCOSE CONTROL FOR PREVENTING AND TREATING DIABETIC NEUROPATHY.” *Cochrane Database of Systematic Reviews*, 2012.

Peiyao Jin, Jin-juan Peng, H. Zou, Weiwei Wang, Jiong Fu, B. Shen, X. Bai, Xun Xu, and Xi Zhang. “A Five-Year Prospective Study of Diabetic Retinopathy Progression in Chinese Type 2 Diabetes Patients with “Well-Controlled” Blood Glucose.” *PLoS ONE*, 2015.

R. Amin, C. Turner, S. Van Aken, T. Bahu, A. Watts, D. Lindsell, R. Dalton, and D. Dunger. “The Relationship Between Microalbuminuria and Glomerular Filtration Rate in Young Type 1 Diabetic Subjects: The Oxford Regional Prospective Study.” *Kidney International*, 2005.

R. Frank. “Can Ophthalmologists Achieve Better Blood Glucose Control in Their Diabetic Patients?” *JAMA Ophthalmology*, 2015.

R. Gilbert, J. Mann, M. Hanefeld, G. Spinas, J. Bosch, S. Yusuf, H. Gerstein, and The Origin trial investigators. “Basal Insulin Glargine and Microvascular Outcomes in Dysglycaemic Individuals: Results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) Trial.” *Diabetologia*, 2014.

Rami Aldafas, Thomas Crabtree, Y. Vinogradova, Jason P Gordon, and I. Idris. “Efficacy and Safety of Intensive Versus Conventional Glucose Targets in People with Type 2 Diabetes: A

Systematic Review and Meta-Analysis." *Expert Review of Endocrinology & Metabolism*, 2023.

S. A. Jiskani, Dolat Singh, K. Meghji, R. Talpur, Jahanzaib Khan, and H. Khanzada. "Microalbuminuria and Its Association with Glycemic Control in Patients with Diabetes Mellitus Type II." *The Professional Medical Journal*, 2020.

S. Bressler, and N. Bressler. "Retinopathy in Patients with Type 1 Diabetes 4 Years After Intensive Therapy." *A M A Archives of Ophthalmology*, 2000.

S. Coca, F. Ismail-Beigi, Nowreen Haq, H. Krumholz, and C. Parikh. "Role of Intensive Glucose Control in Development of Renal End Points in Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis Intensive Glucose Control in Type 2 Diabetes." *Archives of Internal Medicine*, 2012.

S. Genuth, Janie Lipps, G. Lorenzi, D. Nathan, M. Davis, J. Lachin, and P. Cleary. "Effect of Intensive Therapy on the Microvascular Complications of Type 1 Diabetes Mellitus." *Journal of the American Medical Association (JAMA)*, 2002.

S. Holfort, K. Nørgaard, G. R. Jackson, E. Hommel, S. Madsbad, I. C. Munch, K. Klemp, B. Sander, and M. Larsen. "Retinal Function in Relation to Improved Glycaemic Control in Type 1 Diabetes." *Diabetologia*, 2011.

S. Levin, J. Coburn, C. Abraira, W. Henderson, J. Colwell, N. Emanuele, F. Nuttall, C. Sawin, J. Comstock, and Cynthia K. Silbert. "Effect of Intensive Glycemic Control on Microalbuminuria in Type 2 Diabetes. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators." *Diabetes Care*, 2000.

S. Zoungas, H. Arima, H. Gerstein, R. Holman, M. Woodward, P. Reaven, R. Hayward, T. Craven, R. Coleman, and J. Chalmers. "Effects of Intensive Glucose Control on Microvascular Outcomes in Patients with Type 2 Diabetes: A Meta-Analysis of Individual Participant Data from Randomised Controlled Trials." *The Lancet Diabetes and Endocrinology*, 2017.

Sharon D. Solomon, E. Chew, E. Duh, L. Sobrin, Jennifer K. Sun, B. Vanderbeek, C. Wykoff, and T. Gardner. "Erratum. Diabetic Retinopathy: A Position Statement by the American Diabetes Association. Diabetes Care 2017;40:412–418." *Diabetes Care*, 2017.

Sophie Sun, Lucie Hisland, G. Grenet, F. Gueyffier, C. Cornu, N. Jaafari, and R. Boussageon. "Reappraisal of the Efficacy of Intensive Glycaemic Control on Microvascular Complications in Patients with Type 2 Diabetes: A Meta-Analysis of Randomised Control-Trials." *The´rapie (Paris)*, 2021.

T. Harindhanavudhi, M. Mauer, R. Klein, B. Zinman, A. Sinaiko, and M. Caramori. "Benefits of Renin-Angiotensin Blockade on Retinopathy in Type 1 Diabetes Vary With Glycemic Control." *Diabetes Care*, 2011.

Takayoshi Sasako, Kohjiro Ueki, Kengo Miyoshi, Kana Miyake, Tomohisa Aoyama, Yukiko Okazaki, Naoki Ishizuka, Toshimasa Yamauchi, Mitsuhiko Noda, and Takashi Kadowaki. "Effect of a Multifactorial Intervention on Retinopathy in People With Type 2 Diabetes: A Secondary Analysis of the J-DOIT3 Randomized Clinical Trial." *JAMA Ophthalmology*, 2025.

Thomas Crabtree, Jael-Joy Ogendo, Y. Vinogradova, Jason P Gordon, and I. Idris. "Intensive Glycemic Control and Macrovascular, Microvascular,

Hypoglycemia Complications and Mortality in Older (Age ≥60years) or Frail Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis from Randomized Controlled Trial and Observation Studies." *Expert Review of Endocrinology & Metabolism*, 2022.
Tomoki Okuno, Arin Vansomphone*, Elyse Zhang, Hua Zhou, J. Koska, P. Reaven, and Jin J. Zhou. "Association of Both Short-Term and Long-Term Glycemic Variability with the Development of Microalbuminuria in the ACCORD Trial." *Diabetes*, 2023.
Vivek Charu, Jane W. Liang, Glenn M. Chertow, June Li, M. Montez-Rath, P. Geldsetzer, Ian H. de Boer, Lu Tian, and M. Tamura. "Heterogeneous Treatment Effects of Intensive Glycemic Control on Kidney Microvascular Outcomes and Mortality in ACCORD." *Journal of the American Society of Nephrology*, 2023.
W. Herman, B. Braffett, S. Kuo, Joyce M Lee, M. Brandle, A. Jacobson, L. Prosser, and J. Lachin. "What Are the Clinical, Quality-of-Life, and Cost Consequences of 30 Years of Excellent Vs. Poor Glycemic Control in Type 1 Diabetes?" *Journal of Diabetes and Its Complications*, 2018.
W. Shiferaw, T. Akalu, Melaku Desta, A. Kassie, P. Petrucka, H. Assefa, and Y. Aynalem. "Glycated Hemoglobin A1C Level and the Risk of Diabetic Retinopathy in Africa: A Systematic Review and Meta-Analysis." *Diabetes & Metabolic Syndrome*, 2020.
Wei-zhi Chen, C. Hung, Y. Wen, H. Ning, Bing-Ru Gau, and Yu-Yao Huang. "Effect of Glycemic Control on Microalbuminuria Development Among Type 2 Diabetes with High-Normal Albuminuria." *Renal Failure*, 2014.