INPLASY

# Association Between the TG/HDL-C Ratio and Atherogenic Index of Plasma in Relation to Diabetic Retinopathy: A Systematic Review and Meta-Analysis

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## ADMINISTRATIVE INFORMATION

**Support -** No.

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**Conflicts of interest -** The authors declare that they have no conflicts of interest related to this work. No financial or non-financial relationships exist that could be perceived as potential sources of bias or influence in the conduct, analysis, or reporting of this study.

**INPLASY registration number:** INPLASY2025100035

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 October 2025 and was last updated on 10 October 2025.

## INTRODUCTION

**Review question / Objective** Population (P): Adults with type 2 diabetes mellitus (T2DM), irrespective of sex, disease duration, or treatment status.

Intervention / Exposure (I):
Atherogenic lipid indices, including the Atherogenic Index of Plasma (AIP, defined as log10[TG/HDL-C]) and the triglyceride-to–high-density lipoprotein cholesterol (TG/HDL-C) ratio, measured in mmol/L.

Comparator (C):
Patients without diabetic retinopathy (DR–) or those with less advanced stages of retinopathy, depending on study design (e.g., NPDR vs. PDR, DR– vs. DR+).

Outcome (O):
Presence and severity of diabetic retinopathy (DR), as defined by standardized ophthalmic grading systems such as the Early Treatment Diabetic Retinopathy Study (ETDRS) or International Clinical Diabetic Retinopathy (ICDR) scales. Secondary outcomes include quantitative differences in AIP or TG/HDL-C across DR stages and associations with clinical covariates (e.g., HbA1c, BMI, renal function).

Study Design (S):
Observational studies (cross-sectional, case–control, and cohort) reporting quantitative data on AIP or TG/HDL-C in relation to diabetic retinopathy.

Objective:
To systematically evaluate and quantitatively synthesize available evidence regarding the association between the Atherogenic Index of Plasma (AIP) and TG/HDL-C ratio with the

presence and severity of diabetic retinopathy in adults with type 2 diabetes mellitus. The review aims to determine whether these lipid indices serve as potential biomarkers for early detection and risk stratification of DR, identify sources of heterogeneity across studies, and assess the robustness and quality of the evidence using standardized bias and GRADE frameworks.

**Condition being studied** Diabetic retinopathy (DR) is one of the most common and vision-threatening microvascular complications of type 2 diabetes mellitus (T2DM). It results from chronic hyperglycemia-induced damage to the retinal microvasculature, leading to capillary leakage, ischemia, and neovascularization. DR typically progresses from a non-proliferative stage (NPDR)—characterized by microaneurysms, hemorrhages, and cotton-wool spots—to a proliferative stage (PDR) marked by pathological new vessel formation and a high risk of vision loss.

Globally, DR affects nearly one-third of individuals with diabetes, representing a major cause of preventable blindness among working-age adults. The risk of developing DR is strongly influenced by glycemic control, blood pressure, lipid metabolism, and renal function. Increasing evidence suggests that dyslipidemia plays an important pathogenic role in the onset and progression of DR, potentially through endothelial dysfunction, oxidative stress, and chronic inflammation.

Among lipid indices, the Atherogenic Index of Plasma (AIP)—calculated as log10(triglycerides/high-density lipoprotein cholesterol, in mmol/L)—and the TG/HDL-C ratio have emerged as integrated markers of atherogenic dyslipidemia. These indices reflect the balance between triglyceride-rich and anti-atherogenic lipoproteins and have been associated with cardiovascular and renal complications in diabetes. However, their relationship with DR remains inconsistent across studies, partly due to differences in population characteristics, measurement methods, and statistical adjustment.

Understanding whether AIP and TG/HDL-C are reliably associated with DR severity could enhance risk prediction and early screening strategies for diabetic microvascular disease. This systematic review and meta-analysis aims to clarify the quantitative association between these lipid indices and the presence or progression of diabetic retinopathy in adults with T2DM.

## METHODS

**Search strategy** This review focuses on adult patients (≥18 years old) with type 2 diabetes mellitus (T2DM), regardless of sex, disease duration, or treatment regimen. Eligible participants were those enrolled in observational studies—including cross-sectional, case–control, and cohort designs—that reported quantitative data on the Atherogenic Index of Plasma (AIP) and/or the triglyceride-to–high-density lipoprotein cholesterol (TG/HDL-C) ratio in relation to diabetic retinopathy (DR).

Participants were categorized according to DR status based on standardized ophthalmologic grading systems such as the Early Treatment Diabetic Retinopathy Study (ETDRS) or International Clinical Diabetic Retinopathy (ICDR) scales. The primary comparison groups included:

Individuals with diabetes but no retinopathy (DR–)

Patients with non-proliferative diabetic retinopathy (NPDR)

Patients with proliferative diabetic retinopathy (PDR)

Studies including participants with type 1 diabetes, gestational diabetes, or unspecified diabetes type were excluded. Where mixed populations were reported, data specific to T2DM were extracted or requested from the authors when possible. This inclusive approach ensures that the synthesis represents the broad adult T2DM population at risk for microvascular complications, thereby enhancing clinical relevance and external validity.

**Participant or population** This review focuses on adult patients (≥18 years old) with type 2 diabetes mellitus (T2DM), regardless of sex, disease duration, or treatment regimen. Eligible participants were those enrolled in observational studies—including cross-sectional, case–control, and cohort designs—that reported quantitative data on the Atherogenic Index of Plasma (AIP) and/or the triglyceride-to–high-density lipoprotein cholesterol (TG/HDL-C) ratio in relation to diabetic retinopathy (DR).

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**Intervention** The exposures of interest in this review are atherogenic lipid indices, specifically the Atherogenic Index of Plasma (AIP) and the triglyceride-to–high-density lipoprotein cholesterol (TG/HDL-C) ratio.

AIP was defined consistently across studies as log10(triglycerides / high-density lipoprotein cholesterol), with both components expressed in mmol/L. This index reflects the balance between atherogenic triglyceride-rich lipoproteins and protective HDL particles, serving as a surrogate marker of atherogenic dyslipidemia and insulin resistance.

The TG/HDL-C ratio represents a closely related lipid parameter, similarly indicative of metabolic imbalance, endothelial dysfunction, and subclinical inflammation—mechanisms believed to contribute to microvascular injury in diabetic retinopathy.

No active pharmacologic or behavioral intervention was introduced by investigators in the included studies; rather, this review synthesizes observational data evaluating the natural association between these lipid indices and the presence or severity of diabetic retinopathy in adults with type 2 diabetes mellitus.

**Comparator** The primary comparators in this review are groups stratified by diabetic retinopathy (DR) status and severity. Participants with type 2 diabetes mellitus but without retinopathy (DR–) served as the reference group for all primary analyses.

Comparisons were conducted as follows:

DR(–) vs. any DR — to assess whether overall presence of retinopathy is associated with higher AIP or TG/HDL-C levels.

DR(–) vs. NPDR (non-proliferative diabetic retinopathy) — to explore changes associated with early microvascular damage.

DR(–) vs. PDR (proliferative diabetic retinopathy) and NPDR vs. PDR — to evaluate lipid index gradients with advancing disease severity.

Where studies reported multiple subgroups, the analyses used independent contrasts to avoid double-counting shared DR(–) controls. The comparators thus reflect the progressive pathological spectrum of diabetic retinopathy and allow assessment of whether dyslipidemia markers (AIP and TG/HDL-C) increase with microvascular complication burden.

**Study designs to be included** This systematic review includes observational epidemiological studies that quantitatively evaluated the relationship between atherogenic lipid indices (AIP and TG/HDL-C ratio) and diabetic retinopathy (DR) in adults with type 2 diabetes mellitus. Eligible designs comprise:Cross-sectional studies, which assess associations between lipid indices and DR presence or severity at a single time point.Case–control studies, which compare lipid profiles between participants with DR and matched diabetic controls without retinopathy.Prospective or retrospective cohort studies, which evaluate whether.

**Eligibility criteria** Studies were eligible for inclusion if they met all of the following criteria:

Population: Adults (≥18 years) diagnosed with type 2 diabetes mellitus (T2DM) based on recognized clinical or biochemical criteria (e.g., ADA, WHO).

Exposure: Reported data on atherogenic lipid indices, specifically the Atherogenic Index of Plasma (AIP = $\log_{10}$[TG/HDL-C]) and/or the triglyceride-to–high-density lipoprotein cholesterol ratio (TG/HDL-C), with values expressed or convertible to mmol/L.

Outcome: Evaluated the presence or severity of diabetic retinopathy (DR), classified using standardized ophthalmologic grading systems (e.g., ETDRS or ICDR) based on fundus photography, OCT, or fluorescein angiography.

Study design: Observational cross-sectional, case–control, or cohort studies providing quantitative comparisons (e.g., mean ± SD, ORs, or regression coefficients).

Reporting: Sufficient data for effect size estimation and variance computation.

Exclusion criteria included:

Studies involving type 1 or gestational diabetes, non-human or in vitro models, or overlapping cohorts.

Lack of clear DR diagnosis or insufficient lipid data.

Reviews, editorials, conference abstracts, or studies without original data.

Both English and Chinese publications were eligible to ensure comprehensive evidence coverage.

**Information sources** A comprehensive and systematic literature search was conducted across eight electronic databases from inception to July 30, 2025. The databases included four major international sources — PubMed, Embase, Web of Science, and the Cochrane Library — and four leading Chinese databases — CNKI, Wanfang Data, VIP, and SinoMed — to capture both English- and Chinese-language evidence.

To minimize publication and language bias, grey literature was also searched using Google Scholar, ClinicalTrials.gov, and the Chinese Clinical Trial Registry (ChiCTR). Reference lists of all eligible studies and relevant reviews were manually screened to identify additional records not retrieved through database searching.

No restrictions on publication year were applied. However, studies were limited to those published in English or Chinese, as these represent the predominant languages of biomedical research in the target domain.

All retrieved records were exported to EndNote for deduplication, followed by title, abstract, and full-text screening in accordance with the PRISMA 2020 guidelines. The full search strategy, including Boolean operators and filters for each database, is provided in Supplementary Table S1.

**Main outcome(s)** The primary outcome of this systematic review was the association between atherogenic lipid indices and the presence or severity of diabetic retinopathy (DR) in adults with type 2 diabetes mellitus (T2DM). Specifically, quantitative comparisons were made using:

Atherogenic Index of Plasma (AIP) — defined as $\log_{10}$(triglycerides / high-density lipoprotein cholesterol), with all values standardized to mmol/L.

Triglyceride-to–HDL cholesterol ratio (TG/HDL-C) — calculated as the molar ratio of TG to HDL-C.

For each index, the main summary measure was the mean difference (MD) with 95% confidence intervals (CIs) between groups stratified by DR status:

DR(–) vs. any DR,

DR(–) vs. NPDR (non-proliferative DR), and

NPDR vs. PDR (proliferative DR).

Where available, adjusted effect estimates (e.g., odds ratios, regression coefficients) were also extracted and analyzed separately.

Secondary outcomes included dose–response relationships and the potential moderating effects of clinical factors (e.g., HbA1c, diabetes duration, statin use, and region) on the association between lipid indices and DR progression.

**Quality assessment / Risk of bias analysis** The methodological quality and risk of bias of all included studies were evaluated independently by two reviewers using validated domain-based tools tailored to study design.

For cohort and case–control studies, the Newcastle–Ottawa Scale (NOS) was applied, assessing three core domains — selection, comparability, and outcome/exposure. Studies scoring ≥7 points were classified as high quality, 5–6 points as moderate, and ≤4 points as low quality.

For cross-sectional studies, the Agency for Healthcare Research and Quality (AHRQ) checklist was used, which includes 11 items assessing study design, confounding control, and data completeness.

In addition, the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) framework was used to perform domain-level assessment across seven bias domains (confounding, participant selection, exposure classification, deviations from intended exposure, missing data, outcome measurement, and selective reporting).

Discrepancies between reviewers were resolved by consensus or consultation with a third senior researcher.

Sensitivity analyses excluding studies rated as having "serious" or "critical" risk of bias in any ROBINS-I domain were conducted to test the robustness of pooled estimates.

Detailed domain-level ratings are presented in Supplementary Table S2.

**Strategy of data synthesis** Quantitative synthesis was performed using the R software (meta and metafor packages). Continuous outcomes (AIP and TG/HDL-C ratio) were summarized as mean differences (MDs) with 95% confidence intervals (CIs). When effect sizes were reported in other forms (e.g., odds ratios, regression coefficients), they were extracted and analyzed separately to avoid scale bias.

Between-study heterogeneity was evaluated using Cochran's Q test ($p < 0.10$ indicating significance) and $I^2$ statistics (25%, 50%, and 75% denoting low, moderate, and high heterogeneity, respectively). When substantial heterogeneity was present ($I^2 \geq 50\%$), a random-effects model with the restricted maximum likelihood (REML) estimator and Hartung–Knapp adjustment was applied. Otherwise, a fixed-effects inverse-variance model was used.

The between-study variance ($\tau^2$) and 95% prediction intervals (PIs) were calculated and reported in all forest plots.

Subgroup analyses were conducted by DR severity (DR–, NPDR, PDR), study design, and region. Meta-regression explored potential moderators including mean HbA1c, diabetes duration, and statin use.

Publication bias was assessed using funnel plots and Egger's regression test, with trim-and-fill analyses performed as exploratory sensitivity checks.

All analyses adhered to PRISMA 2020 standards for transparent and reproducible meta-analytic reporting.

**Subgroup analysis** To explore potential sources of heterogeneity and clarify differential associations, a series of pre-specified subgroup analyses were conducted.

By Diabetic Retinopathy Severity:
Comparisons were stratified into DR(–), NPDR (non-proliferative diabetic retinopathy), and PDR (proliferative diabetic retinopathy) groups to evaluate whether AIP and TG/HDL-C levels exhibit a graded increase with disease progression.

By Study Design:
Analyses were repeated separately for cross-sectional, case–control, and cohort studies to assess the consistency of directional effects across epidemiologic designs.

By Region and Population Characteristics:
Subgroup analyses compared Asian versus non-Asian cohorts to assess regional variability in lipid metabolism and DR risk.

By Clinical Covariates:
Where data were available, stratification was performed by mean HbA1c, diabetes duration, and statin use categories to identify potential moderators of effect size.

For all subgroup contrasts, independence of comparisons was preserved by ensuring that shared DR(–) control groups were not double-counted. Subgroup-specific $\tau^2$, $I^2$, and prediction intervals were reported to illustrate between-study variance within each stratum.

**Sensitivity analysis** Comprehensive sensitivity analyses were conducted to evaluate the robustness and stability of the pooled estimates.

Leave-one-out analyses were performed to assess the influence of individual studies on the overall pooled effect. Results were visualized through influence and Baujat plots, confirming that no single study disproportionately affected the summary estimate.

To minimize potential small-study effects, analyses were repeated after excluding studies with total sample sizes <100 participants.

Risk-of-bias–based sensitivity analysis excluded studies rated as having serious or critical risk of bias in any ROBINS-I domain to ensure that findings were not driven by methodologically weak evidence.

Alternative model testing compared results using different estimators (DerSimonian–Laird vs. REML–HKSJ) to verify the consistency of conclusions under various random-effects assumptions.

Finally, cumulative meta-analysis was performed where applicable to observe temporal trends and the stability of evidence accumulation over time.

Across all tests, the direction and magnitude of the pooled associations remained consistent, indicating that the overall results were robust to study-level and analytical variations.

**Country(ies) involved** The studies included in this systematic review were conducted across multiple countries, predominantly within Asia. The majority originated from China, reflecting the substantial contribution of Chinese research institutions to the.

**Keywords** Diabetic retinopathy; TG/HDL-C ratio; Atherogenic index of plasma; Type 2 diabetes; Meta-analysis.

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Author 1 - Ye Ye Liang.
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