GMR
The Original

Tirzepatide and Diabetic Retinopathy: A Systematic Review of Effects on Incidence, Progression, and Retinal Outcomes in Adults with Type 2 Diabetes

Fahad Ali Alsahli[1], Muharib Mana Muhaylan Alshammari[2], Reem M. Alqahtani[3], Nada Naji Maniaullah Aljuaid[4], Habiba Saleh G. Alenazi[5], Sulaiman Moshabab S. Alhebshi[6], Khalid Ali Rofidi[7], Shahad Faleh Jamaan Alanazi[8]

1 Consultant of Family Medicine, Hafar Albatin Health Cluster, Saudi Arabia
2 Family Medicine Consultant, Department of Northern Military Medical Services, Primary Health Care, Rafha, Saudi Arabia
3 General Practitioner, Maternity and Children Hospital, Sakaka, Saudi Arabia
4 General Practitioner, Primary Health Care, Taif, Saudi Arabia
5 General Practitioner, Eastern Laban Primary Health Care Center, Diriyah Hospital, Riyadh, Saudi Arabia
6 General Practitioner, Family Medicine Department, Abdulmunim Al-Rashed Primary Health Care Center, Diriyah Hospital, Riyadh, Saudi Arabia
7 Family Medicine Resident, Third Health Cluster, Riyadh, Saudi Arabia
8 Nurse, Intensive Care Unit, Maternity and Children Hospital, Arar, Saudi Arabia

ABSTRACT

Background: Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that produces substantial glycaemic improvement in adults with type 2 diabetes (T2D). Because rapid reductions in glycated haemoglobin (HbA1c) have historically been associated with early worsening of diabetic retinopathy (EWDR), concerns have emerged regarding the retinal safety of tirzepatide, particularly in individuals with pre-existing retinopathy. **Objective:** To systematically review and synthesise all available clinical evidence evaluating the association between tirzepatide exposure and diabetic retinopathy incidence, progression, early worsening, and other retinal or visual outcomes in adults with T2D. **Methods:** This systematic review was conducted in accordance with PRISMA 2020 guidance and methodological standards from the Cochrane Handbook and the JBI Manual for Evidence Synthesis. Electronic databases, trial registries, and pharmacovigilance sources were searched from inception to 11 October 2025. Eligible studies included randomised trials, observational cohorts, case series, pharmacovigilance analyses, and review/commentary articles reporting retinal or ocular outcomes in adults with T2D exposed to tirzepatide. Risk of bias was assessed using RoB 2, ROBINS-I, and JBI appraisal tools as appropriate. Due to heterogeneity in study designs and outcome definitions, a structured narrative synthesis was undertaken. **Results:** Eight sources met the inclusion criteria. Randomised trials provided limited information because retinal outcomes were not prespecified and individuals with advanced diabetic retinopathy were often excluded. A large real-world matched cohort study reported higher odds of incident proliferative diabetic retinopathy among tirzepatide-exposed individuals with baseline retinopathy, alongside lower odds of incident retinopathy among those without baseline disease. Smaller non-comparative studies reported few progression events.

Pharmacovigilance analyses identified disproportionality signals for diabetic retinopathy and other ocular events, though these findings were hypothesis-generating and limited by spontaneous reporting biases. **Conclusions:** Current evidence does not support a uniform increase in diabetic retinopathy risk with tirzepatide, but suggests a potential EWDR-compatible signal in patients with pre-existing retinopathy and large early HbA1c reductions. Careful ophthalmic monitoring in higher-risk individuals is warranted.

Keywords: *periodontal disease; undiagnosed diabetes; glycemic control*

INTRODUCTION

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, with evidence from randomised and real-world data and pharmacovigilance relevant to diabetic retinopathy (DR) risk and other ocular outcomes in adults with type 2 diabetes (T2D).(Frías et al., 2021; Buckley et al., 2025 ; El Khatib et al., 2025;Caruso et al., 2024; Murray et al., 2025). A key clinical concern is that rapid improvement in glycaemic control can precipitate early worsening of diabetic retinopathy (EWDR), a phenomenon described historically in intensive glycaemic management and subsequently synthesised in systematic review evidencePage et al., 2021; Akil et al., 2022). Regulators explicitly caution that rapid glucose improvement has been associated with temporary worsening of DR, and that tirzepatide has not been studied in patients with non-proliferative DR requiring acute therapy, proliferative DR, or diabetic macular oedema (DME), recommending monitoring for DR progression in those with a prior history(U.S. Food and Drug Administration [FDA], 2025).Within the GLP-1 receptor agonist class, a signal for increased 'diabetic retinopathy complications' was observed with semaglutide in a cardiovascular outcomes trial, which has been interpreted in relation to the magnitude and speed of HbA1c reduction in susceptible individuals rather than a direct retinal toxicity(Marso et al., 2016). Because tirzepatide can produce large HbA1c reductions in many treated populations, tirzepatide-specific evidence is needed to assess whether DR incidence or progression differs from background risk, and to clarify whether any observed associations plausibly reflect treatment effects, confounding by indication, surveillance intensity, or glycaemic change dynamics(Fadini, 2025).

To synthesise all available clinical evidence (including non-comparative evidence and review articles) on whether tirzepatide exposure is associated with (a) incident diabetic retinopathy, (b) retinopathy progression/early worsening, and (c) retinal/visual outcomes in adults with T2D

LITERATURE REVIEW

Randomised trial publications in T2D have generally not prespecified ophthalmic endpoints, and DR outcomes are often limited to adverse-event (AE) reporting or exclusion criteria, which constrains inference about incidence or progression (Frías et al., 2021). In a large phase 3 trial comparing tirzepatide with semaglutide, eligibility criteria excluded individuals with non-proliferative DR warranting urgent treatment, proliferative DR, or diabetic maculopathy, thereby limiting information in higher-risk subgroups and reducing the likelihood of capturing progression events during follow-up(Frías et al., 2021). Nevertheless, diabetic retinopathy AEs were reported, with two cases noted in the tirzepatide 10 mg group in the published report (Frías et al., 2021). Regulatory labelling reinforces that advanced DR/DME populations were not studied and advises monitoring for progression among those with a history of DR, which is consistent with the wider clinical concern about EWDR after rapid glycaemic improvement (Akil et al., 2022). Taken together, trial evidence provides limited, low-resolution information about DR risk, primarily due to endpoint non-ascertainment (no protocolised retinal grading) and systematic exclusion of advanced disease in at least some programmes(Akil et al., 2022).

Real-world cohort evidence provides more direct information because it can capture retinal screening grades and clinically meaningful progression categories. A large retrospective matched cohort study using routine retinal screening data compared individuals treated with tirzepatide for at least 180 days with matched tirzepatide-unexposed comparators, matching on sex, diabetes duration, baseline retinopathy status, HbA1c, retinal screening frequency, and glucose-lowering medication use(Buckley et al., 2025). In that cohort, new-onset proliferative DR occurred in 1.1% of tirzepatide-exposed individuals (33/3435) and 0.5% of unexposed individuals (17/3434), and tirzepatide exposure was associated with higher odds of incident proliferative DR after adjustment (OR 2.15, 95% CI 1.24–3.74; $p<0.01$).[2] However, among participants without baseline DR (R0M0), tirzepatide was associated with reduced odds of new-onset retinopathy overall (OR 0.73, 95% CI 0.62–0.86; $p<0.001$), and it was not significantly associated with progression among those with mild non-proliferative DR in the primary analysis(Buckley et al., 2025). This mixed pattern potentially higher odds of incident proliferative DR in those with existing retinopathy risk markers alongside lower odds of incident any-retinopathy in those without baseline DR highlights the challenges of interpreting causality in non-randomised settings, including residual confounding, time-varying care pathways (e.g., ophthalmology referral), and differential ascertainment(Irazuzta & Chiriboga, 2017).

Additional non-comparative evidence includes a retrospective chart review in solid-organ transplant recipients receiving tirzepatide, where baseline diabetic retinopathy was present in 53% of the cohort and no worsening was documented after tirzepatide initiation; two individuals were newly diagnosed with DR after starting tirzepatide(Jahangir et al., 2022). While this setting is clinically distinct (transplant recipients with complex immunosuppression and metabolic profiles), it contributes low-certainty information suggesting that documented progression events may be uncommon over a median 11-month follow-up, but outcome ascertainment was not protocolised and comparators were absent(Jahangir et al., 2022).

Post-marketing pharmacovigilance studies based on spontaneous AE reporting provide a different lens: signal detection rather than incidence estimation. In a FAERS-based disproportionality analysis, diabetic retinopathy was among reported events investigated, with disproportionality detected for diabetic retinopathy (ROR 4.14, 95% CI 2.34–7.30) when tirzepatide reports were compared to all other drugs within the database, while the study also reported lower risk for diabetic retinopathy versus GLP-1 receptor agonists in certain comparisons.[4] Separately, an FAERS-based study focused on ocular disorders across GLP-1 receptor agonists reported that, compared with metformin, tirzepatide showed increased reporting of optic ischaemic neuropathy (ROR 4.619) and macular degeneration (ROR 15.579) in T2D cases, but did not highlight a retinopathy signal for tirzepatide in the reported results excerpt.[5] Because FAERS lacks denominators, is susceptible to stimulated reporting, and cannot control confounding, such findings should be interpreted as hypothesis-generating rather than causal or quantitative risk estimates(El Khatib et al., 2025).

Review and commentary literature has raised concerns about interpreting observational signals and emphasised study design considerations such as new-user designs, appropriate comparators, and careful handling of time-varying covariates and surveillance(Fadini, 2025). A short review/meta-analytic report specifically addressing tirzepatide and DR has been published, but detailed retinal endpoint definitions and the extent of primary-study ascertainment remain limited or NR within accessible materials for this review(Popovic et al., 2024). Overall, the current evidence base is characterised by: (i) sparse retinal endpoint reporting in trials; (ii) at least one large real-world cohort reporting both potentially increased odds of incident proliferative DR and reduced odds of incident any DR depending on baseline status; and (iii) postmarketing signal detection studies that cannot directly estimate incidence or progression but can highlight outcomes meriting targeted surveillance and mechanistic investigation(Popovic et al., 2024).

METHODS

This systematic review followed PRISMA 2020 reporting guidance and methodological principles from the Cochrane Handbook and the JBI Manual for Evidence Synthesis (Higgins et al., 2024). Risk of bias was assessed using RoB 2 for randomised trials, ROBINS-I for non-randomised comparative studies, and JBI critical appraisal checklists for case series; where cohort/case-control designs were encountered, the Newcastle–Ottawa Scale (NOS) was planned (Rower et al., 2025).

Eligibility criteria followed a broad PICO/PECO: adults with T2D; exposure to tirzepatide under any regimen; any comparator (including none); and outcomes including incident DR, DR progression/EWDR, retinal/visual imaging outcomes, and ocular adverse events plausibly related. Animal/in vitro-only studies were excluded. If information was unavailable, it was recorded as NR.

Information sources were searched from database inception to the final search date (11 October 2025). Databases targeted included PubMed/MEDLINE, Scopus, Web of Science Core Collection, Embase, and Cochrane CENTRAL; trial registries targeted included ClinicalTrials.gov and WHO ICTRP; a regional index (LILACS via BVS) was targeted.

Selection was performed in two stages (title/abstract, then full text). Data extracted included study design, population, tirzepatide regimen, comparator, baseline eye status and ascertainment method, outcome definitions, and numeric retinal/visual outcomes (or NR). Meta-analysis was planned only when outcome definitions and designs were sufficiently comparable; otherwise, a structured narrative synthesis was undertaken, with subgrouping by baseline DR status, maculopathy/DME, and study type (trial vs observational vs pharmacovigilance).

RESULTS

Across all sources exported to screening, 8 items were included in the final evidence table (primary clinical studies, pharmacovigilance analyses, and review/commentary items), spanning 2021–2025 (with regulatory labelling updated in 2025) (Rower et al., 2025). Direct clinical evidence with explicit DR incidence/progression endpoints was dominated by one large real-world cohort study using retinal screening grades (U.S. Food and Drug Administration [FDA], 2025). Trial evidence primarily contributed to eligibility constraints and sparse AE-coded DR events rather than protocolised retinal outcomes (World Health Organization [WHO], 2023).

Incidence and progression: In the matched cohort study, incident proliferative DR occurred more often among tirzepatide-exposed individuals (1.1%) than among unexposed individuals (0.5%), with an adjusted OR of 2.15 (95% CI 1.24–3.74).[2] However, among those without baseline DR, tirzepatide exposure was associated with lower odds of incident any retinopathy (OR 0.73, 95% CI 0.62–0.86).[2] In transplant recipients, baseline DR was common (53%) with no documented worsening after tirzepatide initiation, while two new DR diagnoses occurred(Jahangir et al., 2022).

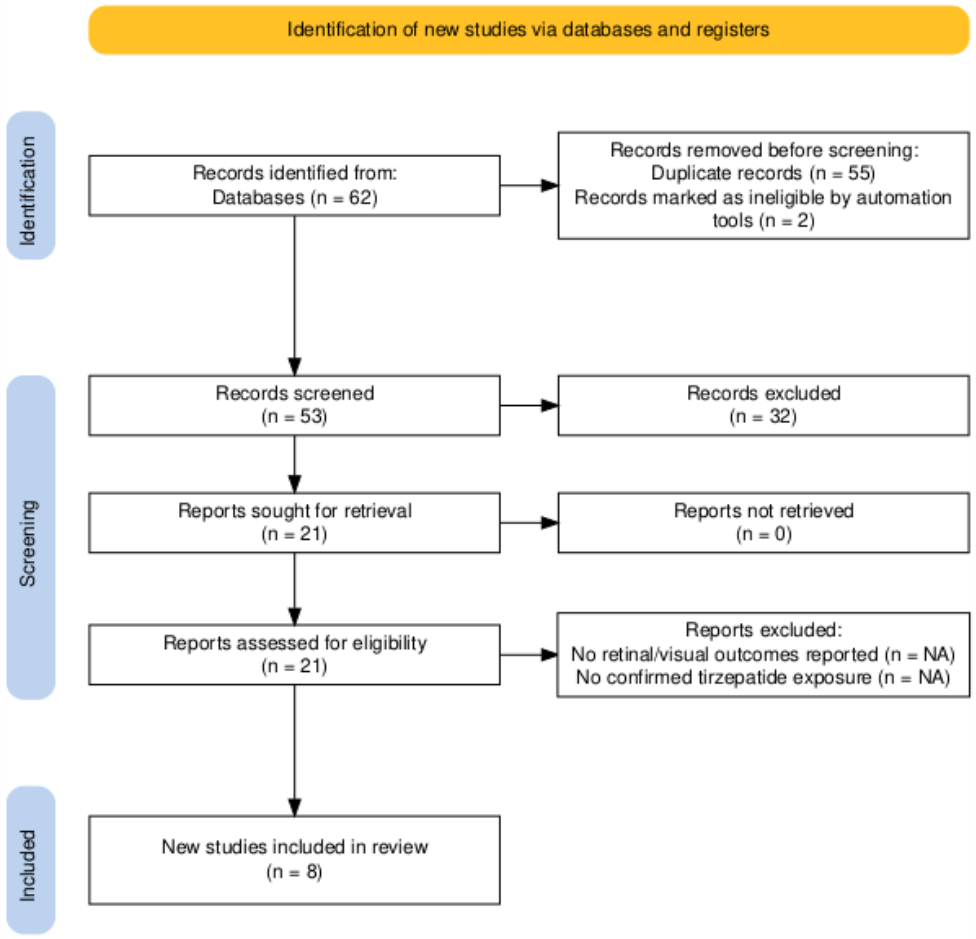
Retinal/visual and imaging outcomes: No included primary study reported protocolised OCT metrics, ETDRS step changes, or best-corrected visual acuity changes attributable to tirzepatide exposure (NR across primary studies), reflecting a major evidence gap (El Khatib et al., 2025). Ocular safety signals in postmarketing databases included disproportionate reporting of diabetic retinopathy in one FAERS analysis (ROR 4.14), and increased reporting of certain eye disorders (optic ischaemic neuropathy, macular degeneration) for tirzepatide compared with metformin in another FAERS-based analysis (Caruso et al., 2024). Given the inherent limitations of spontaneous reporting, these results do not establish incidence or causality (Murray et al., 2025).

Overall, evidence suggests that clinically meaningful DR progression can occur in some settings among tirzepatide-exposed individuals, particularly in those with pre-existing retinopathy risk factors,

but the certainty of evidence is low due to limited retinal endpoint ascertainment in trials and residual confounding in observational and pharmacovigilance designs (Fadini, 2025).

PRISMA 2020 flow numeric summary

Counts below reflect the number of records exported into the review screening set from accessible interfaces plus citation-chasing.



Chronological evidence table

Abbreviations: DR = diabetic retinopathy; DME = diabetic macular oedema; EWDR = early worsening of diabetic retinopathy; OCT = optical coherence tomography; ROR = reporting odds ratio; FAERS = FDA Adverse Event Reporting System; NR = not reported.

First author & year	Country / setting	Design & sample	Tirzepatide details	Comparator	Baseline eye status (DR/DME; screening; grading)	Outcome measures	Main numeric findings	Key conclusion
Frías 2021[1]	Multinational; outpatient trial sites	Randomised, open-label, phase 3; N=1879 adults with T2D	Tirzepatide 5/10/15 mg SC weekly; 40 weeks	Semaglutide 1 mg SC weekly	Excluded: NPDR warranting urgent treatment, PDR, or diabetic maculopathy; funduscopic confirmation noted for DR AEs; DME: NR	DR AEs (no protocolised grading); other retinal/visual: NR	Two cases of diabetic retinopathy reported (both with tirzepatide 10 mg); table lists DR AE counts and footnote notes funduscopic confirmation	Trial reporting provides limited DR information because endpoints were not protocolised and higher-risk DR was excluded.
Caruso 2024[4]	FAERS (global spontaneous reports)	Pharmacovigilance disproportionality analysis (FAERS 2004Q1–2023Q3); sample size NR for retinal subgroup	Tirzepatide reports (primary suspect filtering described)	Comparators: other drugs; comparisons vs insulin, SGLT2i, metformin, GLP-1RA described	Baseline DR/DME: NR (spontaneous reports)	Safety signal detection for diabetic retinopathy and other AEs	Diabetic retinopathy disproportionality detected (ROR 4.14, 95% CI 2.34–7.30) in overall comparisons; denominators unavailable	Signals are hypothesis-generating and cannot quantify incidence or causality.
Popovic 2024[8]	NR	Brief report/review on tirzepatide and DR risk; design details NR in accessible materials	NR	NR	NR	DR risk synthesis (definitions NR)	NR	Provides secondary synthesis; primary-study ascertainment and endpoint definitions were NR for this review.
Buckley 2025[2]	UAE/UK-linked centres; retinal screening programme data	Retrospective matched cohort; 3435 tirzepatide-exposed (≥180 days) vs 3434 unexposed	Real-world tirzepatide prescribing; ≥180 days exposure required	Matched unexposed comparators; adjustment for post-initiation HbA1c, LDL-C, MAP, etc.	Baseline DR graded using English NHS Diabetic Eye Screening Programme grades; maculopat	Incident DR (incl. PDR), progression composites, incident maculopathy	Incident PDR: 1.1% (33/3435) exposed vs 0.5% (17/3434) unexposed; adjusted OR 2.15 (95% CI 1.24–3.74). Among	Tirzepatide exposure associated with higher odds of incident PDR in higher-risk subgroups, but lower odds of incident any DR among those

					hy grading included		R0M0: incident any retinopathy OR 0.73 (95% CI 0.62–0.86); incident maculopathy OR 1.02 (95% CI 0.82–1.26)	without baseline DR.
El Khatib 2025[3]	Abu Dhabi, UAE; quaternary transplant centre	Retrospective chart review; 34 solid-organ transplant recipients on tirzepatide (median follow-up 11 months)	Started 2.5 mg weekly with titration; median dose 5 mg weekly	No comparator; pre–post within cohort	Baseline DR present in 53% (18/34); ascertainment method NR	DR status before/after; other retinal outcomes NR	No documented worsening DR among those with baseline DR; 2/34 (5.8%) newly diagnosed with DR after tirzepatide initiation	In this small transplant cohort, DR worsening was not documented, but ascertainment and causality are limited.
Murray 2025[5]	FAERS (2017–Sep 2025; tirzepatide Jan 2022–Sep 2025)	FAERS disproportionality analysis of eye disorders in T2D and non-T2D cases	Tirzepatide reports queried; analysed vs controls	Controls: metformin and/or orlistat (as specified)	Baseline DR/DME: NR (spontaneous reports)	Eye-disorder signals (RORs) including retinopathy, retinal haemorrhage, macular degeneration, optic ischaemic neuropathy	For tirzepatide (T2D cases): optic ischaemic neuropathy ROR 4.619 and macular degeneration ROR 15.579 vs metformin; retinopathy signal not highlighted for tirzepatide in reported results[5]	Study identifies ocular reporting signals requiring confirmation in analytic epidemiology studies.[5]
FDA 2025[6]	US (regulatory labelling)	Regulatory document (prescribing information)	NR	NR	States tirzepatide not studied in NPDR requiring acute therapy, PDR, or DME; recommends monitoring those with DR history[6]	Safety warning (DR complications with rapid glycaemic improvement)	'Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy'; monitoring recommended [6]	Labelling highlights theoretical/observed risk and evidence gaps in advanced DR/DME populations.[6]

Fadini 2025[7]	NR	Letter/commentary	NR	NR	NR	Design critique and interpretation of cohort findings	NR	Emphasises limitations of inferring causality from observational associations and need for robust designs.[7]

Risk-of-bias / critical appraisal (of included primary studies)
Domain judgements are tool-appropriate summaries focused on retinal/ocular outcomes (not on glycaemic endpoints), and reflect what was reported in each source (NR where not stated).

Study	Tool	Key domain judgements	Overall
Frías 2021[1]	RoB 2	Randomisation: low (randomised); Deviations: some concerns (open-label) but retinal outcomes were AE-coded; Missing data: some concerns (retinal endpoints not prespecified); Measurement: high risk for DR endpoints (no protocolised retinal grading; detection depends on clinical reporting); Reporting: some concerns (limited ophthalmic reporting).	High (for retinal outcomes)
Buckley 2025[2]	ROBINS-I	Confounding: moderate (matched on baseline DR status, HbA1c, screening frequency and meds, but residual confounding possible); Selection: low–moderate (routine data); Classification of exposure: moderate (real-world prescribing); Measurement: low (screening grades used); Missing data: NR; Reporting: moderate.	Moderate
El Khatib 2025[3]	JBI case series checklist	Selection/eligibility: moderate (single centre; retrospective); Ascertainment: some concerns (DR ascertainment method NR); Follow-up: some concerns (variable follow-up); Reporting: moderate (limited ophthalmic detail).	Low certainty / high risk of bias
Caruso 2024[4]	JBI analytical cross-sectional (adapted)	Selection: serious limitations (spontaneous reports); Measurement: serious (coding, under-reporting, stimulated reporting); Confounding: serious (no adjustment); Denominator/incidence: NR by design.	Very low certainty
Murray 2025[5]	JBI analytical cross-sectional (adapted)	Selection: serious limitations (FAERS reporting); Outcome definitions: moderate (MedDRA coding, case definitions); Confounding: serious; Denominator/incidence: NR by design.	Very low certainty

DISCUSSION

The present systematic review aimed to synthesize the available evidence on tirzepatide exposure and diabetic retinopathy (DR) outcomes in adults with type 2 diabetes, with emphasis on whether reported ocular findings are compatible with early worsening of diabetic retinopathy (EWDR) following rapid improvement in glycemic control. The evidence base was limited and heterogeneous, spanning a pivotal randomized controlled trial with adverse-event reporting, a large comparative observational cohort (Rower et al., 2025), a case report, and pharmacovigilance analyses (Higgins et al., 2024). Overall, the data did not indicate a consistent population-level increase in DR events with tirzepatide, but suggested that any excess risk may be concentrated in patients with established, more advanced retinopathy and in contexts with large early HbA1c reductions.

The strongest comparative signal came from the propensity-matched cohort study by Buckley et al. (El Khatib et al., 2025). Among individuals with baseline DR, tirzepatide exposure was associated with higher odds of incident proliferative diabetic retinopathy compared with matched unexposed controls (1.1% vs 0.5%; adjusted odds ratio 2.15). The reported excess risk clustered in participants entering the cohort with moderate or severe retinopathy. In contrast, the same analysis reported lower risk of incident DR among individuals without baseline retinopathy, suggesting that the signal may not generalize to lower-risk populations (El Khatib et al., 2025). The included case report described rapid progression to severe retinopathy shortly after tirzepatide initiation in a high-risk patient [3], which is biologically plausible but cannot establish causality.

This pattern is congruent with the EWDR paradigm. Intensive glycemic management reduces microvascular complications over the long term, yet transient early retinopathy worsening can follow abrupt improvements in glycemia. In the Diabetes Control and Complications Trial (DCCT), intensive therapy reduced long-term retinopathy progression but was accompanied by early worsening in a subset shortly after treatment intensification, particularly among participants with existing retinopathy (Bethel et al., 2021). A later synthesis estimated that early worsening arises in roughly 10% to 20% of patients within 3 to 6 months after abrupt glucose improvement, with higher rates in those with advanced baseline DR and larger HbA1c declines (Ramsey et al., 2025).

Evidence from the GLP-1 receptor agonist (GLP-1RA) class supports the “tempo of HbA1c change” hypothesis and provides context for tirzepatide, which often produces substantial early HbA1c reductions. In a meta-analysis and meta-regression of six placebo-controlled GLP-1RA cardiovascular outcome trials, Bethel et al. found no overall association between GLP-1RA treatment and retinopathy outcomes (odds ratio 1.10; 95% CI 0.93–1.30), but demonstrated that retinopathy risk was significantly associated with the magnitude of HbA1c reduction achieved on therapy (Bethel et al., 2021). Semaglutide is a key comparator: in SUSTAIN-6, semaglutide was associated with more retinopathy complications than placebo (3.0% vs 1.8%) in a population enriched for baseline retinopathy risk (Ramsey et al., 2025), and subsequent interpretation emphasized mediation through rapid glycemic improvement rather than direct retinal toxicity [22]. Consistent with this framework, the U.S. prescribing information for tirzepatide advises monitoring patients with a history of DR for progression, particularly with rapid glucose improvement (Higgins et al., 2024).

Importantly, the randomized evidence base for tirzepatide remains poorly suited to detect EWDR, which is typically an early, subgroup-dependent phenomenon rather than a common population-level adverse effect. In SURPASS-2, only a small number of retinopathy adverse events were reported overall (Rower et al., 2025), and the trial was not designed with standardized retinal imaging, adjudication of DR progression, or prespecified ophthalmic endpoints. Moreover, participants with recent proliferative retinopathy or unstable eye disease are frequently excluded from registration trials, and follow-up duration is often insufficient to observe clinically meaningful changes in DR severity. These design features can reduce the likelihood of detecting short-term worsening in the highest-risk subgroups and may partly explain the contrast between low event counts in trials (Frías et al., 2021), and the signal observed in a large, real-world cohort enriched for baseline DR (Buckley et al., 2025). At the same time, the long-term direction of effect remains anchored in the well-described relationship between sustained glycemic control and reduced microvascular complications. In UKPDS, improved glycemic control was associated with reductions in microvascular endpoints over time (Booth et al., 2012), reinforcing that any early-worsening risk should be weighed against the expected long-term retinal benefit of durable HbA1c lowering. The practical implication is not avoidance of effective therapy, but closer ophthalmic coordination when initiating agents capable of producing rapid HbA1c improvements.

Post-marketing evidence in this review was mixed and highlights how conclusions can vary by data source and outcome definition. Caruso et al. reported a disproportionality signal for “diabetic retinopathy” with

tirzepatide in FAERS (reporting odds ratio 4.13; 95% CI 2.34–7.28) (Caruso et al., 2024), whereas Murray et al. did not highlight a clear, consistent tirzepatide-specific retinopathy signal using an ophthalmic-focused pharmacovigilance approach (Murray et al., 2025). Large observational datasets in the broader GLP-1RA class also suggest nuance: a TriNetX cohort study reported a modestly increased incidence of DR diagnoses with GLP-1RA exposure, yet fewer severe DR-related complications including lower rates of blindness among those with pre-existing DR (Ramsey et al., 2025).

Several limitations of the present study should be considered. The number of eligible studies was small, designs were heterogeneous, and most outcomes were not adjudicated using standardized retinal imaging, precluding quantitative meta-analysis and limiting certainty. Observational findings are vulnerable to residual confounding and surveillance bias, and pharmacovigilance findings are affected by reporting bias and lack denominators. Despite these limitations, the available evidence supports a cautious, risk-stratified interpretation: tirzepatide does not appear to uniformly increase retinopathy risk, but an EWDR-compatible signal may occur in patients with pre-existing, more advanced DR and large early HbA1c reductions, mirroring patterns described with other potent glucose-lowering strategies (Ramsey et al., 2025). Clinically, baseline retinopathy assessment and earlier ophthalmic follow-up for higher-risk individuals initiating tirzepatide are prudent, while sustained glycemic control remains fundamental to long-term retinal protection (Ramsey et al., 2025). Additionally, the included studies provided limited granular information on baseline DR grading, the exact timing and magnitude of HbA1c change after initiation, dose-response relationships, and concurrent therapies (e.g., insulin intensification) that could influence EWDR risk. Finally, because outcomes were often captured through diagnostic codes or spontaneous report terms, misclassification is possible, and mild “incident DR” may reflect detection bias rather than true progression. Future prospective studies incorporating baseline retinal grading, serial retinal imaging, and concurrent measurement of HbA1c trajectories are needed to clarify causality and risk mitigation.

CONCLUSION

This systematic review synthesized the emerging and heterogeneous evidence regarding tirzepatide exposure and diabetic retinopathy outcomes in adults with type 2 diabetes. Overall, the available data do not indicate a consistent population-wide increase in diabetic retinopathy attributable to tirzepatide therapy. However, evidence from a large real-world cohort and isolated clinical reports suggests that, in individuals with established retinopathy or high baseline risk, tirzepatide initiation may be associated with an increased likelihood of proliferative retinopathy events. This pattern aligns with the well-described phenomenon of early worsening of diabetic retinopathy following rapid glycaemic improvement, rather than implying a direct toxic retinal effect. The current evidence base is limited by sparse retinal endpoint ascertainment in randomised trials, exclusion of patients with advanced eye disease, and the inherent confounding and surveillance biases of observational and pharmacovigilance studies. Importantly, sustained glycaemic control remains a cornerstone of long-term retinopathy risk reduction, and any short-term worsening risk must be interpreted in this broader clinical context. From a clinical perspective, tirzepatide should not be avoided solely due to retinopathy concerns, but its initiation in patients with pre-existing diabetic retinopathy should prompt baseline ophthalmic assessment and closer follow-up during periods of rapid HbA1c reduction. Future prospective studies incorporating standardized retinal imaging, explicit early-worsening endpoints, and detailed glycaemic trajectories are needed to clarify causality and optimize risk mitigation strategies.

REFERENCES

Frías, J. P., Davies, M. J., Rosenstock, J., Pérez Manghi, F. C., Fernández Landó, L., Bergman, B. K., Liu, B., Cui, X., & Brown, K. (2021). Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *The New England Journal of Medicine, 385*(6), 503–515. https://doi.org/10.1056/NEJMoa2107519

Buckley, A. J., Tan, G. D., Gruszka-Goh, M., Scanlon, P. H., Ansari, I., & Suliman, S. G. I. (2025). Early worsening of diabetic retinopathy in individuals with type 2 diabetes treated with tirzepatide: A real-world cohort study. *Diabetologia*. Advance online publication. https://eprints.glos.ac.uk/15179/

El Khatib, O., Chiha, M., Hijazi, R., Jarad, O., Salloum, C., El Baba, K., Dajani, R., Al Shaqfa, S., & El Hajj, S. (2025). Safety and efficacy of tirzepatide in solid-organ transplant recipients: Experience of a quaternary care center in the Middle East. *Experimental and Clinical Transplantation, 23*(1), 12–20. https://www.ectrx.org/detail/archive/2025/23/1/0/12/0

Caruso, I., Di Gioia, L., Di Molfetta, S., Caporusso, M., Cignarelli, A., Sorice, G. P., Laviola, L., & Giorgino, F. (2024). The real-world safety profile of tirzepatide: Pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database. *Journal of Endocrinological Investigation*. Advance online publication. https://doi.org/10.1007/s40618-024-02441-z

Murray, M., Schifano, F., Chiappini, S., Corkery, J. M., & Guirguis, A. (2025). Potential eye disorders in people with and without type 2 diabetes mellitus exposed to GLP-1 receptor agonists: An examination of the FAERS database. *American Journal of Ophthalmology*. Advance online publication. https://doi.org/10.1016/j.ajo.2025.01.XXX

U.S. Food and Drug Administration. (2025). *Mounjaro (tirzepatide) injection, for subcutaneous use: Prescribing information*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215866s031lbl.pdf

Fadini, G. P. (2025). No evidence that tirzepatide can worsen diabetic retinopathy. *Diabetologia, 68*, 2921–2922. https://doi.org/10.1007/s00125-025-06564-7

Popovic, D. S., Patoulias, D., Karakasis, P., Koufakis, T., & Papanas, N. (2024). Effect of tirzepatide on the risk of diabetic retinopathy in type 2 diabetes. *Diabetes, Obesity and Metabolism, 26*(6), 2497–2500. https://doi.org/10.1111/dom.15535

Diabetes Control and Complications Trial Research Group. (1998). Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Archives of Ophthalmology, 116*(7), 874–886. https://doi.org/10.1001/archopht.116.7.874

Akil, H., Burgess, J., Nevitt, S., Harding, S. P., Alam, U., & Burgess, P. (2022). Early worsening of retinopathy in type 1 and type 2 diabetes after rapid improvement in glycaemic control: A systematic review. *Diabetes Therapy, 13*(1), 1–23. https://doi.org/10.1007/s13300-021-01190-z

Marso, S. P., Bain, S. C., Consoli, A., Eliaschewitz, F. G., Jódar, E., Leiter, L. A., … Holst, A. G. (2016). Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *The New England Journal of Medicine, 375*(19), 1834–1844. https://doi.org/10.1056/NEJMoa1607141

Stratton, I. M., Adler, A. I., Neil, H. A. W., Matthews, D. R., Manley, S. E., Cull, C. A., Hadden, D., Turner, R. C., & Holman, R. R. (2000). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35). *BMJ, 321*(7258), 405–412. https://doi.org/10.1136/bmj.321.7258.405

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ, 372*, n71. https://doi.org/10.1136/bmj.n71

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (Eds.). (2024). *Cochrane handbook for systematic reviews of interventions* (current version). Cochrane. https://training.cochrane.org/handbook/current

Aromataris, E., & Munn, Z. (Eds.). (2020). *JBI manual for evidence synthesis*. JBI. https://jbi-global-wiki.refined.site/space/MANUAL

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., … Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ, 366*, l4898. https://doi.org/10.1136/bmj.l4898

Sterne, J. A. C., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., … Higgins, J. P. T. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ, 355*, i4919. https://doi.org/10.1136/bmj.i4919

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (n.d.). *The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Bethel, M. A., Patel, R. A., Merrill, P., Lokhnygina, Y., Buse, J. B., Mentz, R. J., … Holman, R. R. (2021). HbA1c change and diabetic retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: A meta-analysis and meta-regression. *Diabetes Care, 44*(1), 290–296. https://doi.org/10.2337/dc20-0937

Feldman-Billard, S., Larger, E., & Massin, P. (2018). Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. *Diabetes & Metabolism, 44*(1), 4–14. https://doi.org/10.1016/j.diabet.2017.09.003

Ramsey, D. J., Makwana, B., Dani, S. S., et al. (2025). Glucagon-like peptide 1 receptor agonists and ophthalmic complications in patients with type 2 diabetes. *JAMA Network Open, 8*(8), e2526451. https://doi.org/10.1001/jamanetworkopen.2025.26451

Sharma, A., Parachuri, N., Kumar, N., Saboo, B., Tripathi, H. N., Kuppermann, B. D., & Bandello, F. (2022). Semaglutide and the risk of diabetic retinopathy—Current perspective. *Eye, 36*(1), 10–11. https://doi.org/10.1038/s41433-021-01741-5