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Composite glycaemic and weight-control target attainment with tirzepatide in adults with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is characterized by progressive deterioration of glycaemic control and is frequently accompanied by overweight or obesity. Achieving glycaemic targets while simultaneously reducing body weight may provide greater metabolic benefit than improvement in glycated haemoglobin (HbA1c) alone. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, has demonstrated substantial effects on both glycaemia and body weight. However, the proportion of patients achieving clinically meaningful combined glycaemic and weight-control targets across randomized controlled trials (RCTs) has not been comprehensively synthesized.

Objective: To systematically review and quantitatively synthesize evidence from RCTs evaluating composite glycaemic and weight-control target attainment among adults with T2DM treated with tirzepatide compared with placebo or active glucose-lowering therapies.

Methods: A systematic literature search will be conducted in PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, Web of Science, and clinical trial registries from database inception through 2026.

Randomized controlled trials enrolling adults with T2DM and comparing tirzepatide with placebo or an active comparator will be eligible. The primary outcomes will be composite attainment of HbA1c <7.0% together with ≥5%, ≥10%, or ≥15% weight loss. Secondary outcomes will include stricter glycaemic thresholds (HbA1c ≤6.5% and <5.7%), composite target attainment according to tirzepatide dose and comparator, and composite outcomes incorporating absence of clinically significant hypoglycaemia. Risk ratios (RRs) with 95% confidence intervals (CIs) will be pooled using random-effects models. Statistical heterogeneity will be assessed using I^2 and τ^2 statistics. Risk of bias will be evaluated using the Cochrane Risk of Bias 2 tool, and certainty of evidence will be assessed using GRADE.

Results: The meta-analysis will synthesize RCT-level evidence on simultaneous glycaemic and weight-control target attainment. Available evidence from the SURPASS clinical development programme indicates that tirzepatide substantially increases the proportion of participants achieving combined HbA1c and weight-loss targets compared with placebo and several active glucose-lowering comparators. The planned quantitative synthesis will determine pooled relative effects across trials and examine whether composite target attainment varies according to tirzepatide dose, treatment duration, comparator, and baseline metabolic characteristics.

Conclusion: This systematic review and meta-analysis will provide a comprehensive assessment of the ability of tirzepatide to achieve simultaneous clinically meaningful glycaemic control and weight reduction in adults with T2DM. By focusing on composite treatment targets rather than isolated changes in HbA1c or body weight, the study may provide a more clinically relevant estimate of the proportion of patients achieving multidimensional treatment goals with tirzepatide.

Keywords: Tirzepatide, Type 2 Diabetes Mellitus, Glycated Haemoglobin, Hba1c, Weight Loss, Obesity, Composite Endpoint, GLP-1 Receptor Agonist, GIP, Systematic Review, Meta-Analysis, Randomized Controlled Trials.

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by chronic hyperglycaemia and is frequently accompanied by overweight or obesity. The coexistence of hyperglycaemia and excess adiposity contributes substantially to cardiometabolic morbidity and complicates long-term disease management. Current treatment strategies therefore increasingly emphasize simultaneous achievement of individualized glycaemic and weight-management goals rather than focusing exclusively on glycated haemoglobin (HbA1c). For many nonpregnant adults with diabetes, an HbA1c target of <7.0% remains an appropriate general goal, while a lower target such as <6.5% may be considered in selected individuals when it can be achieved safely and without excessive treatment burden.[1] The 2026 American Diabetes Association Standards of Care specifically identify weight management as a primary treatment goal alongside glycaemic management in people with T2DM and overweight or obesity.[2]

The clinical importance of weight reduction in T2DM extends beyond cosmetic or anthropometric improvement. Even modest weight loss of approximately 5–7% of baseline body weight can improve glycaemia and other cardiometabolic risk factors, whereas weight loss exceeding 10% is generally associated with greater metabolic benefits and, in some

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individuals, the potential for diabetes remission.[2] Consequently, contemporary approaches to diabetes and obesity increasingly consider clinically meaningful weight-loss thresholds of ≥5%, ≥10%, and ≥15% in addition to conventional glycaemic targets[2,3]. Evaluating these outcomes together may provide a more clinically relevant measure of treatment success because glycaemic improvement without concomitant weight reduction may not address the underlying metabolic burden in individuals with T2DM and excess adiposity.

Tirzepatide is a once-weekly dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that produces glucose-dependent insulinotropic effects while influencing appetite, energy intake and body weight[4,5]. Activation of both incretin pathways provides a pharmacological rationale for simultaneously improving glycaemic control and reducing body weight. Early clinical studies demonstrated substantial reductions in HbA1c and body weight with tirzepatide, establishing the basis for its subsequent evaluation in large phase 3 trials[6]. The SURPASS clinical development programme subsequently demonstrated the efficacy of tirzepatide across a range of treatment settings and comparator therapies. In SURPASS-1, tirzepatide monotherapy produced substantial reductions in HbA1c and body weight compared with placebo in adults with T2DM inadequately controlled with lifestyle intervention alone[7]. SURPASS-2 demonstrated greater reductions in HbA1c and body weight with tirzepatide than once-weekly semaglutide 1 mg, providing direct evidence against an established GLP-1 receptor agonist[8]. In SURPASS-3, tirzepatide was compared with titrated insulin degludec in participants receiving metformin with or without an SGLT2 inhibitor and produced greater improvements in both glycaemic control and body weight[9]. SURPASS-4 similarly demonstrated superior glycaemic and weight outcomes with tirzepatide compared with insulin glargine in patients with T2DM and increased cardiovascular risk[10]. In SURPASS-5, addition of tirzepatide to titrated insulin glargine resulted in substantial HbA1c reductions accompanied by weight loss compared with placebo added to basal insulin[11].

Evidence from the SURMOUNT programme has further strengthened the relevance of tirzepatide for patients in whom diabetes and excess body weight coexist. In SURMOUNT-2, adults with obesity or overweight and T2DM experienced substantial body-weight reductions with tirzepatide compared with placebo over 72 weeks[12]. These findings are particularly relevant because obesity is both a major driver of insulin resistance and an important therapeutic target in T2DM. Mechanistic and clinical reviews have consequently highlighted the potential of dual GIP/GLP-1 receptor agonism to achieve improvements in both metabolic control and body weight that may exceed those observed with conventional glucose-lowering therapies[4,5]. Several systematic reviews and meta-analyses have already established the efficacy and safety of tirzepatide in T2DM. Early pooled analyses demonstrated significant reductions in HbA1c, fasting glucose and body weight compared with placebo or active glucose-lowering therapies[13]. Subsequent systematic reviews incorporating the expanding phase 3 evidence similarly confirmed substantial improvements in glycaemic control and body weight without a corresponding increase in clinically important hypoglycaemia, although gastrointestinal adverse events were more frequent with tirzepatide[14]. More recent comparative analyses have also evaluated tirzepatide against semaglutide and basal insulin,

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confirming its clinically important effects on both HbA1c and body weight[15].

Despite these findings, conventional meta-analyses have generally evaluated glycaemic and weight outcomes separately. Such an approach may underestimate the clinical importance of achieving both outcomes simultaneously. A particularly relevant post-hoc analysis of the SURPASS-1 to SURPASS-5 trials evaluated composite endpoints combining HbA1c thresholds of <7.0%, ≤6.5%, or <5.7% with weight-loss thresholds of ≥5%, ≥10%, or ≥15%, additionally considering the absence of hypoglycaemia[16]. Across the SURPASS trials, substantially larger proportions of tirzepatide-treated participants achieved these combined targets than participants receiving placebo, semaglutide 1 mg, or basal insulin.[16] However, this analysis was conducted as a post-hoc synthesis of the SURPASS programme rather than as a dedicated systematic review and meta-analysis of independently extracted RCT-level composite outcome data.

Therefore, an updated systematic review and meta-analysis specifically addressing composite glycaemic and weight-control target attainment is warranted. Such an approach can quantitatively synthesize randomized evidence across different tirzepatide doses, treatment durations and comparator groups while assessing progressively stringent combinations of glycaemic control and weight loss. The present study consequently aims to determine the efficacy of tirzepatide in achieving simultaneous clinically meaningful glycaemic and weight-control targets in adults with T2DM, with particular emphasis on HbA1c <7.0% combined with ≥5%, ≥10%, and ≥15% weight loss, while also evaluating stricter glycaemic thresholds and composite outcomes incorporating hypoglycaemia where available.

Materials and Methods

Study design and reporting standards

This systematic review and meta-analysis will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. The review will evaluate randomized controlled trials (RCTs) investigating the efficacy of tirzepatide in achieving simultaneous glycaemic and weight-control targets among adults with type 2 diabetes mellitus (T2DM). The methodology will be defined before final data extraction and analysis. Where applicable, the review protocol should be prospectively registered in PROSPERO before completion of the analysis.

Research question

The primary research question was formulated according to the PICO framework**:**

- **Population:** Adults with T2DM.
- **Intervention:** Once-weekly subcutaneous tirzepatide at any approved or investigated dose.
- **Comparator:** Placebo or active glucose-lowering treatment, including GLP-1 receptor agonists, basal insulin and other antihyperglycaemic therapies.
- **Outcomes:** Composite attainment of predefined glycaemic and weight-loss targets.
- **The primary question was:** Among adults with T2DM, does treatment with tirzepatide increase the probability of simultaneously achieving clinically meaningful glycaemic control and weight loss compared with placebo or active glucose-lowering therapy?

Eligibility criteria

Studies were eligible if they fulfilled all of the following criteria:

Randomized controlled clinical trials.

1. Included adults aged ≥18 years with established T2DM.
2. Evaluated once-weekly subcutaneous tirzepatide at any dose.
3. Included a placebo or active glucose-lowering comparator.
4. Reported at least one relevant glycaemic or weight-loss outcome and, where available, data permitting determination of composite target attainment.
5. Had a treatment duration sufficient to evaluate changes in HbA1c and body weight.
6. Were published as full-text articles or had sufficient trial data available from an authoritative clinical-trial report.

Studies were excluded if they were observational studies, case reports, case series, narrative reviews, editorials, letters without primary trial data, conference abstracts without sufficient outcome information, pharmacokinetic studies, animal studies, studies involving participants without T2DM, or duplicate publications of the same trial. For multiple publications from the same trial, the most complete dataset was used, while supplementary publications were consulted when they contained additional relevant composite-outcome information.

Information sources

A comprehensive electronic literature search will be performed in:

- PubMed/MEDLINE
- Embase
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Scopus
- Web of Science Core Collection
- ClinicalTrials.gov

WHO International Clinical Trials Registry Platform, where applicable

The search will cover the period from database inception to September 2026**.** Reference lists of eligible studies and relevant systematic reviews will also be manually screened to identify additional eligible trials.

Search strategy

The search strategy will combine controlled vocabulary and free-text terms related to tirzepatide, T2DM, glycaemic control, weight reduction and randomized trials. A representative PubMed strategy will include combinations of:

("tirzepatide" OR "LY3298176" OR "GIP/GLP-1 receptor agonist") AND ("type 2 diabetes" OR "type 2 diabetes mellitus" OR T2DM) AND ("randomized controlled trial" OR "randomised controlled trial" OR random* OR placebo) AND ("HbA1c" OR "glycated haemoglobin" OR "glycemic control" OR "weight loss" OR "body weight" OR "weight reduction").

The search strategy will be adapted to the indexing requirements of each database. No restriction based on sex, ethnicity or geographical location will be applied. Language restrictions should preferably not be applied during the initial search; studies for which adequate data cannot be reliably extracted will be documented and excluded with reasons.

Study selection

All retrieved records will be imported into reference-management software and duplicate records will be removed. Two reviewers will independently screen titles and abstracts according to the prespecified eligibility criteria. Potentially relevant studies will undergo full-text assessment.

Disagreements between reviewers will be resolved through discussion; if consensus cannot be reached, a

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third reviewer will adjudicate. The study-selection process will be presented using a PRISMA 2020 flow diagram, including the numbers of records identified, duplicates removed, records screened, full-text articles assessed and studies included in the quantitative synthesis.

Data extraction

A standardized data-extraction form will be used. Two reviewers will independently extract the following information:

Study characteristics

- First author
- Publication year
- Trial name
- Country or geographical region
- Study design
- Treatment duration
- Sample size

Participant characteristics

- Mean or median age
- Sex distribution
- Baseline HbA1c
- Baseline body weight and/or BMI
- Duration of diabetes
- Background glucose-lowering therapy
- Baseline cardiovascular risk characteristics, when reported

Intervention characteristics

- Tirzepatide dose: 5, 10 or 15 mg once weekly
- Dose-escalation schedule
- Treatment duration
- Concomitant therapy

Comparator characteristics

- Placebo
- Semaglutide
- Insulin degludec
- Insulin glargine
- Other active comparators

Outcome data

- Number of participants achieving predefined HbA1c thresholds
- Number achieving ≥5%, ≥10% and ≥15% weight loss
- Number achieving combined HbA1c and weight-loss targets
- Hypoglycaemia-related composite outcomes, when reported
- Adverse events and treatment discontinuation, where relevant.

Definition of composite treatment targets

The primary methodological feature of this review will be the evaluation of **simultaneous glycaemic and weight-control target attainment**.

The principal composite outcome will be:

HbA1c <7.0% + ≥5% body-weight reduction from baseline.

Secondary composite endpoints will include:

1. HbA1c <7.0% + ≥10% weight loss.
2. HbA1c <7.0% + ≥15% weight loss.
3. HbA1c ≤6.5% + ≥5% weight loss.
4. HbA1c ≤6.5% + ≥10% weight loss.
5. HbA1c ≤6.5% + ≥15% weight loss.
6. HbA1c <5.7% + ≥5% weight loss.
7. HbA1c <5.7% + ≥10% weight loss.
8. HbA1c <5.7% + ≥15% weight loss.

Where sufficient information is available, additional composite outcomes incorporating absence of clinically significant or severe hypoglycaemia will be evaluated.A composite endpoint will be considered achieved only when both the specified HbA1c criterion and the

specified weight-loss criterion are fulfilled by the same participant**.**

Primary and secondary outcomes

The primary outcome will be the proportion of participants simultaneously achieving HbA1c <7.0% and ≥5% weight loss at the prespecified study endpoint.

Secondary outcomes will include the other predefined combinations of HbA1c and weight-loss thresholds, as well as:

- HbA1c <7.0% alone.
- ≥5%, ≥10% and ≥15% weight loss alone.
- Continuous change in HbA1c.
- Continuous change in body weight.
- Composite target attainment without clinically significant hypoglycaemia.
- Serious adverse events.
- Treatment discontinuation because of adverse events.

Risk-of-bias assessment

The methodological quality of included RCTs will be independently assessed by two reviewers using the **Cochrane Risk of Bias 2 (RoB 2) tool**.

The following domains will be assessed:

- Bias arising from the randomization process.
- Bias due to deviations from intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

Statistical analysis

The principal effect measure for dichotomous composite outcomes will be the risk ratio (RR) with 95% confidence interval (CI)**.** Where appropriate, odds ratios will be converted or analyzed separately according to the available data. Continuous outcomes such as change in HbA1c and body weight will be summarized as mean differences (MDs) with 95% CIs when the same measurement scale is used.Because clinical and methodological differences between trials are anticipated, a random-effects meta-analysis will be used as the primary analytical model. Pooled estimates will be presented using forest plots.

Statistical heterogeneity will be assessed using the I^2 statistic**,** with approximate values of 25%, 50%, and 75% interpreted as low, moderate and high heterogeneity, respectively, while recognizing that I^2 should be interpreted alongside clinical and methodological heterogeneity. Between-study variance will additionally be assessed using τ^2.

Subgroup analyses

Where sufficient studies are available, prespecified subgroup analyses will be undertaken according to:

- Tirzepatide dose (5, 10 and 15 mg).
- Comparator type (placebo versus active comparator).
- GLP-1 receptor agonist comparator versus insulin comparator.
- Treatment duration.
- Baseline HbA1c.
- Baseline BMI.
- Background insulin therapy.
- Study publication period.
- Risk-of-bias category.

Sensitivity analyses

Sensitivity analyses will be performed by:

- Excluding studies judged to have high risk of bias.
- Excluding studies contributing disproportionately to statistical heterogeneity.
- Applying alternative random-effects estimators where appropriate.
- Restricting the analysis to trials with directly reported composite endpoints.

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- Performing leave-one-out analyses to determine whether individual trials materially influence the pooled estimate.

Publication bias and small-study effects

When at least 10 studies are available for a particular meta-analysis, potential small-study effects and publication bias will be explored using funnel plots. Where appropriate, Egger's regression test will be applied. The results will be interpreted cautiously because funnel-plot asymmetry may arise from factors other than publication bias, including clinical heterogeneity and differences in study size.

Certainty of evidence

The certainty of evidence for the principal outcomes will be assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. Evidence will initially be considered high certainty for randomized trials and may be downgraded for risk of bias, inconsistency, indirectness, imprecision or publication bias. The certainty of evidence will be categorized as high, moderate, low, or very low**.**

Ethical considerations

As this study will use data from previously published randomized controlled trials and will not involve direct recruitment, intervention or collection of identifiable participant information, institutional ethical approval and informed consent are not required**.**

Results

Evidence identified from references[1-16]

The evidence base supporting the present systematic review consisted of contemporary diabetes guidelines, mechanistic and clinical studies of tirzepatide, randomized controlled trials from the SURPASS programme, obesity/T2DM evidence from SURMOUNT-2, previous systematic reviews/meta-analyses, and the post-hoc analysis specifically evaluating combined glycaemic and weight-loss targets. The major characteristics and relevant findings of references 1–16 are summarized below.

Table 1: Characteristics and principal findings of the evidence cited in the Introduction

Ref.	Study/source	Year	Study/design	Population/sample	Intervention/comparison	Principal finding relevant to present review
1	ADA Standards of Care—Glycemic Goals	2026	clinical guideline	Adults with diabetes	Evidence-based glycaemic targets	HbA1c <7% remains a general treatment goal for many nonpregnant adults, with individualized targets according to patient characteristics and treatment burden.
2	ADA Standards of Care—Obesity and Weight Management	2026	Clinical guideline	Adults with diabetes and overweight/obesity	Lifestyle and pharmacological weight-management strategies	Weight management is recognized as a major component of diabetes care; clinically meaningful weight reduction is associated with metabolic benefits.
3	ADA Standards of Care—Health Behaviors and Well-being	2026	Clinical guideline	Adults with diabetes	Lifestyle/behavioral interventions	Reinforces comprehensive diabetes management incorporating nutrition, physical activity, weight management and individualized treatment goals.
4	Nauck &	2022	Mechanistic/c	Patients with T2DM	Dual GIP/GLP-1	Tirzepatide provides simultaneous

	D'Alessio		linical review		receptor agonism	glucose-lowering and weight-reducing effects through complementary incretin pathways.
5	Rizvi & Rizzo	2022	Clinical review	Patients with T2DM	Dual GIP/GLP-1 receptor agonists	Dual incretin receptor activation provides a rationale for addressing both glycaemia and body weight.
6	Frias et al.	2018	Phase 2 randomized controlled trial	Adults with T2DM	Tirzepatide vs placebo	Tirzepatide produced substantial dose-dependent reductions in HbA1c and body weight, establishing the clinical basis for phase 3 evaluation.
7	SURPASS-1; Rosenstock et al.	2021	Phase 3 RCT	478 adults with T2DM	Tirzepatide 5/10/15 mg vs placebo	At 40 weeks, HbA1c reductions were approximately 1.87–2.07 percentage points, with body-weight reductions of approximately 7.0–9.5 kg across tirzepatide doses.
8	SURPASS-2; Frías et al.	2021	Phase 3 open-label RCT	1,879 adults with T2DM	Tirzepatide 5/10/15 mg vs semaglutide 1 mg	Tirzepatide produced greater reductions in HbA1c and body weight than semaglutide 1 mg at 40 weeks.
9	SURPASS-3; Ludvik et al.	2021	Phase 3 open-label RCT	1,444 randomized participants	Tirzepatide 5/10/15 mg vs insulin degludec	Tirzepatide produced greater HbA1c reduction and substantial weight loss compared with insulin degludec at 52 weeks.
10	SURPASS-4; Del Prato et al.	2021	Phase 3 open-label RCT	~2,000 adults with T2DM and increased CV risk	Tirzepatide 5/10/15 mg vs insulin glargine	HbA1c reductions with tirzepatide were approximately 2.24–2.58%, while weight decreased by approximately 7.1–11.7 kg, compared with weight gain with insulin glargine.
11	SURPASS-5; Dahl et al.	2022	Phase 3 randomized controlled trial	475 adults with T2DM receiving insulin glargine	Tirzepatide 5/10/15 mg + insulin glargine vs placebo + insulin glargine	Tirzepatide substantially improved HbA1c and produced weight reduction despite background basal insulin therapy.
12	SURMOUNT-2; Garvey et al.	2023	Phase 3 randomized controlled trial	Adults with obesity/overweight and T2DM	Tirzepatide 10/15 mg vs placebo	Demonstrated substantial and clinically meaningful weight reduction with tirzepatide in people with obesity and T2DM.
13	Previous tirzepatide systematic review/meta-analysis	2021	Systematic review/meta-analysis of RCTs	Patients with T2DM	Tirzepatide vs placebo/active comparators	Pooled evidence demonstrated significant improvements in HbA1c and body weight with tirzepatide compared with control therapies.
14	Zhou et al.	2023	Systematic	Randomized tirzepatide	Tirzepatide vs	Confirmed significant glycaemic and

			review/meta-analysis	trials	comparator	weight benefits of tirzepatide, while gastrointestinal adverse events were among the important treatment-related adverse effects.
15	Kaur et al.	2024	Systematic review/network meta-analysis	Adults with T2DM	Tirzepatide vs semaglutide and other therapies	Comparative evidence supported clinically important reductions in HbA1c and body weight with tirzepatide.
16	Lingvay et al.	2023	Post-hoc analysis of SURPASS-1 to -5	Participants from five phase 3 RCTs	Tirzepatide vs placebo, semaglutide 1 mg or basal insulin	Composite attainment of HbA1c <7% + ≥5% weight loss + no hypoglycaemia ranged from 43%–82% with tirzepatide, compared with 4%–5% with placebo, 51% with semaglutide 1 mg and 5% with basal insulin.

Table 2: Individual SURPASS trial efficacy findings relevant to composite target attainment

Trial	Comparator	Duration	Tirzepatide doses	Main glycaemic finding	Main weight finding
SURPASS-1[7]	Placebo	40 weeks	5, 10, 15 mg	HbA1c reduction: 1.87%, 1.89%, 2.07%	Weight reduction: 7.0, 7.8, 9.5 kg
SURPASS-2[8]	Semaglutide 1 mg	40 weeks	5, 10, 15 mg	HbA1c reduction: approximately 2.01%, 2.24%, 2.30%	Weight reduction: approximately 7.6, 9.3, 11.2 kg
SURPASS-3[9]	Insulin degludec	52 weeks	5, 10, 15 mg	Greater HbA1c reduction than insulin degludec	Significant dose-dependent weight reduction
SURPASS-4[10]	Insulin glargine	52 weeks	5, 10, 15 mg	HbA1c reduction: 2.24%, 2.43%, 2.58%	Weight reduction: 7.1, 9.5, 11.7 kg
SURPASS-5[11]	Placebo + insulin glargine	40 weeks	5, 10, 15 mg	Significant HbA1c improvement	Significant weight reduction despite basal insulin

The published SURPASS evidence demonstrates that tirzepatide consistently improves both major components of the proposed composite endpoint—glycaemic control and body weight—across different clinical settings and comparator treatments.

Table 3: Composite glycaemic and weight-control target attainment

Composite endpoint	Evidence from SURPASS-1 to -5[16]	Interpretation
HbA1c <7% + ≥5% weight loss + no hypoglycaemia	43%–82% with tirzepatide	Commonly achieved composite target across tirzepatide trials
HbA1c <7% + ≥10% weight loss + no hypoglycaemia	Significantly greater with tirzepatide than comparators	Demonstrates more substantial combined metabolic response
HbA1c <7% + ≥15% weight loss + no hypoglycaemia	Significantly greater with tirzepatide than comparators	Represents a stringent combined treatment target
HbA1c ≤6.5% + weight-loss target + no hypoglycaemia	Greater with tirzepatide across evaluated thresholds	Supports achievement of more stringent glycaemic control
HbA1c <5.7% + weight-loss target + no	Greater with tirzepatide across evaluated thresholds	Demonstrates that some participants achieved

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hypoglycaemia		normoglycaemic-range HbA1c together with clinically meaningful weight loss

The original post-hoc analysis evaluated nine combinations of three HbA1c thresholds (<7.0%, ≤6.5%, and <5.7%) and three weight-loss thresholds (≥5%, ≥10%, and ≥15%), additionally requiring absence of hypoglycaemia. Across SURPASS-1 to -5, the combined endpoints were achieved significantly more frequently with tirzepatide than with the respective comparators.

Overall, the evidence consistently demonstrates that tirzepatide has effects on both glycaemic control and body weight, providing the biological and clinical basis for evaluating a composite endpoint. The particularly relevant evidence is reference 16, which directly demonstrates substantially greater simultaneous attainment of HbA1c and weight-loss targets with tirzepatide across the SURPASS programme.

Discussion

The present systematic review and meta-analysis was designed to evaluate an increasingly important therapeutic concept in T2DM: simultaneous achievement of clinically meaningful glycaemic control and weight reduction. Rather than considering HbA1c and body weight as independent outcomes, the analysis focuses on composite treatment targets that reflect the multidimensional goals of contemporary diabetes management. The available randomized evidence indicates that tirzepatide consistently improves both components of these composite endpoints, while the dedicated SURPASS post-hoc analysis demonstrates that substantially more patients can achieve combined glycaemic and weight-loss targets with tirzepatide than with several commonly used comparators[12-16].

Glycaemic and weight-control benefits of tirzepatide

The findings are biologically and clinically plausible because tirzepatide simultaneously activates GIP and GLP-1 receptors. This dual incretin mechanism improves glucose-dependent insulin secretion, reduces inappropriate glucagon secretion and influences appetite and energy intake[12,13]. Consequently, the treatment effect is not restricted to HbA1c reduction but extends to clinically meaningful weight loss. Earlier randomized trials consistently demonstrated this dual effect, providing the foundation for evaluating composite outcomes rather than isolated endpoints[13-15].

The SURMOUNT-2 study provides particularly relevant evidence for individuals with the combined phenotype of obesity and T2DM. In this randomized trial, tirzepatide 10 and 15 mg produced mean body-weight reductions of approximately 12.8% and 14.7%, respectively, at 72 weeks, compared with approximately 3.2% with placebo. Moreover, approximately 79–83% of tirzepatide-treated participants achieved at least 5% weight loss compared with 32% receiving placebo[12]. These findings demonstrate that substantial weight reduction can occur even in individuals with established T2DM, a population in whom weight loss may be more difficult to achieve.

Relevance of composite endpoints

An important implication of the present analysis is that single-domain efficacy measures may underestimate the overall clinical benefit of tirzepatide. HbA1c reduction alone does not describe the accompanying change in adiposity, while percentage weight loss alone does not establish whether adequate glycaemic control has been achieved. A composite endpoint requiring both outcomes therefore provides a more clinically integrated assessment of therapeutic response.

This concept is supported particularly strongly by the post-hoc SURPASS-1 to -5 analysis[16]. The investigators

examined combinations of HbA1c thresholds of <7.0%, ≤6.5%, and <5.7% with weight-loss thresholds of ≥5%, ≥10%, and ≥15%, additionally considering freedom from hypoglycaemia. Across the SURPASS programme, substantially greater proportions of participants receiving tirzepatide achieved these combined targets than those receiving the corresponding comparator therapies. The proportion achieving HbA1c <7%, ≥5% weight loss and no hypoglycaemia ranged from approximately 43% to 82% across tirzepatide treatment groups[16].

These observations are important because increasingly stringent composite thresholds provide information about the depth of metabolic response. Achieving HbA1c <7% with ≥5% weight loss represents a clinically meaningful response, whereas achieving the same glycaemic target together with ≥10% or ≥15% weight reduction identifies a subgroup with a substantially greater magnitude of weight response. The progressive decline in the proportion achieving increasingly stringent combinations is therefore expected and should not be interpreted as treatment failure.

Comparison with previous meta-analyses

The findings are consistent with earlier quantitative syntheses demonstrating substantial reductions in HbA1c and body weight with tirzepatide. A systematic review and meta-analysis of phase II/III randomized trials reported a pooled HbA1c reduction of approximately 1.94 percentage points and body-weight reduction of approximately 8.47 kg compared with control therapies[14]. Another meta-analysis involving 6,579 participants similarly demonstrated reductions in HbA1c, fasting glucose and body weight without an overall increase in hypoglycaemia[15].

More recent evidence has expanded these observations. A 2024 meta-analysis involving eight RCTs and 7,491 participants with overweight/obesity and T2DM found significant improvements in body weight, HbA1c, fasting glucose, blood pressure and lipid parameters with tirzepatide compared with GLP-1 receptor agonists, insulin or placebo[17]. A subsequent systematic review including 14 RCTs and 14,713 participants also reported increased attainment of ≥5%, ≥10% and ≥15% weight-loss thresholds with tirzepatide, together with improvements in HbA1c and other cardiometabolic measures[18].

The present analysis extends these observations by placing the simultaneous achievement of glycaemic and weight targets at the centre of interpretation. Thus, it complements rather than duplicates conventional meta-analyses of continuous HbA1c and weight changes.

Comparison with GLP-1 receptor agonists

The comparison with GLP-1 receptor agonists is particularly relevant because semaglutide is an established incretin-based therapy for T2DM. In SURPASS-2, tirzepatide produced greater reductions in HbA1c and body weight than semaglutide 1 mg[13]. The subsequent network meta-analysis comparing tirzepatide with semaglutide across randomized trials similarly evaluated achievement of HbA1c ≤6.5%, HbA1c <7%, and ≥10% weight loss, reinforcing the relevance of composite metabolic outcomes[19].

These findings suggest that the additional GIP receptor component of tirzepatide may contribute to the magnitude of its combined metabolic effects. However, differences between trials in baseline HbA1c, background therapy, treatment duration, comparator dose and patient characteristics should be considered when interpreting cross-trial comparisons.

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Dose-response considerations

An important finding across the evidence base is the apparent dose-response relationship. Higher tirzepatide doses generally produce greater reductions in HbA1c and body weight. A dose-focused network meta-analysis reported progressively greater HbA1c and weight reductions with 10 and 15 mg compared with 5 mg[20]. Similarly, broader network meta-analytic evidence suggests clinically important dose-dependent metabolic effects with incretin-based therapies[21].

For composite endpoints, however, dose-response relationships should be interpreted cautiously. Increasing the dose may increase the probability of achieving stringent weight-loss thresholds but may also increase gastrointestinal adverse events. Thus, the optimal dose should be individualized according to efficacy, tolerability, comorbidities and treatment goals rather than determined solely by weight-loss magnitude.

Safety and Tolerability

The clinical value of achieving simultaneous glycaemic and weight targets must be considered alongside treatment tolerability. Across tirzepatide trials, gastrointestinal adverse events—particularly nausea, diarrhoea and vomiting—have been among the most frequently reported adverse effects. In SURMOUNT-2, these events were generally mild to moderate, and fewer than 5% of participants discontinued treatment because of adverse events.[12]

The relationship between tirzepatide and hypoglycaemia is also clinically important. Because its insulinotropic activity is glucose dependent, clinically significant hypoglycaemia is generally uncommon when tirzepatide is used without insulin or insulin secretagogues. However, the risk can increase when tirzepatide is combined with insulin-based therapy. The composite endpoint incorporating absence of hypoglycaemia, therefore, provides additional clinical context beyond glycaemic and weight outcomes alone[16].

Comparison with insulin-based therapy

The results are particularly relevant when tirzepatide is compared with basal insulin. In SURPASS-3 and SURPASS-4, tirzepatide achieved greater reductions in HbA1c while producing weight loss, whereas insulin-based therapy was associated with weight gain or substantially less weight reduction. This distinction is clinically relevant because weight gain associated with intensification of insulin therapy can complicate management in patients who already have obesity or substantial excess adiposity.

A recent network meta-analysis specifically evaluating patients with T2DM receiving basal insulin found tirzepatide to have important efficacy advantages compared with several GLP-1 receptor agonist regimens for HbA1c and body-weight outcomes[22]. These findings support the relevance of composite endpoints in treatment settings where both glycaemic control and weight trajectory influence therapeutic decision-making.

Clinical Implications

The findings have implications for the way treatment success is conceptualized in T2DM. A patient achieving HbA1c <7% while maintaining or gaining weight represents a different therapeutic outcome from a patient achieving HbA1c <7% together with ≥10% or ≥15% weight loss. Composite endpoints can therefore provide a more patient-centred description of treatment response.

The increasing recognition of diabetes and obesity as interconnected components of cardiometabolic disease further supports this approach. Contemporary clinical management increasingly emphasizes weight reduction, glycaemic control and reduction of cardiovascular and

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renal risk as interconnected therapeutic goals. The expanding evidence base for tirzepatide in obesity, T2DM and cardiometabolic disease therefore makes composite metabolic outcomes increasingly relevant[18,23].

Relationship with emerging cardiovascular and metabolic evidence

The importance of tirzepatide extends beyond HbA1c and body weight. Emerging outcome evidence has expanded investigation into cardiovascular, renal and metabolic consequences of tirzepatide therapy. Recent cardiovascular-kidney-metabolic literature has highlighted the growing evidence surrounding tirzepatide in obesity, heart failure and related cardiometabolic conditions[23]. However, these outcomes should not be conflated with the composite glycaemic-weight endpoint evaluated in the present review. Demonstrating improved metabolic target attainment does not by itself establish reductions in cardiovascular or renal events.

Strengths of the present approach

The major strength of this systematic review is its focus on simultaneous target attainment rather than isolated changes in individual metabolic variables. The use of predefined HbA1c and weight-loss thresholds enables clinically interpretable comparisons across trials. Evaluation of progressively stringent thresholds also allows assessment of the distribution of treatment response rather than relying exclusively on mean changes.

Another strength is the inclusion of both placebo-controlled and active-comparator trials. This permits assessment of whether the observed composite benefits remain evident against established glucose-lowering therapies rather than only against placebo.

Conclusion

Tirzepatide demonstrates a consistent ability to improve glycaemic control and body weight simultaneously in adults with type 2 diabetes mellitus. Across randomized controlled trials, treatment was associated with substantially greater achievement of clinically meaningful HbA1c and weight-loss targets than placebo and several active glucose-lowering comparators. The available evidence also indicates that progressively stringent composite targets—combining HbA1c thresholds with ≥5%, ≥10%, or ≥15% weight loss—can be achieved by a clinically important proportion of tirzepatide-treated patients. These findings support the use of composite glycaemic and weight-control target attainment as a clinically informative measure of treatment response. Nevertheless, individual treatment response and tolerability vary, and composite efficacy should be interpreted alongside safety, comorbidities, treatment duration and patient-specific therapeutic goals.

Limitations and Future Prospects

Limitations

1. Heterogeneity among trials: Differences in baseline HbA1c, body weight, diabetes duration, background glucose-lowering therapy, comparator treatments, tirzepatide dose, and follow-up duration may contribute to clinical and statistical heterogeneity.
2. Limited reporting of composite outcomes: Not all randomized controlled trials directly reported simultaneous HbA1c and weight-loss target attainment. Consequently, some composite estimates may depend on secondary or post-hoc analyses rather than prospectively defined endpoints.
3. Variation in treatment targets: Different HbA1c and weight-loss thresholds were evaluated, making direct

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comparisons between individual composite outcomes more challenging.

4. Duration of follow-up: Most available RCTs had relatively short-to-intermediate follow-up periods. Therefore, the durability of simultaneous glycaemic control and substantial weight loss over several years remains incompletely established.
5. Generalizability: Trial participants may differ from patients encountered in routine clinical practice with respect to comorbidities, adherence, socioeconomic characteristics and treatment complexity.
6. Safety considerations: The present analysis primarily focuses on efficacy and composite target attainment. Rare adverse events and long-term safety outcomes may not be adequately captured by individual RCTs.
7. Potential publication and reporting bias: Although standard methods will be used to identify unpublished or selectively reported evidence, the possibility of publication bias and outcome-reporting bias cannot be completely excluded.

Future Prospects

Future research should prioritize prospectively defined composite endpoints combining glycaemic control, clinically meaningful weight reduction and freedom from clinically important hypoglycaemia. Longer-duration randomized and real-world studies are needed to determine whether simultaneous achievement of these targets is sustained over several years and whether it translates into reductions in cardiovascular, renal and other diabetes-related complications. Comparative studies should also evaluate tirzepatide against newer incretin-based therapies and different treatment strategies using equivalent doses and clinically relevant endpoints. Further research should investigate which baseline characteristics predict successful achievement of stringent composite targets, including ≥10% and ≥15% weight loss. Finally, cost-effectiveness, treatment persistence, quality of life, patient-reported outcomes and real-world adherence should be incorporated into future evaluations to determine the broader clinical and health-system implications of tirzepatide therapy.

Declarations

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