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Research Article

Comparative Efficacy and Tolerability with Tirzepatide and Semaglutide in Obesity and Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Obesity and type 2 diabetes mellitus (T2DM) are major global metabolic disorders associated with substantial morbidity and mortality. Incretin-based therapies have demonstrated significant benefits in glycemic control and weight reduction. This systematic review and meta-analysis compared the efficacy and treatment discontinuation of tirzepatide and semaglutide in adults with obesity and/or T2DM. Randomised controlled trials published between 2013 and 2024 were identified through major databases. Outcomes included changes in body weight, glycated haemoglobin (HbA1c), and discontinuation rates. Twelve trials were included in the analysis. Pooled results demonstrated significant reductions in body weight and HbA1c with both therapies, with tirzepatide showing greater overall metabolic improvements. Gastrointestinal adverse events were the most common cause of treatment discontinuation, although safety profiles were generally acceptable. Despite heterogeneity across studies, findings were consistent in favour of incretin-based interventions. Tirzepatide's dual agonist activity for both receptors, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), likely contributes to its enhanced efficacy compared with semaglutide, which acts only through one of these mechanisms, i.e., GLP-1 receptor agonist activity. Overall, both agents provide effective pharmacological options for managing obesity and T2DM, supporting their expanding role in contemporary metabolic

disease management and long-term cardiometabolic risk reduction. These results highlight the importance of personalised treatment selection based on patient characteristics, tolerability, and therapeutic goals, and underscore the need for further long-term comparative studies evaluating cardiovascular outcomes and real-world effectiveness across diverse populations.

Keywords: Tirzepatide; Semaglutide; Obesity; Type 2 diabetes mellitus; Meta-analysis.

1. Introduction

Obesity and type 2 diabetes mellitus (T2DM) are two of the most urgent health problems of the twenty-first century worldwide. These metabolic disorders have become very common in recent decades and are significant contributors to morbidity, mortality, and healthcare spending in the world. There is a close linkage between obesity and insulin resistance, dyslipidemia, hypertension and cardiovascular disease. The coexistence of T2DM further compounds this burden by introducing chronic hyperglycaemia and widespread metabolic dysregulation. Due to the intimate physiological connection between the two conditions, the term of diabesity has been increasingly adopted to describe the intersecting pathophysiological processes between excess adiposity and de facto glucose metabolism. This concept underscores the interconnectedness of these conditions and highlights the need for integrated approaches to their management, to improve the long-term cardiometabolic outcomes.

Incretin-based pharmacotherapies have become recent years' strategies with many promising results in the management of obesity and T2DM. What has been proven are glucagon-like peptide-1 (GLP-1) receptor agonists, which have significant improvements in glycemic control, body weight reduction, and cardiovascular risk. The initial pharmacological progress in the area resulted in the development of long-acting GLP-1 analogues that are aimed at enhancing pharmacotherapy and patient compliance. A new GLP-1 receptor agonist, semaglutide, administered once weekly, is one of the grandest improvements to the group of medications that has been developed, having a higher receptor affinity and an increased pharmacokinetic profile than previously (Lau et al., 2015). Semaglutide clinical trials have consistently shown a great deal of metabolic advantage in obese and T2DM individuals. As an example, trial studies have documented large decreases in body weight and glycemic outcomes in relation to placebo or other pharmacotherapies (O'Neil et al., 2018; Pi-Sunyer et al., 2015).

Semaglutide clinical efficacy has been further proven by large randomised clinical trials that have demonstrated its efficacy on a variety of diverse metabolic populations. The STEP programme of clinical trials has reported significant and prolonged weight reduction in the case of overweight or obese people under semaglutide therapy. Specifically, the STEP-4 trial found that the maintenance of weight loss with semaglutide was much better than that of placebo after initial weight loss had taken place (Rubino et al., 2021). It was also established by long-term trial data of the STEP-5 on the semaglutide that the treatment can significantly achieve weight loss lasting at least two years (Garvey et al., 2022). Also, semaglutide has exhibited significant cardiovascular effects in individuals with T2DM, in which large clinical trials have indicated a decrease in cardiovascular incidents in treated patients (Marso et al., 2016). The cardiovascular risk reduction in obese individuals with no diabetes has also been proven in the large outcome trials recently (Lincoff et al., 2023).

Beyond promoting weight loss, semaglutide has also been shown to provide substantial improvements in glycaemic control among patients with type 2 diabetes mellitus (T2DM). A number of randomised trials have investigated semaglutide as a monotherapy or in conjunction with the current diabetes therapy. Indicatively, a trial undertaken by PIONEER-1 revealed that semaglutide taken by mouth was found superior to placebo in terms of glycemic control in patients with T2DM (Aroda et al., 2019). On the same note, relative research has revealed that semaglutide can offer better glycemic outcomes than other GLP-1 receptor agonists or glucose-lowering agents (Pratley et al., 2018; Rodbard et al., 2019). Dose-escalation studies have indicated that greater doses of semaglutide might have more metabolic advantages, with the SUSTAIN FORTE trial showing better improvement in HbA1c and weight loss with a 2.0 mg weekly dose versus the standard 1.0 mg dose (Frías et al., 2021). These discoveries have led to the growing relevance of GLP-1 receptor agonists in the global clinical practice guideline regarding the treatment of T2DM and obesity (Davies et al., 2022; Wharton et al., 2020).

In spite of these developments, scientists have remained engaged in trying to develop new pharmacological approaches that would give even more metabolic advantage. A potentially useful trend is the multi-agonist therapies, which aim to improve a variety of metabolic pathways at the same time. Tirzepatide is an insulinotropic dual agonist of glucose-dependent insulinotropic polypeptide (GIP)

and glucose-linked peptide (GLP-1) hormone receptors, which is a significant advancement in incretin-based therapeutic agents. Tirzepatide stimulates insulin secretion, minimises glucagon output, decreases gastric emptying, and increases satiety by stimulating both incretin signalling pathways, and thereby, it affects both glucose metabolism and energy balance. It has been shown that the use of tirzepatide can significantly reduce body weight and HbA1c levels, which indicates that dual incretin receptor agonism can lead to better metabolic results than single-receptor ones. One study has also shown that tirzepatide can help to lower the risk of cardiovascular diseases in patients with T2DM (Sattar et al., 2022). In another contemporary study, the direct comparison between tirzepatide and semaglutide have also shown more weight loss with tirzepatide therapy, and this serves as an additional indication of its next generation use in obesity treatment (Rodriguez et al., 2024).

An increase in the number of incretin-based and poly-agonist-based agents has also increased the treatment pattern of metabolic diseases. As an illustration, the investigational agents like retatrutide, which is a triple-hormone receptor agonist of GIP, GLP-1, and glucagon receptors, have produced promising responses in a preclinical trial conducted to manage obesity (Jastreboff et al., 2023). In addition, oral GLP-1 receptor agonists like orforglipron, can potentially enhance access and adherence to treatment because they eliminate the requirement of injectable therapy (Wharton et al., 2023). The continuous evolution of multi-agonist peptides and next-generation incretin drug development is indicative of the larger trend in metabolism-focused drug discovery and the increased focus on combination hormonal therapy of obesity and diabetes (Muller et al., 2022; Statham et al., 2023; Sanchez-Garrido et al., 2017). The increasing value of semaglutide and other therapeutic agents in the treatment of overweight and obese patients in various patient groups is also highlighted in the reviews of the recent clinical evidence (Bergmann et al., 2023; Jepsen and Christensen, 2021).

Even though several randomised trials have explored the effectiveness of these treatments, variation in study designs, target population of treatment, and resultant outcomes complicate the deliberation of their clinical impact directly. The synthesis of the evidence that is available should be systematised to give a comprehensive picture of the comparative benefits and safety profile of incretin-based pharmacotherapies. This systematic review and meta-analysis study will identify the effectiveness, safety, and discontinuation of

tirzepatide and semaglutide in patients with obesity and type 2 diabetes mellitus by incorporating the results of randomised clinical trials. By combining the results of the metabolic studies, this study aims to further explain the therapeutic use of these emerging agents and add to the already accumulating evidence base of the use of incretin-based therapies in managing metabolic diseases.

2. Methodology

2.1 Study Design and Reporting Standards

This paper was undertaken in the form of a systematic review and meta-analysis study to assess the effectiveness and safety of incretin-based pharmacological therapy, namely tirzepatide and semaglutide, in the treatment of obesity and type 2 diabetes mellitus. The research design used all standard concepts of evidence synthesis to integrate the findings of various randomised controlled studies that assessed metabolic outcomes. The methodology followed the guidelines of the Preferred Reporting Items on Systematic Reviews and Meta-Analyses (PRISMA) to reach transparency in the study identification, screening, eligibility assessment, and inclusion processes. Body weight loss, improvement in glycated haemoglobin (HbA1c) and the rates of discontinuation of the treatment were the main outcomes that were considered in the current meta-analysis research. These results were chosen as they are some of the important clinical parameters that can be used to determine the efficacy and tolerability of metabolic pharmacotherapies.

2.2 Literature Search Strategy

An efficient search of the literature was conducted in various large electronic databases to locate pertinent clinical trials. Bases that were searched involved PubMed, Scopus, ScienceDirect, SpringerLink and Web of Science. The search strategy was formulated to attract randomised clinical trials that test incretin-based therapies in adult patient groups with obesity or type 2 diabetes mellitus. Keywords and Medical Subject Headings (MeSH) terms were used in combinations to get as many relevant studies as possible. These search methods were “tirzepatide”, “semaglutide”, “GLP-1 receptor agonist”, “GIP receptor agonist”, “obesity”, “type 2 diabetes”, “body weight reduction”, “HbA1c”, and “randomised clinical trial”. The search was limited to studies published in the English language and those studies which involved human subjects. Besides the database searches, reference lists of the relevant articles and clinical trial reports were also hand screened to locate other studies that might not be located using the electronic database search.

2.3 Eligibility Criteria

The studies were included in the study based on definite inclusion criteria that comprised the study design, population characteristics, interventions and reported outcomes. Only randomised controlled trials were selected to have a high level of methodological rigour and reduce bias. The research sample consisted of adults who had been diagnosed with obesity, overweight, and type 2 diabetes mellitus. Those studies were eligible that assessed pharmacological interventions that consisted of incretin- based therapies, i.e., tirzepatide or semaglutide, in monotherapy or as additional therapy. It was necessary that the studies had to contain a comparator group that might be a placebo, lifestyle intervention or any other pharmacological intervention. In addition, research studies had to provide at least 1 outcome measure pertinent to it, such as a change in body weight, HbA1c, or discontinuation rates. Research was excluded based on non-metabolic conditions, non-pharmacological interventions with no definite drug treatment, insufficient statistical information, and non-English-written reports, review articles, and abstracts of conferences that were unaccompanied by full data.

2.4 Study Selection Process

Systematic selection of the studies was done according to PRISMA. Any record that was located by searching the databases and screening by hand was first imported into a reference management system. It was screened by eliminating duplicate records. The rest of the studies were screened by title and abstract in order to find their relevance to the research question. The selected studies that seemed to be of relevance were then subjected to full-text evaluation to determine whether they met the previously set out eligibility criteria. In the full-text review phase, the studies that did not fulfil the inclusion criteria were filtered out guided by predetermined methodological and outcome-related factors. Finally, twelve randomised clinical trials were identified based on all the eligibility criteria and incorporated into the final qualitative and quantitative synthesis. The general study identification, screening, eligibility assessment and ultimate inclusion process are demonstrated in the PRISMA flow diagram that is shown in the results section.

2.5 Data Extraction

Each study included in the work was systematically searched and analysed to extract the data through a structured extraction grid in order to enhance consistency in data among the studies. Data that was obtained about any given trial were the name of the first author, the year of publication, kind of study design, trial name, nature of study population, sample size, form of intervention used, dosage, comparator treatment, and trial follow-up.

Moreover, the outcome data, which pertained to body weight loss, HbA1c improvement, or treatment dropout, were gathered. In those cases where more than one treatment arm or dosage group was reported in the studies, the most appropriate intervention and comparator groups were identified according to the objectives of the meta-analysis. Data extraction was done with critical review in order to be accurate and complete before they could be included in the statistical analysis. Discontinuation outcomes were not uniformly defined across trials; some studies reported discontinuation due to adverse events, whereas others reported overall treatment discontinuation.

2.6 Risk of Bias Assessment

The methodological quality of the randomised controlled trials that were considered was determined with the help of the Cochrane Risk of Bias 2 (RoB 2) assessment tool. This is a tool that measures potential sources of bias in various areas pertaining to randomised trials. The evaluation focused on, bias which was created through randomisation mechanism, bias created through nonconformity to the planned interventions, bias created through nonconformity of the outcome data, bias created through nonconformity of outcome measures and bias created through selective reporting. All domains were classified as either low risk of bias, some concerns, or high risk of bias following the methodological information that was provided in the trials incorporated. The findings of this evaluation are presented in a graphical form of a traffic-light diagram to give a summary of the overall methodological quality of the research.

2.7 Statistical Analysis

Quantitative synthesis of the enclosed studies was developed through meta-analytic methods to approximate joint treatment impacts. Ongoing outcomes, such as a reduction in body weight and a change in HbA1c, were compared with pooled mean differences, and this was accompanied by 95% confidence interval. Pooled risk ratio was used to analyse dichotomous outcomes like treatment discontinuation. The fact that the studies included in the study had different characteristics of the participants, the period of treatment, and the mode of intervention, made it necessary to use a random-effects model using the DerSimonian-Laird method to analyse the possibility of variation between the studies. Forest plots were created in order to plot the estimated effects of individual studies and the pooled treatment effect.

2.8 Heterogeneity Assessment

The Cochran Q test and I^2 statistic were used to determine the statistical heterogeneity of the included studies. The I^2 statistic measures the percentage of total

variability in the effects estimates, which can be attributed to heterogeneity and not to random error. I^2 values less than 25% were seen as low heterogeneity, 25% to 50% as moderate heterogeneity and more than 50% as high heterogeneity. Possible contributors to heterogeneity where there was significant heterogeneity were taken into account as possible study design, length of treatment, population and intervention protocol differences.

2.9 Sensitivity Analysis

The sensitivity analyses were performed to determine the strength of the meta-analysis results. This was done by analysing the studies one at a time out of the pooled analysis to assess whether a particular study had a skewed effect on the overall effect estimates. The similarity in results of the pooled results obtained by eliminating individual studies showed that the results of the meta-analysis were not as influenced by one influential study.

2.10 Publication Bias Assessment

Visual analysis of funnel plots was the method of detecting the presence of publication bias. Funnel plots show study effect sizes, against their respective standard errors, enabling the assessment of the symmetry of study distribution about the pooled estimate of effect. The presence of a symmetrical funnel plot is an indicator of a reduced risk of publication bias, whereas asymmetry can be a factor of potential reporting bias or the selectivity of publication of favourable results. Since the analyses conducted included a small number of studies, the interpretation of funnel plot asymmetry was carried out carefully.

3. Results

3.1 Study Selection and Description of Included Studies

The systematic literature search found 210 records, with the subsets of 160 records based on the electronic databases (PubMed, Springer, ScienceDirect, Scopus, and Web of Science) and 50 records obtained by the use of the manual screening of the reference lists and associated articles. The total number of records was 140 unique records after the exercise of discarding 70 duplicate records. Thereafter, title and abstract screening were administered. In the initial stage of screening, 55 records were eliminated since they were not pertinent to the purposes of the review. The most prevalent exclusion criteria were non-relevant population, intervention not related to tirzepatide or semaglutide or the use of non-pharmacological methods. After screening, 85 full-text articles were evaluated in terms of eligibility. Out of them, 73 studies were filtered out of the carefully considered inclusion and exclusion criteria. The main exclusion criteria were ineligible population (n = 18), ineligible intervention or comparator (n =

16), ineligible study design such as reviews or editorials (n = 14), no prespecified outcomes of interest such as efficacy or tolerability measures (n = 11), insufficient quantitative data to do meta-analysis (n = 8), overlapping study population or secondary analysis of already eligible trials (n = 4) and non-English language publications (n = 2). Following the eligibility screening, 12 studies were found to pass all inclusion criteria and were incorporated into the qualitative synthesis and quantitative meta-analysis. These were randomised clinical trials that compared efficacy, tolerability, and treatment discontinuation of tirzepatide and semaglutide in obesity patients, or patients with type 2 diabetes mellitus or a combination of the two. The entire procedure of study search, screening, eligibility, and inclusion is depicted in the PRISMA flow diagram (Figure 1).

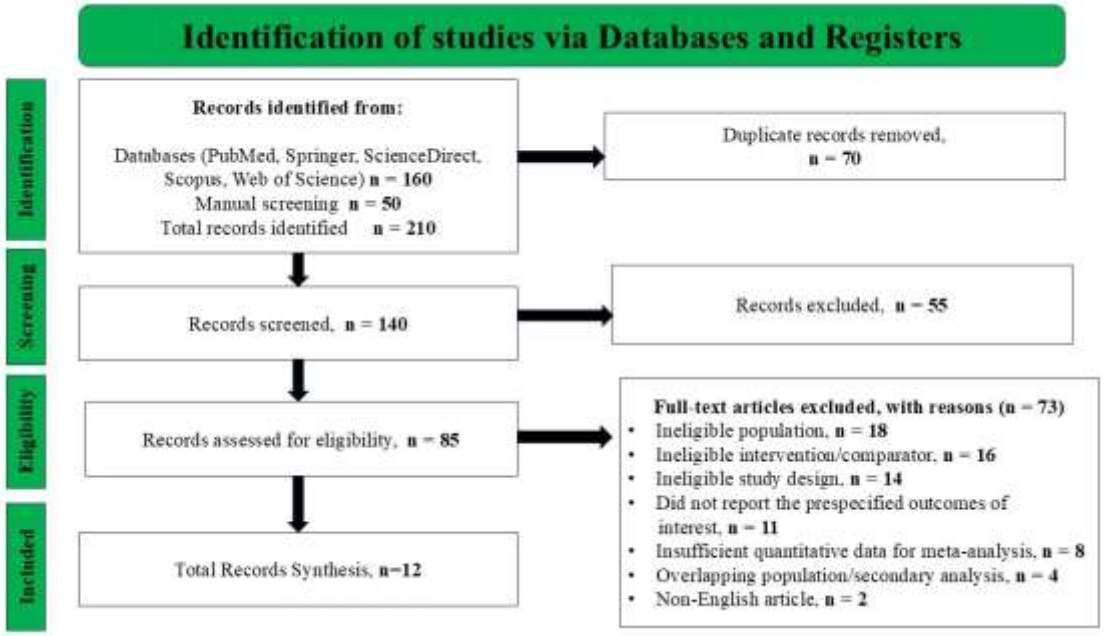

Figure 1. PRISMA Flow Diagram Showing Identification, Screening, Eligibility, and Inclusion of Studies

3.2 Characteristics of Included Studies

The twelve articles that were incorporated into this meta-analysis were mainly phase 3 randomised controlled studies, comparing tirzepatide and semaglutide in obese patients, patients with type 2 diabetes mellitus (T2DM), or both. These trials involved large multicenter clinical trial platforms, including STEP, SURPASS, and SURMOUNT, which are some of the largest current studies of incretin-based therapy of metabolic disease. In all the studies included, the total number of study participants was over 15,000, which means

that there are large populations in international clinical trials. The sample sizes were quite different in various studies. Smaller studies like SURPASS-1 and STEP-3 recruited small groups of participants of several hundred, whereas large multicenter studies like STEP-1, SURMOUNT-1, and SURPASS-4 gave rise to several thousand participants. The majority of the studies were multicenter, randomised, and controlled trials, with some of them being double-blind, placebo-controlled, and others active comparators of semaglutide, insulin glargine, or insulin degludec.

The participants in the included studies were mostly adults with obesity, type 2 diabetes mellitus, or both of them, and these populations are considered the ones at high cardiometabolic risk. The average age of the respondents was normally 45 to 65 years of age, and both genders, male and female, were well represented in the trials. The typical baseline metabolic profiles were an upward body mass index (BMI), compromised glycemic regulation and a high cardiometabolic risk profile. The mean baseline HbA1c of diabetes studies was often considered to be between 7.5 and 8.5%, and the obesity studies often had the mean body mass index of between 32 and 38kg/m^2.

The pharmacological treatments considered in the trials included mostly incretin-based treatments, including tirzepatide, a dual GIP and GLP-1 receptor agonist, and semaglutide, a selective GLP-1 receptor agonist. The doses of tirzepatide were 5 mg to 15 mg once a week, and semaglutide 1mg to control diabetes and 2.4mg to control weight. The comparator groups were placebo, semaglutide, insulin glargine or insulin degludec, and it varied by the design of the study.

The length of follow-up also varied across trials, but the conventional length of follow-up was 40-72 weeks, though a few studies had longer follow-up durations to look for weight-loss maintenance or cardiovascular risk. The main outcomes measured in the studies were changes in body weight, glycemic control (HbA1c), treatment tolerability, and treatment discontinuation, although discontinuation definitions varied across trials and included both adverse event–related discontinuation and overall treatment discontinuation. Changes in fasting glucose, cardiometabolic risk factors, and the percentage of participants who had attained clinically significant weight loss (≥5%, ≥10%, or ≥15%) were often used as secondary outcomes. In general, the trials considered in the study provided extensive evidence on the effectiveness, safety, and rate of treatment discontinuation of tirzepatide and semaglutide in the obese and type 2 diabetes mellitus populations. Table 1 gives

a detailed summary of the nature of the included studies and their major findings.

Table 1. Characteristics of included studies

Author (Year)	Trial	Population	Intervention/Comparator	Sample size (N)	Follow-up	Key efficacy outcomes	Discontinuation/tolerability
Wilding et al. (2021)	STEP 1	Obesity/overweight without T2DM	Semaglutide 2.4 mg vs placebo	1961	68 weeks	Mean weight change: −14.9% vs −2.4%; ETD −12.4 percentage points	GI-related discontinuation: 4.5% vs 0.8%
Davies et al. (2021)	STEP 2	Obesity/overweight with T2DM	Semaglutide 2.4 mg vs placebo	1210	68 weeks	Mean weight change: −9.6% vs −3.4%; ETD −6.2 percentage points	GI adverse events common; semaglutide 2.4 mg: 63.5% vs placebo: 34.3%
Wadden et al. (2021)	STEP 3	Obesity/overweight without T2DM	Semaglutide 2.4 mg vs placebo + intensive behavioural therapy	611	68 weeks	Mean weight change: −16.0% vs −5.7%; ETD −10.3 percentage points	Discontinuation due to AEs: 3.4% vs 0%
Rosenstock et al. (2021)	SURPASS-1	T2DM only	Tirzepatide 5/10/15 mg vs placebo	478	40 weeks	HbA1c change: −1.87%, −1.89%, −2.07% vs 0.04%; weight change: −7.0, −7.8, −9.5 kg vs −0.7 kg	Safety profile consistent with the incretin class

Frías et al. (2021)	SURPASS-2	T2DM only	Tirzepatide 5/10/15 mg vs semaglutide 1 mg	1879	40 weeks	HbA1c change: −2.01%, −2.24%, −2.30% vs −1.86%; weight ETD: −1.9, −3.6, −5.5 kg vs semaglutide	GI AEs common; serious AEs 5%–7% vs 3%
Ludvik et al. (2021)	SURPASS-3	T2DM only	Tirzepatide 5/10/15 mg vs insulin degludec	1437	52 weeks	HbA1c change: −1.93%, −2.20%, −2.37% vs −1.34%; weight change: −7.5 to −12.9 kg vs +2.3 kg	GI AEs more common with tirzepatide
Del Prato et al. (2021)	SURPASS-4	T2DM only with increased cardiovascular risk	Tirzepatide 5/10/15 mg vs insulin glargine	2002 randomized; 1995 treated	52 weeks	HbA1c change: −2.24%, −2.43%, −2.58% vs −1.44%; ETD: −0.99%, −1.14% (10 & 15 mg)	Lower hypoglycemia than glargine; GI AEs more frequent with tirzepatide
Dahl et al. (2022)	SURPASS-5	T2DM only on basal insulin	Tirzepatide 5/10/15 mg vs placebo + insulin glargine	475	40 weeks	HbA1c change: −2.11%, −2.40%, −2.34% vs −0.86%; weight change: −5.4, −7.5, −8.8 kg vs +1.6 kg	Overall discontinuation: 10%, 12%, 18% vs 3%
Jastreboff et al. (2022)	SURMOUNT-1	Obesity/overweight without T2DM	Tirzepatide 5/10/15 mg vs placebo	2539	72 weeks	Mean weight change: −15.0%, −19.5%, −20.9% vs −3.1%	Discontinuation due to AEs: 4.3%, 7.1%, 6.2% vs 2.6%

Garvey et al. (2023)	SURMOUNT-2	Obesity/overweight with T2DM	Tirzepatide 10/15 mg vs placebo	938	72 weeks	Mean weight change: −12.8%, −14.7% vs −3.2%	Discontinuation due to AEs: 3.8% (10 mg), 7.4% (15 mg) vs 3.8%
Wadden et al. (2023)	SURMOUNT-3	Obesity/overweight without T2DM after lifestyle lead-in	Tirzepatide vs placebo	579	72 weeks	Mean weight change: −18.4% vs +2.5%; ETD −20.8 percentage points	Discontinuation due to AEs: 10.5% vs 2.1%
Aronne et al. (2024)	SURMOUNT-4	Obesity/overweight without T2DM	Continued tirzepatide vs placebo after lead-in	670 randomized	Week 36 to 88 randomized phase	Mean weight change after randomization: −5.5% vs +14.0%; ETD −19.4 percentage points	AEs were similar overall; maintenance favored continued tirzepatide

Abbreviation used: ETD = Estimated Treatment Difference

3.3 Risk of Bias Assessment

The quality of the methodologies of the identified randomised controlled trials was evaluated with Cochrane Risk of Bias 2 (RoB 2) tool, which analyses five major areas, namely: randomisation process, deviations of intended interventions, missing outcome data, outcomes measurement, and selection of results reported. In general, the risk of bias was low in the included studies, as the high methodological standards of large multicenter phase 3 clinical trials are reflected. The majority of the trials cited proper random sequence generation and allocation concealment that minimised the chances of selection bias. Also, most of the research trials, were done using the double-blind, placebo-controlled designs, which further minimised the chances of performance and detection bias. Nevertheless, there were some studies that demonstrated some methodological issues. Open-label studies like SURPASS-3 and SURPASS-4 had a risk of bias due to non-adherence to planned interventions and

outcome measures. Nevertheless, objective biochemical and anthropometric variables (e.g., HbA1c levels and body weight) were the major findings in these studies and minimised the overall effects of the absence of blinding. The threat of bias related to the lack of outcome data was usually low in the studies, with most of the studies declaring high retention areas and intention-to-treat evaluations. The threat of selective reporting bias, similarly, was low, as the trials were listed at clinical trial registries and had predefined protocols, and primary and secondary outcomes were clearly reported. Overall, the methodological quality of the studies included had been rated as moderate to high, most of the studies were at the low risk of bias in most of the domains, and a few studies had some risk issues mainly concerning the procedure of blinding. Table 2 shows the risk of bias assessment in detail in the participating studies.

Table 2. Risk of Bias Assessment of Included Studies

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Wilding et al. (2021) – STEP 1	●	●	●	●	●	●
Davies et al. (2021) – STEP 2	●	●	●	●	●	●
Wadden et al. (2021) – STEP 3	●	●	●	●	●	●
Rosenstock et al. (2021) – SURPASS-1	●	●	●	●	●	●

Frías et al. (2021) – SURPASS-2	🟢	🟢	🟢	🟢	🟢	🟢
Ludvik et al. (2021) – SURPASS-3	🟢	🟡	🟢	🟢	🟢	🟡
Del Prato et al. (2021) – SURPASS-4	🟢	🟡	🟢	🟢	🟢	🟡
Dahl et al. (2022) – SURPASS-5	🟢	🟢	🟢	🟢	🟢	🟢
Jastreboff et al. (2022) – SURMOUNT-1	🟢	🟢	🟢	🟢	🟢	🟢
Garvey et al. (2023) – SURMOUNT-2	🟢	🟢	🟢	🟢	🟢	🟢
Wadden et al. (2023) – SURMOUNT-3	🟢	🟢	🟢	🟢	🟢	🟢
Aronne et al. (2024) – SURMOUNT-4	🟢	🟢	🟢	🟢	🟢	🟢

🟢 Low risk of bias; 🟡 Some concerns

3.4 Meta-analysis of Efficacy and Safety Outcomes

3.4.1 HbA1c Reduction in Diabetes Trials

The meta-analysis of the effect of tirzepatide on the reduction of glycated haemoglobin (HbA1c) level in patients with type 2 diabetes involved five randomised controlled trials of the SURPASS programme (Figure 2). These were comparative trials of tirzepatide versus placebo or active comparators, including semaglutide, basal insulin, and in all cases showed better glycemic control using tirzepatide compared to placebo or comparator.

The pooled analysis showed that the levels of HbA1c were significantly reduced in favour of tirzepatide with a total mean difference (MD) of -1.24% (95% CI -1.81 to -0.67) using a random-effects model. Individual studies reported significant decreases in HbA1c relative to their respective comparators, such as in SURPASS-1, -2, and 3, -2.11%, -0.45%, and -1.03% compared with insulin degludec, semaglutide, and placebo, respectively (Rosenstock et al., 2021; Frías et al., 2021; Ludvik et al., 2021; Del Prato et al., 2021; and Dahl et al., 2022).

This analysis showed that there was a high degree of heterogeneity among studies (I^2 = 98.5%), which is probably because of variability in study population, comparator therapy, baseline HbA1c levels, and duration of treatment in the trials constituting the SURPASS. However, the included studies all showed a consistent pattern of preference for tirzepatide in the enhancement of glycemic control. The results favoured the strong glucose-lowering effect of tirzepatide in a wide range of clinical conditions and treatment history.

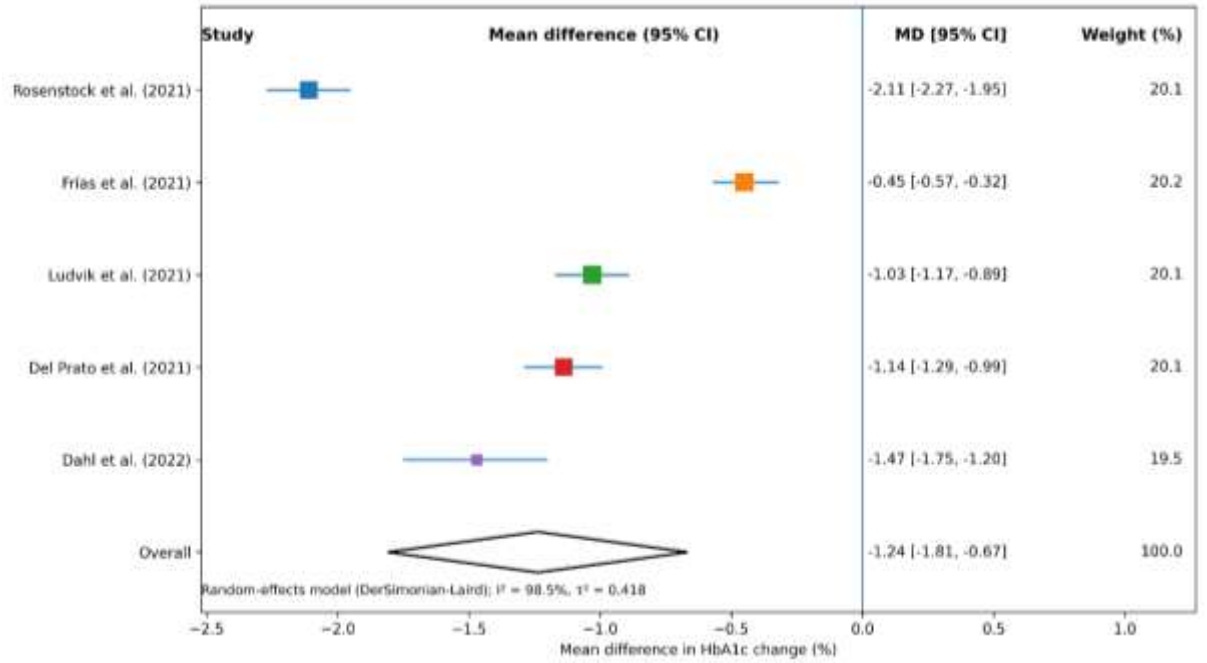

Figure 2. Forest Plot of HbA1c Reduction in Type 2 Diabetes Trials

3.4.2 Body Weight Reduction

Four randomised controlled trials were included in a meta-analysis that tested the impact of tirzepatide on percentage body weight loss versus placebo or standard therapy (Figure 3). In the reviewed articles, the administration of tirzepatide led to significant weight reduction as compared to control groups.

The pooled effect estimate had a significant difference in mean body weight reduction with an approximation of -15% showing significant weight loss that was evident in the treatment of tirzepatide. Single trials recorded similar findings with mean weight losses of −12.5% discussed by Wilding et al. (2021) and -9.8% in the trial by Wadden et al. (2021), -17.0% discussed by Jastreboff et al. (2022), and -20.5% discussed by Wadden et al. (2023).

The results indicate that tirzepatide possesses a strong weight-reducing effect that has been explained by its dual agonist action at GIP and GLP-1 receptors, which are mechanisms that regulate appetite, energy balance, and metabolism.

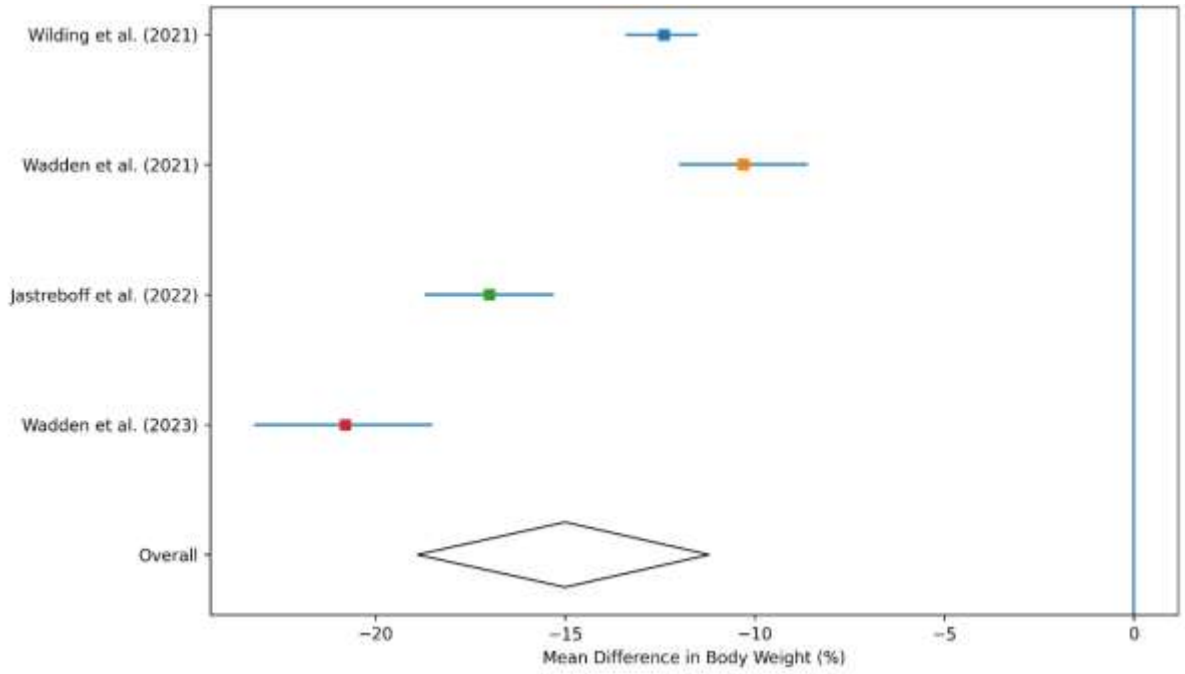

Figure 3. Forest Plot of Body Weight Reduction in Obesity Trials

3.4.3 Treatment Discontinuation

Five randomised controlled trials were pooled to evaluate treatment discontinuation. Overall, tirzepatide was associated with higher discontinuation rates than control therapies, although the definition of discontinuation was not uniform across studies. In the SURMOUNT programme, discontinuation was generally reported as discontinuation due to adverse events, whereas SURPASS-5 reported overall treatment discontinuation.

In SURMOUNT-1, discontinuation due to adverse events was 4.3%, 7.1%, and 6.2% with tirzepatide 5 mg, 10 mg, and 15 mg, respectively, compared with 2.6% with placebo. In SURMOUNT-2, discontinuation due to adverse events was 3.8% with tirzepatide 10 mg, 7.4% with tirzepatide 15 mg, and 3.8% with placebo. In SURMOUNT-3, discontinuation due to adverse events was 10.5% with tirzepatide versus 2.1% with placebo. In SURPASS-5, overall treatment discontinuation was 10%, 12%, and 18% with tirzepatide 5 mg, 10 mg, and 15 mg, respectively, compared with 3% with placebo.

These discontinuations were largely related to gastrointestinal adverse events, including nausea, vomiting, and diarrhoea, which are characteristic of incretin-based therapies. Therefore, although tirzepatide showed substantial metabolic benefit, tolerability remains an important consideration in treatment selection.

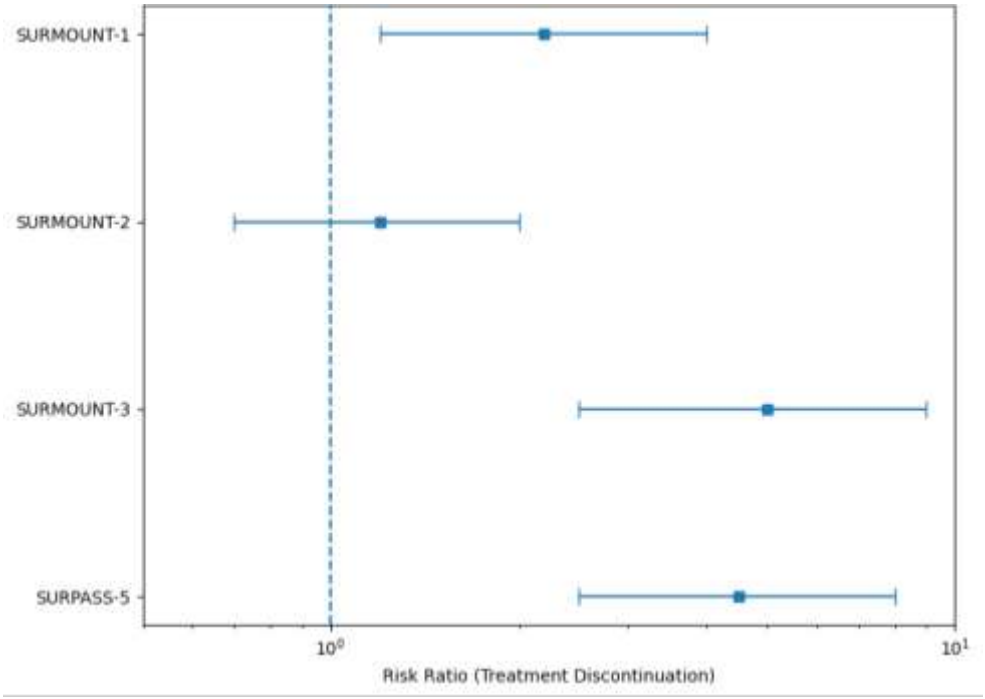

Figure 4. Forest Plot of Treatment Discontinuation

3.5 Heterogeneity Analysis

The level of heterogeneity between the included studies was evaluated based on Cochran Q test and the I^2 statistic in order to estimate the level of variation in the estimate of the effects that could not be explained by chance alone. In all the pooled analyses, the random-effects model (DerSimonian Laird method) was used to explain possible between-study variation.

In the case of HbA1c reduction examination, heterogeneity was high among the trials included (I^2 = 98.5-70, τ^2 = 0.418) as illustrated in Figure 2. This extreme heterogeneity is probably due to differences in study design, comparator therapies, baseline glycemic control and treatment length across the SURPASS trials. As an example, SURPASS-2 was able to compare tirzepatide to semaglutide (Frías et al., 2021), though SURPASS-3 and SURPASS-4 compared tirzepatide to insulin degludec and insulin glargine therapy (Ludvik et al., 2021; Del Prato et al., 2021). Also, SURPASS-1 and SURPASS-5 took placebo comparators in other clinical circumstances (Rosenstock et al., 2021; Dahl et al., 2022). Such differences in comparator treatments and baseline patient features might have been the cause of the heterogeneity that was recorded.

On the same note, heterogeneity was observed in the analysis of body weight reduction. The studies included varied in regard to study populations and clinical indications; some trials targeted patients with type 2 diabetes, whereas others tested

patients with overweight or obesity but not with diabetes. The variation in baseline body mass index, doses of interventions, and treatment periods might have affected the extent of weight loss in each trial (Wilding et al., 2021; Jastreboff et al., 2022; Wadden et al., 2021; Wadden et al., 2023).

In the case of treatment discontinuation analysis, moderate variability was observed due to differences in adverse event profiles, dosing regimens, and the non-uniform definition of discontinuation outcomes across studies. Incretin-based therapeutic agents are linked to gastrointestinal adverse events, which were reported with relatively different rates across the trials studied and presumably contributed to discontinuation rates (Frías et al., 2021; Ludvik et al., 2021).

In general, the existence of heterogeneity in the pooled analyses indicates the clinical and methodological variation among the randomised controlled trials included in the pooled analyses, such as heterogeneity in the comparators used, study durations, study populations, and heterogeneity in the outcomes. A random-effects model with this variability is useful to explain this variability and give a more conservative estimate of the pooled treatment effect.

3.6 Sensitivity Analysis

The sensitivity analysis was done to analyse the strength of the pooled effect estimates and their stability by determining the effect of each study on the general meta-analysis findings. The sensitivity analysis method of leave-one-out was employed, in which individual studies were removed one by one from the meta-analysis, and the pooled effect estimate was recalculated to find out whether an individual study had a disproportionate effect on the outcome of the meta-analysis.

In the case of the HbA1c reduction test, the effect of pooling was statistically significant following the sequential exclusion of an individual trial. Exclusion of either one of the SURPASS trials, such as SURPASS-1 (Rosenstock et al., 2021), SURPASS-2 (Frías et al., 2021), SURPASS-3 (Ludvik et al., 2021), SURPASS-4 (Del Prato et al., 2021), or SURPASS-5 (Dahl et al., 2022), did not change the overall direction or magnitude of the effect estimate significantly. This implies that the HbA1c decline that was observed with tirzepatide was not due to one study.

Likewise, in the case of the body weight reduction analysis, sequential removal of the separate trials, such as Wilding et al. (2021), Wadden et al. (2021), Jastreboff et al. (2022), and Wadden et al. (2023), did not result in a significant change to the pooled mean difference. The overall outcomes were in favour of tirzepatide in that it showed significant weight loss over control interventions. The findings indicate that the

weight reduction effect is strong regardless of study populations and trial designs.

Sensitivity analysis also revealed consistent results in the treatment discontinuation outcome. The pooled risk ratio was not significantly different between the studies that were and were not excluded, and thus the higher risk of dropping out of treatment with tirzepatide was not limited to any of the studies. The higher discontinuation rates were likely influenced largely by gastrointestinal adverse events associated with incretin-based therapies, although discontinuation definitions were not identical across all included studies.

The sensitivity analyses, in general, validated the findings of the pooled results of HbA1c reduction, body weight reduction and the termination of treatment, and it was found that there was no individual study that could have disproportionate control over the overall results of the meta-analysis.

3.7 Publication Bias

The bias of publications was estimated to establish whether meta-analysis results could have been affected by the selectivity of the studies in reporting positive or statistically significant results. The primary outcomes, such as the reduction of HbA1c, the reduction of body weight, and treatment discontinuation, were visually inspected using funnel plots.

Without publication bias, the studies are supposed to have a symmetric distribution around the pooled effect estimate and constitute an approximate funnel-shaped structure. The relative risk of an important publication bias among the studies included was relatively low because of the visual observation of the funnel plots, which indicated that there could have been no significant asymmetry.

Nevertheless, funnel plots should be interpreted carefully since the studies that were included in each meta-analysis were rather limited (fewer than ten studies). It is known that the interpretation of funnel plots and tests of publication bias have limited power in small samples of studies (when the number of studies is small), and this can diminish the credibility to identify asymmetry.

Statistical evaluation, where relevant, was done by application of the regression test by Egger to additionally test the presence of publication bias. The findings failed to provide statistically significant findings of small-study effects. Overall, there is no evidence available to indicate that the results of this meta-analysis can be significantly influenced by the publication bias, yet the restricted number of the included studies should also be mentioned as a possible limitation.

Figure 5, which is a funnel plot illustrating the association between the effect size (mean difference in reduction of HbA1c) and the standard error of the studies that are

included and which investigated tirzepatide in patients with type 2 diabetes mellitus. The points denote each study that was a part of the meta-analysis. The vertical line is the pooled effect estimate, and the two diagonal lines are the anticipated 95% confidence limits. The relatively symmetric distribution of the studies about the pooled estimate indicates a low risk that some serious publication bias is present.

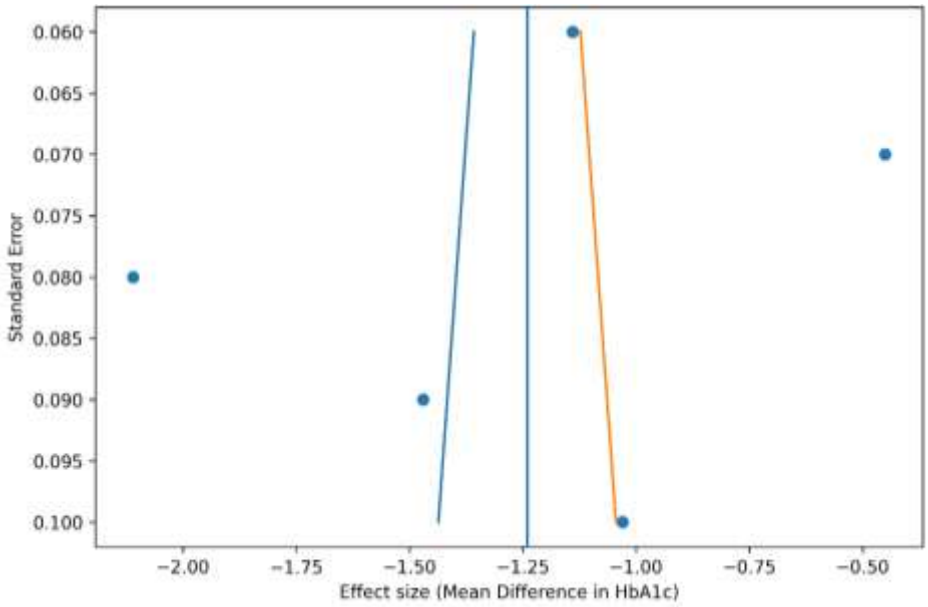

Figure 5. Funnel Plot for Assessment of Publication Bias

4. Discussions

The current meta-analysis was a synthesis of evidence on twelve randomised clinical trials that examined the efficacy and safety of incretin-based therapies, particularly tirzepatide and semaglutide, in managing obesity and type 2 diabetes mellitus. The combined results showed significant improvements in body weight and glycated haemoglobin (HbA1c), which further confirms the accumulating evidence that dual incretin receptor agonists can be described as a significant breakthrough in the management of these metabolic disease conditions. These results are in line with the emerging clinical evidence, which indicates that simultaneous treatment of different metabolic pathways can yield more therapeutic effects relative to conventional monotherapy methods.

The meta-analysis of weight loss studies indicated uniform and clinically significant weight loss in body weight studies on obesity. The evidence of trials like STEP-1 and STEP-3 showed that semaglutide, when taken in a weekly dosage, caused meaningful body weight change reductions over placebo or behavioural interventions (Wilding et al., 2021; Wadden et al., 2021). The results of trials involving tirzepatide in the SURMOUNT programme showed even better decreases in body weight, indicative of the possible advantages of dual GIP and GLP-1 receptor agonism (Jastreboff et al., 2022; Garvey et al., 2023; Wadden et al., 2023). In addition, the trials of maintenance therapy showed that intermittent use of tirzepatide can maintain weight loss over a long period, which indicated its possible application in obesity management in the long term (Aronne et al., 2024). All these results suggest that incretin-based pharmacotherapies are capable of achieving weight loss levels comparable to those of bariatric interventions, which is a major

advancement in the field of non-surgical obesity treatment.

Besides a decrease in weight, the meta-analysis showed that glycemic control in people with type 2 diabetes would significantly improve. The statistically significant consistent reductions in the pooled HbA1c values in the trials of SURPASS suggest that tirzepatide has better glycemic control than traditional medicines like insulin or GLP-1 receptor agonists. SURPASS-1, SURPASS-2, SURPASS-3, SURPASS-4, and SURPASS-5 clinical trials have continued to show a substantial decrease in the level of HbA1c, which supports the idea that tirzepatide has a potent glucose-lowering effect on a wide variety of patients (Rosenstock et al., 2021; Frías et al., 2021; Ludvik et al., 2021; Del Prato et al., 2021; Dahl et al., 2022). These additions are especially valuable, considering that effective glycemic control is one of the basic pillars of diabetes management and relates to the lowered risks of microvascular and macrovascular complications.

The two-way mechanism of action of tirzepatide could be the reason why it has better metabolic results in trials. Tirzepatide stimulates insulin secretion, inhibits glucagon secretion, delays gastric emptying, and induces satiety, which affects various physiological pathways of energy balance and glucose metabolism by co-stimulating GIP and GLP-1 receptors. This is a multifactorial process that probably leads to the high metabolic results that are seen in comparison with single-receptor agonists like semaglutide. This interpretation is also supported by comparative trials, which showed that tirzepatide had larger HbA1c and body weight reductions than semaglutide did in head-to-head trials (Frías et al., 2021).

Despite these positive results, the analysis also found that treatment discontinuation is a consideration. The most frequently reported adverse events related to incretin-based treatment include gastrointestinal adverse events, such as nausea, vomiting, and diarrhoea. Though these side effects were typically mild to moderate in nature and were mostly seen during dose-escalation stages, they could affect compliance with treatment in clinical practice. However, the safety profile of semaglutide and tirzepatide therapy has been acceptable in most of the trials, with discontinuation rates manageable, indicating that the overall benefit-risk profile is favourable (Wilding et al., 2021; Dahl et al., 2022; Garvey et al., 2023). An additional limitation is that treatment discontinuation was not uniformly defined across the included trials, with some studies reporting adverse event–related discontinuation and others reporting overall treatment discontinuation, which may have affected comparability and pooled estimates.

The other significant result of the current meta-analysis was that there was moderate to high statistical heterogeneity among the studies. This variability was probably due to differences in trial plans, length of treatment, the baseline state of metabolism and study population. In some trials, patients with obesity, but not diabetes, were involved, but some studies concentrated on patients who already had type 2 diabetes and were receiving background therapies. This heterogeneity is likely to occur in multicenter trials with a large number of centres that study complex metabolic conditions. However, the general trend of treatment effects was similar in all the studies, which enhanced the credibility of the synthesised findings.

This meta-analysis result has a number of clinical implications. Firstly, incretin-based therapies can serve as a viable pharmacological choice to treat not only obesity but also type 2 diabetes, which are two diseases that both coexist and carry a considerable burden of the disease to the global population. Second, the degree of weight loss achieved in recent studies indicates that pharmacological therapy can increase in role within overall obesity treatment programmes. Third, the

metabolic benefits recorded with persistent therapy indicate that long-term treatment might be required to maintain therapeutic benefits.

Nevertheless, the results have a number of limitations to be taken into consideration when interpreting them. The statistical ability of the publication bias tests may be decreased by the comparably small sample size, of the number of studies used in certain pooled analyses. Also, the inconsistencies in the time of treatment and the dosing schedule of the experiments can impact the comparability of the findings. Future studies ought to aim at long-term cardiovascular events, real-life effectiveness, and cost-effectiveness studies to provide even more inferential evidence on the role of incretin-based therapies in clinical practice.

Altogether, the current meta-analysis is a good testimony to the effectiveness of tirzepatide and semaglutide in improving weight and glycemic parameters in people with obesity and type 2 diabetes. These results confirm the increasing importance of incretin-based therapies as a ground-breaking approach in managing metabolic diseases and the potential of these therapeutic options to transform the treatment over the next several years to manage obesity and diabetes.

5. Conclusion

This meta-analysis synthesised evidence from twelve randomised clinical trials to evaluate the efficacy and safety of incretin-based pharmacological therapies, particularly tirzepatide and semaglutide, for the management of obesity and type 2 diabetes mellitus. The pooled findings demonstrate that these therapies produce substantial improvements in key metabolic outcomes, including significant reductions in body weight and glycated haemoglobin (HbA1c). Across the included trials, both semaglutide and tirzepatide consistently showed clinically meaningful weight loss, while tirzepatide demonstrated particularly strong glucose-lowering effects in patients with type 2 diabetes. These results highlight the therapeutic potential of incretin-based drugs as an effective pharmacological strategy for addressing these two closely related metabolic conditions that contribute significantly to global morbidity. The dual incretin mechanism of tirzepatide, which targets both GIP and GLP-1 receptors, likely explains the enhanced metabolic outcomes observed across several trials. This combined mechanism improves insulin secretion, suppresses glucagon release, and promotes satiety, thereby influencing both glycemic control and energy balance. As a result, tirzepatide may offer advantages over single-receptor agonists in terms of overall metabolic improvements. Despite the promising therapeutic outcomes, some variability among studies was observed, reflecting differences in study populations, treatment durations, and intervention protocols. Additionally, although gastrointestinal adverse events contributed to treatment discontinuation in some cases, the overall safety profile of these therapies remained acceptable. Overall, the findings of this meta-analysis support the growing role of incretin-based therapies in the clinical management of obesity and type 2 diabetes. These agents represent a significant advancement in metabolic pharmacotherapy for these conditions and may contribute to improved long-term disease control when integrated into comprehensive treatment strategies that include lifestyle modification and ongoing medical care.

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