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Review

Efficacy and Safety of Tirzepatide for Weight Management in Non-Diabetic Obese Individuals: A Narrative Review

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Abstract: Obesity remains a global health challenge, requiring long-term, sustainable treatment strategies. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist is the latest clinically approved and commercially available pharmacological option for obesity management, necessitating further research in non-diabetic individuals. This narrative review synthesizes existing clinical evidence on the efficacy and safety of Tirzepatide in non-diabetic obese individuals. A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, ClinicalTrials.gov, and Google Scholar databases to identify relevant clinical trials, meta-analyses, and studies assessing its weight-loss impact from 2022 onwards. Synthesized evidence indicates that Tirzepatide achieved up to 20.9% weight loss over 72 weeks (SURMOUNT-1), 18.4% after lifestyle intervention (SURMOUNT-3), 17.5% in Chinese adults (SURMOUNT-CN), and 25.3% with continued treatment over 88 weeks (SURMOUNT-4). Meta-analyses confirmed higher odds of ≥5%-20% weight loss versus Semaglutide and Liraglutide, significantly reducing body mass index (BMI), waist circumference, blood pressure, and Atherosclerotic Cardiovascular Disease (ASCVD) risk. Health-related quality of life (HRQoL) improved with greater weight loss, and gastrointestinal side effects (nausea, diarrhea, constipation) were common but mild to moderate, with <5% treatment discontinuation. Tirzepatide achieved significant weight loss, cardiometabolic benefits, and improved quality of life in non-diabetic obese individuals, but further research is needed on long-term efficacy, safety, and clinical application.

Keywords: Tirzepatide; GIP and GLP-1 receptor agonist; body mass index; BMI; obesity treatment; overweight; weight loss

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1. Introduction

Obesity is a rapidly growing epidemic, affecting nearly 40% of adults worldwide [1–3]. It has been a primary risk factor for diabetes, hypertension, cardiovascular disease, and many other metabolic diseases [4]. Being overweight incurs significant healthcare expenses and economic impact, predominantly arising from the treatment of related conditions such as diabetes, cardiovascular diseases, and hypertension [5,6]. This situation highlights the necessity for effective clinical management strategies to alleviate this financial burden [7].

Given this, the clinical management of obesity is an essential task demanding an effective strategy [8]. Pharmacological agents can be helpful as tools in obesity management against environmental and epigenetic factors [9]. Only a few long-term treatment options are approved by the US Food and Drug Administration (FDA), while more interventions are at different stages of development and evaluation [10,11].

Among FDA-approved anti-obesity medications, Tirzepatide has demonstrated significant weight-loss efficacy [12,13]. Initially, Tirzepatide was solely used to treat diabetes mellitus (DM). Nevertheless, the recent approval by the United States Food and Drug Administration (FDA) for its use in chronic weight management has resulted in a significant rise in its prescription frequency. It has been authorized for individuals who are categorized as obese, which is defined as having a body mass index (BMI) of 30 or higher, or for those who are classified as overweight and possess at least one weight-related health condition, such as hypertension, elevated cholesterol levels, type 2 diabetes, obstructive sleep apnea, or cardiovascular disease [14].

Tirzepatide is a dual agonist consisting of two native ligands in glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). The proposed mechanisms are related to a decrease in hunger and energy intake, an increase in energy expenditure, an increase in thermogenic activity, inhibition of gastric emptying, and increased glucose metabolism [15,16]. Synergistic action on the targets of GLP-1 and GIP strengthens the role of Tirzepatide as an efficacious pharmaceutical agent for obesity treatment [17].

This review evaluates Tirzepatide's role as a pharmacotherapeutic option by analyzing its efficacy and safety in non-diabetic obese individuals, which aligns with current clinical guidelines for obesity management [18–21].

2. Materials and Methods

2.1. Study Design

This narrative review followed a structured approach for literature synthesis, incorporating findings from clinical trials, systematic reviews, and meta-analyses on Tirzepatide for non-diabetic obesity.

The research methodology followed the structured approach for narrative literature reviews [22–24].

2.2. Research Question

This review explores the effectiveness of Tirzepatide as a modern pharmacotherapeutic agent in promoting weight reduction and enhancing clinical outcomes in the management of obesity, focusing on its efficacy and safety in non-diabetic individuals [25]. This objective is addressed through the research question: What is the efficacy and safety of Tirzepatide for weight loss in non-diabetic obese individuals?

2.3. Literature Search Strategy

Relevant literature was identified through PubMed, Scopus, Web of Science, and Google Scholar database searches. The search terms included combinations of keywords such as "Tirzepatide,"

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"obesity management," "dual GIP/GLP-1 receptor agonist," "weight loss treatment," and "clinical outcomes in obesity."

Boolean search operators were applied: ("Tirzepatide" OR "GLP-1" OR "peptide" OR "medication" OR "weight loss" OR "obesity"). Filters applied: Studies published from 2022 onward, English language, human studies.

2.4. Inclusion Criteria

This review included studies evaluating the efficacy and safety of Tirzepatide in non-diabetic, obese, or overweight individuals. Eligible studies consisted of clinical trials, reviews, meta-analyses, and observational studies published in peer-reviewed journals. Only studies reporting weight loss outcomes, body mass index (BMI) reduction, or changes in metabolic parameters were considered. Additionally, studies assessing waist circumference reduction, cardiometabolic risk factors such as blood pressure, lipid profile, ASCVD risk, treatment discontinuation rates, health-related quality of life (HRQoL), and gastrointestinal adverse effects were included to provide a comprehensive evaluation of Tirzepatide's impact on obesity management. The review considered articles featured in scholarly sources from 2022 to 2025, and only articles published in English were included to ensure consistency in data interpretation.

2.5. Exclusion Criteria

This review excludes studies primarily focusing on diabetic populations to maintain specificity. Additionally, those lacking sufficient data on efficacy, safety, or weight loss outcomes were omitted. Animal studies, in vitro research, case reports, editorials, and opinion pieces were also not included. Duplicate studies or those with overlapping data sets were removed to prevent redundancy and ensure data integrity. Studies with small sample sizes, short follow-up durations, or unclear methodologies were also not included to enhance the reliability of the findings.

2.6. Data Collection and Analysis

Initially, articles were screened based on their titles and abstracts to identify relevant studies, followed by a thorough full-text review to determine eligibility according to the predefined inclusion and exclusion criteria. Extracted data included study details such as author information, publication year, study design, sample size, intervention duration, dosage of Tirzepatide, reported weight loss outcomes, metabolic parameter changes, and safety profiles, including adverse effects and treatment discontinuation rates. The findings were synthesized narratively, focusing on efficacy trends, comparative effectiveness against other weight-loss agents, safety and tolerability profiles, and potential knowledge gaps that warrant further investigation for long-term clinical application.

3. Results

The initial database search retrieved 465 articles. Following a rigorous screening and filtering process based on the inclusion and exclusion criteria, 17 studies were deemed eligible and included in this review. These studies are organized chronologically from the earliest publication in 2022 to the most recent in 2025, ensuring a structured presentation of evolving clinical evidence. The detailed list of selected studies, including key findings on Tirzepatide's efficacy and safety, is presented in **Table 1**.

Table 1. Overview of included studies evaluating Tirzepatide for weight management in non-diabetic obese individuals.

Author Names	Reference Title, Journal, and Year	Study Design	Key Outcomes

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Jastreboff, *et al.* [26]	Tirzepatide Once Weekly for the Treatment of Obesity, N Engl J Med, 2022	Phase 3 double-blind, randomized, controlled trial (SURMOUNT-1)	Tirzepatide demonstrated significant and sustained weight reduction in non-diabetic obese individuals over 72 weeks, with up to 20.9% mean weight loss at the highest dose, improved cardiometabolic measures, and gastrointestinal side effects as the most common adverse events.
Wadden, *et al.* [27]	Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial, Nat Med, 2023	Phase 3, double-blind, randomized, placebo-controlled trial (SURMOUNT-3)	Tirzepatide resulted in a significant additional weight reduction (−18.4%) over 72 weeks in adults who had already achieved ≥5% weight loss through intensive lifestyle intervention, with gastrointestinal side effects being the most common adverse event.
Alkhezi, *et al.* [28]	Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: A network meta-analysis of randomized clinical trials, Obes Rev, 2023	A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials	Tirzepatide demonstrated greater weight loss efficacy than semaglutide and liraglutide, with higher odds of achieving ≥5%-20% weight loss, while all GLP-1 receptor agonists had comparable safety profiles with increased gastrointestinal adverse events.
le Roux, *et al.* [29]	Tirzepatide for the treatment of obesity: Rationale and design of the SURMOUNT clinical development program, Obesity (Silver Spring), 2023	Global phase 3, double-blind, randomized, placebo-controlled trials	The SURMOUNT program evaluates Tirzepatide's efficacy and safety for chronic weight management; initial results from SURMOUNT-1 confirm significant weight reduction, with results from other trials pending.
Aronne, *et al.* [30]	Continued TreatmentwWith Tirzepatide for Maintenance of Weight Reduction in Adults with Obesity The SURMOUNT-4 Randomized Clinical Trial, Jama, 2024	Phase 3, double-blind, randomized, placebo-controlled trial (SURMOUNT-4)	Continued Tirzepatide treatment maintained and enhanced weight reduction (−25.3% over 88 weeks), while withdrawal led to substantial weight regain, with gastrointestinal side effects being the most common adverse events.
Zhao, *et al.* [31]	Tirzepatide for Weight Reduction in Chinese Adults with Obesity: The SURMOUNT-CN Randomized Clinical Trial, Jama, 2024	Phase 3, double-blind, randomized, placebo-controlled trial (SURMOUNT-CN)	Tirzepatide significantly reduced body weight (up to −17.5% at 52 weeks) in Chinese adults with obesity or overweight, with gastrointestinal side effects being the most common but generally mild to moderate.
Qin, *et al.* [32]	Efficacy and safety of once-weekly Tirzepatide for weight management compared to placebo: An updated systematic review and meta-analysis including the latest SURMOUNT-2 trial, Endocrine, 2024	A Systematic Review and Meta-Analysis	Tirzepatide demonstrated dose-dependent weight loss (−8.07% to −11.83%), BMI and waist circumference reduction, and improvements in metabolic parameters, with mild-to-moderate gastrointestinal side effects being the most common adverse events.
Liu, *et al.* [33]	Efficacy and safety of Tirzepatide versus placebo in overweight or obese adults without diabetes: a systematic review and meta-analysis of	A Systematic Review and Meta-Analysis of Randomized Controlled Trials	Tirzepatide significantly reduced body weight, BMI, waist circumference, and blood pressure in overweight or obese adults without diabetes but was associated with a higher risk of gastrointestinal adverse events,

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	randomized controlled trials, Int J Clin Pharm, 2024		highlighting the need for risk-benefit assessment and monitoring.
Rochira, *et al.* [34]	The Effect of Tirzepatide on Body Composition in People with Overweight and Obesity: A Systematic Review of Randomized, Controlled Studies, Diseases, 2024	A Systematic Review of Randomized Controlled Trials	Tirzepatide significantly reduced total fat mass, visceral adipose tissue, and waist circumference in individuals with overweight and obesity, demonstrating superior fat reduction compared to other anti-obesity medications, while its effect on fat-free mass remains uncertain.
St-Pierre, *et al.* [35]	Efficacy and Safety of GLP-1 Agonists on Metabolic Parameters in Non-diabetic Patients with Inflammatory Bowel Disease, Dig Dis Sci, 2024	A Single-Center, Observational Cohort Study	Tirzepatide and other Glucagon-like peptide-1 (GLP-1) agonists significantly reduced body mass index (BMI) and total body weight (TBW) in non-diabetic patients with inflammatory bowel disease (IBD), with nausea and constipation as common side effects, though long-term safety remains unclear.
Hankosky, *et al.* [36]	Tirzepatide reduces the predicted risk of atherosclerotic cardiovascular disease and improves cardiometabolic risk factors in adults with obesity or overweight: SURMOUNT-1 post hoc analysis, Diabetes Obes Metab, 2024	A Post Hoc Analysis of the Phase 3, Randomized, Placebo-Controlled SURMOUNT-1 Trial	Tirzepatide significantly reduced the 10-year predicted risk of atherosclerotic cardiovascular disease (ASCVD) and improved cardiometabolic risk factors in adults with obesity or overweight without diabetes, with greater absolute risk reduction in those with higher baseline risk.
Xie, *et al.* [37]	Seven glucagon-like peptide-1 receptor agonists and polyagonists for weight loss in patients with obesity or overweight: an updated systematic review and network meta-analysis of randomized controlled trials, Metabolism, 2024	A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials	Tirzepatide demonstrated superior efficacy in reducing body weight and waist circumference compared to other GLP-1 receptor agonists, with greater weight loss observed in non-diabetic patients, those with higher BMI, and longer treatment durations. At the same time, no significant increase in serious adverse events was noted.
Pan, *et al.* [38]	Efficacy and safety of Tirzepatide, GLP-1 receptor agonists, and other weight loss drugs in overweight and obesity: a network meta-analysis, Obesity (Silver Spring), 2024	A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials	Tirzepatide demonstrated the highest efficacy for achieving ≥15% weight loss, ranking among the top treatments for weight reduction and metabolic improvements, while GLP-1 receptor agonists and Tirzepatide were associated with increased gastrointestinal adverse effects.
Malhotra, *et al.* [39]	Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity, N Engl J Med, 2024	Phase 3, double-blind, randomized, placebo-controlled trial	Tirzepatide significantly reduced apnea-hypopnea index, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure, improving sleep-related patient-reported outcomes.
Gudzune, *et al.* [40]	Association between weight reduction achieved with Tirzepatide and quality of life in adults with obesity: Results from the SURMOUNT-1	A Post Hoc Analysis of the Phase 3, Randomized, Placebo-Controlled SURMOUNT-1 Trial	Tirzepatide treatment significantly improved health-related quality of life (HRQoL), physical function, and psychosocial well-being, with greater weight reduction associated with greater improvements in adults with overweight or obesity.

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	study, Diabetes Obes Metab, 2025		
Packer, *et al.* [41]	Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity, N Engl J Med, 2025	International, double-blind, randomized, placebo-controlled trial	Tirzepatide reduced the risk of cardiovascular death or worsening heart failure, improved Kansas City Cardiomyopathy Questionnaire scores, and enhanced health status in patients with heart failure with preserved ejection fraction and obesity.
Hamza, *et al.* [42]	Tirzepatide for overweight and obesity management, Expert Opinion on Pharmacotherapy, 2025	Review of Findings from the Global SURMOUNT-3, along with trials (SURMOUNT-CN and SURMOUNT-J)	Tirzepatide enables significant weight loss (≥20%), demonstrates clinically relevant improvements in obesity-related complications, and has a well-tolerated safety profile, with ongoing trials further evaluating its long-term efficacy, cardiovascular outcomes, and cost-effectiveness.

4. Discussion

As obesity is a major global health challenge, the demand for pharmacological interventions that offer substantial, sustained weight reduction with an acceptable safety profile has intensified [43]. This review evaluates Tirzepatide's efficacy and safety in non-diabetic obese individuals, synthesizing findings from multiple high-quality clinical trials and meta-analyses. As a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, tirzepatide demonstrates clinically significant weight loss, with results approaching those seen with bariatric interventions [44,45]. Its unique mechanism of action and ability to drive clinically meaningful improvements in weight and metabolic parameters position it as an advancement in obesity pharmacotherapy [46]. The discussion that follows examines the depth of its clinical impact, key considerations for its role in long-term obesity management, and the remaining gaps in knowledge that warrant further investigation.

Efficacy of Tirzepatide for Weight Loss

Tirzepatide has been shown to provide significant and sustained weight loss in multiple randomized controlled trials. SURMOUNT-1, a phase 3 trial, reported a mean weight loss of up to 20.9% over 72 weeks, making it one of the most effective pharmacotherapies for obesity management in non-diabetic individuals [26].

Further studies confirmed Tirzepatide's superior efficacy in promoting additional weight loss beyond lifestyle interventions. In SURMOUNT-3, participants who had already achieved ≥5% weight loss through an intensive lifestyle intervention experienced an additional mean reduction of 18.4% over 72 weeks, demonstrating Tirzepatide's role as an effective adjunct to behavioral modifications [27]. Similarly, in a Chinese population, SURMOUNT-CN found that Tirzepatide achieved a mean weight reduction of 17.5% over 52 weeks, indicating its efficacy consistent across different ethnic groups [31].

Long-term weight maintenance is another crucial factor in obesity management [29]. SURMOUNT-4 demonstrated that continued Tirzepatide treatment over 88 weeks resulted in a weight loss of 25.3%, whereas participants who discontinued the drug experienced substantial weight regain, reinforcing the importance of sustained pharmacologic intervention to prevent weight rebound [30].

Comparative Effectiveness Against Other Anti-Obesity Agents

Multiple meta-analyses have positioned Tirzepatide as one of the most effective weight loss pharmacotherapies. A network meta-analysis of randomized controlled trials confirmed that Tirzepatide induced greater weight loss than semaglutide and liraglutide, with higher odds of achieving ≥5%-20% weight loss [28]. Another meta-analysis evaluating dose-dependent efficacy

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found that Tirzepatide 15 mg achieved the highest efficacy in weight reduction, outperforming GLP-1 receptor agonists in absolute weight loss and metabolic improvements [38].

In terms of body composition, a systematic review found that Tirzepatide significantly reduced total fat mass, visceral adipose tissue, and waist circumference, outperforming other GLP-1 receptor agonists and dual hormone receptor agonists, although its effect on fat-free mass remains unclear [34].

Impact on Cardiometabolic Risk Factors

Beyond weight loss, Tirzepatide has been associated with significant improvements in cardiometabolic health. The SURMOUNT-1 post hoc analysis found that Tirzepatide significantly reduced the 10-year predicted risk of atherosclerotic cardiovascular disease (ASCVD) while also improving lipid profiles, glycated hemoglobin (HbA1c), and blood pressure [36]. Given the high prevalence of cardiovascular complications in obesity, this finding suggests that Tirzepatide may offer long-term cardioprotective benefits.

Additionally, a study evaluating Tirzepatide's impact on metabolic parameters in non-diabetic patients with inflammatory bowel disease (IBD) found that BMI and total body weight significantly decreased, with no significant changes in liver enzymes or inflammatory markers, supporting its potential metabolic benefits beyond obesity [35].

Tirzepatide significantly reduced the apnea-hypopnea index (AHI), body weight, and inflammatory markers in patients with moderate-to-severe obstructive sleep apnea [39]. In patients with heart failure with preserved ejection fraction, Tirzepatide reduced the risk of cardiovascular mortality and disease progression while also improving health status scores [41]. These findings highlight its potential beyond weight loss in managing obesity-related complications.

Health-Related Quality of Life Improvements

Tirzepatide's weight reduction effects have been linked to improved health-related quality of life (HRQoL). A post hoc analysis of SURMOUNT-1 reported that higher weight loss percentages correlated with significant improvements in physical function, psychosocial well-being, and overall HRQoL [40]. Participants who achieved ≥20% weight loss showed the greatest improvements, reinforcing the psychosocial benefits of effective obesity management.

Safety and Tolerability of Tirzepatide

Despite its strong efficacy, Tirzepatide was associated with gastrointestinal side effects, including nausea, diarrhea, and constipation, which were mostly mild to moderate and transient. Across trials, less than 5% of participants discontinued treatment due to adverse events, suggesting a favorable tolerability profile [26,27].

Network meta-analyses confirmed that Tirzepatide and GLP-1 receptor agonists were associated with increased gastrointestinal adverse effects compared to placebo, though no significant increase in serious adverse events or withdrawal rates was observed [37,38].

Given the relatively short follow-up durations in clinical trials, long-term safety data remain a critical research gap. Further studies are necessary to assess the potential risks of prolonged Tirzepatide use, particularly regarding cardiovascular and renal outcomes.

Clinical Implications and Future Research Directions

While Tirzepatide has demonstrated strong efficacy in non-diabetic obesity management, several areas require further investigation. Comparative studies against emerging anti-obesity agents like Retatrutide are needed to determine optimal treatment strategies [28]. Long-term studies beyond 88 weeks should assess weight maintenance with continued or intermittent use [30]. Further research should explore its effects on fat-free mass and metabolic adaptation [34] and evaluate real-world adherence, accessibility, and cost-effectiveness to inform clinical decision-making [38]. Additionally, its role in managing obesity-related complications such as obstructive sleep apnea and metabolic dysfunction-associated steatohepatitis (MASH) warrants further study [42]. Moving forward, Tirzepatide represents a transformative advancement in obesity pharmacotherapy, but continued research is essential to refine treatment guidelines, optimize patient selection, and ensure long-term sustainability.

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Limitations

While Tirzepatide has shown a favorable short-term safety profile, its long-term safety and efficacy remain uncertain. The available data primarily come from trials, leaving gaps in understanding weight maintenance, metabolic adaptation, and potential long-term adverse effects. Additionally, the cost-effectiveness of Tirzepatide remains uncertain, and its financial impact on healthcare systems requires further evaluation to determine its long-term affordability and accessibility [13]. Also, the safety and tolerability of Tirzepatide in pediatric obesity remain unverified, as current clinical trials have primarily focused on adult populations [47]. Further research is needed to assess its sustained benefits, comparative effectiveness against newer agents, and long-term impact.

Addressing these gaps will help define Tirzepatide's long-term impact and integration into obesity care.

5. Conclusions

Tirzepatide has emerged as one of the most effective pharmacologic treatments for obesity, achieving record weight loss, cardiometabolic benefits, and improved quality of life in non-diabetic individuals. While it is generally well-tolerated, gastrointestinal side effects remain a consideration, and long-term safety and effectiveness studies are needed to establish its full therapeutic potential and optimal role in clinical practice. Despite its strong efficacy, Tirzepatide's long-term clinical role remains an area of ongoing research, with key considerations including patient selection criteria, optimal dosing strategies, long-term adherence, and the potential need for continued treatment to sustain weight loss effects. Ongoing clinical trials will shape its future outlook, comparative effectiveness studies against emerging therapies, and regulatory developments, ultimately defining its place in the evolving landscape of obesity management.

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Abbreviations

The following abbreviations are used in this manuscript:

US FDA	United States Food and Drug Administration
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
BMI	Body Mass Index
ICD-10	International Statistical Classification of Diseases-10
ASCVD	Atherosclerotic Cardiovascular Disease
HRQoL	Health-related Quality of Life

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