RCMOS – Revista Científica Multidisciplinar O
Saber. ISSN: 2675-9128. São Paulo - SP.
Ano VII, v.1 2026 | submissão: 17/07/2026 | aceito: 20/07/2026 | publicação: 23/07/2026

Pharmacological and Physiological Impact of Tirzepatide and GLP-1 Receptor Agonists in Non-Diabetic Individuals: A Meta-Analysis

Impacto Farmacológico e Fisiológico do Uso de Tirzepatida e de Agonistas do Receptor de GLP-1 em Indivíduos Não Diabéticos: Uma Metanálise

Impacto Farmacológico y Fisiológico del Uso de Tirzepatida y de Agonistas del Receptor de GLP-1 en Individuos No Diabéticos: Un Metanálisis

Eduarda Parzianello Lubi – Universidade de Passo Fundo (UPF)
Nicole Parzianello Lubi – Centro Universitário AFYA Pato Branco

Abstract:
Off-label use of glucagon-like peptide-1 receptor agonists (GLP-1RA) and of the dual GIP/GLP-1 agonist tirzepatide by individuals without a diagnosis of type 2 diabetes mellitus has grown substantially in recent years, driven mainly by demand for weight loss. This article aimed to gather, through a narrative meta-analysis, pharmacological, physiological and clinical evidence on the effects of tirzepatide and GLP-1RA in non-diabetic populations. Three studies published between 2024 and 2026 were analyzed: a dissertation on the use of tirzepatide for obesity treatment, an article on the regulatory risks of approving incretin-based drugs for childhood obesity in Brazil, and a study on cardiovascular outcomes associated with this therapeutic class, complemented by landmark clinical trials (SURMOUNT, SELECT and SURPASS-CVOT). Results indicate that dual activation of GIP and GLP-1 receptors promotes greater weight loss than selective GLP-1 agonism, with improvement of cardiometabolic parameters even in patients without diabetes, although the incidence of gastrointestinal events, the lack of long-term safety data and the regulatory weaknesses observed in vulnerable populations reinforce the need for careful prescription and continuous clinical monitoring.

Keywords:
Tirzepatide. Glucagon-Like Peptide 1. Pharmacology. Obesity. Patient Safety.

Resumo:
O uso off-label de agonistas do receptor de GLP-1 (GLP-1RA) e do agonista dual GIP/GLP-1 tirzepatida por indivíduos sem diagnóstico de diabetes mellitus tipo 2 cresceu de forma expressiva nos últimos anos, motivado sobretudo pela busca de emagrecimento. Este artigo teve como objetivo reunir, por meio de uma metanálise narrativa, evidências farmacológicas, fisiológicas e clínicas sobre os efeitos da tirzepatida e dos GLP-1RA em populações não diabéticas. Foram analisados três estudos publicados entre 2024 e 2026: um trabalho de conclusão de curso sobre o uso da tirzepatida no tratamento da obesidade, um artigo sobre os riscos regulatórios da aprovação de fármacos incretinomiméticos para obesidade infantil no Brasil e um estudo sobre desfechos cardiovasculares associados a essa classe terapêutica, complementados por ensaios clínicos de referência (SURMOUNT, SELECT e SURPASS-CVOT). Os resultados indicam que a ativação dual dos receptores de GIP e GLP-1 promove perda ponderal superior à dos agonistas seletivos de GLP-1, com melhora de parâmetros cardiometabólicos mesmo em pacientes sem diabetes, porém a incidência de eventos gastrointestinais, a ausência de dados de segurança em longo prazo e as fragilidades regulatórias observadas em populações vulneráveis reforçam a necessidade de prescrição criteriosa e monitoramento clínico contínuo.

Palavras-chave:
Tirzepatida. Peptídeo 1 Semelhante ao Glucagon. Farmacologia. Obesidade. Segurança do paciente.

RCMOS – Revista Científica Multidisciplinar O
Saber. ISSN: 2675-9128. São Paulo - SP.
Ano VII, v.1 2026 | submissão: 17/07/2026 | aceito: 20/07/2026 | publicação: 23/07/2026

Resumen:
El uso fuera de indicación de agonistas del receptor de GLP-1 (GLP-1RA) y del agonista dual GIP/GLP-1 tirzepatida por individuos sin diagnóstico de diabetes mellitus tipo 2 ha crecido de forma considerable en los últimos años, motivado principalmente por la búsqueda de pérdida de peso. Este artículo tuvo como objetivo reunir, mediante un metanálisis narrativo, evidencias farmacológicas, fisiológicas y clínicas sobre los efectos de la tirzepatida y de los GLP-1RA en poblaciones no diabéticas. Se analizaron tres estudios publicados entre 2024 y 2026: un trabajo de conclusión de curso sobre el uso de la tirzepatida en el tratamiento de la obesidad, un artículo sobre los riesgos regulatorios de la aprobación de fármacos incretinomiméticos para la obesidad infantil en Brasil y un estudio sobre desenlaces cardiovasculares asociados a esta clase terapéutica, complementados por ensayos clínicos de referencia (SURMOUNT, SELECT y SURPASS-CVOT). Los resultados indican que la activación dual de los receptores de GIP y GLP-1 promueve una pérdida de peso superior a la de los agonistas selectivos de GLP-1, con mejoría de los parámetros cardiometabólicos incluso en pacientes sin diabetes; sin embargo, la incidencia de eventos gastrointestinales, la ausencia de datos de seguridad a largo plazo y las fragilidades regulatorias observadas en poblaciones vulnerables refuerzan la necesidad de una prescripción cuidadosa y un seguimiento clínico continuo.

Palabras clave:
Tirzepatida. Péptido 1 Similar al Glucagón. Farmacología. Obesidad. Seguridad del paciente.

1 Introduction

Obesity is recognized by the World Health Organization as a chronic, multifactorial, and progressive disease associated with an increased risk of type 2 diabetes, arterial hypertension, dyslipidemia, cardiovascular diseases, and several types of cancer. Over the last two decades, the development of incretin-mimetic drugs has substantially changed the therapeutic landscape of excess weight, shifting the focus of treatment from exclusively behavioral interventions to pharmacological strategies with high weight-loss efficacy.

Among these drugs, tirzepatide stands out as the first molecule developed to act simultaneously as an agonist of the glucose-dependent insulinotropic polypeptide (GIP) receptor and the glucagon-like peptide-1 (GLP-1) receptor. Initially approved for glycemic control in patients with type 2 diabetes mellitus, the use of tirzepatide rapidly expanded, first off-label and subsequently through regulatory approval, to the treatment of obesity in individuals with and without a diagnosis of diabetes.

The growing use of GLP-1RA and tirzepatide by metabolically healthy people, often for aesthetic purposes, raises relevant questions about the pharmacokinetic profile, the physiological mechanisms involved, and the magnitude of adverse effects in this specific segment of the population, which differs from the original target population of pivotal clinical trials conducted predominantly in diabetic patients.

Ano VII, v.1 2026 | submissão: 17/07/2026 | aceito: 20/07/2026 | publicação: 23/07/2026

This article aims to conduct a narrative meta-analysis of recent scientific literature on the pharmacological and physiological impact of tirzepatide and GLP-1 receptor agonists in non-diabetic individuals, discussing the mechanism of action, clinical efficacy, safety, regulatory aspects, and cardiovascular repercussions of this therapeutic class.

2 Theoretical Framework

2.1 Physiology of the Incretin System

GLP-1 and GIP are peptide hormones secreted by enteroendocrine cells of the small intestine in response to nutrient intake, constituting the so-called "incretin effect": the greater insulin secretion observed after oral glucose administration compared with intravenous administration. GLP-1 stimulates glucose-dependent insulin secretion, inhibits glucagon release, delays gastric emptying, and acts on hypothalamic nuclei and the vagus nerve, promoting satiety. GIP, in turn, acts predominantly on pancreatic β cells and adipose tissue, participating in the regulation of lipid metabolism and bone density, although its isolated action on appetite is less consistent than that of GLP-1.

Tirzepatide was designed as a linear peptide of 39 amino acids, structurally derived from the GIP sequence, to which a 20-carbon diacidic fatty moiety was attached, extending its plasma half-life to approximately five days and allowing weekly subcutaneous administration. Its simultaneous activation of both incretin receptors produces a synergistic effect on glycemic homeostasis and on the hypothalamic circuits controlling appetite, resulting in reduced caloric intake regardless of the patient's glycemic status.

2.2 Clinical Pharmacology in Non-Diabetic Populations

In individuals without diabetes, the response to tirzepatide and GLP-1RA tends to be dominated by their effects on appetite and gastric emptying, since the baseline risk of hypoglycemia is reduced by the absence of pancreatic β-cell dysfunction. Studies from the SURMOUNT program, conducted in adults with overweight or obesity with and without type 2 diabetes, demonstrated body-weight reductions ranging from 15% to approximately 21% at the highest doses of tirzepatide after 72 weeks, values higher than those obtained with selective GLP-1 agonists over the same treatment period. This difference is attributed to the additional action of GIP on lipid metabolism and adipose-tissue thermogenesis, which enhances the anorexigenic effect mediated by GLP-1.

Conversely, dose titration in non-diabetic individuals usually follows the same gradual escalation schedule used in diabetic patients, beginning with 2.5 mg weekly and increasing in 2.5 mg increments every four weeks, a strategy specifically intended to reduce the incidence of gastrointestinal events, the adverse effects most frequently reported for this pharmacological class.

2.3 Safety, Adverse Events, and Regulatory Status

The most common adverse reactions associated with the use of tirzepatide and other GLP-1RA are gastrointestinal, including nausea, vomiting, diarrhea, and constipation, and are generally concentrated during dose adjustment. Less frequent but clinically relevant reactions include cholecystitis, acute pancreatitis, hypotension, dizziness, and hypersensitivity reactions. Rapid weight loss has also been associated with cases of malnutrition and concerns regarding loss of lean mass among users without a formal clinical indication for treatment.

In the regulatory field, expansion of GLP-1 agonist use beyond glycemic control has brought debates about the appropriateness of extrapolating evidence obtained in adult populations to more vulnerable groups, such as adolescents. The approval of liraglutide and semaglutide for adolescents with obesity in Brazil, for example, was based on a limited number of clinical trials sponsored by the pharmaceutical industry responsible for marketing the drugs, without robust long-term outcome data. This led public-health researchers to recommend caution and to advocate prioritizing non-pharmacological strategies — grounded in social justice, adequate nutrition, and physical activity — before medicalizing obesity in young populations.

3 Materials and Methods

This is a narrative meta-analysis based on a critical reading and qualitative synthesis of three open-access scientific publications selected because they complementarily address the pharmacological, regulatory, and cardiovascular aspects of the use of tirzepatide and GLP-1 receptor agonists: (i) a specialization course completion paper from the Adolfo Lutz Institute on the use of tirzepatide in treating obesity and overweight; (ii) an article published in Cadernos de Saúde Pública on the public-health risks arising from the approval of drugs to treat childhood obesity in Brazil; and (iii) a review study published in Arquivos Brasileiros de Cardiologia on cardiovascular outcomes associated with incretin-mimetic therapies.

The synthesis of these sources was complemented by consultation of landmark randomized clinical trials widely cited in the international literature on the topic, including the SURMOUNT-1 through SURMOUNT-5 studies, the SELECT study — which evaluated cardiovascular outcomes of semaglutide in individuals with overweight or obesity without diabetes — and the SURPASS-CVOT study, focused on the cardiovascular evaluation of tirzepatide. The three base articles were read in full when the complete text was available, or through their structured abstracts and results published in indexed databases. Extracted data were organized by thematic axis (mechanism of action, efficacy, safety, and regulation) to allow qualitative comparison across the studies.

Findings concerning adult or adolescent participants without a previous diagnosis of type 2 diabetes mellitus who were treated with tirzepatide or GLP-1 receptor agonists for body-weight control were considered eligible for discussion. Data referring exclusively to populations with uncontrolled diabetes were excluded, because this article focuses on the pharmacological and physiological impact of this therapeutic class outside the glycemic context that originally motivated its development.

4 Results and Discussion

4.1 Weight-Loss Efficacy in Non-Diabetic Individuals

The collected data confirm that the magnitude of weight loss achieved with tirzepatide in participants without diabetes tends to be greater than that observed in diabetic participants, a finding attributed to lower peripheral resistance to incretin effects in this population. In the SURMOUNT-1 study, participants with obesity but without type 2 diabetes experienced a mean weight reduction of up to 20.9% at the maximum dose, compared with a variation of only 3.1% in the placebo group over 72 weeks. Similar results were described in the direct comparison between tirzepatide and semaglutide (SURMOUNT-5), in which the former demonstrated superiority in reducing body weight and waist circumference among participants without diabetes.

These findings reinforce the role of the GIP component as an enhancer of the GLP-1 effect on satiety and energy expenditure, supporting the physiological hypothesis that dual activation of the two incretin receptors produces an additive effect, rather than merely an isolated additive effect, on the hypothalamic circuits that regulate energy balance.

Ano VII, v.1 2026 | submissão: 17/07/2026 | aceito: 20/07/2026 | publicação: 23/07/2026

4.2 Cardiovascular and Metabolic Effects

Studies of cardiovascular outcomes in populations without diabetes, such as the SELECT trial with semaglutide, demonstrated an approximately 20% reduction in the incidence of major cardiovascular events — myocardial infarction, stroke, and death from cardiovascular causes — in individuals with overweight or obesity and established cardiovascular disease, regardless of the presence of diabetes. Specifically for tirzepatide, the SURPASS-CVOT program, conducted in diabetic patients with established atherosclerotic disease, showed non-inferiority to dulaglutide for this composite outcome, while complementary analyses of the SURMOUNT studies indicate improvement in parameters associated with cardiovascular risk — systolic and diastolic blood pressure, triglycerides, HDL cholesterol, and non-HDL cholesterol — even in participants without diabetes, suggesting a cardiometabolic benefit that extends beyond the isolated effect of weight loss.

Nevertheless, the literature recognizes that data on cardiovascular outcomes specific to tirzepatide in exclusively non-diabetic populations remain more limited than the evidence already consolidated for selective GLP-1 agonists, which is identified as an important gap to be addressed by longer follow-up studies.

4.3 Safety, Off-Label Use, and Regulatory Weaknesses

Gastrointestinal adverse events remain the main practical limitation to the use of tirzepatide and GLP-1RA; they are more intense during dose escalation and are generally transient. However, analysis of regulatory data reveals an additional concern: expansion of these drugs to non-diabetic populations — especially adolescents — was supported, in many cases, by a limited number of clinical trials sponsored by the pharmaceutical industry itself, without sufficient follow-up to characterize long-term risks such as effects on bone development, body composition, and mental health.

In Brazil, health surveillance authorities have responded to this scenario with stricter control measures, such as the requirement for prescriptions in two copies for GLP-1 agonists and the dual GIP/GLP-1 agonist, introduced in 2025 by the Brazilian Health Regulatory Agency in response to the increase in reports of adverse events related to use outside approved indications. This measure reinforces the interpretation found in the reviewed literature that broader access to these therapies must be accompanied by active health surveillance and individualized clinical follow-up, especially when use is motivated exclusively by aesthetic goals and occurs outside a formal medical indication.

Final Considerations

The meta-analysis of the reviewed studies indicates that tirzepatide and GLP-1 receptor agonists produce pharmacological and physiological effects in non-diabetic individuals that are consistent with those observed in diabetic patients, with substantial weight loss and improved cardiometabolic parameters, without the baseline risk of hypoglycemia associated with pancreatic β-cell dysfunction. Dual activation of GIP and GLP-1 receptors gives tirzepatide an efficacy advantage over selective GLP-1 agonists, supported by synergistic physiological mechanisms controlling appetite and energy expenditure.

On the other hand, extending the use of these molecules beyond their original indication for glycemic control reveals important gaps in long-term safety and weaknesses in the regulatory approval process for more vulnerable populations, such as adolescents. It is therefore recommended that the use of tirzepatide and GLP-1RA in non-diabetic individuals remain conditional on careful medical indication, continuous clinical monitoring, and the production of independent scientific evidence that deepens knowledge of the long-term adverse effects of this therapeutic class.

References

ARONNE, L. J. et al. Tirzepatide as compared with semaglutide for the treatment of obesity. The New England Journal of Medicine, v. 393, n. 1, p. 26–36, 2025.

FONSECA DE OLIVEIRA, F.; YANO, H. M. Uso da tirzepatida no tratamento da obesidade e sobrepeso. 2025. Trabalho de Conclusão de Curso (Especialização em Vigilância Laboratorial em Saúde Pública) – Instituto Adolfo Lutz, São Paulo, 2025.

GARVEY, W. T. et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. The Lancet, v. 402, n. 10402, p. 613–626, 2023.

JASTREBOFF, A. M. et al. Tirzepatide once weekly for the treatment of obesity. New England Journal of Medicine, v. 387, n. 3, p. 205–216, 2022.

KOSIBOROD, M. N. et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. The New England Journal of Medicine, v. 390, n. 15, p. 1394–1407, 2024.

LIU, L.; SHI, H.; XIE, M.; SUN, Y. X.; NAHATA, M. C. The efficacy and safety of tirzepatide in patients with diabetes and/or obesity: systematic review and meta-analysis of randomized clinical trials. Pharmaceuticals, v. 18, n. 5, p. 668, 2025.

SATTAR, N. et al. Tirzepatide and major adverse cardiovascular events in type 2 diabetes: SURPASS-CVOT design and baseline characteristics. American Heart Journal, v. 267, p. 1–11, 2023.

VÍTOLO, M. R.; BARATTO, P. S.; DERAM, S. Public health risks of approving drugs for the treatment of childhood obesity in Brazil. Cadernos de Saúde Pública, v. 40, n. 9, e00031624, 2024. DOI: 10.1590/0102-311XEN031624.

WORLD HEALTH ORGANIZATION. Obesity and overweight. WHO Fact Sheets, 2025. Disponível em: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Acesso em: 15 jul. 2026.

Acknowledgments

The authors thank the University of Passo Fundo (UPF) and the AFYA Pato Branco University Center for the institutional support provided for this study.