USE OF DUAL AND TRIPLE INCRETIN AGONISTS (TIRZEPATIDE AND RETATRUTIDE) IN THE TREATMENT OF OBESITY AND TYPE 2 DIABETES MELLITUS

USO DOS AGONISTAS DUPLOS E TRIPLOS DE INCRETINAS (TIRZEPATIDA E RETATRUTIDA) NO TRATAMENTO DA OBESIDADE E DIABETES TIPO 2

USO DE AGONISTAS DE INCRETINA DOBLES Y TRIPLES (TIRZEPATIDA Y RETARTIDA) EN EL TRATAMIENTO DE LA OBESIDAD Y LA DIABETES TIPO 2

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ABSTRACT

Obesity and type 2 diabetes mellitus (T2DM) represent major global public health challenges, requiring more effective and integrated therapeutic strategies. In this context, dual and triple incretin agonists have emerged as innovative approaches by targeting multiple metabolic pathways simultaneously. This study aimed to provide a critical and comparative analysis of tirzepatide and retatrutide in the treatment of obesity and T2DM, based on recent scientific evidence. This narrative critical-analytical review was conducted through a structured search in PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Cochrane Library, including studies published between 2016 and 2025. A total of 20 studies were included, comprising clinical trials, systematic reviews, meta-analyses, and narrative reviews. The findings indicate that tirzepatide demonstrates well-established efficacy in glycemic control and weight reduction, whereas retatrutide shows greater potential for weight loss, likely related to increased energy expenditure mediated by glucagon receptor activation. However, this apparent superiority is accompanied by a higher incidence of adverse events and limited long-term evidence. The lack of direct head-to-head clinical trials and methodological heterogeneity across studies limit definitive conclusions regarding their comparative effectiveness. Therefore, although dual and triple incretin agonists represent a significant advancement in the management of obesity and T2DM, further long-term and head-to-head comparative studies are required to define their role in clinical practice.

Keywords: Obesity. Type 2 Diabetes Mellitus. Tirzepatide. Retatrutide. Incretin Agonists.

RESUMO

A obesidade e o diabetes mellitus tipo 2 (DM2) constituem importantes desafios de saúde pública global, demandando abordagens terapêuticas mais eficazes e integradas. Nesse contexto, os agonistas duplos e triplos de incretinas emergem como estratégias inovadoras ao atuarem simultaneamente em múltiplas vias metabólicas. O presente estudo teve como objetivo realizar uma análise crítica e comparativa do uso da tirzepatida e da retatrutida no tratamento da obesidade e do DM2, com base em evidências científicas recentes. Trata-se de uma revisão narrativa de caráter crítico-analítico, conduzida por meio de busca estruturada nas bases PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect e Cochrane Library, contemplando estudos publicados entre 2016 e 2025. Foram incluídos 20 estudos, entre ensaios clínicos, revisões sistemáticas, meta-análises e revisões narrativas. Os resultados indicam que a tirzepatida apresenta eficácia consolidada no controle glicêmico e na redução de peso corporal, enquanto a retatrutida demonstra maior potencial para perda ponderal, possivelmente relacionado ao aumento do gasto energético mediado pela ativação do receptor de glucagon. Entretanto, essa aparente superioridade ocorre em paralelo a maior incidência de eventos adversos e à limitada disponibilidade de evidências de longo prazo. A ausência de estudos comparativos diretos e a heterogeneidade metodológica dificultam a definição do posicionamento ideal dessas terapias. Conclui-se que, embora representem um avanço significativo, os agonistas duplos e triplos de incretinas ainda demandam estudos

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adicionais, especialmente de longo prazo e com comparação direta, para consolidação de seu papel na prática clínica.

Palavras-chave: Obesidade. Diabetes Mellitus Tipo 2. Tirzepatida. Retatrutida. Incretinas.

RESUMEN

La obesidad y la diabetes mellitus tipo 2 (DM2) constituyen importantes desafíos para la salud pública mundial, que exigen enfoques terapéuticos más eficaces e integrados. En este contexto, los agonistas de incretinas duales y triples emergen como estrategias innovadoras al actuar simultáneamente sobre múltiples vías metabólicas. Este estudio tuvo como objetivo realizar un análisis crítico y comparativo del uso de tirrizepatida y retatrutida en el tratamiento de la obesidad y la DM2, con base en la evidencia científica reciente. Se trata de una revisión narrativa crítico-analítica, realizada mediante una búsqueda estructurada en las bases de datos PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect y Cochrane Library, que abarca estudios publicados entre 2016 y 2025. Se incluyeron veinte estudios, entre ellos ensayos clínicos, revisiones sistemáticas, metaanálisis y revisiones narrativas. Los resultados indican que la tirzepatida tiene una eficacia consolidada en el control glucémico y la reducción del peso corporal, mientras que la retatrutida demuestra un mayor potencial para la pérdida de peso, posiblemente relacionado con un mayor gasto energético mediado por la activación del receptor de glucagón. Sin embargo, esta aparente superioridad se acompaña de una mayor incidencia de efectos adversos y una disponibilidad limitada de evidencia a largo plazo. La ausencia de estudios comparativos directos y la heterogeneidad metodológica dificultan la definición del posicionamiento ideal de estas terapias. Se concluye que, si bien representan un avance significativo, los agonistas de incretinas duales y triples aún requieren más estudios, especialmente estudios a largo plazo con comparación directa, para consolidar su papel en la práctica clínica.

Palabras clave: Obesidad. Diabetes Mellitus Tipo 2. Tirzepatida. Retatrutida. Incretinas.

1 INTRODUCTION

Obesity and type 2 diabetes mellitus (DM2) are multifactorial chronic conditions whose increasing prevalence imposes substantial challenges to health systems, not only because of their epidemiological magnitude, but also because of the complexity of their pathophysiological mechanisms and the limitation of conventional therapeutic strategies to promote sustained metabolic control. The interdependence between insulin resistance, β cell dysfunction, and neuroendocrine changes in appetite reinforces the need for therapeutic approaches that transcend single targets, since traditional interventions often have limited efficacy and low long-term adherence (ULLAH; TAMANNA, 2025; CARUSO et al., 2024).

In this context, incretin-based therapies have emerged as a relevant advance by integrating glycemic regulation and weight control in the same physiological axis. However, although GLP-1 receptor agonists have partially redefined the clinical management of these conditions, accumulating evidence suggests that modulation of this pathway alone may not be sufficient to achieve optimal metabolic outcomes in a significant portion of patients. This limitation has driven the development of multimodal agonists, whose purpose lies in the simultaneous activation of different hormone receptors, with a potential synergistic effect on multiple metabolic axes (BAILEY; FLATT; CONLON, 2024; GOGINENI et al., 2024).

The introduction of double incretin agonists, particularly tirzepatide, represents a milestone in this paradigm by combining the activation of GLP-1 and GIP receptors. Although the clinical results indicate superiority in glycemic parameters and weight reduction compared to conventional therapies, it remains to be debated whether such benefits reflect a qualitative advance in the modulation of the disease or just a quantitative intensification of already known effects. In addition, the heterogeneity of clinical responses and the need for continuous treatment raise questions about the sustainability of these effects in the real world (LEMPESIS; LIU; DALAMAGA, 2022; GALLWITZ, 2022; THIRIVEEDI et al., 2025).

The evolution to triple agonists, such as retatrutide, further amplifies this complexity by incorporating glucagon receptor activation, associated with increased energy expenditure and potential intensification of weight loss. Although initial data suggest superior efficacy, especially in obesity-related outcomes, this advantage occurs in parallel with a still-consolidating safety profile and an increase in the incidence of adverse events. Thus, the comparison between double and triple agonists is not restricted to the magnitude of the effects, but involves a critical analysis of the balance between efficacy, safety, and clinical applicability, especially considering the absence of robust long-term data and the limitation of direct comparative studies (GOLDNEY et al., 2025; FERNANDEZ; LAKSHMI; PAPPACHAN, 2025; SINHA; GHOSAL, 2025).

In addition, issues related to the cost, access, and feasibility of incorporating these therapies into health systems remain relevant barriers, particularly in resource-limited contexts. The current literature, although promising, still lacks consensus regarding the optimal positioning of these drugs in therapeutic algorithms, as well as on their sustained effects on harsh clinical outcomes, such as mortality and macrovascular complications. Thus, the incorporation of these technologies should be interpreted with caution, avoiding premature extrapolations of results obtained in controlled clinical trials (YAN; YU; BLAISE, 2025; MELSON et al., 2024).

In view of this scenario, the present study aims to carry out a critical and comparative analysis of the use of double and triple incretin agonists, with emphasis on tirzepatide and retatrutide, evaluating their impacts on the treatment of obesity and DM2 in the light of the available scientific evidence, as well as discussing their limitations, controversies and implications for contemporary clinical practice.

2 METHODOLOGY

This is a **critical-analytical narrative review**, with a qualitative approach, aimed at the synthesis and comparative analysis of the available evidence on the use of double and triple incretin agonists, with emphasis on tirzepatide and retatrutide, in the treatment of obesity and type 2 diabetes mellitus (DM2).

The bibliographic search was carried out in the **PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect and Cochrane Library databases**, covering publications in the period from **2016 to 2025**. Controlled descriptors and free terms combined by Boolean operators were used, including: *"tirzepatide", "retatrutide*", *"dual incretin agonist", "triple incretin agonist", "GLP-1/GIP receptor agonist", "obesity"* and *"type 2 diabetes".* The strategy was complemented by a manual search in the reference lists of the selected studies.

Original studies, randomized controlled trials, systematic reviews, meta-analyses, and narrative reviews published in peer-reviewed journals addressing the clinical, metabolic, and safety effects of tirzepatide and/or retatrutide were included. Duplicate studies, publications outside the established period, articles without access to full text or reliable abstract, and those without direct relationship to the topic were excluded. Abstracts of congresses were considered in a complementary way.

At the end of the selection process, **20 studies** were included for analysis, most of which were narrative and systematic reviews, as well as meta-analyses and clinical trials relevant to the topic. The selection of studies was carried out through sequential screening of available titles, abstracts, and full texts.

The included articles were analyzed in terms of design, population characteristics, interventions, clinical outcomes (glycemic control, weight loss, and cardiometabolic parameters), and safety profile. Data synthesis was conducted descriptively, with emphasis on the comparison between double and triple incretin agonists.

The analysis considered the heterogeneity of the designs, populations, and outcomes evaluated, as well as the limited availability of direct comparative studies and long-term data. These aspects were incorporated into the interpretation of the findings, with a focus on the consistency and applicability of the evidence.

3 RESULTS AND DISCUSSION

The analysis of the included studies shows that incretin agonists represent a significant advance in the management of obesity and type 2 diabetes mellitus (DM2), although the magnitude and nature of these benefits vary according to the pharmacological profile of the therapies. In this context, tirzepatide, as a dual agonist of GLP-1 and GIP receptors, demonstrates consistent efficacy in reducing glycated hemoglobin (HbA1c), often higher than 2%, consolidating itself as one of the most potent pharmacological interventions for glycemic control currently available (LEMPESIS; LIU; DALAMAGA, 2022; THIRIVEEDI et al., 2025). This performance is reiterated in meta-analyses, in which tirzepatide is superior to GLP-1 agonists alone and other antidiabetic therapies, suggesting that the simultaneous modulation of multiple incretinal pathways may amplify traditional metabolic effects (YAN; YU; BLAISE, 2025; SINHA; GHOSAL, 2025). However, although retatrutide also promotes relevant glycemic improvement, the available data indicate that its differential does not lie primarily in this outcome, but rather in its broader metabolic action, which limits direct comparisons based exclusively on glycemic parameters and suggests a possible dissociation between glycemic control and other metabolic effects (GOLDNEY et al., 2025; FERNANDEZ; LAKSHMI; PAPPACHAN, 2025).

This distinction becomes even more evident when analyzing weight loss, a central aspect in the contemporary approach to obesity. Tirzepatide promotes significant weight reductions, often greater than 15–20%, approaching results observed in bariatric interventions in certain clinical settings (MELSON et al., 2024; MADSBAD; HOLST, 2025). However, the introduction of retatrutide, with its additional action on the glucagon receptor, seems to further enhance this effect, with initial studies showing losses of more than 20%, possibly related to increased energy expenditure in addition to appetite suppression (GOLDNEY et al., 2025; SINHA; GHOSAL, 2025). Still, this apparent superiority of triple agonists should be interpreted with caution, since the data derive mostly from short-term

studies and highly selected populations, which raises doubts about the sustainability of the effects and their reproduction in real clinical practice scenarios.

The comparison between tirzepatide and retatrutide, therefore, transcends the isolated analysis of specific outcomes and requires an integrated assessment between efficacy and safety. While tirzepatide has a more consolidated profile, with well-documented benefits in both glycemic control and weight reduction, retatrutide emerges as a potentially more potent strategy, but still accompanied by greater clinical uncertainty (GALLWITZ, 2022; ZAFFINA et al., 2023; WINKLER et al., 2023). This difference is also reflected in the profile of adverse events, since, although both therapies share predominantly gastrointestinal side effects, evidence suggests a higher frequency of these events with retatrutide, possibly due to the simultaneous activation of multiple hormonal pathways (BAILEY; FLATT; CONLON, 2024; GOGINENI et al., 2024; SINHA; GHOSAL, 2025; FERNANDEZ; LAKSHMI; PAPPACHAN, 2025). This aspect reinforces the need to weigh incremental efficacy and tolerability, especially considering that therapeutic adherence is a critical determinant of success in the treatment of chronic conditions.

In addition, the absence of randomized controlled trials with direct comparison between double and triple agonists limits the ability to establish unequivocal superiority between these approaches. Although indirect analyses suggest greater weight reduction with retatrutide and robust glycemic performance with tirzepatide, these inferences remain conditioned by methodological limitations, including heterogeneity of studies, differences in the populations evaluated, and variability in the outcomes considered (YAN; YU; BLAISE, 2025; SALHAB et al., 2025). In this scenario, the expansion of the therapeutic arsenal does not necessarily translate into clarity in clinical decision-making, but rather into greater complexity in the individualization of treatment.

This scenario is even more challenging when considering factors extrinsic to pharmacological efficacy, such as cost, access, and large-scale applicability. Studies highlight that, despite the significant metabolic benefits, the incorporation of these therapies may be limited by economic and structural barriers, particularly in health systems with restricted resources (CARUSO et al., 2024; ULLAH; TAMANNA, 2025). In addition, the scarcity of long-term data on relevant clinical outcomes, such as mortality and major cardiovascular events, prevents definitive conclusions about the real impact of these interventions on the natural history of the disease (YAN; YU; BLAISE, 2025; MELSON et al., 2024).

Thus, although double and triple incret agonists represent a significant evolution in the treatment of obesity and DM2, the current literature still does not support a clear

consensus regarding the ideal positioning of these therapies. Tirzepatide is a more consolidated and predictable option, while retatrutide appears as a promising alternative, but still dependent on more robust evidence to validate its clinical superiority. Thus, the contemporary scenario is characterized less by a replacement of therapeutic paradigms and more by an expansion of possibilities, whose effective application will depend on future evidence that clarifies its real comparative advantages and limitations.

4 CONCLUSION

Double and triple incretin agonists represent a relevant advance in the treatment of obesity and type 2 diabetes mellitus, by promoting integrated metabolic effects that include both glycemic control and weight reduction. Tirzepatide, as a representative of dual agonists, presents more consolidated evidence, with consistent efficacy and a relatively well-established safety profile, positioning itself as a robust therapeutic option in current clinical practice. On the other hand, retatrutide, as a triple agonist, demonstrates superior potential, especially with regard to the magnitude of weight loss, although it is still associated with greater uncertainty regarding its safety and long-term applicability.

The comparative analysis between these therapies shows that the apparent superiority of triple agonists does not translate, so far, into clinical consensus, since the incremental benefits observed occur in parallel with important limitations, including a higher incidence of adverse events, scarcity of long-term data, and absence of clinical trials with direct comparison. In this context, the choice between double and triple agonists should be guided by an individualized evaluation, considering not only efficacy, but also factors such as tolerability, patient profile, and feasibility of continuous use.

In addition, aspects related to cost, access, and sustainability of treatment emerge as critical elements for the incorporation of these therapies in different health systems. The current literature, although consistent in terms of metabolic benefits, still does not allow us to clearly establish the impact of these interventions on more relevant clinical outcomes, such as mortality and cardiovascular complications, which limits the definition of their definitive role in therapeutic algorithms.

Thus, multimodal incretin agonists should be understood as part of an expanding therapeutic scenario, in which the increase in available options does not necessarily imply an immediate replacement of existing approaches, but rather greater complexity in clinical decision-making. Future studies, especially direct comparative clinical trials and long-term investigations, will be key to elucidate the relative advantages between double and triple

agonists and consolidate their position in the treatment of obesity and type 2 diabetes mellitus.

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