

USE OF GLP-1 RECEPTOR AGONIST “WEIGHT-LOSS PENS” AND PANCREATIC COMPLICATIONS: IMPLICATIONS FOR CLINICAL PRACTICE

USO DE AGONISTAS DO RECEPTOR DE GLP-1 (“CANETAS PARA PERDA DE PESO”) E COMPLICAÇÕES PANCREÁTICAS: IMPLICAÇÕES PARA A PRÁTICA CLÍNICA

USO DE AGONISTAS DEL RECEPTOR DE GLP-1 («PLUMAS PARA PERDER PESO») Y COMPLICACIONES PANCREÁTICAS: IMPLICACIONES PARA LA PRÁCTICA CLÍNICA

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ABSTRACT

The use of glucagon-like peptide-1 (GLP-1) receptor agonists, popularly known as “weight-loss pens,” has expanded significantly in the treatment of obesity, establishing itself as one of the leading therapeutic innovations in contemporary medicine, in line with the growing recognition of obesity as a chronic, complex, and multifactorial disease. These drugs offer substantial benefits in reducing body weight, improving glycemic control, and positively affecting cardiovascular outcomes, which has driven their expanding use beyond classic indications, including off-label and aesthetic contexts. However, concerns have arisen regarding their safety, particularly the possible development of pancreatic complications, such as acute pancreatitis, reported in clinical trials, pharmacovigilance analyses, and observational studies. This study aimed to analyze, through a narrative literature review, the available evidence on the association between GLP-1 receptor agonist use for weight loss and pancreatic complications, discussing implications for clinical practice. Searches were conducted in PubMed/MEDLINE, Scopus, and Web of Science, using combined descriptors, including articles published in the last ten years in English, Portuguese, and Spanish. The results confirm consistent efficacy of these medications in weight reduction and cardiometabolic outcomes, but reveal heterogeneity regarding pancreatitis risk: while pharmacovigilance databases and case series identify safety signals warranting clinical vigilance, propensity score-matched analyses and large cohorts do not confirm a consistent increase in risk. Proposed pathophysiological mechanisms, including altered incretin signaling and exocrine pancreatic effects, remain insufficiently elucidated amid confounding factors such as obesity and diabetes, which independently raise pancreatitis risk. It is concluded that, although no definitive consensus exists, a cautious clinical approach, based on individualized risk assessment, continuous monitoring, and rational use of these therapies, is essential to ensure patient safety.

Keywords: GLP-1 Receptor Agonists. Obesity. Pancreatitis. Patient Safety.

RESUMO

O uso de agonistas do receptor de peptídeo semelhante ao glucagon-1 (GLP-1), popularmente conhecidos como "canetas para perda de peso", expandiu-se significativamente no tratamento da obesidade, consolidando-se como uma das principais inovações terapêuticas da medicina contemporânea, em consonância com o crescente reconhecimento da obesidade como uma doença crônica, complexa e multifatorial. Esses fármacos oferecem benefícios substanciais na redução do peso corporal, na melhora do controle glicêmico e em desfechos cardiovasculares, o que impulsionou sua utilização para além das indicações clássicas, abrangendo contextos *off-label* e estéticos. No entanto, surgiram preocupações quanto à sua segurança, particularmente em relação ao possível desenvolvimento de complicações pancreáticas, como a pancreatite aguda, relatadas em ensaios clínicos, análises de farmacovigilância e estudos observacionais. Este estudo teve como objetivo analisar, por meio de uma revisão narrativa da literatura, as evidências disponíveis sobre a associação entre o uso de agonistas do receptor de GLP-1 para perda de peso e complicações pancreáticas, discutindo as implicações para a prática clínica. Foram realizadas buscas nas bases PubMed/MEDLINE, Scopus e Web of Science, utilizando descritores combinados e incluindo artigos publicados nos últimos dez anos em inglês, português e espanhol. Os resultados confirmam a eficácia consistente desses medicamentos na redução de peso e em desfechos cardiometabólicos, mas revelam heterogeneidade quanto ao risco de pancreatite: enquanto bancos de dados de farmacovigilância e séries de casos identificam sinais de segurança

que justificam vigilância clínica, análises pareadas por escore de propensão e grandes coortes não confirmam um aumento consistente do risco. Os mecanismos fisiopatológicos propostos, incluindo a alteração na sinalização de incretinas e efeitos no pâncreas exócrino, permanecem insuficientemente esclarecidos em meio a fatores de confusão como obesidade e diabetes, que, por si sós, elevam o risco de pancreatite. Conclui-se que, embora não exista um consenso definitivo, uma abordagem clínica cautelosa — baseada na avaliação individualizada de risco, no monitoramento contínuo e no uso racional dessas terapias — é essencial para garantir a segurança do paciente.

Palavras-chave: Agonistas do Receptor de GLP-1. Obesidade. Pancreatite. Segurança do Paciente.

RESUMEN

El uso de agonistas del receptor del péptido similar al glucagón tipo 1 (GLP-1), conocidos popularmente como «plumas para perder peso», se ha expandido significativamente en el tratamiento de la obesidad, consolidándose como una de las principales innovaciones terapéuticas de la medicina contemporánea, en consonancia con el creciente reconocimiento de la obesidad como una enfermedad crónica, compleja y multifactorial. Estos fármacos ofrecen beneficios sustanciales en la reducción del peso corporal, la mejora del control glucémico y los resultados cardiovasculares, lo que ha impulsado su uso más allá de las indicaciones clásicas, abarcando contextos de uso fuera de indicación (*off-label*) y estéticos. Sin embargo, han surgido preocupaciones sobre su seguridad, particularmente respecto al posible desarrollo de complicaciones pancreáticas, como la pancreatitis aguda, reportadas en ensayos clínicos, análisis de farmacovigilancia y estudios observacionales. Este estudio tuvo como objetivo analizar, mediante una revisión narrativa de la literatura, la evidencia disponible sobre la asociación entre el uso de agonistas del receptor de GLP-1 para la pérdida de peso y las complicaciones pancreáticas, discutiendo sus implicaciones para la práctica clínica. Se realizaron búsquedas en PubMed/MEDLINE, Scopus y Web of Science utilizando descriptores combinados, e incluyendo artículos publicados en los últimos diez años en inglés, portugués y español. Los resultados confirman una eficacia consistente de estos medicamentos en la reducción de peso y en los resultados cardiometabólicos, pero revelan heterogeneidad respecto al riesgo de pancreatitis: mientras que las bases de datos de farmacovigilancia y las series de casos identifican señales de seguridad que justifican la vigilancia clínica, los análisis emparejados por puntuación de propensión y las grandes cohortes no confirman un aumento consistente del riesgo. Los mecanismos fisiopatológicos propuestos, que incluyen la alteración de la señalización de las incretinas y los efectos sobre el páncreas exocrino, aún no se han esclarecido suficientemente debido a factores de confusión como la obesidad y la diabetes, que aumentan el riesgo de pancreatitis de forma independiente. Se concluye que, aunque no existe un consenso definitivo, resulta esencial adoptar un enfoque clínico cauteloso —basado en la evaluación individualizada del riesgo, el monitoreo continuo y el uso racional de estas terapias— para garantizar la seguridad del paciente.

Palabras clave: Agonistas del receptor de GLP-1. Obesidad. Pancreatitis. Seguridad del Paciente.



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INTRODUCTION

The use of injectable weight-loss medications, popularly known as “weight-loss pens,” has expanded markedly in recent years, driven by advances in clinical evidence and by the growing centrality of GLP-1 receptor agonists in the treatment of obesity and metabolic disorders. Drugs of this class, initially developed and incorporated into the management of type 2 diabetes mellitus, have progressively come to occupy a relevant place in obesity treatment, in line with the contemporary understanding of this condition as a chronic, complex, and multifactorial disease, rather than merely the result of isolated behavioral choices (Rubino *et al.*, 2025; Moiz *et al.*, 2025).

In this context, drugs such as semaglutide and liraglutide have demonstrated significant efficacy in weight reduction, acting through appetite modulation, increased satiety, delayed gastric emptying, and improvement of metabolic parameters related to glycemic homeostasis. Recent clinical trials and systematic reviews show not only sustained weight loss but also relevant cardiometabolic benefits, including in populations with overweight or obesity and increased cardiovascular risk. However, the expanding use of these drugs beyond their classic indications, including in off-label contexts and for aesthetic purposes, has reignited discussions about the safety, monitoring, and rational use of these therapies (Wilding *et al.*, 2021; Lincoff *et al.*, 2023; Liu, 2024; Aldawsari *et al.*, 2023; Al-Qaaneh *et al.*, 2025).

Pancreatic complications associated with the use of these drugs, particularly acute pancreatitis, have been reported in clinical studies, pharmacovigilance analyses, and observational investigations, although the causal relationship remains controversial. The most recent literature reflects precisely this scenario of interpretive tension: on the one hand, case series and signals from pharmacovigilance databases support ongoing clinical vigilance; on the other, propensity score-matched analyses and large cohorts do not confirm a consistent increase in risk across all populations studied. From a pathophysiological standpoint, the hypotheses discussed include alterations in incretin signaling, effects on the entero-insular axis, and possible repercussions on inflammatory and exocrine pancreatic pathways, which reinforces the need for a critical and individualized reading of the available evidence (Guo *et al.*, 2024; Ayoub *et al.*, 2025; Ilias *et al.*, 2025; Liu, 2024).

Given this scenario, it becomes essential to understand the potential risks associated with the use of the so-called weight-loss pens, particularly regarding their pancreatic repercussions

and their implications for the safe clinical management of patients. The growing demand for these medications, coupled with the expansion of their use in different care and non-care settings, requires health professionals to adopt a critical stance grounded in evidence and guided by careful assessment of the risk-benefit ratio. Thus, this study aims to analyze, through a narrative literature review, the available evidence on the use of these drugs and their association with pancreatic complications, discussing their implications for contemporary clinical practice.

METHOD

This is a narrative literature review of a qualitative, descriptive-analytical nature, which sought to synthesize and critically interpret the scientific evidence related to the use of GLP-1 receptor agonists and their possible associations with pancreatic complications. This methodological approach makes it possible to integrate different types of studies, including clinical trials, observational studies, and case reports, providing a comprehensive and contextualized view of the phenomenon under investigation. It also favors a critical discussion of the findings in light of clinical practice.

The search was conducted in the PubMed/MEDLINE, Scopus, and Web of Science databases, using descriptors combined through Boolean operators, such as: “GLP-1 receptor agonists,” “semaglutide,” “liraglutide,” “weight loss drugs,” “pancreatitis,” and “pancreatic complications.” Articles published in the last 10 years, in English, Portuguese, and Spanish, were included, with priority given to studies of clinical and methodological relevance. Duplicate studies, editorials, letters to the editor, and articles that did not directly address the proposed theme were excluded. The guiding question, structured according to the PICO strategy, was: “What is the available evidence on the association between the use of GLP-1 agonists for weight loss and the development of pancreatic complications?”

RESULTS

The analysis of the included studies showed that GLP-1 receptor agonists have consistent efficacy in reducing body weight, with an additional positive impact on glycemic control and relevant cardiovascular outcomes. Randomized clinical trials demonstrate significant reductions in body mass index, in addition to improvements in metabolic markers such as glycated

hemoglobin and lipid profile (Wilding *et al.*, 2021; Lincoff *et al.*, 2023). These findings consolidate the role of these drugs as one of the main therapeutic innovations in the treatment of obesity and its associated comorbidities, also impacting major cardiovascular outcomes (Moiz *et al.*, 2025; Collins *et al.*, 2024). Furthermore, improvements in patient-reported quality of life and greater treatment adherence are observed when compared to exclusively behavioral interventions, which reinforces their relevance in contemporary clinical practice (Wilding *et al.*, 2021).

On the other hand, part of the literature points to a possible association between the use of these medications and an increased risk of acute pancreatitis, although the findings are heterogeneous and, at times, conflicting (Wen *et al.*, 2025; Ayoub *et al.*, 2025). While some studies suggest a slight increase in risk, others find no statistically significant difference when compared to control groups, or even suggest the absence of a consistent association (Masson *et al.*, 2024; Ayoub *et al.*, 2025). Case reports and analyses of pharmacovigilance databases also describe episodes of pancreatitis in patients using semaglutide and liraglutide, highlighting the importance of clinical monitoring and active surveillance, especially in higher-risk populations (Guo *et al.*, 2024; Nature, 2026). Additionally, some studies suggest that the duration of drug exposure may influence the emergence of these events, particularly during the initial periods of treatment, although this association still lacks robust confirmation (Springer, 2025).

Given this scenario, the main findings of the analyzed studies were systematized in Table 1, which comparatively summarizes the evidence related to the clinical efficacy of GLP-1 agonists and the potential pancreatic risks associated with their use. The table allows visualization of the heterogeneity of the results, highlighting methodological differences, study populations, and outcomes analyzed, contributing to a more integrated and critical understanding of the available literature.

Table 1. Main findings of the studies included in the narrative review on GLP-1 receptor agonists and pancreatic complications

Author/Year	Study design / Type of evidence	Main focus	Principal findings	Clinical implications
Wilding <i>et al.</i> (2021)	Randomized clinical trial	Once-weekly semaglutide in adults with overweight or obesity	Demonstrated significant and sustained weight loss, with favorable effects on metabolic parameters and patient-reported outcomes.	Reinforces the effectiveness of GLP-1 receptor agonists as an important therapeutic strategy for obesity management.
Lincoff <i>et al.</i> (2023)	Randomized clinical trial	Cardiovascular outcomes of semaglutide in obesity without diabetes	Reported reduction in major cardiovascular events in individuals with obesity, supporting benefits beyond weight reduction alone.	Suggests that GLP-1 receptor agonists may offer cardiometabolic protection in selected patients.
Moiz <i>et al.</i>	Narrative review	Expanding role of	Highlighted the growing	Supports the view that these

(2025)		GLP-1 receptor agonists	relevance of GLP-1 receptor agonists in obesity treatment, emphasizing efficacy, metabolic benefits, and emerging clinical applications.	drugs have reshaped contemporary obesity management.
Collins et al. (2024)	General clinical review	Pharmacological profile of GLP-1 receptor agonists	Summarized mechanisms of action, therapeutic indications, and beneficial effects on glycemic control and weight reduction.	Provides a broad clinical basis for the safe and evidence-based use of this drug class.
Wen et al. (2025)	Systematic review and meta-analysis	Risk of pancreatitis associated with GLP-1 receptor agonists	Identified heterogeneous findings regarding pancreatitis risk, with no definitive consensus across studies.	Indicates the need for cautious interpretation and individualized clinical assessment.
Ayoub et al. (2025)	Propensity score-matched observational study	Pancreatitis risk in a comorbidity-free subgroup with type 2 diabetes	Did not confirm a consistent increase in pancreatitis risk among GLP-1 receptor agonist users in the analyzed subgroup.	Suggests that the association may be influenced by baseline comorbidities and confounding factors.
Masson et al. (2024)	Updated meta-analysis	Semaglutide and acute pancreatitis risk	Reported no statistically robust evidence of a consistent increase in acute pancreatitis risk.	Supports a cautious but not alarmist clinical interpretation of pancreatic safety concerns.
Guo et al. (2024)	Pharmacovigilance analysis and case series	Acute pancreatitis reports associated with different GLP-1 receptor agonists	Identified reported cases of acute pancreatitis in real-world databases, highlighting safety signals that deserve monitoring.	Reinforces the importance of pharmacovigilance and clinical surveillance, especially in higher-risk individuals.
Nature (2026)	Scientific news analysis / commentary	Severe complications potentially associated with obesity drugs	Discussed emerging concerns regarding serious adverse events, including pancreatic complications, in the context of expanding drug use.	Highlights the growing public health relevance of safety monitoring as use becomes more widespread.
Springer (2025)	Observational clinical study	Pancreatic events and mortality associated with GLP-1 receptor agonists	Suggested that pancreatic events may vary according to exposure time and patient profile, although evidence remains inconclusive.	Points to the importance of longitudinal follow-up and risk stratification during treatment.

Source: Prepared by the authors (2026), based on the studies included in the narrative review.

DISCUSSION

The growing use of GLP-1 receptor agonists in the management of obesity represents a paradigmatic shift in contemporary clinical practice, offering an effective, relatively safe alternative with broad metabolic benefits. Recent reviews highlight that this therapeutic class has transformed obesity treatment by combining substantial weight loss with relevant cardiometabolic gains, even expanding interest in other conditions associated with metabolic risk (Moiz *et al.*, 2025; Kunutsor; Seidu, 2025). However, this therapeutic expansion also imposes new challenges, particularly regarding long-term safety and the rational use of these medications. Critical analysis of potential adverse effects becomes essential in a scenario of increasing medicalization of obesity (Moiz *et al.*, 2025; Kunutsor; Seidu, 2025).

Pathophysiological Mechanisms and Biological Plausibility of Pancreatic Complications

The possible relationship between GLP-1 agonists and pancreatitis has been the subject of intense scientific investigation, with different hypotheses proposed to explain this association. From a pathophysiological standpoint, safety reviews and pharmacovigilance analyses indicate that uncertainty remains regarding the exact mechanism, although possible effects on the exocrine pancreas, incretin signaling, and modulation of local inflammatory pathways are discussed, especially in metabolically vulnerable individuals (Smits; Van Raalte, 2021; Guo *et al.*, 2024). These hypotheses remain relevant above all because the occurrence of severe pancreatic events, although uncommon, continues to be closely monitored in observational studies and pharmacovigilance databases (Smits; Van Raalte, 2021; Guo *et al.*, 2024).

In addition, experimental studies and safety reviews suggest that earlier concerns involved possible structural pancreatic changes and effects on the exocrine compartment, although evidence in humans remains limited and inconclusive. In this regard, authors emphasize that definitive conclusions about pancreatic safety are still hindered by the low incidence of events, methodological heterogeneity among studies, and limited comparability between experimental models and real clinical contexts (Smits; Van Raalte, 2021; Moiz *et al.*, 2025). Thus, the direct extrapolation of experimental findings to clinical practice should be undertaken with caution (Smits; Van Raalte, 2021).

It is important to emphasize that conditions frequently associated with the use of these medications, such as obesity and type 2 diabetes mellitus, are themselves independent or risk-amplifying factors for pancreatic outcomes. A meta-analysis of cohort studies showed an increased risk of acute pancreatitis among individuals with diabetes, while recent reviews on the obesity-pancreas axis reinforce that obesity aggravates systemic inflammation, peripancreatic lipolysis, and pancreatic injury, acting as a relevant confounding element in the interpretation of events observed during GLP-1 use (Aune; Vatten, 2020; Zacharia *et al.*, 2025). This aspect makes it difficult to distinguish between direct causality and indirect association, reinforcing the need for more robust studies that adequately control for confounding variables and allow more definitive conclusions (Aune; Vatten, 2020; Zacharia *et al.*, 2025).

Clinical Implications, Safety, and Rational use in Medical Practice

From a clinical standpoint, the prescription of weight-loss pens should be based on rigorous criteria, including a detailed assessment of the patient’s profile, presence of comorbidities, and clinical history, especially regarding prior pancreatic disease. Recent guidelines and narrative reviews emphasize that appropriate patient selection and risk stratification are fundamental steps for the safe use of GLP-1 agonists (Davies *et al.*, 2022; Kunutsor; Seidu, 2025). Individualized therapy is essential to maximize benefits and minimize risks, ensuring a patient-centered approach. In addition, institutional protocols can help standardize prescribing and follow-up for these individuals. Shared decision-making with the patient should also be encouraged as a strategy for adherence and safety, especially in long-term therapies (Davies *et al.*, 2022).

Early identification of signs and symptoms suggestive of pancreatitis, such as persistent abdominal pain, nausea, vomiting, and elevated pancreatic enzymes, is essential for the immediate discontinuation of the medication and the initiation of appropriate treatment. Clinical guidelines for the management of acute pancreatitis emphasize the importance of early recognition and discontinuation of potential triggering agents (Tenner *et al.*, 2013; Boxhoorn *et al.*, 2020). In this regard, continuous clinical follow-up and patient education are indispensable components of care. The implementation of periodic laboratory monitoring strategies can contribute to the early detection of subclinical changes. Furthermore, multiprofessional collaboration strengthens the safe management of these cases, especially in scenarios of greater clinical complexity (Boxhoorn *et al.*, 2020).

Additionally, the growing trivialization of the use of these drugs for aesthetic purposes, often without professional supervision, represents a significant public health problem. Recent studies point to a significant increase in the off-label use of GLP-1 agonists, driven by social media and the pursuit of rapid aesthetic results, often dissociated from appropriate clinical indication (Al-Qaaneh *et al.*, 2025; Ilias; Zabuliene; Rizzo, 2025). Self-medication and indiscriminate use significantly increase the risk of adverse events, reinforcing the need for regulation, health education, and ethical conduct on the part of professionals. Educational campaigns and public policies can play a fundamental role in raising public awareness. In this context, professional responsibility plays a central role in curbing inappropriate use and promoting the rational use of these therapies (Ilias; Zabuliene; Rizzo, 2025).

FINAL CONSIDERATIONS

The use of weight-loss pens represents a significant advance in the treatment of obesity, offering relevant clinical benefits and contributing to the management of a highly prevalent condition with global impact. However, the possibility of pancreatic complications, although not yet fully clarified, requires heightened attention from health professionals.

The analysis of the available evidence suggests that, although warning signs exist in the literature, there is no definitive consensus on the increased risk of pancreatitis associated with the use of these drugs. This uncertainty reinforces the importance of conducting further studies with more robust methodological designs and long-term follow-up.

Thus, it is incumbent upon health professionals to adopt a critical, ethical, and evidence-based stance, promoting the rational use of these therapies and ensuring patient safety as the central axis of clinical practice. The incorporation of these technologies must be accompanied by active surveillance and a commitment to quality of care.

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