ASSOCIATION BETWEEN GLP-1 ANALOGUES AND PANCREATITIS: AN INTEGRATIVE REVIEW OF CURRENT EVIDENCE

ASSOCIAÇÃO ENTRE ANÁLOGOS DE GLP-1 E PANCREATITE: REVISÃO INTEGRATIVA DAS EVIDÊNCIAS ATUAIS

ASOCIACIÓN ENTRE ANÁLOGOS DE GLP-1 Y PANCREATITIS: UNA REVISIÓN INTEGRAL DE LA EVIDENCIA ACTUAL

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) receptor agonists have been widely used in the treatment of Type 2 Diabetes Mellitus and obesity due to their effectiveness in glycemic control and weight reduction. However, concerns regarding their pancreatic safety, particularly the risk of acute pancreatitis, have been raised in the scientific literature. This study aimed to analyze the association between the use of GLP-1 analogues and the occurrence of pancreatitis through an integrative literature review. The search was conducted in PubMed/MEDLINE, SciELO, and LILACS, including studies published between 2016 and 2026. Original articles, observational studies, systematic reviews, meta-analyses, and clinical guidelines available in full text were included. The results demonstrated that GLP-1 analogues have a well-established efficacy profile; however, findings regarding pancreatitis risk are heterogeneous. Observational studies suggest a possible association, whereas systematic reviews do not demonstrate a statistically significant increase in risk, indicating a low absolute risk and no definitive causal relationship. It is concluded that, although a direct causal association cannot be established, caution is recommended when prescribing these drugs, especially in patients with risk factors, and further studies are needed to better clarify this potential relationship.

Keywords: GLP-1. Acute Pancreatitis. Type 2 Diabetes Mellitus. Obesity. Drug Safety.

RESUMO

Os análogos do GLP-1 têm sido amplamente utilizados no tratamento do Diabetes Mellitus tipo 2 e da obesidade, em virtude de sua eficácia no controle glicêmico e na redução do peso corporal. Entretanto, questionamentos acerca de sua segurança pancreática, especialmente quanto ao risco de pancreatite aguda, têm sido levantados na literatura científica. O presente estudo teve como objetivo analisar a associação entre o uso de análogos do GLP-1 e a ocorrência de pancreatite, por meio de uma revisão integrativa da literatura. A busca foi realizada nas bases de dados PubMed/MEDLINE, SciELO e LILACS, incluindo estudos publicados entre 2016 e 2026. Foram incluídos artigos originais, estudos observacionais, revisões sistemáticas, metanálises e diretrizes clínicas disponíveis na íntegra. Os resultados evidenciaram que os análogos do GLP-1 apresentam perfil de eficácia consolidado; contudo, os achados referentes ao risco de pancreatite mostram-se heterogêneos. Estudos observacionais sugerem possível associação, enquanto revisões sistemáticas não demonstram aumento estatisticamente significativo do risco, indicando baixo risco absoluto e ausência de relação causal definida. Conclui-se que, embora não seja possível estabelecer associação causal direta, recomenda-se cautela na prescrição, especialmente em pacientes com fatores de risco, sendo necessários estudos adicionais para melhor elucidação dessa possível relação.

Palavras-chave: GLP-1. Pancreatite Aguda. Diabetes Mellitus Tipo 2. Obesidade. Segurança Medicamentosa.

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RESUMEN
Los análogos del GLP-1 se han utilizado ampliamente en el tratamiento de la diabetes mellitus tipo 2 y la obesidad debido a su eficacia en el control glucémico y la reducción del peso corporal. Sin embargo, en la literatura científica se han planteado dudas sobre su seguridad pancreática, especialmente en lo que respecta al riesgo de pancreatitis aguda. Este estudio tuvo como objetivo analizar la asociación entre el uso de análogos del GLP-1 y la aparición de pancreatitis mediante una revisión integradora de la literatura. La búsqueda se realizó en las bases de datos PubMed/MEDLINE, SciELO y LILACS, incluyendo estudios publicados entre 2016 y 2026. Se incluyeron artículos originales, estudios observacionales, revisiones sistemáticas, metaanálisis y guías clínicas disponibles en su totalidad. Los resultados mostraron que los análogos del GLP-1 tienen un perfil de eficacia consolidado; sin embargo, los hallazgos sobre el riesgo de pancreatitis son heterogéneos. Los estudios observacionales sugieren una posible asociación, mientras que las revisiones sistemáticas no demuestran un aumento estadísticamente significativo del riesgo, lo que indica un riesgo absoluto bajo y la ausencia de una relación causal definida. Se concluye que, si bien no es posible establecer una relación causal directa, se recomienda precaución en la prescripción, especialmente en pacientes con factores de riesgo, y se necesitan más estudios para dilucidar mejor esta posible relación.

Palabras clave: GLP-1. Pancreatitis Aguda. Diabetes Mellitus Tipo 2. Obesidad. Seguridad Farmacológica.

1 INTRODUCTION

Type 2 diabetes mellitus (DM2) and obesity are important global public health problems, associated with high morbidity and mortality and substantial socioeconomic impacts. These conditions share complex pathophysiological mechanisms, including insulin resistance, chronic low-grade inflammation, and systemic metabolic dysfunctions, which reinforces the need for more effective, integrated, and multi-axis therapeutic approaches (VOGT et al., 2025; CHRIST et al., 2025).

In this scenario, recent advances in metabolic pharmacotherapy have boosted the use of drugs based on glucagon-like peptide type 1 (GLP-1), especially its receptor agonists (GLP-1RA), which demonstrate high efficacy in glycemic control and body weight reduction (STAICO et al., 2023; PACHECO et al., 2025). These agents act by modulating the incretin axis, promoting glucose-dependent insulin secretion, glucagon suppression, delayed gastric emptying, and increased satiety, contributing significantly to the management of T2DM and obesity (BARROS et al., 2021; LIMA MACIEL et al., 2026). In addition, evidence from clinical studies and cardiovascular outcome analyses indicate additional benefits, especially in reducing major cardiovascular events, increasing its therapeutic relevance (VOGT et al., 2025).

However, the rapid expansion of the clinical use of GLP-1 receptor agonists, including molecules such as semaglutide and liraglutide, has been accompanied by growing questions about their safety profile, particularly with regard to pancreatic adverse events (MAGALHÃES et al., 2025). Acute pancreatitis, an inflammatory condition of the pancreas with variable clinical presentation, can progress from mild and self-limiting forms to severe conditions, associated with organ dysfunction and increased mortality (MATOS et al., 2025).

From the pathophysiological point of view, it has been hypothesized that GLP-1 agonists may influence pancreatic dynamics through stimulation of ductal and acinar cells, in addition to possible effects on cell proliferation and the inflammatory microenvironment, although such mechanisms remain controversial and not fully elucidated in the current literature. At the same time, classical etiological factors, such as gallstones, alcoholism, and metabolic disorders, continue to be the main determinants of pancreatitis, which complicates the causal attribution to drug use.

In this context, the possible association between GLP-1 receptor agonists and pancreatitis has been extensively investigated through observational studies, pharmacovigilance databases, and systematic reviews. However, the findings remain inconsistent, reflecting methodological heterogeneity, the presence of confounding biases, and limitations inherent to the designs used (SILVA et al., 2024; FONSECA et al., 2024).

Although some studies suggest increased risk, more robust analyses indicate that the absolute risk of pancreatitis associated with these agents is low, and it is not possible to establish a definitive causal relationship to date (FONSECA et al., 2024).

In addition, it should be considered that individuals with DM2 and obesity have an increased baseline risk for pancreatic diseases, which represents an important confounding factor and makes it difficult to interpret the available findings (INDIANI et al., 2025). Such a scenario highlights the need for critical analysis of the evidence, with attention to methodological limitations and the clinical applicability of the results.

Given this scenario, there is a gap in the consolidation of the available evidence, especially with regard to the magnitude of the risk, the consistency of the findings, and the pathophysiological mechanisms potentially involved. Thus, the present study aims to analyze, through an integrative review of the literature, the association between the use of GLP-1 receptor agonists and the occurrence of pancreatitis, seeking to critically synthesize the most recent evidence and contribute to a more robust evaluation of the safety of these drugs in clinical practice.

2 METHODOLOGY

The present study is characterized as an integrative literature review, with a qualitative and descriptive approach, conducted according to the steps proposed by Whittemore and Knafl (2005), which include: identification of the problem, search in the literature, evaluation of data, analysis and synthesis of results.

The search was carried out in the PubMed/MEDLINE, SciELO and LILACS databases, including studies published in the period from 2016 to 2026. Controlled and uncontrolled descriptors in English and Portuguese were used, based on the terms MeSH (Medical Subject Headings) and DeCS (Health Sciences Descriptors), including: "GLP-1 receptor agonists", "GLP-1 analogs", "pancreatitis", "acute pancreatitis", "diabetes mellitus type 2" and "obesity", as well as their counterparts in Portuguese.

The search strategy was structured using Boolean operators (AND and OR), according to the following model: ("GLP-1 receptor agonists" OR "GLP-1 analogs") AND ("pancreatitis" OR "acute pancreatitis") AND ("diabetes mellitus type 2" OR "obesity"), adapted according to the specificities of each database.

The following inclusion criteria were established: original articles, randomized clinical trials, observational studies, systematic reviews, meta-analyses, and clinical guidelines that directly addressed the association between GLP-1 analogues and pancreatitis; studies published in the delimited period; and articles available in full. Duplicate studies, isolated

case reports, studies with low methodological rigor, and those that did not have a direct relationship with the research objective were excluded.

The selection of studies was carried out in stages, including reading of titles, abstracts and, subsequently, full texts, according to the previously defined eligibility criteria. After this stage, the selected studies were read in full to extract the relevant data.

The data were organized and analyzed in a descriptive manner, and were later grouped into thematic categories, according to the convergence of the findings, including: metabolic efficacy, weight reduction, safety profile, and association with pancreatitis. This process allowed the comparison between the studies and the identification of patterns, divergences, and gaps in the literature.

Finally, the synthesis of the data was carried out in a critical and integrative manner, enabling the construction of a comprehensive analysis of the available evidence, with emphasis on the safety and risk of pancreatitis associated with the use of GLP-1 receptor agonists, contributing to evidence-based clinical practice.

3 RESULTS

The search in the databases resulted in the identification of relevant studies on the association between GLP-1 receptor agonists and the occurrence of acute pancreatitis. After applying the eligibility criteria, publications were included between 2016 and 2026, covering different methodological designs, including observational studies, systematic reviews, and pharmacovigilance analyses.

In general, studies have shown that GLP-1 receptor agonists are associated with improved glycemic control in individuals with type 2 diabetes mellitus, with a consistent reduction in glycated hemoglobin levels, a finding observed recurrently in different study designs (VOGT et al., 2025).

In the context of body weight, evidence indicated an association between the use of GLP-1 analogues and weight reduction in overweight and obese individuals. Studies have attributed this effect to appetite modulation and delayed gastric emptying, resulting in increased satiety and reduced caloric intake (LIMA MACIEL et al., 2026). Additionally, sustained weight loss over time has been described, as well as improvement in metabolic parameters, including insulin resistance and lipid profile (RAMOS et al., 2024; SANT'ANA, 2023). Among the most frequently reported drugs, semaglutide and liraglutide stood out, consistently associated with the metabolic outcomes described (STAICO et al., 2023).

Regarding the safety profile, studies have reported that the adverse effects most frequently associated with the use of GLP-1 receptor agonists are gastrointestinal in nature,

including nausea, vomiting, and abdominal discomfort, especially in the early stages of treatment (LACERDA LEOPOLDINO et al., 2025). In addition, comparative studies have described favorable effects on cardiovascular outcomes in patients with associated comorbidities (MAGALHÃES et al., 2025).

Regarding the occurrence of pancreatitis, observational studies and pharmacovigilance analyses have reported cases in patients using GLP-1 receptor agonists, particularly among individuals with previous risk factors, such as obesity and metabolic disorders (SILVA et al., 2024). Reviews involving specific drugs, such as semaglutide, have also described the occurrence of pancreatitis, without establishing a direct causal relationship (LEITE et al., 2024).

On the other hand, systematic reviews indicated the absence of a statistically significant increase in the risk of pancreatitis associated with the use of these drugs, with a description of low absolute risk in the studies analyzed (FONSECA et al., 2024). Similar findings have been reported in other investigations, which have highlighted the inconsistency of the results and the methodological heterogeneity among the available studies (MATOS et al., 2025).

Additionally, it has been described that individuals with type 2 diabetes mellitus and obesity have an increased baseline risk for pancreatic diseases, and this factor is pointed out as a potential confounding variable in the analysis of the association between the use of GLP-1 receptor agonists and the occurrence of pancreatitis (INDIANI et al., 2025). Finally, studies have highlighted the need for clinical monitoring during the use of these drugs, especially in the face of the occurrence of rare adverse events (CHRIST et al., 2025).

4 DISCUSSION

The analysis of the included studies shows that GLP-1 receptor agonists have consistent efficacy in the management of type 2 diabetes mellitus and obesity, with a significant impact on the reduction of glycemic levels and body weight. These findings were observed recurrently across different methodological designs, including observational studies and clinical trials, which reinforces the robustness of the available evidence (VOGT et al., 2025; LIMA MACIEL et al., 2026). Similarly, Ramos et al. (2024) and Sant'Ana (2023) describe sustained weight reduction, while Magalhães et al. (2025) report additional benefits in cardiovascular outcomes, expanding the spectrum of clinical applicability of these drugs.

Despite the well-established metabolic benefits, the pancreatic safety of GLP-1 receptor agonists remains a point of debate in the literature. Observational studies and data from pharmacovigilance, such as those presented by Silva et al. (2024), suggest a possible

association between the use of these drugs and the increased incidence of acute pancreatitis, especially in individuals with previous risk factors. Convergently, Leite et al. (2024) report cases of pancreatitis associated with the use of semaglutide, indicating the need for clinical monitoring.

On the other hand, evidence from systematic reviews and analyses with greater methodological rigor do not consistently corroborate this association. Fonseca et al. (2024) demonstrate the absence of a statistically significant increase in the risk of pancreatitis among users of GLP-1 analogues, while Matos et al. (2025) highlight that the current evidence is insufficient to establish a direct causal relationship. This contrast between the findings suggests the influence of methodological factors, including heterogeneity among studies, selection bias, and possible confounding *by indication phenomena*, in which the clinical condition that indicates the use of the drug may be associated with the outcome investigated.

In addition, individuals with type 2 diabetes mellitus and obesity have an increased baseline risk for pancreatic diseases, which can act as an important confounding variable and make it difficult to interpret the results (INDIANI et al., 2025). This aspect reinforces the need for caution in attributing causality, especially in observational studies.

From the pathophysiological point of view, it has been proposed that GLP-1 receptor agonists may influence pancreatic function through modulation of acinar and ductal cells, in addition to potential effects on the pancreatic inflammatory microenvironment. However, such mechanisms remain controversial and have not yet been fully elucidated, which limits the interpretation of the available clinical findings.

Regarding the global safety profile, Lacerda Leopoldino et al. (2025) highlight that the most frequent adverse effects are gastrointestinal in nature, while pancreatic events are considered rare. In consonance, Christ et al. (2025) point out that, in the general context, these drugs have a favorable safety profile, particularly when considering their metabolic benefits.

Another relevant aspect refers to the growing incorporation of these drugs in clinical practice. Staico et al. (2023) and Pacheco et al. (2025) highlight the wide use of agents such as semaglutide and liraglutide, which may contribute to greater detection of rare adverse events in post-marketing studies, influencing the perception of risk associated with these drugs.

Thus, it is observed that the literature presents conflicting results regarding the association between GLP-1 receptor agonists and pancreatitis. While some studies suggest a possible increase in risk, more robust evidence does not consistently confirm this

relationship. In this context, the available findings indicate that the risk of pancreatitis associated with these drugs remains low, although it cannot be completely ruled out.

Thus, the interpretation of the data should consider the methodological limitations of the studies, as well as the clinical characteristics of the populations evaluated. Overall, current evidence suggests that the benefit-risk profile of GLP-1 receptor agonists is favorable in most clinical settings, provided their use is accompanied by adequate monitoring and therapeutic individualization.

5 CONCLUSION

GLP-1 analogues have been consolidated as an important therapeutic strategy in the management of type 2 diabetes mellitus and obesity, demonstrating consistent efficacy in glycemic control and body weight reduction, in addition to additional metabolic benefits widely described in the literature. These factors have contributed to its increasing incorporation into clinical practice.

However, the possible association with acute pancreatitis remains a controversial topic. Although observational studies and clinical reports suggest a possible increased risk, evidence from systematic reviews and meta-analyses does not demonstrate a consistent causal association, indicating that the absolute risk described is low.

In this context, the available findings suggest that the benefit-risk profile of GLP-1 analogues is globally favorable in most clinical scenarios, provided that their use is carried out in a judicious and individualized manner. Caution is advised in patients with a prior history of pancreatitis or with multiple predisposing factors, in whom the indication should be carefully evaluated.

Finally, the need for additional studies with greater methodological rigor and long-term follow-up is highlighted, in order to elucidate more definitively the possible relationship between the use of these drugs and pancreatic events, contributing to a safer and evidence-based clinical practice.

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