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Review Article

Serious adverse effects on gastrointestinal tract associated with GLP-1 agonists available in Brazil: a literature review

Efeitos adversos graves no trato gastrointestinal associados aos agonistas de GLP-1 disponíveis no Brasil: uma revisão da literatura

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ABSTRACT: Objective: The present work proposes an overview of the serious adverse effects related to GLP-1 receptor agonists available in Brazil. **Methods:** To this end, a literature review was carried out, using the Pubmed database, bringing together the most current body of evidence on the association between GLP-1 agonists and the following topics: biliary diseases, gastroparesis and intestinal obstruction. **Results:** In total, 17 articles were consulted and addressed in the discussion. Side effects on the bile duct, stomach and intestine cannot be ruled out. **Conclusions:** Further studies are still needed to confirm the causal relationship between the facts.

KEYWORDS: Adverse Effects; Glucagon-like Peptide-1 Receptor Agonists; Biliary Tract; Gastrointestinal Tract.

RESUMO: Objetivo: O presente trabalho propõe uma visão geral acerca dos efeitos adversos graves relacionados aos agonistas do receptor de GLP-1 disponíveis no Brasil. **Métodos:** Para tanto, foi feita uma revisão da literatura no idioma inglês, através do banco de dados Pubmed, reunindo o corpo de evidências mais atual sobre a associação entre os agonistas de GLP-1 e os seguintes temas: doenças biliares, gastroparesia e obstrução intestinal. **Resultados:** Ao todo, 17 artigos foram consultados e abordados na discussão. Não estão descartados efeitos colaterais na via biliar, no estômago e no intestino. **Conclusões:** Ainda são necessários novos estudos que confirmem a relação causal entre os fatos, sendo as evidências atuais insuficientes para mitigar as dúvidas.

PALAVRAS-CHAVE: Efeitos Adversos; Agonistas do Receptor de Peptídeo-1 Semelhante a Glucagon; Trato Biliar; Trato Gastrointestinal.

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INTRODUCTION

Since their launch in the early 2000s, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become one of the leading drug classes for the treatment of Type 2 Diabetes Mellitus (T2DM) and obesity. Several studies have shown that their benefits go beyond glycemic control and weight loss, with well-established positive cardiovascular effects, including reduced cardiovascular mortality, fatal and non-fatal myocardial infarctions, and strokes[1–4]. After being recommended as the first-line treatment for diabetes in patients with known atherosclerotic disease or high cardiovascular risk[5], drugs such as Liraglutide, Dulaglutide, and Semaglutide—the GLP-1 RAs currently available in Brazil—gained prominence and became increasingly prescribed by clinicians worldwide.

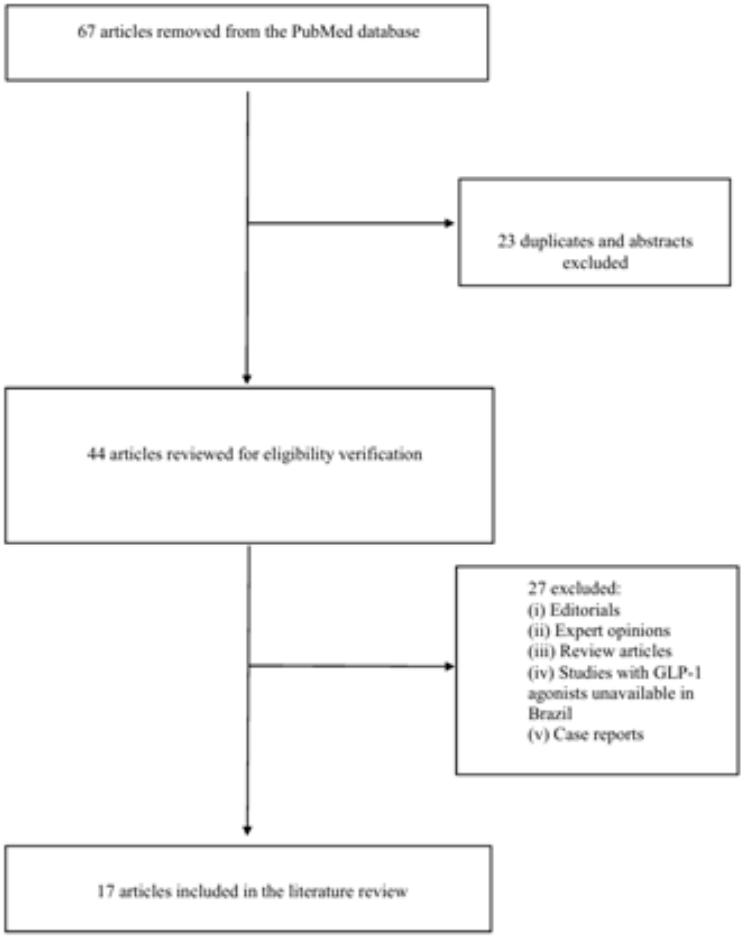
With this growing popularity, the adverse reactions associated with this drug class have become more evident. Although initial clinical trials reported milder side effects, such as nausea and vomiting[6], concerns about more severe adverse reactions grew over time. After Elashoff et al. published a study suggesting a possible association between these drugs and thyroid and pancreatic disorders, including neoplasms[7], several subsequent studies sought to clarify the actual severe side effects attributable to GLP-1 receptor agonists—such as gastrointestinal complications—in order to better understand their real safety profile, clinical applicability, and contraindications in specific contexts.

Therefore, the objective of this literature review is to compile the existing scientific evidence on the severe adverse effects associated with GLP-1 receptor agonists, aiming to assess the current understanding of these effects and determine which of them, in light of the latest evidence, should guide clinical decision-making regarding the use of these drugs.

METHODS

The articles used in this review were retrieved from the PubMed database using the following keywords: “Gallbladder Diseases” OR “Intestinal Obstruction” OR “Gastroparesis” OR “Gastrointestinal Contents” AND “Glucagon-like Peptide-1 Receptor Agonists.” The selection process continued until mid-January 2024. Initially, 67 English-language articles were found without any date restrictions. However, after a careful review of titles and abstracts, 50 articles were excluded, including duplicates. Studies focusing strictly on GLP-1 receptor agonists that are not available in Brazil, as well as editorials, expert opinions, review articles, and case reports, were excluded—although their reference lists were reviewed, and relevant articles were appropriately included in the review.

FIGURE 1 – Flowchart of Study Selection



RESULTS

Biliary Tract

Our literature review highlights eleven studies addressing biliary tract alterations associated with GLP-1 receptor agonists as an adverse event, with nine of them showing a positive association[8–16], while the remaining two found no such correlation[17–18].

TABLE 1 – Results of Selected Studies for Review on the Biliary Tract

Biliary Tract		
Reference	**Study Design**	**Comments**
Monami et al, 2017 [8]	Systematic Review	Systematic review and meta-analysis with 113 RCTs and a total of 59,850 type 2 diabetes (T2D) patients. There was an increased risk of cholelithiasis with GLP-1 RA compared to placebo and active comparators (MH-OR 1.3, 95% CI 1.01 - 1.68, I(2) < 0.001, p = 0.041).
Pizzimenti et al, 2016 [9]	Pharmacovigilance Study	Pharmacovigilance study with 200 cases of acute cholecystitis possibly related to incretin-based therapy in the EudraVigilance database since the drug approval date in the European Union.
Woronow et al, 2022[10]	Pharmacovigilance Study	Pharmacovigilance study with 36 cases of acute cholecystitis possibly related to GLP-1 RA in the FAERS database between 2005 and 2021.
Faillie et al, 2016 [11]	Cohort	Cohort with 71,369 T2D patients followed for an average of 3.2 years. There was an increased risk of biliary duct and gallbladder diseases with GLP-1 RA compared to the use of two other oral antidiabetic agents (adjusted HR 1.79, 95% CI 1.21 - 2.67).
Abrahami et al, 2018 [12]	Cohort	Cohort with 154,162 T2D patients followed for a median of 4.6 years. There was a non-significant increase in cholangiocarcinoma with GLP-1 RA compared to other second- or third-line antidiabetic drugs (HR 1.97, 95% CI 0.83 - 4.66).
Dong et al, 2022 [13]	Cohort	National retrospective cohort with 78,253 T2D patients. There was an increased risk of biliary diseases (acute cholecystitis or cholecystectomy, choledocholithiasis, and acute cholangitis) with GLP-1 RA compared to iSGLT-2 in both on-treatment and intention-to-treat analyses for the composite outcome (HR 1.2, 95% CI 0.93 - 1.56 and HR 1.27, 95% CI 1.05 - 1.53, respectively).
Nauck et al, 2019 [14]	Post-hoc Analysis	Post-hoc analysis of the multinational LEADER RCT (9,340 patients in the intervention group and 4,672 in the placebo group followed for 3.5 to 5 years). There was an increased risk of biliary disease with liraglutide versus placebo (HR 1.6, 95% CI 1.23 - 2.09, p < 0.001).
He et al, 2022 [15]	Systematic Review	Systematic review and meta-analysis with 76 RCTs and a total of 103,371 patients using GLP-1 for T2D or weight loss. There was an increased risk of biliary disease (RR 1.37, 95% CI 1.23 - 1.52). The risk was increased with higher doses and longer durations of treatment (RR 1.56, 95% CI 1.36 - 1.78 and RR 1.4, 95% CI 1.26 - 1.56, respectively).
Nreu et al, 2020 [16]	Systematic Review	Systematic review and meta-analysis with 43 RCTs and a total of 74,846 patients followed for at least 52 weeks. There was an increased risk of cholelithiasis with GLP-1 RA compared to placebo and active comparators (MH-OR 1.28, 95% CI 1.11 - 1.48).
Sodhi et al, 2023 [17]	Cohort	Cohort with 5,411 patients undergoing treatment for weight loss. No significant increase in the risk of biliary disease (cholecystitis, cholelithiasis, and choledocholithiasis) with GLP-1 RA compared to Bupropion-Naltrexone (HR 1.5, 95% CI 0.89 - 2.53).
Ueda et al, 2021 [18]	Cohort	Scandinavian cohort with 585,876 patients (222,577 using iDPP-4, 96,813 using GLP-1 RA, and the rest using sulfonylurea). No significant increase in the risk of cholangiocarcinoma with GLP-1 RA compared to sulfonylurea (adjusted HR 1.25, 95% CI 0.89 - 1.76).

Stomach

In our review, a total of four studies investigated delayed gastric emptying as an adverse effect of GLP-1 receptor agonists. Among them, three reported a positive association[17,19–20], while only one found no significant increase in the risk of this event[21].

TABLE 2 - Results of the selected studies for the review on the stomach

Stomach		
Reference	**Study Design**	**Comments**
Sodhi et al, 2023 [17]	Cohort	Cohort with 5,411 patients undergoing weight-loss treatment. There was an increased risk of gastroparesis with GLP-1 RA compared to Bupropion-Naltrexone (HR 3.67, 95% CI 1.15 - 11.9).
Kobori et al, 2023 [19]	Case-Control	Case-control study with 1,128 T2DM patients who underwent esophagogastroduodenoscopy between 2020 and 2022. There was an increase in residual gastric content with GLP-1 RA after propensity score matching (5.4% vs. 0.49%, p = 0.004).
Silveira et al, 2023 [20]	Cohort	Cohort including 404 esophagogastroduodenoscopies (33 in the Semaglutide group and 371 in the non-Semaglutide group) performed between 2021 and 2022. There was an increase in residual gastric content with Semaglutide used for T2DM and weight loss (24.2% vs. 5.1%, p < 0.001).
Stark et al, 2022 [21]	Cohort	Cohort with 177 patients who underwent esophagogastroduodenoscopy (59 using GLP-1 and 118 in the control group). There was no significant increase in residual gastric content with GLP-1 RA (OR 4.22, 95% CI 0.87 - 20.34).

Intestine

In our review, four studies explored the risk of intestinal obstruction associated with GLP-1 receptor agonists. Three of them demonstrated a positive association[17,22–23], while one[24] failed to find any relationship between the drug and the investigated adverse event.

TABLE 3 - Results of Selected Studies for Review on the Intestine

Intestine		
Reference	**Study Design**	**Comments**
Sodhi et al, 2023 [17]	Cohort	Cohort study with 5,411 patients undergoing weight loss treatment. There was an increased risk of intestinal obstruction with GLP-1 RA for weight loss (HR 4.22, 95% CI 1.02 - 17.40).
Gudin et al, 2020 [22]	Pharmacovigilance Stud	Pharmacovigilance study with 452 cases of intestinal obstruction possibly related to incretin-based therapy in the VigiBase database between 2007 and 2018. Intestinal obstructions were more frequently reported with incretin-based therapy compared to other antidiabetic drugs (ROR 4.52, 95% CI 3.87 - 5.28).
Faillie et al, 2022 [23]	Cohort	Cohort study with 25,617 new users of GLP-1 RA and 67,261 new users of SGLT2 inhibitors. There was an increased risk of intestinal obstruction with GLP-1 RA compared to SGLT-2 inhibitors (HR 1.69, 95% CI 1.04 - 2.74).
Ueda et al, 2023 [24]	Cohort	Scandinavian cohort study with 121,254 new users of GLP-1 RA compared to 185,027. There was no increased risk of intestinal obstruction with GLP-1 RA compared to SGLT-2 inhibitors (HR 0.83, 95% CI 0.69 - 1.01).

DISCUSSION

This literature review highlights potential complications associated with the use of GLP-1 receptor agonists available in Brazil. There appears to be an increased risk of biliary disease, gastroparesis, increased gastric contents during esophagogastroduodenoscopy, and intestinal obstruction among GLP-1 RA users. The following paragraphs discuss the findings in detail.

Biliary Tract

In 2006, a group of researchers discovered that the epithelial cells of the biliary system in rats express GLP-1 receptors[25]. Moreover, they found that this receptor is functionally active, participating in cholangiocyte proliferation while also protecting these cells from apoptosis[26]. This discovery raised concerns within the scientific community about whether incretin-based therapies could be implicated in biliary and gallbladder diseases. Growing reports from adverse event databases further fueled this concern[9–10].

Subsequent studies indicated that these concerns were indeed justified. The results of later meta-analyses[15–16] provide

sufficient warning that the overall risk of biliary events may be increased with GLP-1 RAs. However, not all biliary diseases seem to be associated with this drug class. Notably, a multinational cohort study concluded that GLP-1 RAs do not increase the risk of cholangiocarcinoma[18], suggesting that, to date, there is no evidence of an elevated risk for this highly lethal neoplasm.

The studies reviewed here are also valuable in helping to elucidate the pathophysiological mechanisms behind this association. It is well known that significant weight loss, by supersaturating bile cholesterol, increases the risk of gallstones, and for some time, this was considered the primary explanation for the association. However, studies have shown that this is not the full picture. A post-hoc analysis of the LEADER trial demonstrated that adjusting for baseline body weight and weight change only slightly attenuated the effect of liraglutide on the risk of gallbladder- or biliary tract-related events[14]. Additionally, in their discussion, the authors pointed out that in the "Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes" (SUSTAIN-6) trial, despite greater weight loss compared to LEADER, there was no difference between semaglutide and placebo regarding biliary disorders.

Beyond weight changes, another hypothesis is that gallbladder motility—and consequently, bile emptying—may play a role in GLP-1 RA-induced cholelithiasis. An experimental study demonstrated that GLP-1 inhibits the secretion of cholecystokinin (CCK), a hormone closely related to bile secretion[27]. Contrary to this finding, two randomized, double-blind, placebo-controlled studies found no changes in gallbladder emptying in patients treated with liraglutide for T2DM[28] or for overweight and obesity[29].

Just as the pathogenesis remains unclear, the implications of GLP-1 receptor agonists on the biliary tract are not yet fully understood. Based on the presented studies, particularly that of He et al.[15], clinicians should be attentive to adverse events involving the gallbladder and biliary tract, especially following significant weight loss, prolonged treatment duration, and high dosages.

Stomach

The impact of the incretin system on gastric emptying is closely linked to the role of GLP-1 receptor agonists as antidiabetic drugs[30]. Although some recent studies suggest that this mechanism may be less critical in reducing postprandial glucose levels with long-acting GLP-1 RAs[31]—and even some evidence indicates that the magnitude of delayed gastric emptying may decrease with prolonged receptor stimulation[32–33]—gastric stasis still appears to directly influence the safety and tolerability of these drugs. In clinical practice, there has been an increasing number of case reports linking treatment with these medications to gastroparesis[34] and aspiration of gastric contents during general anesthesia[35–37].

One of the key strengths of the studies included in this review is the use of more reliable methods for evaluating gastrointestinal emptying. Previously published studies that reported no delay in gastric emptying[38] or a delay limited to the first hour[39–40] often relied on tests with limited practical utility, such as the acetaminophen absorption test. In contrast, the three studies referenced here[19–21], which utilized esophagogastroduodenoscopy (EGD), provide stronger evidence and allow for a better correlation with a severe clinical outcome—namely, the risk of gastric content aspiration.

Despite the growing evidence suggesting a potential adverse effect of GLP-1 RAs on stomach motility, it is essential to acknowledge possible confounding factors. For example, Kobori et al.[19], using a population of exclusively diabetic patients, admitted that despite matching groups by glycated hemoglobin levels, critical information such as a prior diagnosis of diabetic neuropathy was not available.

Additionally, Sodhi et al.[17] presented a cohort study evaluating gastroparesis as an adverse event, confirming that the risks associated with gastric stasis are not limited to surgical settings.

Given the limited number of studies supporting this association and the potentially severe nature of pulmonary aspiration, it is reasonable to conclude that prescribing physicians should advise suspending GLP-1 receptor agonists for at least one week before elective surgical procedures, in line with recent recommendations from the American Society of Anesthesiologists (ASA)[41]. Furthermore, healthcare professionals should encourage patients to report any gastrointestinal side effects, such as nausea, vomiting, bloating, and abdominal pain, during anesthesia assessment and preoperative preparation, as these symptoms may indicate an additional risk.

Intestine

The effects of GLP-1 receptor agonists on the gastrointestinal tract are well known and extend beyond their inhibitory effect on gastric emptying. Previous studies have shown reduced intestinal motility with liraglutide, increasing the amount of gastrointestinal residue observed via capsule endoscopy[42]. Given this, it is biologically plausible that GLP-1 receptor agonists could be implicated in cases of intestinal obstruction.

Currently, the evidence remains insufficient to determine the exact role of GLP-1 RAs in this risk. The conflicting results from two large cohort studies[23–24] make it difficult to provide a definitive answer. However, these discrepancies may be explained by factors such as study size and different additional risk factors. For example, in the cohort by Faillie et al.[23], the authors found an increased risk when patients were also using other medications that affect intestinal motility, including antidepressants, antipsychotics, iron supplements, opioids, diuretics, calcium channel blockers, 5-HT3 antagonists, and aluminum-containing antacids, with this finding approaching statistical significance.

For now, while awaiting further research, it would be prudent to avoid combining medications that may have a synergistic effect leading to intestinal obstruction.

CONCLUSIONS

Given the above, it is reasonable to conclude that our

understanding of the potentially severe side effects of GLP-1 receptor agonists remains limited. This may be partly due to the unknown actions of incretin hormones on various organs. Nevertheless, this study attempts to explore, through a critical analysis of the current body of evidence, what is known about these adverse effects on the gastrointestinal tract.

A limitation of our study is the difficulty in evaluating individual drugs within this class separately, as it is now recognized that the tolerability and safety of specific GLP-1 RAs vary based on their molecular structure. However, we believe these details do not significantly impact the quality of our analysis.

For now, the benefits of GLP-1 RAs seem to outweigh their risks for most patients. It is important to emphasize that the adverse events discussed here are not definitively proven, and even if later confirmed, they remain uncommon. The number of studies is still insufficient to completely resolve these uncertainties. However, the growing number of users presents an opportunity for the development of randomized clinical trials aimed at addressing each of the concerns raised in this article.

We encourage physicians to closely monitor their patients and periodically reassess the efficacy, tolerability, and safety of GLP-1 receptor agonists, particularly when prescribed for weight loss, as the risk-benefit ratio may differ from that of patients using them for diabetes.

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