International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
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ARTICLE TITLE	GLP-1 RECEPTOR AGONISTS AND THE RISK OF CHOLELITHIASIS: A LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.1(49).2026.5421
RECEIVED	15 February 2026
ACCEPTED	21 March 2026
PUBLISHED	27 March 2026
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GLP-1 RECEPTOR AGONISTS AND THE RISK OF CHOLELITHIASIS: A LITERATURE REVIEW

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ABSTRACT

Background: Gallstone disease is a chronic condition characterized by the formation of calculi within the biliary tract. It represents a common health issue, particularly among obese populations or those with type 2 diabetes. An increasing number of clinical evidence suggests a potential association between an elevated risk of gallstone development and the chronic use of GLP-1 receptor agonists.
Objective: The aim of this study was to analyze the impact of GLP-1 receptor agonist therapy on the risk of biliary complications, with particular emphasis on gallstone disease. Selected clinical studies and meta-analyses were reviewed, and the mechanisms of gallstone formation, as well as their clinical implications for patient management and therapy selection, were evaluated.
Methods: We analyzed the effects of GLP-1 receptor agonists on gallstone development, gallbladder function, gastrointestinal hormonal regulation, and the impact of rapid weight loss, based on widely available randomized clinical trials and meta-analyses.
Results: GLP-1 receptor agonists are associated with an increased risk of gallstone formation, primarily due to the promotion of rapid weight loss, as well as their effects on gastrointestinal hormonal regulation and gallbladder function, particularly in obese individuals and those with type 2 diabetes.
Conclusions: Chronic therapy with GLP-1 receptor agonists constitutes a risk factor for the development of gallstone disease. However, further long-term clinical studies in larger populations are needed to clarify the underlying mechanisms of this association.

KEYWORDS

Gallstone Disease, Obesity, GLP-1 Receptor Agonists, Liraglutide, Semaglutide, Type 2 Diabetes

CITATION

Julia Pająk, Anna Kamosińska, Antoni Majda, Natalia Sitko, Paulina Makowska, Joanna Gontarczyk, Alicja Laske, Martyna Sowa, Kacper Kucharski, Adam Kowal, Julia Sokołowska, Marcel Dawidowicz. (2026) GLP-1 Receptor Agonists and the Risk of Cholelithiasis: A Literature Review. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.5421

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) represent a modern class of incretin-based therapies consisting of synthetic peptide analogues. They mimic the effects of the endogenous gastrointestinal hormone glucagon-like peptide-1 (GLP-1) [1], which is physiologically secreted by intestinal endocrine cells in response to nutrient intake [2].

The therapeutic effects of GLP-1 receptor agonists include an insulinotropic effect, characterized by increased glucose-dependent insulin secretion. Additionally, these agents suppress glucagon secretion, delay gastric emptying, and reduce food intake through central nervous system mechanisms [3, 4]. The diverse effects of GLP-1 receptor agonists promote weight reduction, making them valuable therapeutic options in the pharmacological management of type 2 diabetes, obesity, dyslipidemia, and metabolic disorders [1, 5].

Despite their well-documented therapeutic effects, the use of GLP-1RAs is also associated with potential adverse effects. Studies indicate, among other things, an increased risk of gallbladder and biliary tract disorders, including cholelithiasis [6]. The mechanisms underlying this phenomenon include effects on gallbladder motility and gastrointestinal hormone regulation, particularly through modulation of cholecystokinin secretion. Such effects promote bile stasis, facilitating the formation of biliary deposits. Additionally, rapid weight loss induced by GLP-1 receptor agonist therapy may lead to cholesterol supersaturation of bile, thereby increasing the risk of gallstone formation [7, 8]. The precise relative risk of developing gallstone-related disorders associated with GLP-1 receptor agonist use remains unclear.

This review aims to summarize the current literature regarding the relationship between GLP-1 receptor agonist therapy and gallstone risk, focusing specifically on pathophysiological mechanisms, predisposing factors, and clinical data.

Pathogenesis of Gallstone Disease

Gallstone disease is one of the most common gastrointestinal disorders, representing a significant public health concern in developed countries [9, 10]. The global prevalence of this disease is estimated at 6% of the adult population, with higher rates observed in women and in South America [10]. In high-income countries, it affects 10–15% of the adult Caucasian population, while in the United States, 10–20% of adults are affected [11]. Additionally, up to 80% of individuals with gallstones remain asymptomatic, with the condition often detected incidentally during abdominal ultrasonography performed for unrelated pathologies or during screening examinations [12]. In recent years, the prevalence of gallstone disease has also increased in the pediatric population, currently ranging from 1.9% to 4%. This rise may be related to the growing prevalence of childhood obesity and more widespread use of ultrasonographic examinations [13].

Mechanisms of Gallstone Formation

Gallstone disease is characterized by the formation of calculi, most commonly located in the gallbladder, and less frequently in the intrahepatic or extrahepatic bile ducts [13]. Gallstones are classified according to their predominant constituent into cholesterol, pigment, and mixed types, with cholesterol stones being the most common [14]. The formation of cholesterol gallstones is a complex, multistep process. A key element in their pathogenesis is an imbalance among the main constituents of bile, including cholesterol, bile acids, and phospholipids. Excessive secretion of cholesterol into bile or a relative deficiency of bile acids leads to the formation of lithogenic bile, which promotes crystallization. The process begins with cholesterol supersaturation of bile, followed by crystallization and deposition of cholesterol monohydrate, which forms the initial nidus for cholesterol gallstone formation. In subsequent stages, these structures aggregate and gradually enlarge, eventually accumulating in the gallbladder as gallstones [14].

An important factor contributing to gallstone formation is impaired gallbladder motility. Reduced contractility leads to bile stasis, prolonging the contact time of its constituents and thereby promoting cholesterol crystallization and aggregation of the forming crystals [12, 15, 16]. Regular and adequate gallbladder emptying is considered an important mechanism for preventing excessive bile accumulation and, consequently, gallstone formation [12]. Additionally, nucleating factors present in bile play a significant role in gallstone formation. Among these, mucins - high-molecular-weight glycoproteins secreted by the epithelium of the gallbladder and bile ducts - form a viscous gel that acts as a matrix, facilitating local cholesterol accumulation, initiating crystallization, and promoting the gradual growth and enlargement of developing gallstones [17].

Major Risk Factors

The development of gallstone disease also depends on predisposing factors that increase susceptibility to gallstone formation. In addition to molecular mechanisms, disease progression is influenced by important metabolic, hormonal, and genetic factors.

Obesity, particularly abdominal obesity, promotes excessive cholesterol secretion into bile, leading to bile supersaturation and increased susceptibility to gallstone formation. This occurs through elevated plasma insulin levels (hyperinsulinemia), which stimulate the activity of HMG-CoA reductase, the enzyme responsible for cholesterol synthesis. As a result, the liver secretes excessive amounts of cholesterol into bile. Additionally, excess adipose tissue is associated with impaired gallbladder contractility, further increasing the risk of bile stasis. [18]

Women are at higher risk of gallstone disease than men, reflecting the influence of sex hormones on lipid metabolism and gallbladder motility. Hormonal risk factors primarily include the lithogenic effects of estrogens. Population-based epidemiological studies have shown that the use of hormone replacement therapy, as well as other forms of estrogen exposure, is associated with a statistically increased risk of gallstone development [19, 20].

Additionally, gallstone disease has a significant genetic component, with its prevalence varying according to ethnic background and population. A study by Goodloe R. et al. demonstrated that polymorphisms in lipid-related genes are associated with gallstone risk, with the ABCG5 rs6756629 variant being significantly correlated with an increased risk in certain populations [21]. Analyses of geographic and ethnic differences indicate that the prevalence of gallstone disease varies, with particularly high rates observed among Native Americans and populations of European descent, and lower rates reported in African and Asian populations [22]. Furthermore, family studies have shown that the presence of gallstone disease in first-degree relatives

significantly increases the likelihood of its occurrence, further highlighting the role of genetic factors in the disease's etiology [23].

The risk of developing gallstone disease increases with age, particularly after the age of 40-50 years, which may result from the cumulative effects of metabolic and hormonal factors, as well as prolonged exposure to environmental influences. Additional risk modifiers include rapid weight loss, a diet high in saturated fats, pregnancy, and disorders affecting fat absorption, all of which may further contribute to gallstone formation [22, 24].

Mechanism of Action of GLP-1 Receptor Agonists on the Biliary Tract

Gallbladder diseases, including gallstone disease, represent a significant health concern, particularly in individuals with obesity and type 2 diabetes [22]. These patients often present with risk factors for gallbladder disease, such as insulin resistance, dyslipidemia, and metabolic disorders, which predispose to abnormal bile composition and an increased risk of gallstone formation [25].

According to U.S. clinical practice guidelines for obesity, the Food and Drug Administration (FDA) has approved several pharmacotherapies for obesity management, including liraglutide, a glucagon-like peptide-1 receptor agonist [26].

GLP-1 receptor agonists represent one of the key classes of drugs used in the treatment of type 2 diabetes [27]. Their actions include modulation of central nervous system centers responsible for appetite and satiety regulation, effects on the release of neurotransmitters and peptides, and interactions with mechanisms controlling hunger and energy expenditure. In the peripheral system, GLP-1 receptor agonists improve glycemic control by enhancing insulin secretion, suppressing glucagon release, and delaying gastric emptying. Additionally, they exert beneficial effects on lipid profiles, reduce adipose tissue inflammation, limit ectopic fat deposition, and regulate the release of gut hormones [28]. Gut hormones, such as ghrelin, peptide YY, and cholecystokinin, are involved in the regulation of appetite and digestive processes. GLP-1 receptor agonists influence their activity in the gastrointestinal tract by modulating their secretion and enhancing mechanisms responsible for satiety [29].

Cholecystokinin is secreted by I cells in the proximal small intestine and regulates the intestinal phase of gallbladder emptying through CCK1 receptors located in the gallbladder musculature [30]. It is released in response to dietary fats, stimulating gallbladder contraction and relaxation of the sphincter of Oddi, thereby enabling bile flow into the duodenum. Consequently, cholecystokinin plays a critical role in regulating gallbladder motility and emptying [28]. Disruptions in cholecystokinin secretion or CCK1 receptor signaling can lead to impaired gallbladder contractility, bile stasis, and an increased risk of gallstone formation [31]. Evidence from the literature suggests that this mechanism may contribute to gallstone pathogenesis; however, its role in the context of pharmacological therapy with GLP-1 receptor agonists remains under investigation [32].

Additionally, the rapid weight loss observed during GLP-1 receptor agonist therapy, associated with increased adipose tissue mobilization, may promote bile stasis and elevate the risk of gallstone formation. This process results in the release of substantial amounts of cholesterol into bile, potentially leading to its supersaturation and crystallization [33, 34].

Clinical Evidence

In recent years, numerous randomized clinical trials and meta-analyses have been published investigating the relationship between GLP-1 receptor agonist therapy and the development of biliary tract disorders. Results from many of these studies suggest a potential influence of this pharmacotherapy on gallstone formation.

In a meta-analysis by He L. et al., which included 76 clinical trials involving over 100,000 patients with type 2 diabetes or obesity, GLP-1 receptor agonist therapy was associated with an increased incidence of gallbladder and biliary tract disorders, including gallstones and cholecystitis. The authors observed that the risk of these complications was higher with higher drug doses, longer treatment duration, and therapies aimed at weight reduction. This association was primarily noted in studies evaluating liraglutide, dulaglutide, subcutaneous semaglutide, and exenatide. In the discussion, the authors suggested that the increased risk could be partly related to delayed gallbladder emptying due to reduced postprandial cholecystokinin (CCK) levels, referring to the hypothesis proposed by Rehfeld et al. in 2018 [34].

A study conducted by Jens F. Rehfeld and colleagues aimed to elucidate the mechanism by which native GLP-1 may increase the risk of adverse biliary events, such as gallstone formation or cholecystitis. The study included 10 healthy individuals and 10 patients with type 1 diabetes, in whom postprandial cholecystokinin

(CCK) levels were assessed. In the control group receiving saline infusions, postprandial CCK levels increased, whereas in the GLP-1 infusion group, levels decreased in both healthy participants and patients with diabetes. These results indicate that GLP-1 may inhibit postprandial CCK secretion, which could consequently impair gallbladder contractility, thereby potentially promoting gallstone formation and cholecystitis [30].

Interestingly, a slightly different outcome was reported by Nerild H.H. and colleagues in a double-blind clinical trial investigating the effects of liraglutide therapy on hormones regulating gallbladder function. The study included 52 individuals with obesity, who were randomly assigned to receive liraglutide (n = 26) or placebo (n = 26) for 12 weeks. Postprandial levels of gut hormones were assessed in all participants, revealing that liraglutide treatment increased cholecystokinin (CCK) levels while decreasing fibroblast growth factor 19 (FGF19) and glucagon-like peptide 2 (GLP-2) compared to placebo. The authors suggested that these hormonal changes could contribute to impaired gallbladder function by delaying its refilling, potentially promoting gallstone formation in individuals with obesity [35].

These observations are supported by other large, randomized clinical trials. An analysis of data from the international LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), conducted by Michael A. Nauck and colleagues, initially focused on cardiovascular outcomes in patients treated with liraglutide. The authors also investigated the relationship between GLP-1 receptor agonist therapy and the risk of gallbladder and biliary tract events. These events were categorized into four main groups: uncomplicated gallstones, complicated gallstones, cholecystitis, and biliary obstruction. The results demonstrated that liraglutide use significantly increased the risk of these conditions, with a 60% higher hazard in treated individuals (hazard ratio [HR] 1.60). The authors further emphasized the need for additional research to elucidate the mechanisms underlying this effect [36].

Table 1. Summary of evidence from clinical trials and meta-analyses on the impact of GLP-1 receptor agonists on gallbladder motility and gallstone-related outcomes.

Study	Study design	Population (n)	Intervention	Follow-up	Outcomes assessed	Key findings	Interpretation
Nerild et al., 2023	Double-blind randomized controlled trial	52	Liraglutide vs placebo	12 weeks	Postprandial gut hormones and gallbladder motility	↑ CCK, ↓ FGF19, ↓ GLP-2; delayed gallbladder refilling	Mechanistic evidence suggesting impaired gallbladder motility as a potential pathway leading to gallstone formation
LEADER trial (Nauck et al., 2019)	Randomized controlled trial (post hoc analysis)	9340	Liraglutide vs placebo	Median 3.8 years	Gallbladder-related adverse events (cholelithiasis, cholecystitis)	Increased risk of gallbladder events (HR ~1.60 vs placebo)	Clinical evidence confirming increased incidence of gallbladder disease
He et al., 2022	Systematic review and meta-analysis of RCTs	>100 000	GLP-1 receptor agonists	Variable	Cholelithiasis, cholecystitis	Significantly increased risk, particularly at higher doses and with longer treatment duration	Class effect of GLP-1 RAs on gallbladder disease risk

Clinical significance

The most important risk factors for the development of gallstone disease in patients treated with GLP-1 receptor agonists include the drug dose, duration of therapy, and the rate of weight loss.

The analysis conducted by Chao Tao et al., covering the period from the first quarter of 2004 to the second quarter of 2024 and based on the international FAERS (FDA Adverse Event Reporting System) database, demonstrated a markedly higher incidence of cholecystitis and gallstone cases in women (58.72% of all reports) compared to men (37.07%). Moreover, the majority of adverse events reported in association with GLP-1 receptor agonist use occurred predominantly in patients aged 45 years and older [37].Research by Salem A.E. et al. showed that among 229 patients treated with GLP-1 receptor agonists, 78 individuals (34%) developed cholelithiasis. The cumulative incidence of cholelithiasis was 33.6%. The analysis also revealed that in patients with a BMI > 30, the incidence rate of cholelithiasis was 39.8% [38]. It was also shown that the risk is higher with the use of high drug doses and longer therapy duration, particularly in cases associated with significant body weight reduction [38].

The rate of weight loss proved to be a significant factor. In a study by Weinsier R.L. et al., it was shown that very rapid weight loss (>1.5 kg per week) is also an important risk factor for cholesterol gallstone formation [39].

In a study conducted by Ramírez-Mejía M.M. et al., it was suggested that although weight loss itself promotes gallstone formation, in patients treated with GLP-1 receptor agonists the risk remains elevated even after accounting for the effects of weight loss, which may indicate a direct impact of the drugs on gallbladder motility [25].

To minimize the risk of gallstone development in patients treated with GLP-1 receptor agonists, preventive measures are recommended. Primarily, gradual weight reduction at an optimal rate of 0.5-1.0 kg per week should be pursued [40, 41]. Patients should also be advised to limit fat intake and to distribute their daily fat consumption evenly across several meals to avoid provoking sudden gallbladder contractions [41]. In selected cases, pharmacological prophylaxis with ursodeoxycholic acid (UDCA) is appropriate, as it reduces cholesterol secretion into bile and lowers bile cholesterol saturation [25]. This facilitates the dissolution of cholesterol crystals and can effectively prevent the formation of new gallstones, especially during periods of rapid weight loss [42].

Data limitations and future research directions

Despite the growing number of clinical trials and meta-analyses investigating the impact of GLP-1 receptor agonists on gallstone development, interpretation of the available data requires consideration of significant limitations. Most importantly, some of the analyzed studies were originally designed to assess clinical outcomes other than the risk of gallbladder disease. Events related to biliary disorders were evaluated secondarily, with the corresponding data primarily derived from adverse event reports or post hoc analyses [34, 36]. This may represent a methodological limitation related to the lack of precision and insufficient reporting of biliary events, which were not predefined safety outcomes in most of the included studies. Additionally, analyses conducted on a small number of reported events may have insufficient statistical power within subgroups, limiting the ability to draw definitive conclusions [34]. An important aspect is also that the analyzed data originate from studies conducted in specific patient populations - primarily individuals with type 2 diabetes and high cardiovascular risk [34, 36]. Observed differences in risk between groups, particularly the increased risk in studies focusing on weight reduction, suggest the need for research assessing individual risk factors in specific patient populations [34]. Moreover, despite numerous hypotheses in the literature - including changes in gut hormone secretion, disturbances in gallbladder motility, and the effects of rapid weight loss - the exact mechanism underlying the observed increased risk of gallstone formation remains not fully elucidated. Therefore, further studies are needed to more precisely clarify the underlying effects of GLP-1 receptor agonists on gallstone development [36].

Conclusions

GLP-1 receptor agonists are commonly prescribed pharmacotherapeutic agents in patients with type 2 diabetes and obesity. However, recent studies indicate that chronic use of these medications may be associated with an increased risk of biliary complications, including gallstone disease. The exact mechanism underlying this phenomenon is multifactorial and not yet fully elucidated. The main factors thought to underlie this phenomenon are impaired gallbladder motility, alterations in gut hormone signaling (notably cholecystokinin),

and cholesterol supersaturation of bile. Nonetheless, additional research is necessary to elucidate the mechanisms of this association.

The risk of developing complications is particularly high in patients experiencing rapid weight loss and in those undergoing long-term therapy with high doses of these drugs. Traditional risk factors for gallstone disease, such as obesity, female sex, advanced age, and a history of cholelithiasis, further increase the likelihood of its occurrence. Therefore, regular monitoring of patients receiving GLP-1 receptor agonists for biliary symptoms is recommended. While these agents offer numerous benefits, clinicians should exercise caution when selecting therapy and carefully consider the individual risk profile of each patient.

Declaration on the use of AI: In preparing this work, the authors used Gemini for the purpose of improving language and readability, text formatting, and verification of bibliographic styles. After using this tool/service, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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