Review

GLP-1 Receptor Agonists and Cholelithiasis: A Comprehensive Review

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Abstract

GLP-1 receptor agonists (GLP-1 RAs) have emerged as a novel class of antidiabetic medications, displaying potential in optimizing glycemic control and offering cardiovascular advantages for individuals with type 2 diabetes. Moreover, GLP-1 receptor agonists are utilized in the treatment of childhood and adolescent obesity. Currently, there are seven GLP-1 receptor agonists available, including exenatide twice-daily, exenatide extended-release (ER) once-weekly, lixisenatide once-daily, liraglutide once-daily, dulaglutide once-weekly, semaglutide once-weekly, and oral semaglutide once-daily.

Aim of this systematic review is to provide an all-inclusive analysis of the existing literature exploring the association between GLP-1 receptor agonists and cholelithiasis, assess the risk of cholelithiasis induced by GLP-1 RAs, and establish its significance. A thorough examination was conducted using the PubMed database with the keywords: "glp-1 receptor agonists" AND "glp-1" AND "cholelithiasis." No further filters were applied. The last research was conducted on 26 November 2023.

Based on the research findings, it has been determined that the utilization of Glp-1 RAs in the management of type 2 diabetes and obesity may be connected to a heightened susceptibility to cholelithiasis. However, further extensive investigations are necessitated to conclusively ascertain the statistical significance of this increased risk in relation to the use of GLP-1 RAs for obesity treatment.

Keywords: glp-1, glp-1 receptor agonists, cholelithiasis, obesity, type 2 diabetes

Introduction

GLP-1 receptor agonists exhibit insulinotropic and glucagon static properties, exhibiting considerable efficacy correlated with glucose levels. Consequently, they effectively reduce elevated plasma glucose concentrations.(2) Since 2005, GLP-1 RAs have been approved for the treatment of type 2 diabetes and are currently recommended in the initial stages of the treatment protocol. This recommendation is based on the proven benefits of GLP-1 RAs, which include weight reduction, glycemic efficacy, and favorable cardiovascular and renal health outcomes, as indicated in the latest guidelines.(5) Additionally, GLP-1 receptor agonists have a central mechanism of action that effectively decreases appetite and food consumption, making them a valuable therapeutic option for addressing obesity.(9) However, there have been reports of gallbladder-related adverse events (such as cholelithiasis and cholecystitis) in clinical trials that study the metabolic effects of GLP-1Ras.

Materials and Methods

Detailed research was conducted through the published bibliography via PubMed database. The keywords used for the search were “medical”, “cannabis”, “in”, “cancer” and “pain”. Data were extracted utilizing a common data elicitation form, using the aforementioned keywords. The study was made with respect to the PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources guidelines. Specifically, as regards the PRISMA, the records that were initially identified through PubMed search were 124. These results derived

after applying a filter of the last 5 years. There were 3 additional ones through review of references. Also, the full text articles assessed for eligibility were 14, and the records excluded articles, title and abstract non relevant were 110. There was 1 extra suitable article derived from the similar articles. All the reports assessed for eligibility were relevant, but 1 of them was written in german, so it was excluded. No duplicates were found. Finally, 17 references fulfilled the above-mentioned criteria and used in the present work.

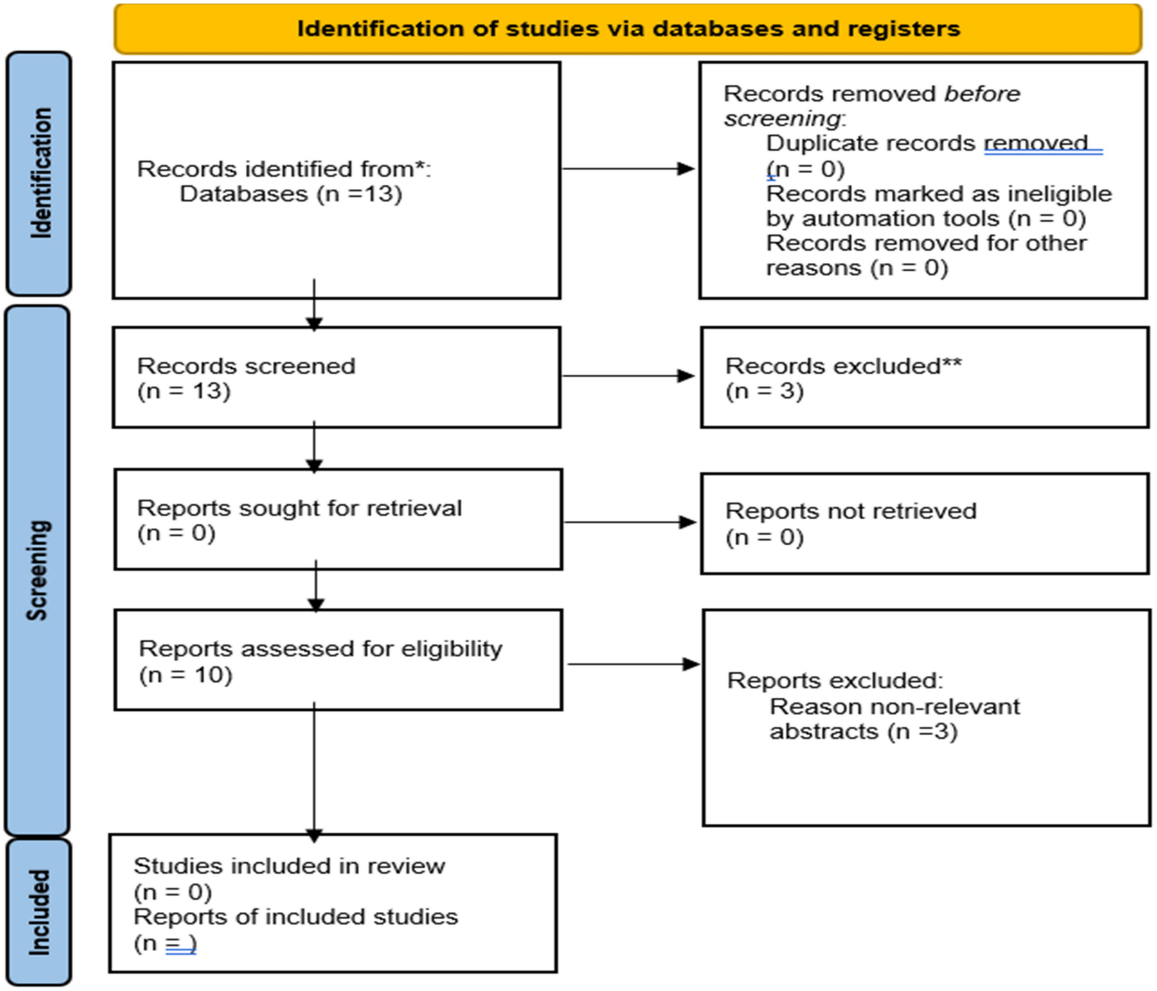

Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and oth
**: title and abstract non relevant

Results

Research has shown that GLP-1 receptor agonists have been associated with an increased risk of cholelithiasis among patients. While some studies have found this risk to be significant, others have been unable to provide definitive evidence. As a result, a clear conclusion cannot be drawn at this time. However, when considering the favorable effects of these drugs on glucose metabolism, blood pressure, body weight, and cardiovascular and renal health, the overall risk/benefit profile of these agents for treating type 2 diabetes and obesity patients is beneficial. It is recommended to assess the presence of gallstones and risk factors for cholelithiasis in all patients before initiating incretin-based therapy.

Studies	Regimen	Patients sample size	Control sample size	Cholelithiasis cases
1	Semaglutide	201	67	5 (4%)
2	Semaglutide	*	*	*
3	GLP-1 Ra	17,232	14,8772	141 for GLP-1 Ra group 99 for control group
4	Liraglutide Semaglutide Dulaglutide Exenatide Albiglutide Oral semaglutide Lixisenatide	12411 8598 9855 9536 6878 5355 4983	9093 5062 7528 9501 7149 3291 4032	276 for GLP-1 Ra group 119 for control group 190-92 153-102 190-154 36-30 28-21 39-26
5	Tirzepatide	4621	2215	1394-235
6	Subcutaneous semaglutide Oral semaglutide	3150 4116	1657 2236	29-8 30-18
7	Subcutaneous semaglutide Oral semaglutide	1642 1591	1644 1592	36-27 4-2
8	GLP-1 Ra	Not mentioned	Not mentioned	Not mentioned
9	Liraglutide	Not mentioned	Not mentioned	37

Table: Data derived from the summary of product characteristics, as the manuscripts did not describe these data.

Discussion

Semaglutide, a Glp-1 RA that has undergone investigation, is being used as a subcutaneous treatment once a week at a dose of 2.4 mg in adults with obesity, in combination with lifestyle intervention. This treatment has demonstrated clinically proven benefits in improving cardiometabolic risk factors and promoting weight loss. Out of a group of 201 participants, only five individuals (4%) in the semaglutide group experienced acute cholelithiasis, whereas none of the 67 participants in the placebo group had a similar occurrence. However, the researchers did not consider this percentage to be statistically significant.(1) Additionally, a separate study revealed that cholelithiasis was observed with greater frequency in the group receiving semaglutide compared to the group receiving a placebo (0.6% versus 0.1% with placebo).(2) In the same study, findings indicated an elevated risk of cholelithiasis (2.5% versus 1.0%) among patients receiving liraglutide, a Glp-1 RA employed in the treatment of obesity.(2) There is documented evidence of a 28% increased risk for cholelithiasis with GLP-1RA treatment. However, it remains uncertain whether this risk is consistent across all agents.(2) Recently released data confirmed that therapy with GLP-1 receptor agonists is associated with a significantly increased risk of cholelithiasis (MH-OR [95% CI] 1.30 [1.01-1.68], P = .041).(3) Further research has verified that the administration of GLP-1 RAs is correlated with heightened risks of cholelithiasis (RR, 1.27; 95% CI, 1.10-1.47; I2 = 0%). A detailed breakdown of these risks for each individual agent is also provided.(4) In comparison to the control group, randomization to liraglutide and dulaglutide treatments showed an elevated risk for gallbladder or biliary diseases (RR, 1.79; 95% CI, 1.45-2.25 and RR, 1.35; 95% CI, 1.06-1.73 respectively). Randomization to subcutaneous semaglutide and exenatide also demonstrated an increased risk, although it was not statistically significant (RR, 1.28; 95% CI, 0.99-1.65 and RR, 1.23; 95% CI, 1.00-1.52 respectively). On the other hand, oral semaglutide, lixisenatide, and albiglutide did not exhibit an increased risk. Notably, higher doses of subcutaneous semaglutide (≥1.0 mg) were associated with an increased incidence of gallbladder or biliary diseases (RR, 1.58; 95% CI, 1.13-2.22).(4) Moreover, the utilization of GLP-1 RAs exhibited a substantial correlation with elevated risks of

cholelithiasis at higher dosages (RR, 1.56; 95% CI, 1.36-1.78), nonetheless, no notable association was observed at lower dosages (RR, 0.99; 95% CI, 0.74-1.33; P = .006 for interaction).(4) A lengthier period of treatment with GLP-1 RAs (greater than 26 weeks) was found to have a higher probability of increasing the risk for gallbladder or biliary disease (relative risk (RR), 1.40; 95% confidence interval (CI), 1.26-1.56). However, a shorter duration of treatment (equal to or less than 26 weeks) did not exhibit the same association (RR, 0.79; 95% CI, 0.48-1.31; p=0.03 for interaction).(4) Tirzepatide, a dual glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA), has obtained approval from the US Food and Drug Administration in May 2022.(5) In various studies, incidents of cholelithiasis were observed, but the combined proportion was found to be statistically insignificant at 0.95% (95% CI, 0.51%-1.52%) with the 5-mg dose.(5) Additionally, it should be noted that the incidence of cholelithiasis showed a further decrease with the administration of both 10- and 15-mg doses, however, no statistically significant differences were found between these two doses.(5) Reports of cholelithiasis were higher with both formulations of semaglutide (oral-subcutaneous) versus comparators, consistent with a meta-analysis that reported a significant increase in cholelithiasis with GLP-1RAs versus comparators.(6) In the context of Asian patients with type 2 diabetes, a notable correlation between GLP-1RAs and heightened risk of cholelithiasis was observed, particularly among patients over the age of 60, female patients, and those undergoing treatment for more than 120 days following initiation.(7) Liraglutide, but not dulaglutide, was associated with an elevated risk.(7) Moreover, calculating Mantel-Haenszel odds ratio (MH-OR, 95%CI), GLP1-RA significantly increased the risk of cholelithiasis (MH-OR 1.28 [1.11, 1.48]).(8) Cholelithiasis was detected in 2.5% of patients who received liraglutide, compared to 1.0% of patients who received a placebo.(9) A possible mechanism of biliary sludge and bile stone formation could be decreased gallbladder motility. Exenatide and albiglutide, based on acute intervention studies, demonstrated a reduction in gallbladder emptying induced by cholecystokinin. Changes in bile salts, specifically altered deoxycholic acid levels in plasma following liraglutide treatment, may lead to supersaturated bile. Nevertheless, the clinical implications of these alterations remain uncertain.(2,10)

Conclusion

The usage of GLP-1 RAs has been approved for the treatment of type 2 diabetes since 2005. In recent years, these agents have also been included in the treatment protocol for weight loss and obesity. Due to this reason, not many studies have been done regarding to treatment of obesity with GLP-1 RAs. So, we cannot extract with assurance that the increased risk of cholelithiasis, due to these agents, is statistically significant. It is imperative to evaluate the overall beneficial risk/benefit profile of treatment for each patient, considering their individual risk factors. This approach ensures that treatment is tailored to each patient's needs and that the benefits outweigh any potential risks.

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