GLP-1 RECEPTOR AGONISTS ARE ASSOCIATED WITH AN INCREASED RISK OF BILIARY PANCREATITIS

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BACKGROUND

- Glucagon-like peptide-1 receptor (GLP-1) agonists have been linked to increased risk of biliary disease[1]
- GLP-1 agonists can possibly increase the risk of biliary pancreatitis
- Evidence supporting this association is limited.

METHODS

- The TriNetX US Collaborative Network was utilized for this study.
- Adult patients without pre-existing pancreaticobiliary disease who received injectable GLP-1 agonists were compared to those without GLP-1 agonist use for development of biliary diseases.
- Only the patients with ≥ 6 refills of GLP-1 agonists were included in the study to ensure adequate drug exposure.
- Patients with pre-existing pancreaticobiliary diseases, hemolytic anemia, pregnancy, alcohol use disorder, nicotine dependence, or exposure to medications known to increase the risk of pancreatitis or biliary disease were excluded.
- We performed propensity score matching to match on biodemographic variables and comorbidities including obesity, hypertension, diabetes mellitus, hyperlipidemias, hypercalcemia, and celiac disease.

Table 1. Comparison of Biliary Disease in GLP-1 users vs non-GLP-1 Users Over 5-Year Interval

	Before Matching				After Matching			
Outcome	GLP-1 Risk (n, %)	Non-GLP-1 Risk (n, %)	P-value	Odds Ratio (95% CI)	GLP-1 Risk (n, %)	Non-GLP-1 Risk (n, %)	P-value	Odds Ratio (95% CI)
Number of patients	163,543	956,269			138,881	138,881		
Biliary pancreatitis	193 (0.12%)	542 (0.06%)	<0.001	2.083 (1.768–2.456)	157 (0.11%)	121 (0.09%)	0.031	1.298 (1.024–1.645)
Cholecystectomy	1,834 (1.12%)	4,881 (0.51%)	<0.001	2.211 (2.095–2.333)	1,523 (1.10%)	1,123 (0.81%)	<0.001	1.360 (1.259–1.470)
Cholelithiasis	4,501 (2.75%)	13,282 (1.39%)	<0.001	2.009 (1.942–2.079)	3,680 (2.65%)	3,142 (2.26%)	<0.001	1.176 (1.121–1.234)
Choledocholithiasis	68 (0.04%)	229 (0.02%)	<0.001	1.737 (1.325–2.277)	55 (0.04%)	53 (0.04%)	0.847	1.038 (0.712–1.513)
Cholecystitis	1,302 (0.80%)	3,837 (0.40%)	<0.001	1.992 (1.870–2.122)	1,074 (0.77%)	880 (0.63%)	<0.001	1.222 (1.118–1.337)

GLP-1: glucagon-like peptide-1 receptor

KEY RESULTS

- GLP-1 agonist use was associated with an increased 5-year risk of cholelithiasis, cholecystitis, biliary pancreatitis, as well as the need for cholecystectomy (Table 1).
- In subgroup analysis, the increased risk of biliary disease, including biliary pancreatitis, was higher after 6 months of therapy, while no significant difference was noted within the first 6 months of treatment initiation.

REFERENCES

1. He L, et al. Association of glucagon-like peptide-1 receptor agonist use with risk of gallbladder and biliary diseases. *JAMA Intern Med.* 2022;182(5):513–519. doi:10.1001/jamainternmed.2022.0338.
2. Mozaffarian D, et al. Nutritional priorities to support GLP-1 therapy for obesity: a joint advisory from major societies. *Am J Clin Nutr.* 2025;122(1):344–367. doi:10.1016/j.ajcnut.2025.04.023.
3. Jalleh RJ, et al. Physiology and pharmacology of effects of GLP-1–based therapies on gastric, biliary and intestinal motility. *Endocrinology.* 2025;166(1):bqae155. doi:10.1210/endocr/bqae155.

DISCUSSION

- This study demonstrates that GLP-1 agonists are associated with an elevated risk of cholelithiasis, choledocholithiasis, cholecystitis, biliary pancreatitis, as well as undergoing cholecystectomy.
- GLP-1 agonists increase the risk of biliary diseases by 1) Inducing rapid weight loss especially within first 6 months.[2] 2) Reducing the mobility and delay emptying of gallbladder.[3]
- The observation that the difference in biliary diseases was not observed within first 6 months of therapy supports the likelihood of a multifactorial or cumulative pathophysiologic process, rather than weight loss alone.

CONCLUSIONS

- Our findings underscore the need for continued monitoring of biliary disease risk in patients receiving long-term GLP-1 agonist therapy as these agents are long-term therapies.
- Further studies are warranted to investigate the underlying mechanism and to define strategies for prevention of biliary complications.