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Tirzepatide-Associated Biliary Injury: Mechanistic Insights and Clinical Implications

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Abstract
Tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide-1 (GLP-1) receptor agonist, has demonstrated unprecedented efficacy in glycemic control and weight reduction, with HbA1c reductions of 1.24–2.58% and weight loss of 5.4–11.7 kg in the SURPASS clinical trial program. However, emerging evidence indicates an increased incidence of biliary complications, particularly in patients with prior bariatric surgery. This comprehensive analysis synthesizes clinical data, mechanistic pathophysiology, and pharmacological mechanisms underlying tirzepatide-associated gallbladder dysfunction, with emphasis on recognition of severe complications such as gallbladder perforation. We present an integrated assessment of this rare but life-threatening adverse effect and propose evidence-based clinical surveillance protocols.

Keywords: Tirzepatide; gallbladder perforation; cholecystitis; GLP-1 receptor agonist; biliary disease; bariatric surgery; dual GIP/GLP-1 agonist

Introduction

Tirzepatide is a first-in-class dual GIP/GLP-1 receptor agonist approved by the FDA in 2022 for type 2 diabetes and in 2023 for chronic weight management. Given once weekly, it significantly lowers HbA1c (≈1.9–2.6%) and body weight (≈6–13 kg), as shown in the SURPASS trials. Its dual action improves insulin secretion and sensitivity, suppresses glucagon, delays gastric emptying, and reduces appetite. While common gastrointestinal side effects are usually mild, emerging data suggest a potential increased risk of biliary disease, especially in patients with prior bariatric surgery or liver-related metabolic conditions.

This image shows **tirzepatide simultaneously binding to GIP and GLP-1 receptors** on the cell membrane.

Dual receptor activation explains its enhanced effects on **glucose control and weight loss** compared to single-agonist therapies.

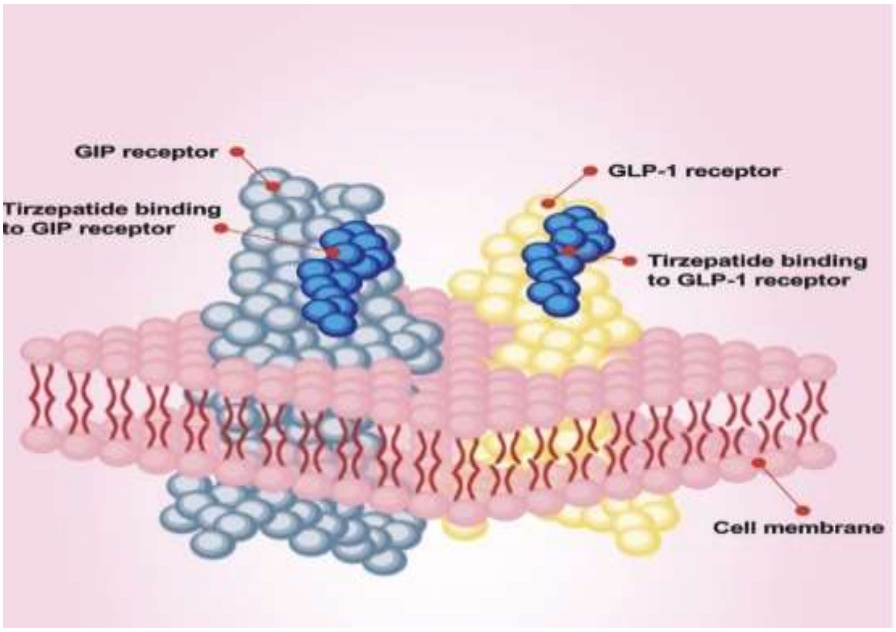

Fig 1 Tirzepatide binds to both GIP and GLP-1 receptors on the cell membrane.

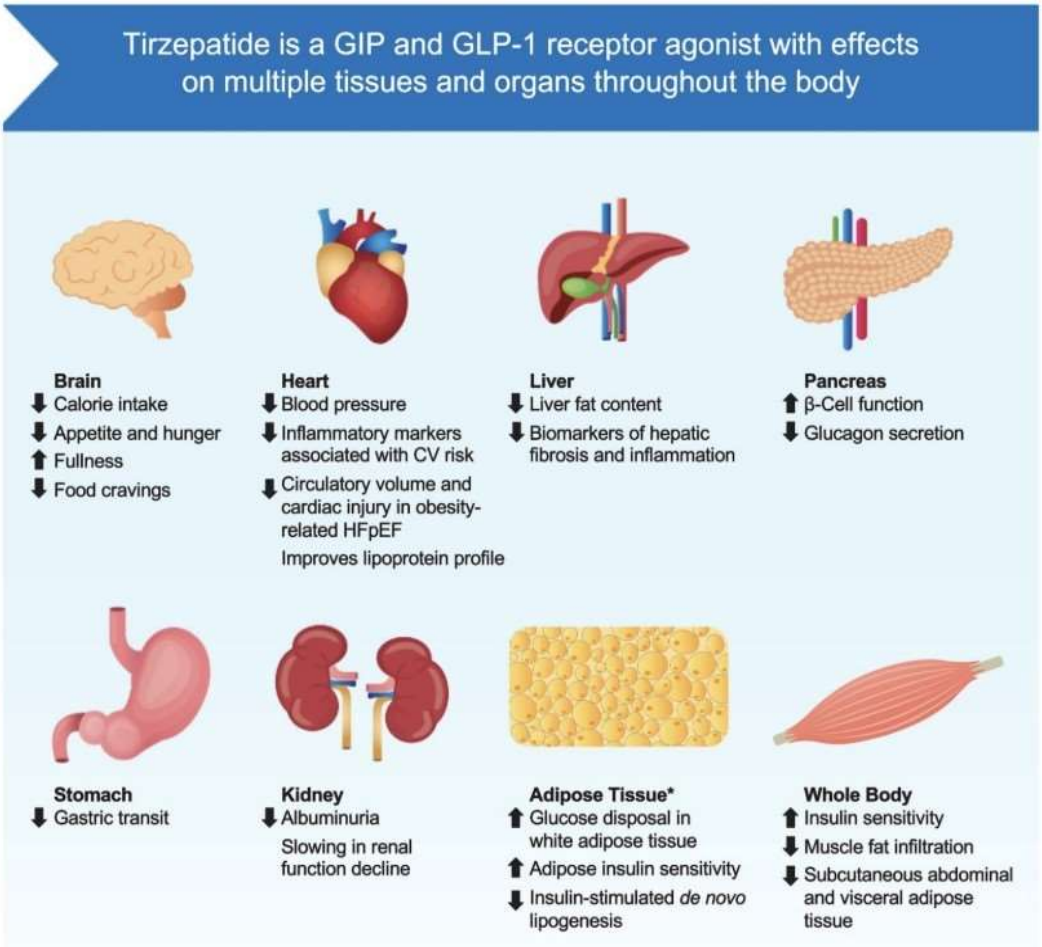

FIG 2 Tirzepatide exerts beneficial effects on multiple organs and tissues throughout the body. CV cardiovascular, GIP glucose-dependent insulinotropic polypeptide, GLP-1 glucagon-like peptide-1, HFpEF heart failure with pre- served ejection fraction

Tirzepatide is also under investigation for reducing morbidity and mortality in individuals with obesity and overweight without diabetes. Meta-analyses of randomized trials show that GLP-1–based therapies, including tirzepatide, are associated with an increased risk of gallbladder and biliary diseases, particularly in weight-loss settings and at higher doses. Proposed mechanisms include reduced gallbladder contractility from GLP-1–mediated CCK suppression, rapid weight-loss–induced changes in bile composition, and altered bile acid and cholesterol metabolism. Although most cases are mild, rare severe complications such as gallbladder perforation can occur, highlighting the need for careful risk stratification, monitoring, and early intervention in high-risk patients.

Mechanistic Pathophysiology of Tirzepatide-Associated Biliary Dysfunction

The gallbladder concentrates and stores bile and empties after meals in response to cholecystokinin (CCK). GLP-1 and GIP receptors are expressed in the gut, pancreas, and central nervous system, and emerging evidence also shows GIP receptor expression in gallbladder smooth muscle and biliary epithelium, although its functional role is not yet clearly defined.

Activation of the GLP-1 receptor suppresses CCK secretion from intestinal enteroendocrine cells, leading to reduced gallbladder contraction and delayed bile emptying. With long-acting agents such as tirzepatide, sustained dual GIP/GLP-1 receptor stimulation may prolong gallbladder hypomotility, increasing bile stasis and the risk of gallstone formation. The associated weight loss and appetite suppression are largely mediated through central nervous system pathways, particularly hypothalamic centers regulating energy balance.

Rapid Weight Loss and Cholesterol Supersaturation

Rapid weight loss strongly promotes cholesterol gallstone formation by increasing hepatic cholesterol secretion into bile and causing cholesterol supersaturation of bile salts and phospholipids. With tirzepatide, accelerated fat loss releases stored cholesterol, increases hepatic synthesis, and maintains intestinal cholesterol absorption, together creating a highly lithogenic bile environment. Simultaneous GLP-1–mediated suppression of cholecystokinin reduces gallbladder contraction and alters mucin composition, promoting bile stasis, sludge, and crystal nucleation. Clinical data from bariatric and pharmacologic weight-loss settings show a clear dose–response relationship between the rate of weight loss and gallstone risk, particularly during early, rapid weight reduction. Tirzepatide-induced appetite suppression and central nervous system effects drive these weight changes, while metabolic adaptation further modifies energy balance during sustained therapy.

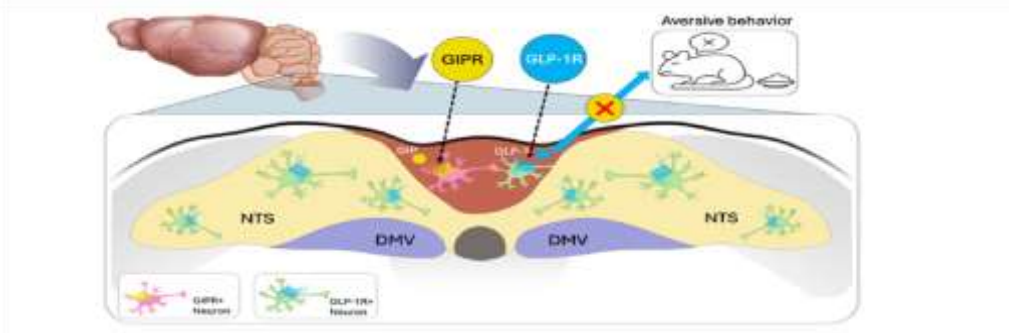

fig 3 the diagram illustrates the brainstem circuitry linking peripheral gut hormones gip (glucose-dependent insulinotropic polypeptide) and glp-1 (glucagon-like peptide-1) to aversive behavior in mice

Case Presentation and Clinical Correlation

A 55-year-old female with a 15-year history of type 2 diabetes mellitus presented to the emergency department with 4 days of progressive right hypochondrial pain radiating to the back, accompanied by vomiting for 4 days, fever (temperatures to 38.8°C), and anorexia. The patient had undergone laparoscopic sleeve gastrectomy 7 years prior for morbid obesity, achieving initial weight loss of 68 kg with subsequent partial weight regain of approximately 15 kg over the following 6 years. Initial diabetes control post-bariatric surgery was achieved with metformin monotherapy; however, progressive glycemic deterioration necessitated sequential addition of a GLP-1 receptor agonist (liraglutide 1.8 mg daily) 3 years prior, achieving modest HbA1c improvement from 8.1% to 7.3%.

Two months prior to presentation, the patient was transitioned from liraglutide to tirzepatide 2.5 mg weekly due to persistent obesity (BMI 33.2 kg/m², weight 87 kg) and inadequate glycemic control (baseline HbA1c 7.8%).

Tirzepatide was titrated to 5 mg at week 4, then to 10 mg at week 8 (the dose scheduled at the time of clinical presentation). The patient reported progressive nausea, constipation, and decreased appetite beginning at week 2 of tirzepatide initiation, consistent with anticipated

GLP-1 receptor agonist gastrointestinal adverse effects. Weight loss was rapid: 2.8 kg at 4 weeks, 5.1 kg at 8 weeks,

and an estimated 6.2 kg by the time of presentation at week 12—representing approximately 7.1% body weight loss over 12 weeks (0.59% per week or 1.1 kg/week). No baseline abdominal ultrasonography was performed prior to tirzepatide initiation, and the patient reported no prior episodes of biliary colic or abdominal pain prior to the current presentation.

On physical examination at presentation, the patient was febrile (38.8°C), tachycardic (120 bpm), normotensive (110/70 mmHg), with normal oxygen saturation (99% on room air). Abdominal examination revealed marked right upper quadrant tenderness to palpation, positive Murphys sign (inspiratory arrest during palpation of the right upper quadrant), and mild peritoneal signs (rebound tenderness in the right upper quadrant without frank guarding or rigidity). No palpable mass or hepatomegaly was appreciated.

Laboratory investigations revealed: leukocyte count 14,200/µL (87% neutrophils, left shift present), C-reactive protein 18.2 mg/dL (normal <5 mg/dL), serum amylase 180 U/L (normal 30–110 U/L),serum lipase 340 U/L (normal <60 U/L), total bilirubin 1.8 mg/dL (normal <1.2 mg/dL), direct bilirubin 1.1 mg/dL, alkaline phosphatase 102 U/L (normal

<90 U/L), gammaglutamyl transferase 118 U/L (normal <50 U/L), AST 68 U/L (normal <35 U/L), ALT 72 U/L (normal <40 U/L), albumin 3.6 g/dL (normal 3.5–5.5 g/dL), prothrombin time 12.8 seconds (normal <13 seconds), and creatinine 0.9 mg/dL (baseline 0.8 mg/dL, normal for age and sex). Viral hepatitis serologies (HBsAg, anti-HCV,anti- HAV) were negative. Transabdominal ultrasonography revealed gall bladder sludge with wall edema suggestive of calculus cholecystitis.divarication of recti noted in supraumbilical and umbilical region. Pericholecystic free fluid noted .?mucosal wall discontinuity noted.possible perforation. MRCP showed bileduct diameter of 9mm and sludge noted in biliary duct with acute mild pancreatitis with acute cholecystitis .

Given the clinical presentation consistent with the findings and concern for potential complications in a post-bariatric surgery patient.she underwent ERCP+SLUDGE EXTRACTION+STENTING+LAPAROSCOPIC CHOLECYSTECTOMY

broad-spectrum intravenous antibiotics ,analgesics and supportive care was done and drain was removed on day 2 and patient was discharged on day 4

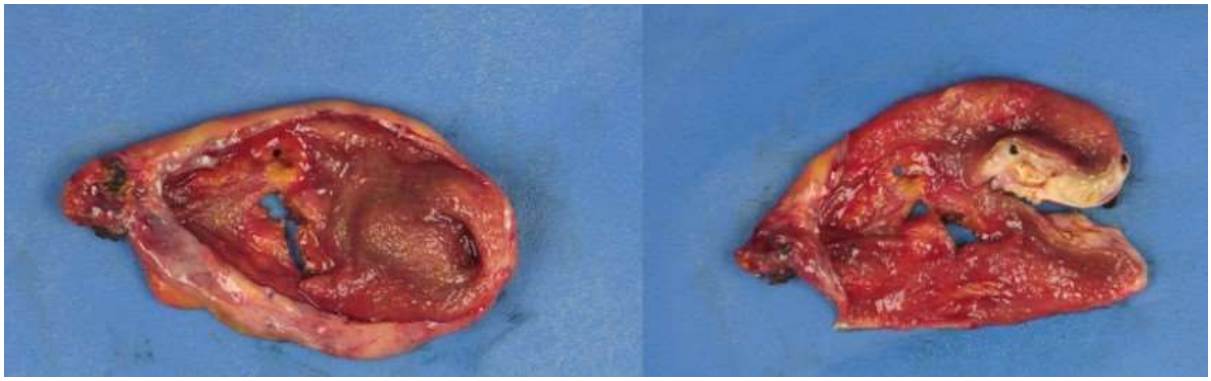

Fig 4 mages showing perforation of gallbladder

DISCUSSION

The classic presentation of biliary colic consists of intermittent right upper quadrant or epigastric pain, often radiating to the right shoulder or interscapular region, typically lasting 30 minutes to several hours, frequently precipitated by fatty meal consumption, and potentially associated with nausea or vomiting. Pain is typically colicky in nature (waxing and waning) rather than constant, reflects partial cystic duct obstruction by migrating gallstones, and resolves spontaneously when the stone either passes back into the gallbladder fundus or becomes transiently lodged without complete obstruction. Approximately 80% of patients with biliary colic have underlying cholelithiasis on imaging; however, ~20% may present with acalculous cholecystitis or functional biliary disorder (postcholecystectomy syndrome or sphincter of Oddi dysfunction), requiring more specialized diagnostic testing (hepatobiliary scintigraphy with CCK stimulation, manometry).

When a gallstone remains impacted within the cystic duct for >6–12 hours, inflammation of the gallbladder wall ensues due to bile stasis, bacterial infiltration (most commonly Escherichia coli, Klebsiella pneumoniae, and Bacteroides fragilis), and release of inflammatory mediators

Gallbladder Perforation. Progression of acute cholecystitis to gallbladder perforation occurs in 6–12% of cases and represents a surgical emergency with high morbidity and mortality. Perforation results from ischemic necrosis of the gallbladder wall, most commonly at the fundus (the most distal aspect with regard to blood supply), and can be classified into three types based on clinical presentation and temporal dynamics:

- Type I Perforation: Acute perforation during initial cholecystitis event, typically within 7–10 days of symptom onset, in patients without chronic cholecystitis history; often occurs in acalculous cholecystitis, particularly in critically ill patients, those with malignancy, diabetes mellitus, immunosuppression, or atherosclerotic heart disease; represents approximately 40–50% of all perforations.
- Type II Perforation: Subacute/chronic perforation with pericholecystic abscess formation; manifests as persistent fever and right upper quadrant mass despite appropriate antibiotic therapy; represents approximately 10–20% of cases.
- Type III Perforation: Chronic perforation with cholecystoenteric fistula formation, typically to the duodenum (most common site; 60% of cases), colon, or less commonly other bowel segments; may present with pneumobilia (air in the biliary tree) or gallstone ileus (small bowel obstruction caused by a large gallstone eroding through the fistula tract and lodging in the distal ileum, typically at the ileocecal valve).

FIG 4 Types of perforation: Neimers classification

Conclusion and Future Directions

The emergence of tirzepatide as a highly effective agent for glycemic control and weight reduction in patients with type 2 diabetes and obesity represents a substantial therapeutic advance. However, the increased incidence of biliary complications—particularly in high-risk subgroups including post-bariatric surgery patients, those with dyslipidemia, and those achieving rapid weight loss—necessitates careful risk-benefit analysis, enhanced

pretreatment screening, and intensified clinical surveillance. The mechanistic contributions of GLP-1-mediated gallbladder hypomotility, CCK suppression, rapid weight loss-induced cholesterol supersaturation, and pharmacological alterations in hepatic cholesterol metabolism warrant further investigation through prospective mechanistic studies employing advanced imaging (e.g., dynamic ultrasound with CCK stimulation, MRI-PDFF for gallbladder mucin quantification), serological biomarkers, and proteomic approaches.

Future research priorities include: (1) prospective randomized trials comparing tirzepatide to alternative agents in post-bariatric surgery patients with careful monitoring for biliary outcomes; (2) genomic and proteomic studies to identify molecular predictors of tirzepatideassociated biliary disease; (3) health services research examining optimal surveillance strategies (baseline imaging, interval monitoring) and cost-effectiveness of varying approaches; (4) mechanistic studies in animal models and human ex vivo systems examining direct effects of tirzepatide on gallbladder myocyte contractility, intracellular calcium dynamics, and mucin synthesis

Until such evidence is generated, we recommend systematic risk assessment of all patients prior to tirzepatide initiation, with particular vigilance in post-bariatric surgery populations; baseline and periodic monitoring (clinical assessment, serological markers, and in high-risk cases imaging); careful education of patients regarding symptoms warranting urgent evaluation; and a low threshold for diagnostic imaging and specialist consultation

(gastroenterology, hepatology, or general surgery) when biliary pathology is suspected.

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