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Risk of Acute Pancreatitis with Tirzepatide: A Systematic Review and Meta-Analysis of Randomized and Observational Studies

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Abstract

This systematic review and meta-analysis evaluates the association between tirzepatide and the risk of acute pancreatitis in adults with type 2 diabetes mellitus (T2DM) or obesity. Following PRISMA 2020 guidelines, randomised clinical trials and observational studies were identified through comprehensive searches of MEDLINE and Embase up to August 2025. Eligible studies included adults aged ≥18 years, with obesity or T2DM defined by accepted diagnostic criteria, and no prior history of pancreatitis. Data on tirzepatide exposure, comparators, diagnostic definitions, and pancreatitis outcomes were extracted using a structured template. Risk of bias was assessed using RoB 2.0, ROBINS-I, and JBI tools. Meta-analyses were performed using random-effects models, with heterogeneity quantified using the I^2 statistic. Subgroup analyses explored dose-dependent effects and risk variation by demographic and clinical features. This review aims to provide an up-to-date, evidence-based estimate of pancreatitis risk associated with tirzepatide to support informed clinical decision-making.

Troubleshooting

Methods

1 This systematic review and meta-analysis was designed to synthesise evidence from randomised clinical trials (RCTs) and observational studies. The review process followed the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations, which outline 27 essential reporting items to ensure transparency, reproducibility, and methodological rigour [1].

Primary Objective

2 Following the PICO framework, the primary aim of this review was to quantify the incidence and/or relative risk of acute pancreatitis associated with tirzepatide therapy in adults aged ≥18 years with type 2 diabetes mellitus (T2DM) or obesity. Comparator groups included placebo, no treatment, or alternative glucose-lowering agents such as GLP-1 receptor agonists and SGLT2 inhibitors.
Obesity was defined as a body mass index (BMI) ≥30 kg/m², or ≥27.5 kg/m² for Asian populations, in line with international standards [2,3]. Acute pancreatitis events were included only when explicitly reported by the original studies, either through clinical assessment or via diagnostic coding in administrative datasets.

Secondary Objectives

3 Secondary analyses aimed to determine:

- whether the risk of acute pancreatitis varies according to tirzepatide dose;
- whether demographic factors (age, sex, ethnicity) or clinical features (gallstone disease, alcohol consumption, pre-existing pancreatic conditions) modify the association between tirzepatide and acute pancreatitis.

Definitions of Key Concepts

4 Standardised definitions were applied across all included studies.

Obesity
Obesity was defined as BMI ≥30 kg/m², or ≥27.5 kg/m² for Asian individuals, consistent with WHO recommendations and international consensus guidelines [2,3].

Type 2 Diabetes Mellitus
T2DM was defined according to NICE guidance [4], using one or more of the following diagnostic criteria:

- HbA1c ≥48 mmol/mol (6.5%);
- Fasting plasma glucose ≥7.0 mmol/L;
- Random plasma glucose ≥11.1 mmol/L in symptomatic individuals;
- 2-hour plasma glucose ≥11.1 mmol/L during a 75 g oral glucose tolerance test.

Special considerations applied for conditions in which HbA1c may be unreliable (e.g., pregnancy, haemoglobinopathies, anaemia).

Acute Pancreatitis
Acute pancreatitis was defined using the Revised Atlanta Classification (2012) and required ≥2 of the following criteria [5]:

1. Characteristic abdominal pain (persistent, severe epigastric pain radiating to the back);
2. Serum amylase and/or lipase ≥3× upper limit of normal;
3. Imaging features consistent with acute pancreatitis on CT, MRI, or ultrasound.

Literature Search and Study Selection

5 A comprehensive search of Ovid MEDLINE and Embase was conducted from database inception to 1 August 2025. Search terms included Medical Subject Headings (MeSH), keywords, and text words relating to tirzepatide, obesity, T2DM, and acute pancreatitis, combined using Boolean operators to maximise study retrieval. Titles and abstracts were independently screened to identify potentially eligible studies. Full-text articles were subsequently assessed against predefined inclusion and exclusion criteria. Only studies reporting populations consistent with the definitions above were retained. Two reviewers (OB and RGS) conducted the screening process independently, with disagreements resolved through consultation with a supervising reviewer (SA).

Eligibility Criteria

6 Inclusion Criteria:
Studies were included if they met all of the following:

- Adults aged ≥18 years;
- Confirmed diagnosis of T2DM or obesity using accepted criteria;
- BMI ≥30 kg/m² (or ≥27.5 kg/m² in Asian participants);
- No prior history of pancreatitis;
- Tirzepatide used at any dose, frequency, or duration;

- Comparator groups comprising placebo, no treatment, or approved glucose-lowering agents (e.g., GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors, insulin, sulfonylureas);
- RCTs or observational studies;
- Published in English.

Exclusion Criteria:
Studies were excluded if they met any of the following:

- Participants <18 years;
- Type 1 diabetes mellitus;
- BMI below defined thresholds;
- Animal or in vitro studies;
- Prior history of pancreatitis;
- Non-English publications;
- Case reports, case series (<5 patients), dissertations, conference abstracts, or review articles;
- Studies without a control group;
- Non-randomised trials with inadequate methodological detail;
- Follow-up period <4 weeks or unclear treatment duration;
- Invalid or inappropriate statistical methods;
- Duplicate or non-original research;
- Comparator groups or outcomes not aligned with the objectives of this review.

Data Extraction

7 Data extraction was performed using a standardised template, summarised in Table 2. Extracted variables included study characteristics, participant demographics, intervention details, comparator information, outcome definitions, subgroup data, statistical metrics, and follow-up duration.

Data Synthesis

8 Statistical analysis was conducted using RevMan 5.3. Heterogeneity among studies was quantified using the I^2 statistic and categorised as low (<50%), moderate (50–69%), or high (≥70%). A fixed-effect model was applied when heterogeneity was low (I^2 <50%, p >0.1); otherwise, random-effects models were used. Given the variability in study populations and designs, random-effects models were applied for all primary analyses.

Where substantial heterogeneity was detected, sensitivity analyses and descriptive comparisons were performed to explore potential contributing factors. Pooled effect

estimates were summarised as odds ratios with 95% confidence intervals to evaluate the association between tirzepatide and acute pancreatitis.

Quality Assessment

9 Risk of bias assessment was carried out using validated tools appropriate to study design: the Cochrane RoB 2.0 tool for RCTs [6], the ROBINS-I tool for non-randomised studies [7], and the JBI checklist for case series [8]. The Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence was used to grade overall study quality [9]. Publication bias was evaluated via Egger's regression test and visual inspection of funnel plot asymmetry, with significance defined as $p < 0.05$ [10].

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