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Authors' Affiliation:
[1]Collegium Medicum, Jan Kochanowski University, Kielce, Poland
[2]The University Hospital in Krakow, Poland
[3]St. Alexander Hospital in Kielce, Poland

***Corresponding author**
Filip Maj
Collegium Medicum, Jan Kochanowski University, Kielce, Poland; Email: filip.jacek.maj@gmail.com

Contact:

Filip Maj:	filip.jacek.maj@gmail.com
Anna Klasa:	klasa.annamaria@gmail.com
Justyna Gręda:	justyna.jurek26@gmail.com
Karol Mateusz Wojnarowski:	wojnarowskikarol@gmail.com
Bartosz Zieliński:	bartoszzielinski1912@gmail.com

Orcid:

Filip Maj	0009-0009-8448-9467
Anna Klasa	0009-0005-0461-0599
Justyna Gręda	0009-0006-5072-1035
Karol Mateusz Wojnarowski	0009-0001-7683-7945
Bartosz Zieliński	0009-0005-5954-6037

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DISCOVERY SCIENTIFIC SOCIETY

The impact of tirzepatide on the development of pancreatitis: a literature review

Filip Maj[1*], Anna Klasa[2], Justyna Gręda[3], Karol Mateusz Wojnarowski[3], Bartosz Zieliński[3]

ABSTRACT

Background: Tirzepatide, a dual GIP/GLP-1 receptor agonist is a new drug used in type 2 diabetes and obesity. However, concerns persist about its potential association with pancreatitis due to the expression of GLP-1 receptors in pancreatic cells. This review evaluates the available evidence on tirzepatide's pancreatic safety profile. *Materials and methods:* The MEDLINE database was searched. The search query used was "tirzepatide AND pancreatitis" with one filter "free full text". The initial search returned 41 results. After screening abstracts, 32 results were chosen for complete text analysis, of which 6 met the inclusion criteria and were included in the study. *Results:* Across all studies, pancreatitis incidence was consistently low (<1%) with no dose-dependent relationship. While some studies reported elevated pancreatic enzymes, these changes did not correlate with clinical pancreatitis. Real-world data confirmed no disproportionate reporting of pancreatitis cases. *Conclusions:* Current evidence suggests that tirzepatide does not increase the risk of pancreatitis compared to other antidiabetic drugs. Although, to confirm this hypothesis, further studies with longer follow-ups and larger patient groups are needed.

Keywords: tirzepatide, pancreatitis, gip/glp-1 receptor agonist, type 2 diabetes mellitus, obesity

1. INTRODUCTION

Obesity is a multifactorial and chronic disease that poses a serious public health threat. One of the main challenges is the rapidly increasing global prevalence and associated comorbidities such as type 2 diabetes mellitus (T2DM), cardiovascular disease, and non-alcoholic fatty liver disease. According to data, 650 million adults and 340 million children are obese. Projections indicate a further increase in prevalence, particularly in developing regions (Cai et al., 2024; Ghusn & Hurtado, 2024; Gong et al., 2025). In addition to the metabolic consequences, obesity is associated with a high cardiovascular risk and the development of diabetes, which can lead to death (Cai et al., 2024).

Given the low efficacy of lifestyle modification and the high risk of bariatric surgery, anti-obesity drugs (AOM) are becoming an increasingly integral part of

obesity treatment. Among them, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and more recently dual GLP-1/glucose insulinotropic polypeptide (GIP) receptor agonists, have shown efficacy in lowering glycaemia and reducing body weight. Tirzepatide, a novel dual GIP/GLP-1 receptor agonist, was approved by the US Food and Drug Administration (FDA) in 2022 to treat T2DM. It was also approved in 2023 for the treatment of obesity, following favorable results in the SURPASS and SURMOUNT trials (Cai et al., 2024; Caruso et al., 2024; Ghusn & Hurtado, 2024; Mishra et al., 2023).

Tirzepatide increases insulin secretion, inhibits glucagon release, delays gastric emptying and stimulates feeling of fullness through activation of the dual incretin receptor. Its component GIP specifically increases adipose tissue sensitivity to insulin and lipid buffering, while GLP-1 contributes to appetite regulation and delayed gastric motility (Kamrul-Hasan et al., 2024; Mishra et al., 2023). These effects cause a higher effectiveness of tirzepatide in reducing body weight and HbA1c compared to traditional GLP-1 RA (Caruso et al., 2024).

However, despite the sound effect of the treatment, there are still concerns about the safety of the impact on the exocrine pancreas. GLP-1 receptors are expressed in pancreatic islet cells and pancreatic duct cells, where chronic stimulation can induce hyperplasia or low-grade inflammation. This could potentially increase the risk of acute pancreatitis. Although early GLP-1-based therapies raised the alarm about pancreatitis, and exendin-4 analogs have been shown to alter the expression of pancreatic genes involved in inflammatory responses, it remains unclear whether tirzepatide, with its dual receptor activity and stronger affinity for GIP, is associated with a similar risk (Kamrul-Hasan et al., 2024).

Previous reports, including those sent to the FDA's safety system (FAERS), make it hard to be sure about the risks. In some studies chance of gallbladder or bile duct problems when using tirzepatide was higher. Pancreatitis still seems to be rare, and the overall risk does not appear higher than with other drugs like basal insulin or GLP-1 receptor agonists. Still, many of the trials analyzed in past reviews didn't specifically examine pancreatic risks, which leaves essential gaps in the data (Caruso et al., 2024; Kamrul-Hasan et al., 2024).

This study focuses on whether there might be a link between tirzepatide use and pancreatitis in people living with type 2 diabetes or obesity. By drawing on findings from clinical trials and post-marketing safety reports, the goal is to offer more reliable insights for clinicians weighing possible inflammatory risks.

2. MATERIALS AND METHODS

2.1. Data collection

The MEDLINE database was searched. The following search query was used: "tirzepatide AND pancreatitis" with one filter "free full text". Five independent researchers screened the results. The initial search returned 41 results. After screening abstracts, 32 results were chosen for complete text analysis, of which 6 met the inclusion criteria and were included in the study. All included studies are from January 2023 to January 2025.

2.2. Selection criteria

A flowchart of study inclusion is presented in Figure 1. Inclusion and exclusion criteria studies were included in the analysis if predefined PICO criteria were met (Table 1).

Table 1. PICO criteria used in the study

PICO	Description
Patients	Children and adults with type 2 diabetes or obesity receiving antidiabetic treatment
Intervention	Treatment with tirzepatide
Comparisons	Placebo or other interventions not involving tirzepatide
Outcomes	Incidence or risk of developing pancreatitis

2.3. Quality assessment

This review was performed according to PICO (Patients, Interventions, Comparisons, Outcomes) guidelines.

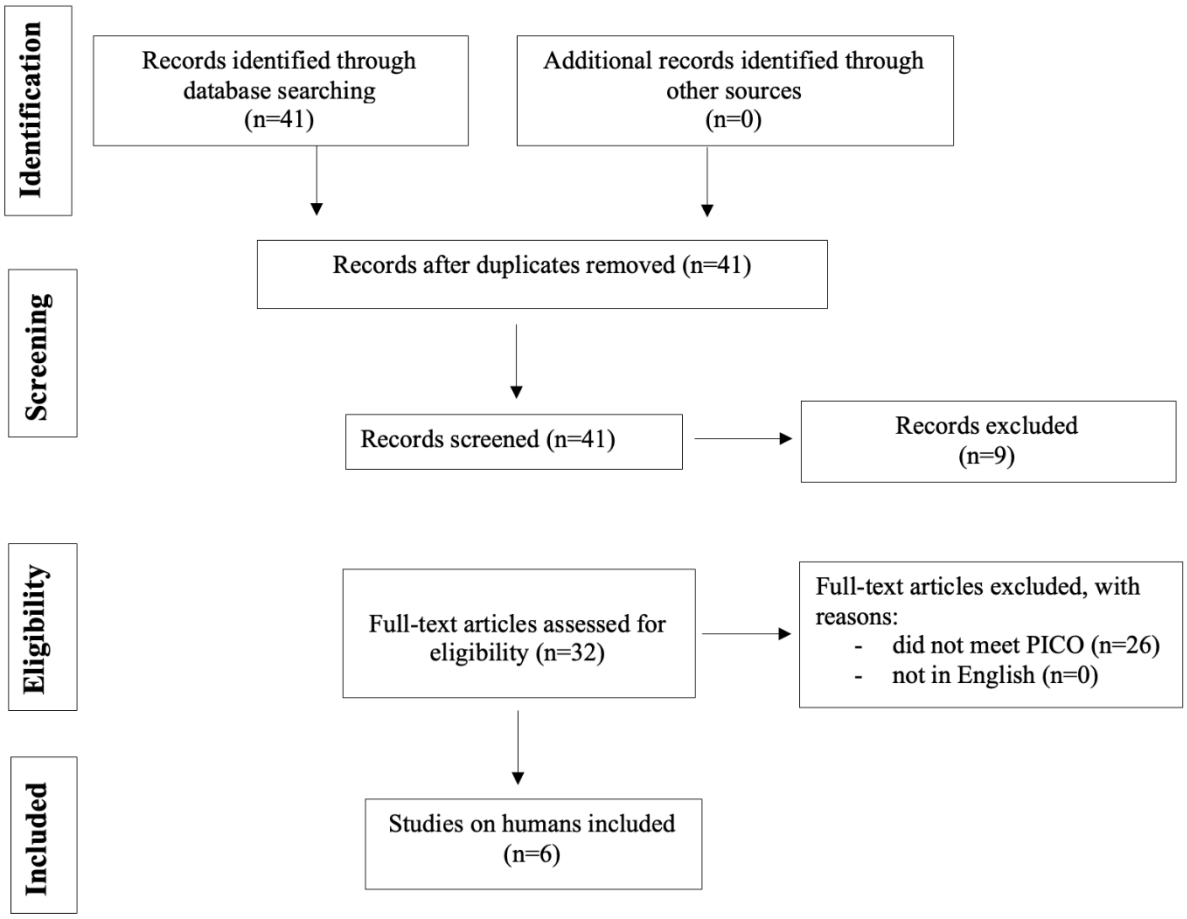

Figure 1. PRISMA protocol for data acquisition

3. RESULTS AND DISCUSSION

3.1. Characteristics of studies

This section provides a detailed overview of the six studies analyzed in this review. Each study evaluated the incidence of pancreatitis preceded by tirzepatide treatment. The consensus across all studies suggests that tirzepatide does not affect the development of pancreatitis more than placebo or other drug groups. However, differences in study design, patient selection, and methodology contribute to the variability in reported results.

3.1.1. Study Descriptions

Cai et al., (2024) analyzed 8142 patients treated with tirzepatide. Adverse effects in the form of pancreatitis were reported in 10 patients. Based on the available data. The risk of pancreatitis associated with tirzepatide appears to be comparable to that observed with GLP-1 receptor agonists, but higher than that seen with insulin or placebo. This suggests that while tirzepatide does not substantially increase the risk relative to other incretin-based therapies, it may carry a modestly elevated risk of pancreatitis when compared to non-incretin treatments such as basal insulin or placebo.

The strength of this study is the relatively large group of patients treated with tirzepatide, altenative drugs and the placebo group. A key limitation of this study is that the difference in pancreatitis incidence between tirzepatide and the control groups was small. Caruso et al., (2024) Examined 20,409 patients treated with tirzepatide. Adverse effects in the form of pancreatitis were reported in 218 patients. Real-world data from the FAERS database suggest that tirzepatide does not increase the risk of pancreatitis compared to other glucose-lowering medications. Tirzepatide has a high glucose-lowering efficacy. The study showed that it increased the risk of gastrointestinal side effects, while it had no effect on the higher incidence of pancreatitis. The results show that tirzepatide is safe for the pancreas.

This study reveals potential correlation between tirzepatide and pancreatitis. One of the biggest strengths is using the FAERS database, which shows real-world adverse event. Because of it we got all adverse events, including rare events such as pancreatitis. SURPASS program did not show higher risk of pancreatitis with tirzepatide use. However, there are also limitations. The FAERS database is a spontaneous report, so there could be potential missing data. In many cases, the time of symptoms, drug dose, patient history, or comorbidities are missing. In addition, the relatively short follow-up period - about the first 16 months after approval of tirzepatide - may not be sufficient to capture adverse events of late onset. All the data suggest that tirzepatide is safe. However, further safety studies and long-term studies are needed to definitively rule out the risk of pancreatitis associated with the use of tirzepatide.

Ghusn & Hurtado, (2024) Studied 497 patients treated with tirzepatide. Adverse effects in the form of pancreatitis were reported in 1 patient. Based on current clinical trial data, tirzepatide does not appear to increase the risk of pancreatitis. In a study comparing different doses of tirzepatide and placebo, four cases of pancreatitis were reported, with one case occurring in each group, including the placebo arm, suggesting no dose or drug regimen dependence. None of these events was classified as severe. This contrasts with other GLP-1 receptor agonists, such as liraglutide and semaglutide, where more cases of pancreatitis were observed. However, these were often associated with pre-existing conditions such as gallstones or a history of pancreatitis. Moreover, systematic reviews and meta-analyses have consistently shown that while GLP-1-based therapies can lead to mild elevations in pancreatic enzyme levels, they are not associated with a significant increase in the incidence of acute pancreatitis or pancreatic cancer. Overall, the current evidence supports the pancreatic safety of tirzepatide.

The study evaluating the impact of tirzepatide on the development of pancreatitis has several strengths. Firstly, cases of pancreatitis were evenly distributed across all treatment groups, including the placebo group, which suggests no connection between tirzepatide and pancreatitis. Secondly, including different tirzepatide doses could show the difference in adverse events. However, there are also limitations. There were low numbers of pancreatitis, which reduced the precision of the conclusions. The observation time may not be enough to detect longer-term risks. Moreover, the study lacks detailed information about participants' risk factors, such as prior history of pancreatitis, gallstones, or hypertriglyceridemia. Finally, as the data are derived from clinical trials, the findings may not fully apply to real-world populations where patients often have more complex medical histories.

Gong et al., (2025) Included 8173 patients treated with tirzepatide. Adverse effects in the form of pancreatitis were reported in 18 patients. This meta-analysis examined data from 12 randomized controlled trials involving patients with type 2 diabetes or obesity to assess the association between tirzepatide and biliary diseases, including pancreatitis, cholelithiasis, and cholecystitis. The results showed no significant increase in pancreatitis risk (RR = 1.29, 95% CI: 0.66–2.53), consistent findings across different dosages (5 mg, 10 mg, 15 mg). However, tirzepatide was linked to a higher incidence of gallbladder/biliary diseases, particularly gallstones at the 5 mg dose. This study gives a lot of important clinical information and reveals the need for further long-term research.

The study analysis is characterised by a detailed methodology. It has a high-quality randomized controlled trial with a large sample of patients. The researchers used the Cochrane Collaboration's risk of bias tool and I^2 statistics to ensure methodological validity. Unlike previous studies, this meta-analysis focused on biliary complications. In addition, examination of the effect of individual drug doses showed a dose dependency. Risks were higher at lower drug doses. Despite its strengths, this study also has limitations. It has a short follow-up time (12-72 weeks), which may not be enough to assess long-term biliary risk. The exclusive reliance on RCTs may limit the applicability of the results. The results show that higher doses of medication reported zero adverse events, which raises questions about the validity of these results. One hypothesis may be that this study has insufficient data. Patients from different ethnic and geographical groups may further introduce variability that is not considered.

Kamrul-Hasan et al., (2024) Investigated 4328 patients treated with tirzepatide. Adverse effects in the form of pancreatitis were reported in 10 patients. This meta-analysis of 17 randomized controlled trials found no significant increase in pancreatitis risk with tirzepatide compared to placebo, insulin, or GLP-1 receptor agonists (RR = 1.29, 95% CI: 0.66–2.53). While tirzepatide caused greater rises in pancreatic enzymes (amylase and lipase), these changes did not affect the development of pancreatitis. The findings suggest that tirzepatide's pancreatic safety profile is comparable to other diabetes treatments. The study provides strong evidence through a complex assessment of 17 randomised controlled trials that tirzepatide is safe for the pancreas. Standardized criteria for assessing pancreatitis were used in all studies.

By comparing tirzepatide against multiple control groups (placebo, insulin, and GLP-1 receptor agonists), the analysis shows clinically relevant safety indicators. The dose-specific evaluation (5 mg, 10 mg, and 15 mg) enhances practical applicability for prescribing decisions. Significantly, consistent results across all studies (I^2 = 0%) increase confidence in the conclusions. The use of

adjudication-confirmed pancreatitis cases rather than just laboratory abnormalities represents a particular strength in outcome assessment.

Several constraints should be considered when interpreting these findings. The relatively short duration of included trials (12-72 weeks) may not capture potential long-term pancreatic effects. The analysis was limited to controlled trial data, excluding real-world evidence that might differ from others. While pancreatic enzyme elevations were documented, the clinical significance of these biochemical changes needs longer observation. The study population differences provide potential variability in pancreatitis risk that wasn't fully characterized. These factors suggest the need for ongoing pharmacovigilance as tirzepatide use expands in clinical practice.

Mishra et al., (2023) analyzed 4419 patients treated with tirzepatide. Adverse effects in the form of pancreatitis were reported in 22 patients. This meta-analysis evaluated the risk of acute pancreatitis associated with tirzepatide, a dual GIP and GLP-1 receptor agonist, across 10 clinical trials. Total frequency of acute pancreatitis was low (<1%) for all tirzepatide doses (5 mg: 0.39%; 10 mg: 0.36%; 15 mg: 0.32%), with no significant dose-dependent increase. Elevated lipase levels were more frequent with higher doses (15 mg: 6.86%), but clinical pancreatitis remained rare. These findings suggest that tirzepatide does not substantially increase the risk of acute pancreatitis compared to placebo. The study provides a comprehensive analysis of tirzepatide-related adverse events, including rare outcomes like pancreatitis, using rigorous meta-regression methods. It has data from multiple studies to maintain correct judgment. An analysis comparing not only placebo but also different doses of Tirzepatide provides insight into the broader context of Tirzepatide's adverse effects.

Limitations of the study are based on short-term study data. This limits insight into the long-term risk of pancreatitis. Differences in the reporting of AEs across studies may influence imprecise interpretations. In addition, the low prevalence of pancreatitis reduces statistical precision. Based on these studies, tirzepatide - a dual GIP and GLP-1 receptor agonist - does not appear to be associated with a higher risk of pancreatitis compared to placebo or other antidiabetic medications. The analyzed research shows a low incidence of pancreatitis, generally below 1% across all tirzepatide dosage groups, with no clear dose-dependent relationship. While some studies observed slightly elevated levels of pancreatic enzymes (amylase and lipase), these changes did not translate into clinically significant cases of pancreatitis. The findings from randomized controlled trials are further supported by real-world data analyses, including reports from the FAERS database, which found no disproportionate reporting of pancreatitis events. However, it should be noted that most of the studies had relatively short follow-up periods, usually less than 72 weeks, and included mainly controlled populations rather than actual patients with complex comorbidities.

Therefore, while current evidence suggests tirzepatide has a favorable pancreatic safety profile, continued pharmacovigilance and longer-term observational studies would be valuable to confirm these findings fully, particularly in broader patient populations and over extended treatment durations. Clinicians should maintain awareness of potential gastrointestinal side effects while recognizing that available data do not indicate a substantial pancreatitis risk with tirzepatide therapy.

3.2 Analysis

In the study by Cai et al., (2024), 8142 patients were treated with tirzepatide, 10 of them developed pancreatitis. The incidence of pancreatitis during tirzepatide therapy was 0.12%. In the study by Caruso et al., (2024), 20409 patients were treated with tirzepatide, 218 of them developed pancreatitis. The incidence of pancreatitis during tirzepatide therapy was 1.07%.

In the study by Ghusn and Hurtado (2024), 497 patients were treated with tirzepatide, and 1 of them developed pancreatitis. The incidence of pancreatitis during tirzepatide therapy was 0.20%. In the study by Gong et al., (2025), 8173 patients were treated with tirzepatide, 18 of them developed pancreatitis. The incidence of pancreatitis during tirzepatide therapy was 0.22%.

In the study by Kamrul-Hasan et al., (2024), 4328 patients were treated with tirzepatide, 10 of them developed pancreatitis. The incidence of pancreatitis during tirzepatide therapy was 0.23%. In the study by Mishra et al., (2023), 4419 patients were treated with tirzepatide, 22 of them developed pancreatitis. The incidence of pancreatitis during tirzepatide therapy was 0.49%. Based on Figure 2, we can see that the Percentage of pancreatitis was between 0.12% and 1.07%.

This literature review provides information on the association between tirzepatide and the risk of pancreatitis. However, this study has several limitations that must be considered. One of the biggest limitations is the short observation time, typically 12 to 72 weeks. Especially given that chronic exposure to incretin-based therapies can, in theory, induce progressive pancreatic changes. The clinical trial data may not fully capture real-world scenarios. Patients often present with more complex comorbidities and concomitant medications that could potentially modify pancreatitis risk.

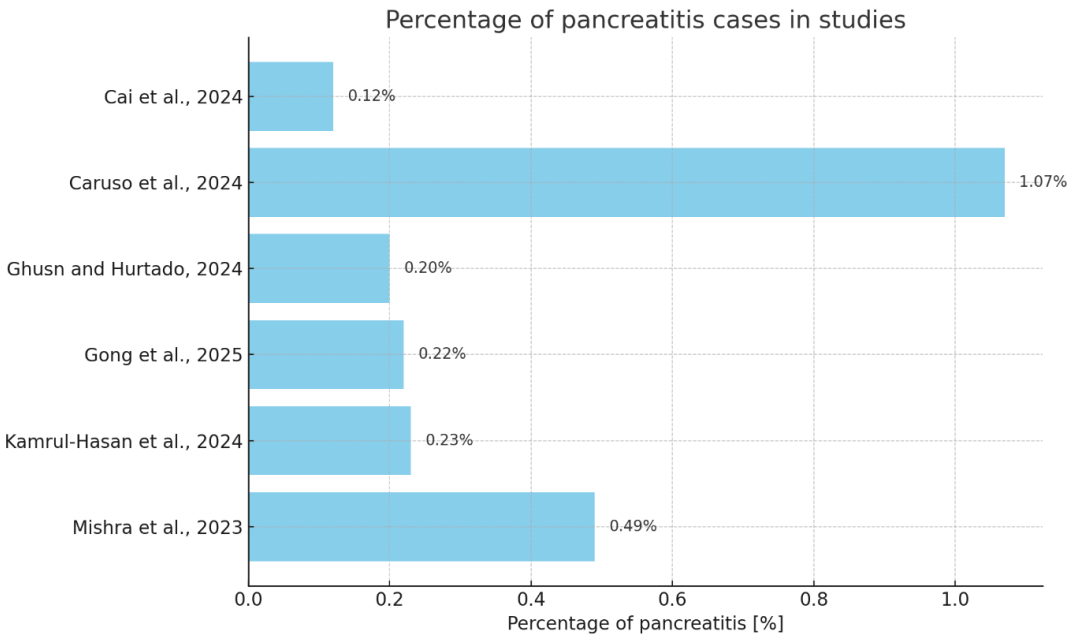

Figure 2. Percentage of pancreatitis cases in studies

Another significant limitation is the systematic exclusion of high-risk populations in most clinical trials. Patients with pre-existing pancreatic conditions, severe hypertriglyceridemia, or a history of pancreatitis were typically excluded from participation. This has resulted in missing data for anticoagulant-treated patients. Reliance on spontaneous reporting systems such as FAERS introduces potential reporting bias. This system belongs to voluntary reporting from providers, which may not include comprehensive clinical details. Furthermore, the observed heterogeneity in study designs, including differences in pancreatitis diagnostic criteria and monitoring protocols, complicates direct comparisons between studies and may falsify risk.

There are several opportunities to improve future research in this area. Extending the duration of observation in current trials would provide key data on long-term pancreatic safety. Prospective registries specifically designed to monitor tirzepatide-treated patients with pre-existing pancreatic risk factors could fill essential evidence gaps. Standardization of pancreatitis diagnostic criteria and monitoring protocols improves data comparison. Future use of more advanced imaging techniques and biomarker panels could be more sensitive in detecting pancreatic lesions.

From a clinical practice perspective, current evidence suggests that, although tirzepatide shows a favorable pancreatic safety profile in clinical trials. Careful monitoring remains advisable, particularly in the initial phase of treatment. Doctors should be alert to all symptoms of pancreatitis. Particularly in patients with known risk factors, while recognizing that the absolute risk appears low based on the available data. These findings support the continued use of tirzepatide in appropriate patient populations, with the assumption that ongoing pharmacovigilance and further studies will continue to improve our knowledge.

4. CONCLUSIONS

Summary data from multiple studies show that treatment with tirzepatide is not associated with an increased incidence of pancreatitis, compared to placebo and other antidiabetic drug groups. The incidence of pancreatitis in all studies was low, less than 1% of treated patients. Moreover, there was no visible dose dependence. Although some studies reported moderate elevations in pancreatic enzymes, these biochemical changes did not correlate with clinical cases of pancreatitis. Tirzepatide can be considered a safe therapeutic option for appropriate patients with type 2 diabetes or obesity, with pancreatic safety comparable to other incretin-based therapies. Routine monitoring of pancreatic enzymes appears unnecessary in asymptomatic patients, although clinicians should be alert to symptoms of pancreatitis. This is especially important at the start of treatment.

Future studies should focus on a longer follow-up time and consider a high-risk population to provide more definitive safety conclusions. Until such data are available, the weight of the current evidence supports the reasonable use of tirzepatide in clinical practice, with appropriate monitoring and awareness of potential adverse effects. The favourable benefit-to-risk profile observed in this analysis suggests that concerns about pancreatitis should not deter clinicians from considering tirzepatide when clinically indicated. However, continuous monitoring and further research remain essential components of responsible pharmacotherapy.

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Author's Contributions
Filip Maj - study design, data collection, statistical analysis, interpretation of data, manuscript preparation, literature review
Anna Klasa - study design, data collection, statistical analysis, interpretation of data, manuscript preparation, literature review
Justyna Gręda - data collection, literature review
Karol Mateusz Wojnarowski - data collection, literature review
Bartosz Zieliński - data collection, literature review

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Not applicable.

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Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data associated with this study are present in the paper.

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