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DUAL BENEFITS AND RISKS: TIRZEPATIDE'S IMPACT ON PANCREATIC FUNCTION

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Abstract

Tirzepatide is a new GLP-1 and GIP receptor agonist. We have seen good results in managing type 2 diabetes and obesity using Tirzepatide by improving glycemic control and promoting significant weight loss. The effects on the pancreas include enhanced glucose-dependent insulin secretion, reduced glucagon production, and potential protective actions on beta-cell function and survival among other. Rare cases of acute pancreatitis, such as severe necrotizing pancreatitis, have been reported however. Thus, we need close monitoring of patients for abdominal pain, nausea, or vomiting. While tirzepatide has benefits for metabolic health, its use requires careful supervision to lower the potential pancreatic risks. This highlights the importance of balancing its therapeutic advantages with vigilant monitoring for adverse effects.

Rezumat

Tirzepatida este un nou agonist al receptorilor GLP-1 si GIP. Rezultatele obținute în gestionarea diabetului de tip 2 și obezității cu tirzepatida sunt promițătoare, prin îmbunătățirea controlului glicemic și promovarea unei pierderi semnificative în greutate. Efectele asupra pancreasului includ stimularea secreției de insulină dependentă de glucoză, reducerea producției de glucagon și acțiuni potențial protectoare asupra funcției și supraviețuirii celulelor beta, printre

Internal Medicine

General Reviews

altele. Totuși, au fost raportate cazuri rare de pancreatită acută, precum pancreatita necrozantă severă. Prin urmare, este necesară monitorizarea atentă a pacienților pentru dureri abdominale, greață sau vomă. Deși tirzepatida are beneficii pentru sănătatea metabolică, utilizarea sa necesită o supraveghere riguroasă pentru a reduce riscurile potențiale asupra pancreasului. Acest lucru subliniază importanța echilibrării avantajelor terapeutice cu monitorizarea atentă a efectelor adverse.

Introduction

Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Besides the treatment of diabetes, it is also indicated in obesity, one of the main factors that disrupt metabolic health. By activating both receptors, tirzepatide enhances insulin secretion, suppresses glucagon release, and promotes weight loss, leading to improved glycemic control and cardiovascular outcomes.[1]

Tirzepatide reduces hemoglobin A1c (HbA1c) levels and body weight in patients with type 2 diabetes mellitus (T2DM). A systematic review [2] reported that tirzepatide achieved better weight loss results compared to other treatments, with patients experiencing important and massive reductions in body weight.

Besides glycemic control, tirzepatide helps with reducing cardiovascular risk factors. Studies [3] indicate reductions in systolic blood pressure, low-density lipoprotein (LDL) cholesterol, and triglycerides, resulting in a lower risk of major adverse cardiovascular events (MACE).

Gastrointestinal symptoms, including nausea, diarrhoea, vomiting, and constipation, are among the most frequently reported adverse events, typically presenting as mild to moderate and transient in nature[4].

Tirzepatide and the side effects on the pancreas

The mechanism of action of tirzepatide allows it to have multiple effects on metabolic pathways. These effects include : enhanced glucose-dependent insulin secretion from pancreatic beta cells, suppression of glucagon release from alpha cells, and significant improvements in insulin sensitivity. It is also great for weightloss, a crucial factor in managing the cardiovascular

and metabolic complications associated with obesity and T2DM. Clinical trials have consistently demonstrated tirzepatide's superior efficacy in reducing haemoglobin A1c levels and achieving substantial weight loss compared to existing therapeutic options. Despite these therapeutic benefits, the use of tirzepatide, an incretin-based therapy, has been associated with rare but severe adverse effects, including acute pancreatitis. While the pathophysiological mechanisms between tirzepatide and pancreatic inflammation are not fully understood, its actions on pancreatic receptors and its impact on hormonal and metabolic homeostasis may contribute to the development of pancreatitis in certain individuals.

A case report[5] presented a case of necrotizing pancreatitis associated with tirzepatide therapy, a rare but severe adverse reaction to this dual GIP and GLP-1 receptor agonist. The patient developed fulminant necrotizing pancreatitis shortly after initiating tirzepatide treatment. The progression was rapid towards a fatal outcome despite medical intervention. This shows there is a potential mechanisms by which tirzepatide may contribute to pancreatic inflammation. One of the factors to blame is the pharmacodynamic effects on pancreatic hormones such as insulin and glucagon. By stimulating insulin secretion and suppressing glucagon release, tirzepatide alters the metabolic and hormonal status of the pancreas, which may exacerbate or trigger inflammatory responses in certain individuals. This is particularly critical in patients with predisposing factors such as obesity, gallbladder disease, a prior history of pancreatitis, or other conditions that compromise pancreatic health.

Another case reports [6] a 38-year-old woman undergoing tirzepatide treatment for prediabetes who developed mild acute pancreatitis. Unlike the severe case, this instance was less critical and resolved with conservative management, including stopping tirzepatide treatment. The symptoms occurred shortly after the patient began treatment, suggesting a causal link. This shows that even patients without a history of pancreatitis or significant comorbidities may still be at risk. It also reinforces the need for healthcare providers to educate patients about early warning signs of pancreatitis, such as persistent nausea, vomiting, and abdominal pain.[6]

The incidence of pancreatitis and gallbladder or biliary diseases in patients treated with incretin-based therapies is also highlighted. [7] While the overall risk of pancreatitis was found to be low, the study identified a slightly elevated risk compared to control groups. The exact mechanism is unknown, however, it is thought that the incretin effect, which stimulates pancreatic beta cells and alters glucagon secretion, might contribute to the development of pancreatic inflammation. However, it was noted that the benefits of tirzepatide in improving metabolic health often outweigh the risks when the therapy is properly monitored.[7]

Physiopathological and biochemical mechanisms responsable for the increased risk of pancreatitis during tirzepatide use

The development of pancreatitis during the use of tirzepatide so far is thought be caused by a combination of physiological and biochemical mechanisms that affect the pancreas. Although the precise mechanism remains unknown, there are a few pathways that can provide insight into how this may occur.

Tirzepatide enhances the secretion of insulin from pancreatic beta cells and suppresses glucagon release from alpha cells in a glucose-dependent manner. While this improves glycemic control, the overstimulation of pancreatic islets may lead to cellular stress, especially in individuals with underlying issues such as chronic inflammation, obesity, or insulin resistance. Long overstimulation will exacerbate pancreatic workload and inflammation, increasing the risk of pancreatitis.[8]

GLP-1 receptor activation also influences exocrine pancreatic functions. It alters the secretions of pancreatic ducts, leading to ductal obstruction or impaired enzyme outflow. This can cause digestive enzymes such as trypsin to activate prematurely within the pancreas, leading to autodigestion and inflammation—a sign of acute pancreatitis. [9]

Another study [10] investigated the impact of GLP-1 receptor activation on pancreatic masses. The researchers observed that GLP-1 receptor agonists increased pancreatic masses by promoting cellular proliferation. While this effect could be beneficial for enhancing insulin secretion, it also raises concerns about the potential for inducing pancreatic ductal proliferation, which may lead to ductal obstruction and impaired enzyme outflow. Such modifications can result in early activation of digestive enzymes within the pancreas, leading to autodigestion and inflammation characteristic of acute pancreatitis. Tirzepatide slows gastric emptying and reduces appetite, which contributes to significant weight loss. However, rapid weight loss is associated with the formation of gallstones or biliary sludge, which are well-known risk factors for pancreatitis. These substances can obstruct the common bile duct or the pancreatic duct, leading to reflux of bile and activation of pancreatic enzymes, triggering acute inflammation.[11]

GLP-1 receptor agonists, including tirzepatide, can induce localized inflammation in the pancreas due to their effects on immune cell modulation. It is suggested that incretin therapies could influence inflammatory cytokines and chemokines in the pancreatic microenvironment, sensitizing the tissue to inflammatory insults.[12]

Some individuals may have genetic factors that make them more susceptible to drug-induced pancreatitis. Conditions such as chronic pancreatitis, a history of gallbladder disease, or excessive alcohol use could amplify the risk when combined with tirzepatide's pharmacological effects.[13]

Table 1, ,,Pathways leading to Pancreatitis with Tirzepatide", concisely group and show all of the secondary effects of Tirzepatide usage, depending on the pathways used. Additionally, table 2, ,,Distribution of Risk Factors Leading to Pacreatitis with Tirzepatide" presents the risk factors as percentages.

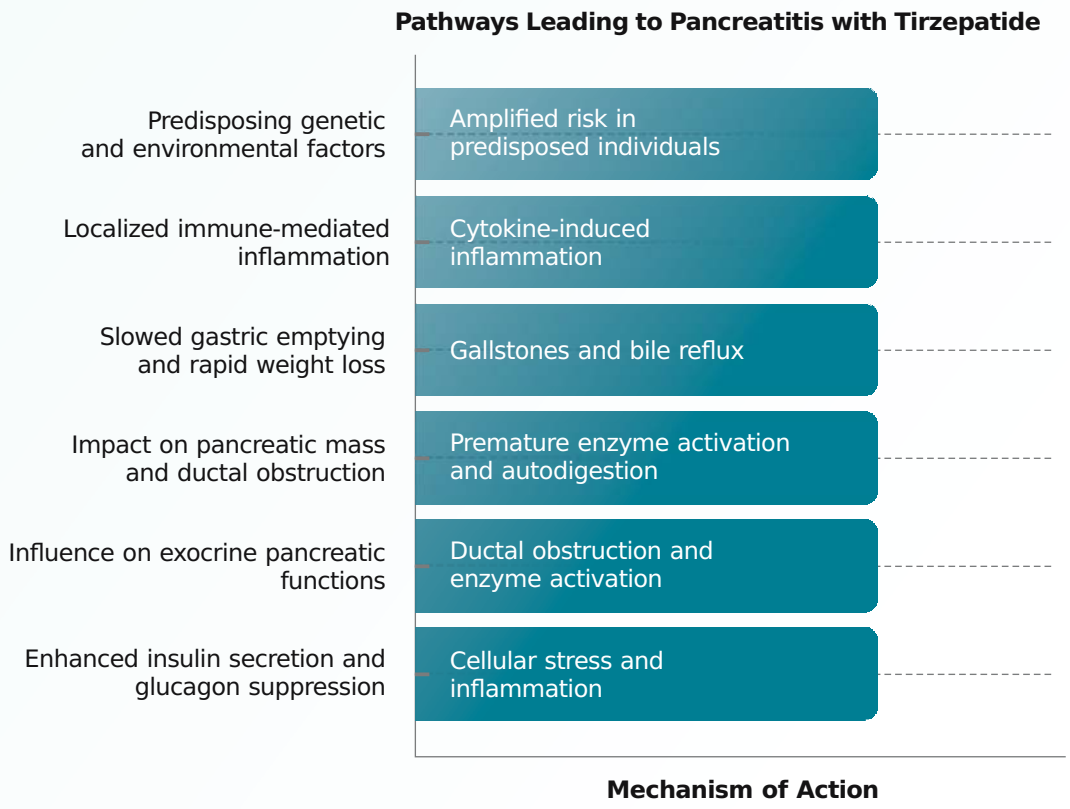

Figure 1. *Pathways Leading to Pancreatitis with Tirzepatide*

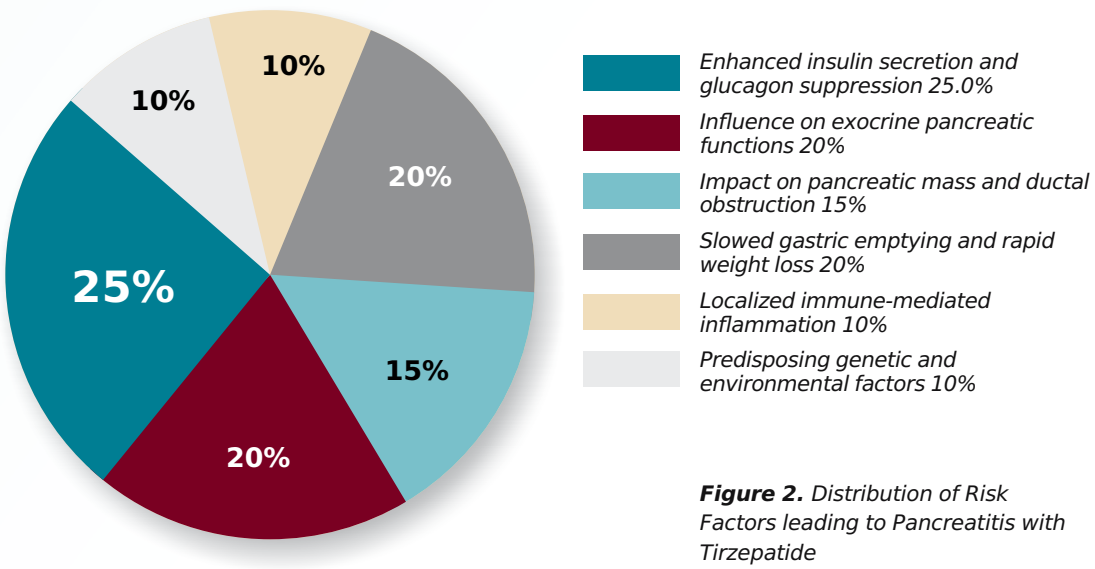

Figure 2. *Distribution of Risk Factors leading to Pancreatitis with Tirzepatide*

Obesity, cognitive function impairment and pancreatic reactions - the surprising triad

As stated before [2] [4], obesity is one of the risk factors involved in a multitude of diseases and is one of the criteria for starting therapy with Tirzepatide, seeing that its pharmacological action works on obesity as well. However, obese patients need special care due to how the excess fat affects the organism as a whole, leading to metabolic issues as well that affect the pancreas.

A study [14] explores the connection between sleep deprivation, obesity, and pancreatic function. This shows that poor sleep is linked to metabolic disorders such as type 2 diabetes and obesity, due to metabolic dysregulation and immune responses affecting pancreatic islet cells. These cells are crucial for insulin production and glucose regulation, suggesting that sleep deprivation may impair pancreatic function, contributing to obesity and diabetes.

Additionally [15], clinicians discuss how lack of sleep serves as a risk factor for cardiometabolic disorders, including obesity and diabetes. Sleep deprivation induces metabolic changes similar to ageing, affecting various tissues and pancreatic function.

One of the less-known side effects of obesity is the disturbance of sleep patterns and sleep-related pathologies [16]. Sleep is essential for cognitive processes, including learning and memory consolidation. Insufficient sleep disrupts these functions, leading to impaired memory retention and reduced learning capacity. Ensuring adequate sleep is critical for maintaining cognitive health, and understanding the complex interactions between sleep, hormones, and brain function. Insufficient sleep disrupts neural mechanisms essential for retaining and processing information, leading to diminished cognitive performance. [17].

Factors such as age, hormonal differences, and sex influence the extent of these effects, with women and older individuals exhibiting increased susceptibility. Understanding the interactions between sleep patterns, hormonal regulation, and cognitive health highlights the critical importance of sufficient sleep in maintaining optimal brain function and mitigating the risks of cognitive decline.

It was also found that fibrinogen and C-reactive protein (CRP) levels are elevated during exacerbations of Chronic Obstructive Pulmonary Disease (COPD) in patients classified as groups C and D. [18] Patients with COPD are usually obese as well, triggering other diseases such as pancreatic reactions. Higher concentrations of these fibrinogen and CRP are associated with increased disease severity and a greater likelihood of hospital admissions. Elevated levels also correlate with a heightened risk of future exacerbations and worse outcomes.

The interplay between obesity, sleep deprivation, and metabolic health highlights the versatile challenges these conditions present.

Obesity, a risk factor for numerous diseases, exacerbates metabolic disturbances, including those affecting pancreatic function. Sleep deprivation compounds these issues by disrupting metabolic regulation, increasing the risk of type 2 diabetes and other cardiometabolic disorders.

Additionally, sleep disturbances can impair cognitive processes, with hormonal and age-related factors influencing susceptibility. In patients with conditions such as COPD, the combined effects of obesity and metabolic dysregulation further worsen outcomes, as evidenced by elevated fibrinogen and CRP levels during exacerbations. Addressing obesity and sleep deprivation as interconnected health concerns is essential for improving overall metabolic health, preventing complications, and enhancing the management of conditions like COPD. Emphasizing the importance of adequate sleep, targeted therapeutic interventions, and personalized care strategies can mitigate the cascading effects of these interconnected health issues.

Conclusion

Tirzepatide has demonstrated great efficacy in enhancing glycemic control, promoting significant weight loss, and improving cardiovascular health. Its dual action as a GIP and GLP-1 receptor agonist leads to enhanced insulin secretion, suppressed glucagon release, and improved insulin sensitivity, providing substantial metabolic benefits.

Even so, rare but serious adverse effects, especially acute pancreatitis, are associated to long term tirzepatide treatment. While the mechanisms linking the drug to pancreatitis remains unknown, several pathways have been identified. Overstimulation of pancreatic islets due to enhanced insulin secretion may induce cellular stress, especially in patients with conditions such as chronic inflammation, obesity, or insulin resistance. GLP-1 receptor activation influences exocrine pancreatic functions, leading to ductal obstruction, impaired enzyme outflow, and premature activation of digestive enzymes within the pancreas.

This will prompt inflammation and autodigestion. Rapid weight loss associated with tirzepatide increases the risk of gallstone formation, which can obstruct the pancreatic or biliary ducts, further exacerbating the risk of pancreatitis. Case reports have illustrated both severe necrotizing pancreatitis and milder, reversible cases linked to tirzepatide therapy. These shows the importance of identifying patient-specific risk factors, such as a history of gallbladder disease or genetic predispositions and maintaining vigilant monitoring during treatment.

In conclusion, while tirzepatide offers to change benefits for managing type 2 diabetes and obesity, its use requires a balanced approach to minimize risks. Rigorous monitoring, patient education, and personalized medical assessments are essential to optimize outcomes and ensure safety. Continued research is vital to further elucidate the mechanisms underlying these adverse effects and refine clinical guidelines for tirzepatide's use.

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Internal Medicine

General Reviews

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