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Is GLP-1 receptor agonist therapy safe for patients with intraductal papillary mucinous neoplasm?

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Summary

Glucagon-like peptide-1 receptor agonists are increasingly used in the management of obesity and diabetes. Their potential risks, however, particularly regarding pancreatitis and pancreatic cancer, remain contentious. Despite numerous studies and meta-analyses indicating no significant correlation between GLP-1 RA therapy and the incidence of acute pancreatitis or pancreatic cancer, gaps in the literature persist regarding their effects in patients with frequent pancreatic conditions, such as intraductal papillary mucinous neoplasms, a disease with potential for malignant transformation. Further rigorous clinical studies addressing the safety of GLP-1 receptor agonists in patients with intraductal papillary mucinous neoplasms should be conducted to understand the potential risks and benefits, establish clear guidelines for clinical practice and ultimately ensure the safety of these medications in this potentially vulnerable patient population.

Introduction

Despite numerous studies exploring the relationship between GLP-1 receptor agonists and pancreatic complications, a definitive correlation remains unclear [1–3]. As the indications for GLP-1 receptor agonist therapy expand to include obesity patients, their use in patients with intraductal papillary mucinous neoplasms – one of the most common cystic pancreatic neoplasms – is increasing. This article reviews existing literature on the association between GLP-1 receptor agonists, pancreatitis and pancreatic cancer, with a focus on implications for intraductal papillary mucinous neoplasm patients, and highlights the urgent need for further clinical studies and the establishment of clear guidelines for this patient group.

Pancreatitis and pancreatic cancer

Initially developed for diabetes, GLP-1 receptor agonists have gained prominence in obesity treatment due to their efficacy in weight loss and improving metabolic parameters. Early clinical trials raised concerns about potential side effects, notably acute pancreatitis and pancreatic cancer. Acute pancreatitis remains a possible adverse effect in Wegovy® (the only GLP-1 receptor agonist approved for obesity in several countries), yet no direct correlation between GLP-1 receptor agonists and pancreatitis has been demonstrated [1–3]. Most clinical trials exclude patients with a history of acute pancreatitis. When acute pancreatitis occurs, it typically develops after 2–6 months of therapy at varying doses, suggesting that the weight loss itself – potentially causing gallstones – could be the trigger, rather than GLP-1 receptor agonist therapy [4].

A recent meta-analysis by Masson et al. [1], which included 21 trials and 34,721 patients on semaglutide, found no increased risk of acute pancreatitis. Similarly, a further meta-analysis from Nreu et al. [5] failed to show a significant correlation between GLP-1 receptor agonists and pancreatic cancer.

Exocrine pancreas growth in animal models

Studies conducted on rodents with GLP-1 receptor agonists have produced inconsistent findings. These range from worsening pancreatitis [6] and triggering inflammation in pancreatic acinar cells [7], to promoting the growth of pancreatic duct glands [8, 9] or reducing chemically induced pancreatitis while increasing levels of anti-inflammatory cytokines [10].

Additionally, there has been limited research on nonhuman primates that indicates any impact on the exocrine pancreas. In studies where a GLP-1 receptor agonist was administrated at doses exceeding normal levels for more than 10 weeks, no alterations in pancreatic structure were identified [11, 12].

Intraductal papillary mucinous neoplasm of the pancreas

Intraductal papillary mucinous neoplasm is one of the most common cystic neoplasms affecting the pancreas, characterised by its potential for malignant transformation. The incidence of intraductal papillary mucinous neoplasms has been increasing significantly, largely due to the enhanced detection capabilities offered by cross-sectional imaging

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techniques [13]. Chronic pancreatitis is recognised as a relevant risk factor for the development of intraductal papillary mucinous neoplasm, likely due to the inflammatory changes that alter the pancreatic ductal epithelium [14, 15]. Furthermore, a retrospective cohort study and meta-analysis by Xu et al. [16] demonstrated an association between acute pancreatitis and high-grade dysplasia in patients with intraductal papillary mucinous neoplasms, emphasising the importance of closely monitoring patients with these conditions.

Moreover, intraductal papillary mucinous neoplasms can be classified into different types, such as main-duct and branch-duct intraductal papillary mucinous neoplasms, which vary in their risk of progression to invasive cancer. Understanding these classifications is crucial when considering treatments like GLP-1 receptor agonists, as patients with main-duct intraductal papillary mucinous neoplasms may have a higher risk of malignant transformation [17, 18]. MRI along with physical examination, assessment of serum tumour markers and new-onset diabetes are the preferred ways to provide surveillance for non-resected intraductal papillary mucinous neoplasm [18].

A case reported by Shi [19] involved a woman in her 60s with diabetes, treated with dulaglutide for 16 months. Routine screening revealed elevated serum CA19-9 and CA242 levels, but no evidence of hepatobiliary, gastrointestinal or pancreatic neoplasms. Discontinuation of dulaglutide normalised her markers within 6 weeks. This elevation in a patient under surveillance for intraductal papillary mucinous neoplasm and treated with GLP-1 receptor agonists could complicate the differentiation between benign conditions and malignant transformation, making clinical interpretation challenging.

Despite the controversial link between acute pancreatitis and use of GLP-1 receptor agonists, we were unable to find any literature that specifically addresses the use of GLP-1 receptor agonists in patients diagnosed with intraductal papillary mucinous neoplasms. Further research is essential to elucidate the safety profile of GLP-1 receptor agonists in this context, particularly in light of intraductal papillary mucinous neoplasm's characteristics that may influence treatment outcomes and risk assessments.

Conclusions

While GLP-1 receptor agonists have shown promise in the management of obesity and diabetes, their potential risks, particularly regarding pancreatitis and pancreatic cancer, remain contentious. Despite numerous studies and meta-analyses indicating no significant correlation between GLP-1 receptor agonist therapy and the incidence of acute pancreatitis or pancreatic cancer, gaps in the literature persist regarding their effects in patients with existing pancreatic conditions, such as intraductal papillary mucinous neoplasms. The notable simultaneous rise in intraductal papillary mucinous neoplasm and obesity incidence, alongside the established link between chronic pancreatitis and intraductal papillary mucinous neoplasm development, emphasises the need for further investigation into the safety profile of GLP-1 receptor agonists in this population. The potential growth of pancreatic duct glands associated with GLP-1 RA usage, reported in rodent models, could also have implications in intraductal papillary mucinous neoplasm patients. Further rigorous clinical studies addressing the safety of GLP-1 receptor agonists in patients with existing pancreatic conditions, such as intraductal papillary mucinous neoplasms, should be conducted to better understand the potential risks and benefits, establish clear guidelines for clinical practice and ultimately ensure the safety of these medications in this potentially vulnerable patient population.

Author contributions
The initial idea for the manuscript was conceived by ML and LB. ML was responsible for searching the available literature, drafting the manuscript and, along with LB, directly accessed and verified the data. PI, JLF, MA and LB contributed to the revision of the manuscript. All authors had full access to the data, take responsibility for accuracy and integrity and approved the final version of the manuscript submitted for publication.

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