

# Incretin-based Antidiabetic Therapy and Pancreatitis: A Case Series

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## ABSTRACT

Dipeptidyl peptidase-4 (DPP-4) inhibitors, commonly referred to as gliptins, are a class of oral antihyperglycemic agents used for the management of type 2 diabetes mellitus. They work by inhibiting the enzyme DPP-4, which leads to increased levels of incretin hormones such as glucagon-like peptide-1 (GLP-1). On the contrary, glucagon-like peptide 1 receptor agonists (GLP-1RA) are the newest treatment for diabetes mellitus (DM). Many of these incretin-based agents have shown positive results in their respective cardiovascular outcome trials (CVOT). Acute pancreatitis is a condition that has been a subject of concern in relation to incretin-based therapies, as reported in some randomized clinical trials. Here, we present three such cases of pancreatitis related to this antidiabetic therapy.

**Keywords:** Acute pancreatitis, Case report, Diabetes mellitus, GLP-1 agonist.

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## INTRODUCTION

Acute pancreatitis is the acute inflammation of the pancreas associated with varying involvement of the surrounding regional tissues or organs linked directly or indirectly to it.<sup>1</sup> It is characterized by deep-seated abdominal pain, which has a typical feature of radiating to back, along with nausea and/or vomiting and biochemical examinations reveals elevated pancreatic enzymes. Among the different etiologic factors, such as alcohol consumption, hypertriglyceridemia, and other drug-induced cases are the least reported worldwide. It is estimated that drugs are responsible for 0.1–2% cases of drug-induced acute pancreatitis.<sup>2</sup> Although meta-analyses have reported conflicting findings, novel incretin-based (both GLP-1 analogue and DPP4 inhibitors) antidiabetic therapy is known to be associated with acute pancreatitis and pancreatic cancer.<sup>3</sup> We report three such cases where pancreatitis is thought to be triggered by such a group of agents.

## CASE DESCRIPTION

### Case 1

A 53-year-old male with type 2 diabetes for 7 years was on tab glimepiride (2 mg) and metformin (1500 mg) for the last 2 years but not having adequate glycemic control. He is a nonsmoker and nonalcoholic. After a recent visit to the endocrine OPD of one private hospital, Kolkata on September 1, 2022, the treating physician added tablet sitagliptin 100 mg sustained release tablet to his regimen. On October 12, 2022, this patient suffered from an episode of acute abdominal pain and mild nausea for the first time, subsequently similar episode of abdominal pain was experienced by him on October 14, 2022 following a heavy meal. This time he was rushed to the emergency of a government medical college and treated conservatively with intravenous fluids, analgesics, and antiemetics. Investigation reports revealed serum Amylase-243 U/L and lipase-310 U/L. Among other parameters, TLC was 11000/cu.mm. Liver enzymes and electrolytes were within the normal limit. Radiological findings showed no abnormalities. The provisional diagnosis

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made by the clinician was acute pancreatitis. After stabilizing, he was discharged on October 17, 2022 from the hospital. Upon referral, clinical pharmacological consultation was carried out and causality assessment was found to be “probable” according to WHO-UMC scale. The offender drug was thought to be sitagliptin which was withdrawn from his antidiabetic regimen, and he was advised to visit endocrinology OPD with all the reports.

### Case 2

A 52-year-old female with diabetes was diagnosed 2 years back, and she was on oral medication like glimepiride (2 mg OD), metformin (1000 mg OD), voglibose (0.3 mg OD), and vildagliptin (50 mg BD), atorvastatin (10 mg OD). Among which, tab vildagliptin was added 1 month back for better glycemic control by the treating physician. She presented with upper abdominal pain and vomiting at the emergency ward of a tertiary care hospital on December 26, 2022. She has hypertriglyceridemia which was not well controlled

despite having tab atorvastatin (triglyceride: 495 mg/dL). Routine investigation showed raised amylase (232 U/L) and lipase (280 U/L) enzyme. Liver function test showed normal LDH, AST, and ALT. Serum electrolytes were normal except serum calcium, which was found to be on the higher side (8.8 mmol/L). Kidney function test and complete blood count were normal. Radiological findings were normal. Detailed history taking revealed that the patient has a history of cholangitis/pancreatitis due to common bile duct calculi back in 2003, for which she had to undergo on endoscopic retrograde cholangiopancreatography (ERCP). Clinical pharmacological consultation was done and causality assessment revealed that this could be a case of acute pancreatitis where the cause was possibly oral vildagliptin which is a Dipeptidyl peptidase 4 inhibitor. Along with WHO-UMC scale, causality assessment was done using Naranjo scale also, and both showed the result "possible" for vildagliptin. The suspected drug was stopped and she was advised to do an endocrinological consultation.

### Case 3

A 56-year-old male with diabetes and hypertension for last 5 years and h/o smoking for an unknown duration presented with nausea and vomiting and upper abdominal pain at the emergency ward of a private hospital on February 2, 2023. He was on tablet glimepiride 4 mg, acarbose 25 mg and tab metformin 1000 mg for the last 3 years. After detailed history taking, it was found that as the patient was obese (BMI 31) and having a symptom of congestive cardiac failure, with a left ventricular ejection fraction (LVEF) of 36% on echocardiography, the treating physician on December 12, 2022 decreased the dose of tablet glimepiride and put him on once weekly dulaglutide (1.5 unit/week subcutaneous injection). Detailed laboratory investigations showed highly elevated levels of serum amylase (277 U/L) and mildly elevated serum lipase levels (102 U/L). Serum electrolytes were normal except calcium was on the lower side, for example, 6.7 mmol/L. The total leucocyte count was 15000/cu.mm. In addition to that CT abdomen findings showed a bulky edematous pancreas.

The patient was treated with intravenous antibiotics and analgesics. Glycemic control was achieved by insulin therapy. The causality assessment result was probable in WHO-UMC scale for injectable dulaglutide. He was discharged after getting stabilized on February 6, 2023.

### CONCLUSION

The clinical use of incretin-based therapy has indeed increased over the past decade due to their favorable characteristics and cardiovascular benefits. Additionally, GLP agonists have a favorable effect on body weight, making them a preferred option for patients who are overweight or obese. However, concerns have been raised about the potential association between these agents and an increased risk of pancreatic cancer and acute pancreatitis. Acute pancreatitis due to drug is often overlooked because of difficulty in appreciating a drug as its cause. A careful clinical assessment, detailed history, and causality assessment of drug reaction will help in early diagnosis and management. These points should be taken in to consideration before initiating treatment for conditions like diabetes. Future studies are needed to identify which subset of the population is more prone for this adverse drug reaction.

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