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CASE REPORT

A Case Report on Acute Pancreatitis Associated with Sitagliptin Therapy in Type 2 Diabetes Mellitus

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Abstract: Acute pancreatitis is a rare but clinically significant adverse drug reaction associated with incretin-based therapies. A 58-year-old male with a 10 year-long history of type 2 diabetes mellitus experienced a sudden onset of severe epigastric pain, nausea, and vomiting exactly fourteen days after the addition of sitagliptin to a long-term regimen of metformin and rosuvastatin. Diagnostic evaluation revealed serum amylase levels of 420 U/L and lipase levels of 780 U/L, while contrast-enhanced computed tomography confirmed diffuse pancreatic enlargement and peripancreatic inflammatory changes. The exclusion of gallstones, alcohol consumption, and hypertriglyceridemia pointed toward a drug-induced etiology. Immediate cessation of sitagliptin coupled with aggressive fluid resuscitation and analgesic therapy resulted in the rapid resolution of symptoms and normalization of biochemical markers within 72 hours. While dipeptidyl peptidase-4 inhibitors offer excellent glycemic control with minimal hypoglycemia, the potential for pancreatic acinar cell injury and ductal proliferation remains a subject of ongoing pharmacovigilance. Early clinical recognition of epigastric distress in patients newly started on incretin mimetics is vital for preventing progression to necrotizing pancreatitis or systemic inflammatory response syndrome. This case shows the need for diligent post-marketing monitoring and the role of clinical suspicion in managing unanticipated adverse events in diabetic patients.

Keywords: Sitagliptin; Dipeptidyl peptidase-4 inhibitors; Drug-induced pancreatitis; Incretin therapy; Pharmacovigilance.

1. Introduction

Type 2 diabetes mellitus (T2DM) is defined as a complex metabolic syndrome characterized by chronic hyperglycemia resulting from a combination of peripheral insulin resistance and a progressive decline in pancreatic beta-cell function [1]. The global health burden of T2DM has reached unprecedented levels, affecting hundreds of millions of individuals and contributing significantly to cardiovascular morbidity and mortality [2]. Current projections by international health organizations suggest that the prevalence will continue to rise, necessitating the development and implementation of diverse pharmacological strategies to achieve optimal glycemic targets [3].

The management of T2DM has been transformed by the discovery of the incretin effect, which refers to the significantly greater insulin response observed following oral glucose administration compared to intravenous glucose infusion [4]. This effect is primarily mediated by two intestinal hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [5]. These hormones enhance insulin secretion from beta cells in a glucose-dependent manner and suppress the inappropriate secretion of glucagon from alpha cells during hyperglycemic states [6].

The clinical utility of native GLP-1 is limited by its rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4), which results in a half-life of less than two minutes [7]. DPP-4 inhibitors, such as sitagliptin, were developed to prolong the activity of endogenous incretins by preventing their cleavage [8]. These agents improve postprandial and fasting glycemic levels without the significant risk of weight gain or hypoglycemia typically associated with sulfonylureas or exogenous insulin by maintaining higher physiological concentrations of GLP-1 and GIP [9].

While sitagliptin was the first DPP-4 inhibitor to receive regulatory approval and has shown a favorable safety profile in large-scale cardiovascular outcome trials, post-marketing surveillance has identified potential risks regarding pancreatic health [10]. Acute pancreatitis is an inflammatory disorder that can range from a mild, self-limiting condition to severe necrotizing disease [11].

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Although biliary lithiasis and chronic ethanol abuse are the primary drivers of pancreatic inflammation, drug-induced pancreatitis remains an important diagnostic consideration, particularly when temporal relationships between drug initiation and symptom onset are evident [12].

2. Case Presentation

2.1. Clinical History and Initial Assessment

A 58-year-old male with a 10-year history of T2DM presented to the emergency department reporting acute, unrelenting epigastric pain that had persisted for 48 hours. The pain was described as sharp, radiating to the mid-back, and was exacerbated by oral intake. The patient also reported persistent nausea and five episodes of non-bilious, non-bloody emesis. His previous diabetic management consisted of metformin (1000 mg twice daily). Two weeks prior to this presentation, sitagliptin (100 mg once daily) had been added to his regimen due to a rising HbA1c level.

Table 1. Current Medication Regimen at Time of Admission

Medication	Dosage	Frequency	Indication
Metformin	1000 mg	Twice daily	Type 2 Diabetes Mellitus
Sitagliptin	100 mg	Once daily	Type 2 Diabetes Mellitus (Added 14 days prior)
Telmisartan	40 mg	Once daily	Hypertension
Rosuvastatin	20 mg	Once daily	Hyperlipidemia

The patient's medical history was notable for hypertension and dyslipidemia, for which he was receiving telmisartan (40 mg daily) and rosuvastatin (20 mg daily). He was a non-smoker and explicitly denied the use of alcohol or tobacco. There was no history of gallstone disease, recent abdominal trauma, or family history of pancreatic or lipid disorders. Upon physical examination, the patient appeared in moderate distress. His blood pressure was 110/68 mmHg, heart rate was 104 beats per minute, and respiratory rate was 24 breaths per minute. Abdominal examination revealed significant tenderness in the epigastrium with associated guarding, though no rebound tenderness or Cullen's sign was observed.

Table 2. Vital Signs and Physical Findings upon Presentation

Clinical Parameter	Recorded Value	Reference Range / Status
Body Temperature	37.1 °C	Afebrile
Blood Pressure	110/68 mmHg	Normotensive
Heart Rate	104 beats/min	Tachycardic
Respiratory Rate	24 breaths/min	Tachypneic
Oxygen Saturation	97%	Normal (Room Air)
Abdominal Exam	Epigastric tenderness	Guarding present; No rebound

2.2. Diagnostic Evaluation and Laboratory Findings

Laboratory investigations at the time of admission were critical in establishing the diagnosis. The serum amylase was significantly elevated at 420 U/L (reference: 30–110 U/L), and serum lipase was markedly increased at 780 U/L (reference: 10–140 U/L). A random blood glucose measurement was 178 mg/dL. Renal function was at the upper limit of normal with a serum creatinine of 1.2 mg/dL. Importantly, serum triglycerides (165 mg/dL) and calcium (9.1 mg/dL) were within ranges that made hypertriglyceridemic or hypercalcemic pancreatitis unlikely.

To confirm the clinical and biochemical suspicion, a contrast-enhanced computed tomography (CECT) scan of the abdomen was performed. The imaging showed diffuse swelling and edema of the pancreatic parenchyma with associated stranding of the peripancreatic fat. No gallstones were visualized in the gallbladder or the common bile duct, and there were no signs of pancreatic necrosis or pseudocyst formation. These findings collectively fulfilled the Atlanta criteria for the diagnosis of acute pancreatitis.

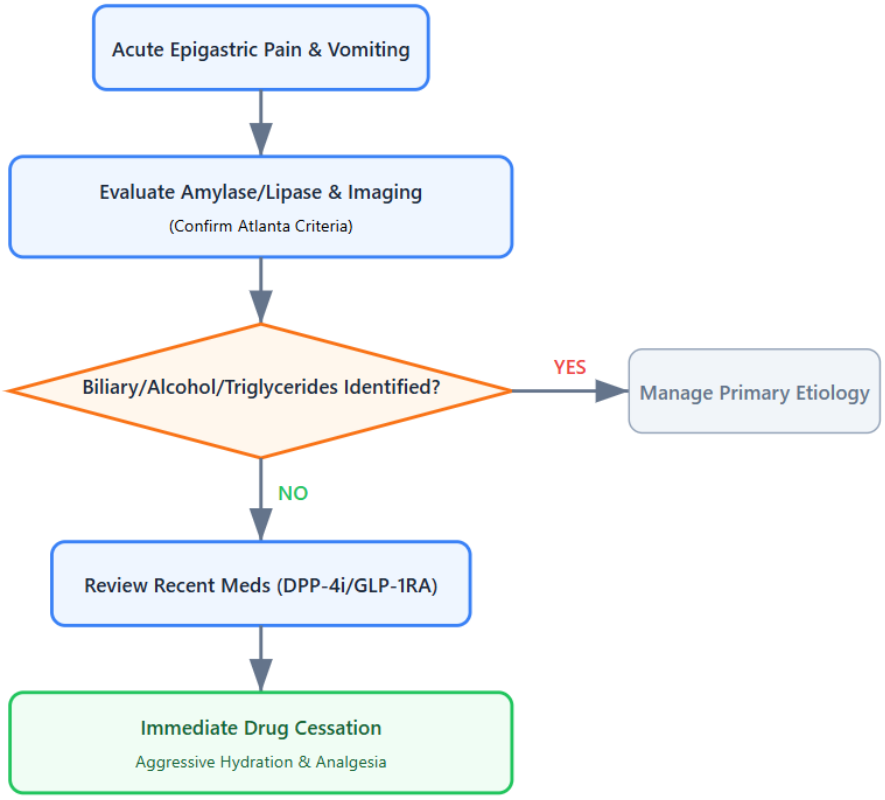

Figure 1. Diagnosis and Management of Suspected Drug-Induced Pancreatitis

Table 3. Laboratory Investigations upon Admission

Laboratory Parameter	Result	Reference Range	Clinical Significance
Serum Amylase	420 U/L	30–110 U/L	Highly Elevated
Serum Lipase	780 U/L	10–140 U/L	Highly Elevated (>3x ULN)
Blood Glucose (Random)	178 mg/dL	70–140 mg/dL	Hyperglycemic
Serum Creatinine	1.2 mg/dL	0.6–1.2 mg/dL	Upper limit of normal
Serum Triglycerides	165 mg/dL	<150 mg/dL	Mildly elevated; Non-etiologic
Serum Calcium	9.1 mg/dL	8.6–10.2 mg/dL	Normal
White Blood Cell Count	12.4 x 10^3/µL	4.0–11.0 x 10^3/µL	Mild Leukocytosis

3. Management and Outcome

Upon confirmation of acute pancreatitis, the patient was immediately admitted to the intensive care unit for close hemodynamic monitoring and supportive care. The primary intervention was the absolute cessation of sitagliptin, identified as the likely offending agent based on the temporal sequence of events. Metformin was also temporarily withheld to prevent potential metabolic complications, such as lactic acidosis, during the acute inflammatory phase.

Table 4. Clinical Management and Supportive Interventions

Intervention Category	Specific Action Taken	Rationale
Pharmacological	Immediate cessation of Sitagliptin	Removal of suspected offending agent
Fluid Resuscitation	Isotonic Saline at 250 mL/hr	Maintain pancreatic perfusion; prevent necrosis
Analgesia	Intravenous Fentanyl (PCA)	Management of severe visceral pain
Gastrointestinal	Initial NPO followed by low-fat diet	Reduction of pancreatic secretory demand
Metabolic	Temporary withdrawal of Metformin	Prevention of potential lactic acidosis

Management followed a standardized protocol for acute pancreatitis. Aggressive fluid resuscitation was initiated with isotonic crystalloids at a rate of 250 mL/hour for the first 24 hours to ensure adequate pancreatic perfusion and minimize the risk of organ failure. Pain control was achieved using intravenous opioids (fentanyl) via a patient-controlled analgesia (PCA) pump. The patient was initially placed on "nil per os" (NPO) status to facilitate bowel rest, followed by the gradual reintroduction of a low-fat diet as symptoms abated.

The clinical response to the discontinuation of sitagliptin and supportive therapy was rapid and significant. Within 24 hours, the patient reported a marked reduction in epigastric pain and a complete cessation of nausea. By the third day of hospitalization, serum amylase and lipase levels had returned to 142 U/L and 195 U/L, respectively.

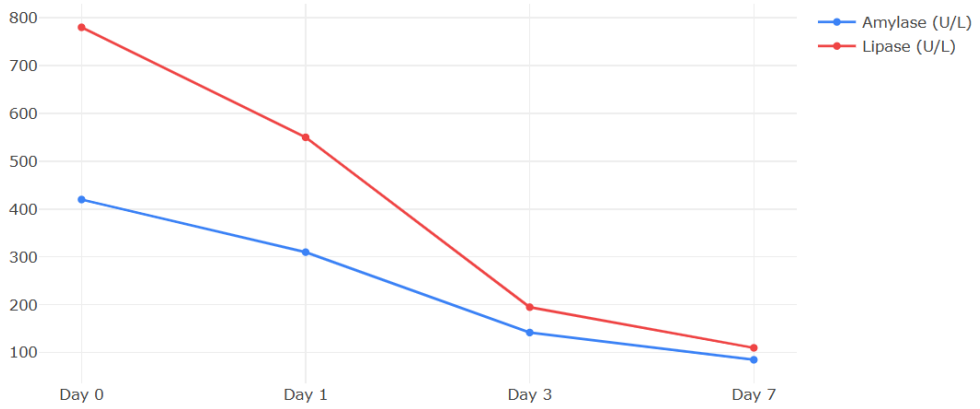

Figure 2. Longitudinal Trend of Pancreatic Enzymes During Hospitalization

By day five, the patient was tolerating a regular diet and was hemodynamically stable without the need for supplemental analgesia. He was discharged on the seventh day. His glycemic management was transitioned to a regimen involving intensified metformin therapy and the introduction of a long-acting insulin analog, under close endocrinological supervision. A follow-up evaluation at four weeks confirmed no recurrence of abdominal symptoms, and repeated pancreatic enzyme levels were within normal physiological limits.

4. Discussion

4.1. Mechanisms of Incretin-Associated Pancreatic Injury

The association between dipeptidyl peptidase-4 (DPP-4) inhibitors and acute pancreatitis remains a complex subject in clinical pharmacology. Several biological mechanisms have been hypothesized to explain how these agents might induce pancreatic inflammation. One prevalent theory suggests that prolonged GLP-1 receptor activation may lead to a low-grade chronic inflammatory state within the pancreatic parenchyma [13]

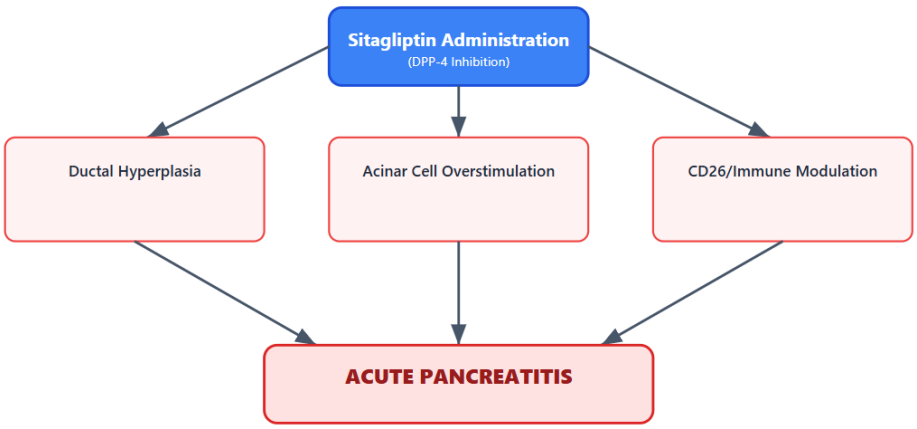

Figure 3. Pathophysiological Mechanisms of Sitagliptin-Induced Pancreatic Injury

Incretin-based therapies are known to promote the proliferation of pancreatic ductal cells. Some histopathological studies in animal models and human tissue have showed that sustained exposure to high levels of GLP-1 achieved through DPP-4 inhibition results in increased pancreatic mass and ductal hyperplasia [14]. This proliferation can theoretically lead to the obstruction of small pancreatic ducts, causing increased intraductal pressure and subsequent activation of digestive enzymes within the acinar cells, a hallmark of acute pancreatitis [15]

Apart from structural changes, DPP-4 is also known as CD26, a protein expressed on the surface of various immune cells. Inhibition of this enzyme may alter the levels of several pro-inflammatory cytokines and chemokines that are substrates for DPP-4, potentially modulating the local immune response within the pancreas and lowering the threshold for acute injury [16]

4.2. Evaluating the Strength of the Association

The temporal relationship in this case is particularly compelling. The patient had been stable on his previous medications for years, and the onset of symptoms occurred exactly 14 days after the introduction of sitagliptin. According to the Naranjo adverse drug reaction probability scale, this case achieves a score indicating a "probable" association [17]

Table 5. Naranjo Adverse Drug Reaction Probability Scale for Sitagliptin

Question	Score Assigned	Rationale for Score
Previous conclusive reports on this reaction?	+1	Documented in post-marketing surveillance
Did the ADR appear after the drug was given?	+2	Symptoms onset 14 days post-initiation
Did the ADR improve when the drug was stopped?	+1	Rapid resolution within 72 hours of cessation
Did the ADR reappear when drug was restarted?	0	Not performed (ethically contraindicated)
Are there alternative causes?	+2	Gallstones, alcohol, and lipids ruled out
Total Score	6	Classification: Probable ADR

Large-scale cardiovascular outcome trials for sitagliptin, such as the TECOS trial, did not find a statistically significant increase in the incidence of pancreatitis compared to placebo [18]. However, meta-analyses of post-marketing data and case-control studies have occasionally highlighted a higher reporting rate for pancreatic adverse events in patients treated with incretin mimetics compared to those on other antidiabetic agents [19]. This discrepancy often suggests that while the absolute risk is low, certain patient populations may possess a idiosyncratic vulnerability to these drugs.

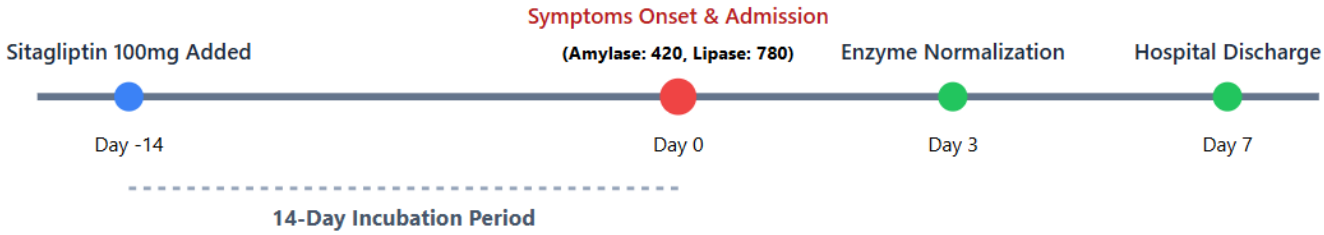

Figure 4. Chronological Sequence of Clinical Events and Pharmacological Exposure

4.3. Diagnostic Challenges in Drug-Induced Pancreatitis

Identifying drug-induced pancreatitis (DIP) requires the systematic exclusion of more common etiologies. In this patient, the absence of gallstones on high-resolution imaging and the lack of alcohol consumption effectively ruled out approximately 80% of typical cases [20]. Normal calcium and triglyceride levels eliminated metabolic triggers. The rapid resolution of the condition upon drug withdrawal referred to as "dechallenge" is a diagnostic hallmark of DIP. However, a "rechallenge" with the drug to confirm the diagnosis is ethically contraindicated in clinical practice due to the risk of severe recurrence [21]

5. Conclusion

This case reinforces the clinical reality that sitagliptin, despite its widespread utility and safety, can be a causative factor in acute pancreatitis. The sudden onset of severe abdominal symptoms shortly after the initiation of therapy should immediately alert the clinician to the possibility of a drug-induced event. Early recognition and the swift discontinuation of the offending agent are paramount to achieving favorable outcomes and preventing systemic complications. As the prevalence of type 2 diabetes continues

to grow and the use of incretin-based therapies expands, ongoing pharmacovigilance and detailed reporting of such cases remain essential for refining our understanding of pancreatic safety. Physicians are encouraged to maintain a high index of suspicion and to counsel patients on the importance of reporting gastrointestinal distress when starting new glycemic interventions.

Compliance with ethical standards

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Conflict of interest statement

The authors declare that they have no conflicts of interest or competing interests regarding the publication of this manuscript, or any financial or personal relationships with institutions or products mentioned in the study.

Statement of ethical approval

Ethical approval (IEC/RGUHS/2025/116) for this case report was obtained from the Institutional Ethics Committee. The study was conducted in accordance with the ethical standards of the institutional research committee and with the principles of the Declaration of Helsinki.

Statement of informed consent

Informed consent was obtained from the patient included in the study

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