

## CASE REPORT

# Sitagliptin-induced pancreatitis – a longer road than expected

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## Introduction

Sitagliptin, a dipeptidyl peptidase IV (DPP-IV) inhibitor, enhances control of type 2 diabetes by prolonging the duration of active incretin hormones such as glucagon-like peptide 1 (GLP-1) in the bloodstream [1, 2]. GLP-1 stimulates both the synthesis of insulin and its release from pancreatic beta cells, and it also reduces release of glucagon from pancreatic alpha cells. GLP-1 is released from intestinal cells in response to food intake, and it usually has a half-life of less than 5 min due to rapid inactivation by the DPP-IV enzyme [1]. Because of the meal-dependent nature of GLP-1 secretion, DPP-IV inhibitors are less likely to cause hypoglycemia than insulin secretagogues such as sulfonylureas. Pancreatitis is a known, although rare, side effect of DPP-IV inhibitors. DPP-IV-induced pancreatitis has previously been reported anywhere between several weeks to 8 months after initiating the medication.

## Case History/Exam

Our patient is a 57-year-old African American female with a past medical history significant for type 2 diabetes mellitus,

### Key Clinical Message

Sitagliptin-induced pancreatitis can occur at any time after the initiation of therapy, even after several years. Patients taking sitagliptin who present with signs and symptoms of mild or severe pancreatitis should immediately discontinue sitagliptin and use an alternate medication regimen for control of type 2 diabetes.

### Keywords

Sitagliptin, dipeptidyl peptidase IV inhibitor, pancreatitis, type II diabetes mellitus.

itus, hypertension, gastro-esophageal reflux disease, and cholecystitis status post cholecystectomy thirty years prior to the presentation, who presented with 4 days of epigastric abdominal pain. The pain was sharp and stabbing, did not radiate, and was worse with eating. There were no associated fevers, chills, sweats, chest pain, shortness of breath, nausea, or vomiting, although the patient did report early satiety over the same time period. The patient denied any history of hyperlipidemia, hypercalcemia, recent travel, insect bites, trauma, alcohol or drug use. She also denied any prior episodes of pancreatitis. She was admitted to the hospital for cholecystitis in 1983, and her gallbladder was surgically removed at that time. Her medications on admission included sitagliptin 100 mg per os (PO) daily, glipizide XL 10 mg PO with breakfast, and glipizide XL 5 mg PO with dinner. The patient had been on sitagliptin for more than 3 years. Her last hemoglobin A1c was 9%. Other medications included lisinopril 20 mg PO daily and esomeprazole 40 mg PO daily.

On admission, the patient's height, weight, and body mass index were 1.676 m, 114.76 kg, and 40.8 kg/m<sup>2</sup>, respectively. Her vital signs included a temperature of 37.4°C (99.3°F), blood pressure of 149/92 mmHg, heart

rate of 114 beats/min, and oxygen saturation of 96% on room air. On exam, her abdomen was tender to palpation in the epigastrium without rebound, guarding or palpable masses. Her white blood cell count was  $10.2 \times 10^9/L$  (10200/ $\mu L$ ), alanine aminotransferase 53 U/L, lipase 1129 U/L, and blood glucose 19.94 mmol/L (359 mg/dL). Her total cholesterol was 4.11 mmol/L (159 mg/dL), triglycerides 3.72 mmol/L (144 mg/dL), high-density lipoproteins 1.50 mmol/L (58 mg/dL) and low-density lipoproteins 1.86 mmol/L (72 mg/dL). Serum amylase level was not checked as it is not routinely drawn in our institution. Ultrasonography of the patient's abdomen (right upper quadrant) revealed diffusely increased echogenicity of the liver without focal parenchymal abnormality or discrete masses. The intrahepatic bile ducts were not dilated, and the gallbladder was surgically absent. The visualized pancreas appeared normal in size and appearance without peripancreatic fluid collections.

## Investigations and Treatment

The patient was diagnosed with acute pancreatitis. She was treated with intravenous fluids and intravenous morphine, and she remained nil per os (NPO). Sitagliptin and glipizide were discontinued, and the patient was started on an insulin regimen. By hospital day 2, the patient's abdominal pain started to improve, and she was started on a clear liquid diet. By hospital day 3, the patient was tolerating a general diet and her abdominal pain had resolved. Her white blood cell count decreased to  $6.04 \times 10^9/L$  (6040/ $\mu L$ ), her alanine aminotransferase normalized to 38 U/L, and her lipase decreased to 102 U/L (see Table 1). The patient received diabetic education, and she was discharged on an insulin regimen.

## Follow-Up

There has been no recurrence of pancreatitis in the 6 months since discontinuation of sitagliptin.

## Discussion

There have been six published case reports of pancreatitis attributed to GLP-1-dependent diabetic therapies, includ-

ing DPP-IV inhibitors as well as synthetic GLP-1 receptor agonists such as exenatide [3–8]. In response to pancreatitis reported in post-marketing surveillance through the Adverse Event Reporting System (AERS), the FDA has issued revised prescribing information for sitagliptin stating that cases of acute pancreatitis have been reported with use, to monitor closely for signs and symptoms of pancreatitis, and to use sitagliptin with caution in patients with a history of pancreatitis [9].

It was initially suggested that the risk for pancreatitis from GLP-1-dependent drugs may be due to the inherently increased risk in diabetic patients of developing pancreatitis. However, evaluation of the FDA adverse event reporting database revealed that pancreatitis is more likely to be reported in patients taking sitagliptin or exenatide than in patients using other therapies for type 2 diabetes (RR 1.86, [95% CI 1.54–2.24],  $P < 0.001$  for sitagliptin) [10]. A subsequent analysis of reports of pancreatitis to the FDA by the Institute for Safe Medication practices found that DPP-IV inhibitors were much more likely to be associated with reported pancreatitis than sulfonylureas or metformin (OR 20.8) [11]. The most recently published evidence, a population-based matched case-control study of 1269 cases of acute pancreatitis, showed a significantly increased odds ratio of acute pancreatitis in patients with current (within the past thirty days) or recent (within the past 2 years, but more than thirty days prior to the onset of pancreatitis) exenatide or sitagliptin use (*current use* adjusted OR 2.24 [95% CI, 1.36–3.69],  $P = 0.01$ ; *recent use* adjusted OR 2.01 [95% CI 1.37–3.18],  $P = 0.01$ ) [12]. Although there are some conflicting data from claims-based analysis, these reports taken together support a correlation between sitagliptin use and the risk of acute pancreatitis [13, 14]. Based on the data published by Singh et al., and histopathology data published by Butler et al., the FDA recently reviewed clinical and animal data regarding the risk of pancreatitis and pancreatic cancer associated with incretin-based therapies [12, 15]. The FDA did not find an increased risk of pancreatitis in their review, and they considered the labeling already in place regarding reports of pancreatitis appropriate [16]. Continued assessment of this association is ongoing.

The mechanism by which GLP-1 therapies may cause pancreatitis has been poorly characterized to date. Small

**Table 1.** Laboratory findings of patient on days 1 and 3 of hospitalization.

Parameter	Day 1	Day 3	Reference values
White blood cell count	$10.2 \times 10^9/L$ (10,200/ $\mu L$ )	$6.04 \times 10^9/L$ (6040/ $\mu L$ )	$4.0 - 10.0 \times 10^9/L$ (4000 – 10,000/ $\mu L$ )
Alanine aminotransferase	53 U/L	38 U/L	0 – 40 U/L
Lipase	1129 U/L	102 U/L	10 – 52 U/L
Blood glucose	19.94 mmol/L (359 mg/dL)	13.83 mmol/L (249 mg/dL)	3.3 – 5.5 mmol/L (60 – 99 mg/dL)

**Table 2.** Previously published case reports.

Author	DPP-IV inhibitor	Days of DPP-IV therapy	Other diabetic medications	Description
Kunjathaya <i>et al.</i> [3]	Vildagliptin	3 weeks	Glimepiride, metformin	Severe necrotizing pancreatitis
Iyer <i>et al.</i> [4]	Sitagliptin	"A few weeks"	Exenatide	Severe necrotizing pancreatitis
Garg <i>et al.</i> [5]	Sitagliptin	12 weeks	Gliclazide, metformin	Acute severe pancreatitis
Saraogi <i>et al.</i> [6]	Vildagliptin	6 months	Metformin	Mild pancreatitis
Girgis <i>et al.</i> [7]	Sitagliptin, vildagliptin	7 months	Metformin	Acute necrotic pancreatitis
Sue <i>et al.</i> [8]	Sitagliptin	8 months	Metformin, voglibose	Severe acute pancreatitis

DPP-IV, dipeptidyl peptidase IV.

but statistically significant increases in levels of amylase and, to a greater extent, lipase have been reported in observational studies of patients on DPP-IV inhibitors or exenatide [17]. Lipase elevations generally returned to control levels after discontinuation of the associated agent. The elevations in lipase may reflect subclinical pancreatic inflammation, but this phenomenon has not been adequately studied.

Animal studies have yielded conflicting results. One small study of transgenic rats showed an association between sitagliptin and fibrotic exocrine pancreatic changes, including one rat that developed focal necrotizing pancreatitis. However, this association was not found in a larger subsequent study using transgenic mice [18, 19]. It is possible that these animal studies have not been sufficiently powered to detect this rare adverse effect. DPP-IV is also expressed on the surface of T-cells as T-cell activation antigen CD26, and it has wide-ranging enzymatic and nonenzymatic functions in the immune system [20]. However, correlation between these effects and inflammatory responses in the pancreas has not been established [21].

The case reported here is notable for the duration of therapy prior to the onset of pancreatitis and the mild clinical course. The patient was taking sitagliptin for more than 3 years prior to developing acute pancreatitis. This is significantly longer than previously reported cases, which have ranged from a few weeks to 8 months after initiation of DPP-IV inhibitor therapy (see Table 2). Although many of the previously published case reports have described patients with severe necrotizing pancreatitis (see Table 2), this case demonstrates that acute pancreatitis induced by DPP-IV inhibitors may also be relatively mild. As in our patient, the majority of reported cases of pancreatitis associated with DPP-IV inhibitor therapy have resolved with discontinuation of the drug, with the exception of one patient who had a complicated hospital course after pancreatic necrosectomy, and one patient who clinically deteriorated and died [4, 8].

The patient in this case had also been prescribed lisinopril for eighteen months, which has had a reported association with pancreatitis. Angiotensin-converting enzyme (ACE) inhibitors are thought to cause pancreatitis related

to localized angioedema of the pancreas or via a direct toxic injury to the pancreas [22, 23]. Reported cases of pancreatitis due to ACE-inhibitors have generally occurred early in therapy, and symptoms have recurred when the patient was re-challenged with the drug [22–25]. In this case, it is unlikely that lisinopril contributed to the patient's presentation, as her symptoms resolved completely without cessation of lisinopril, and there has been no recurrence of symptoms with continuation of the drug.

## Conclusion

We have presented a patient with no identifiable risk factors for pancreatitis other than sitagliptin use, who presented with pancreatitis based on clinical symptoms and laboratory data. Her symptoms and laboratory abnormalities improved with supportive management and discontinuation of sitagliptin, and she has not had any recurrence of pancreatitis after 6 months of follow-up. This case is unusual in that the patient had been on sitagliptin for 3 years prior to developing pancreatitis, which is more than 2 years longer than other reported cases of pancreatitis due to sitagliptin. Further, most other reported cases of sitagliptin-associated pancreatitis were severe and/or necrotizing, while our patient's course was relatively benign. Medical providers should consider pancreatitis as an etiology of abdominal pain in patients who have been taking sitagliptin for any length of time, even if the patient's presentation is not severe. If sitagliptin-induced pancreatitis is suspected, at any point after initiating treatment with sitagliptin, providers should consider alternative agents for the treatment of type 2 diabetes mellitus.

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## Conflict of Interest

None declared.

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