Clinical Case Report

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Linagliptin-related pancreatitis in a diabetic patient with biliary calculus

A case report

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Abstract

Rationale: Dipeptidyl peptidase-4 inhibitors are commonly used drugs for the treatment of type 2 diabetes mellitus. While acute pancreatitis cases induced by saxagliptin, sitagliptin, and vildagliptin (all of which are members of the dipeptidyl peptidase-4 group) have been reported, there is no clear evidence suggesting that linagliptin may cause pancreatitis, and information in this regard is limited to a few studies. Moreover, no pancreatitis cases have been reported that were directly associated with linagliptin.

Patient concerns: We present a case of linagliptin-related pancreatitis in a 79-year-old male diabetic patient with biliary calculi. The patient, who was diagnosed with acute pancreatitis 4 months after initiating linagliptin 5 mg/d treatment, was admitted to our hospital.

Diagnoses: The patient's pancreatic enzymes were high. Ultrasonography showed multiple biliary calculi, and abdominal computed tomography showed edematous pancreatitis.

Interventions: Linagliptin was discontinued and clinical improvement was achieved with standard acute pancreatitis treatment.

Outcomes: This is the 1st case report suggesting that linagliptin might be associated with the risk of pancreatitis and could be an etiologic cause of pancreatitis, similar to the other members of its group.

Lessons: While the results of previous studies stated that there was no data to prove a causal relationship between dipeptidyl peptidase-4 inhibitors and pancreatitis, concerns regarding this subject have continued to arise. Therefore, new and comprehensive studies are needed to determine the long-term effects of dipeptidyl peptidase-4 inhibitors on type 2 diabetes mellitus patients and to shed light on the side effects of these medications.

Abbreviations: DPP-4 = dipeptidyl peptidase-4, FDA = Food and Drug Administration, GLP-1 = glucagon-like peptide-1, T2DM = type 2 diabetes.

Keywords: biliary calculus, dipeptidyl peptidase-4 inhibitors, linagliptin, pancreatitis, type 2 diabetes mellitus

1. Introduction

With their increasing popularity in the recent years, dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin), also known as gliptins, are incretin-based therapies that provide good glycemic control in patients with type 2 diabetes mellitus (T2DM).[1] These antihyperglycemic agents, which can be used as monotherapy or in combination with other drugs, have been approved for over a decade regarding their efficacy and safety.[2]

In general, these agents pose a low risk of hypoglycemia and they do not cause weight gain.[3] Possible side effects of long-term DPP-4 inhibitor use are not yet clearly known. Approved by the United States Food and Drug Administration (FDA) in 2006, gliptins do not appear to be directly consistent with the increase of pancreatitis risk in patients with T2DM according to studies regarding the safety and tolerability of these agents.[4,5] However, given the limited number of studies and case reports, the possibility of pancreatitis has yet to be ruled out. Here, we present a geriatric case of a patient with cholelithiasis who developed pancreatitis after linagliptin treatment, and we discuss whether the pancreatitis had a biliary origin or was caused by linagliptin use.

2. Case presentation

A 79-year-old male was admitted with complaints of severe, sharp, persistent abdominal pain radiating to the back, and nausea lasting for 2 days. He denied alcohol consumption. His medical history indicated T2DM for 15 years and coronary artery disease for 5 years. Linagliptin (5 mg/d) had been added to his treatment regimen 4 months prior to the admission. On physical examination, epigastric tenderness was detected. His medications included *acetylsalicylic acid*, metoprolol, ramipril + chlorothiazide combination, insulin glargine, metformin, and linagliptin. Laboratory tests revealed leukocytosis and increased c-reactive protein, creatinine, aspartate aminotransferase, alanine aminotransferase, amylase, lipase, bilirubin total, bilirubin direct, lactate dehydrogenase, alkaline phosphatase, and gam-

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Table 1

Summary of the patient's initial laboratory data.

Parameters	Value	Normal range
Leukocytes, cells/μL	14.210	4–11
CRP, mg/L	42.3	<5
Creatinine, mg/dL	1.9	0.5–1.3
AST, U/L	706	5–34
ALT, U/L	357	10–49
Amylase, U/L	986	30–118
Lipase, U/L	1120	0–78
Bilirubin T, mg/dL	3.15	0.3–1.2
Bilirubin D, mg/dL	1.56	0–0.3
LDH, U/L	650	120–246
ALP, U/L	145	45–129
GGT, U/L	328	0–73

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRP = C-reactive protein, GGT = gamma-glutamyl transferase, LDH = lactate dehydrogenase.

ma-glutamyl transferase levels. Electrolytes and lipids were within normal limits. The results of the laboratory tests are shown in Table 1.

In the abdominal ultrasonography, multiple calculi (the largest was 7 mm in diameter) were observed in the gallbladder, and the gallbladder wall was observed to be 5 mm thickness and was edematous. The diameter of the ductus choledochus was normal, and no calculi were observed in its lumen. Pancreatitis was diagnosed by abdominal computed tomography (Fig. 1) and laboratory tests. As the patient had metal prosthesis in his knee joint, magnetic resonance cholangiopancreatography could not be taken. The application of metformin, ramipril + chlorothiazide combination, and linagliptin was discontinued secondary to acute renal failure and pancreatitis.

He was treated with bowel rest, hydration, and pain control. The glucose level was regulated using insulin. Oral feeding was reintroduced gradually. Leukocytes, c-reactive protein, creatinine, amylase, lipase, and liver enzymes returned to normal levels. The patient was still being treated with ramipril + chlorothiazide, metoprolol, insulin, and metformin without any recurrent abdominal pain. The patient provided written informed consent for publication of the case details.

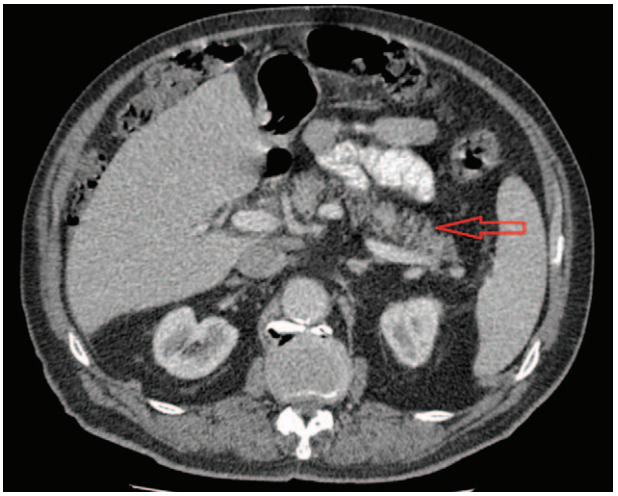

Figure 1. Axial view of the computerized tomography scan of the abdomen. There was a slight increase in pancreatic size and irregularity in the contour of the pancreas. There was a slight decrease in parenchyma density. Obliteration was not observed in the fat planes nor was necrosis observed. No fluids had collected in the abdomen or pelvis, and the peripancreatic fat planes did not appear inflammation.

3. Discussion

In this article, we presented an acute pancreatitis case which may have been induced by linagliptin, which we could not find any other case reports of. Therefore, our case is the 1st one to present possible causation between linagliptin and acute pancreatitis. The fact that our patient also had biliary calculi suggests the possibility of biliary pancreatitis. However, the 79-year-old patient had not had any prior pancreatitis episodes. Because gallstone formation is a chronic phenomenon which occurs over a long period of time, even if linagliptin did not directly induce pancreatitis, it may have facilitated the biliary calculi that then caused pancreatitis. Nevertheless, this prediction cannot be proven with a single case.

Recently, articles discussing the possible risk of DPP-4 inhibitors for pancreatitis have started to be published; thus, there are serious concerns regarding their safety profiles. While both animal studies and the results of clinical trials and meta-analyses indicate that patients with T2DM using DPP-4 inhibitor do not have increased risk of pancreatitis, whether this applies for all DPP-4 inhibitors has yet to be clarified. Furthermore, acute pancreatitis cases that developed after saxagliptin, sitagliptin, and vildagliptin therapy have been reported.[6–9]

Linagliptin is a potent and selective DPP-4 inhibitor. In clinical trials, when combined with metformin + sulphonylurea or metformin + pioglitazone as the 3rd antihyperglycemic agent in patients with T2DM with inadequate glycemic control, linagliptin improved glycemic control and was well tolerated. Moreover, it carried a low risk of hypoglycemia and was not shown to cause weight gain.[10–13]

In a trial published in 2014 involving 7400 patients in which the tolerability and safety profile of linagliptin was investigated, the possibility of pancreatitis development was found to be equal to the placebo group.[13] In another trial, increased risk of pancreatitis was not observed for any of the 5 DPP-4 inhibitor groups, and it was stated that when compared to other glucose-lowering agents, gliptins did not increase the incidence of pancreatitis.[14] In a study by Tinahones et al of patients with inadequate glycemic control, sodium-glucose co-transporter-2 inhibitors and metformin were combined with linagliptin; as a result, linagliptin improved glycemic control and was well-tolerated, with only 1 patient developing acute pancreatitis.[15]

Despite these study data, the FDA requires that the labels of all incretin-based therapy agents include a warning note regarding the possible risk of pancreatitis. The effects of glucagon-like peptide-1 (GLP-1) on gastrointestinal motility, including gallbladder and biliary tract, are well known. It has been reported that liraglutide, a GLP-1 receptor agonist, may contribute to the synthesis of gallstones in the long term and may lead to an increase in the incidence of acute pancreatitis.[16] Based on the pancreatitis risk, is the use of incretin-based therapies in patients with gallstones a safe medication? Moreover, compared to the patients without T2DM, those with T2DM have a 2- to 3-fold higher risk of pancreatitis.[17–19] Therefore, the choice of antidiabetic agent is crucial, and adding a medical therapy which may cause pancreatitis could increase this already existing risk. Unfortunately, in clinical practice it is not possible to perform ultrasonography for each patient before initiating DPP-4 inhibitor therapy.

In a study by Chang et al, DPP-4 inhibitors, sulfonylureas, and metformin were compared regarding their risk of acute pancreatitis. Metformin was found to be safer than the other 2 groups.[20] There have been no reports that insulin glargine may be associated with the risk of pancreatitis. In this case, the patient was given linagliptin without knowing that he had biliary calculi, and thus he developed acute pancreatitis. In patients who have a long history of diabetes and biliary calculi, particularly in geriatric patients, it should be remembered that linagliptin, or more precisely DPP-4 inhibitors, may increase the risk of pancreatitis.

Author contributions

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Investigation: Nurhayat Ozkan Sevencan, Aysegul Ertinmaz Ozkan.
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