Pancreatitis with Pancreatic Tail Swelling Associated with Incretin-based Therapies Detected Radiologically in Two Cases of Diabetic Patients with End-Stage Renal Disease

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Abstract

We herein report two cases of pancreatitis associated with incretin-based therapies in end-stage renal disease (ESRD) patients undergoing dialysis. A 75-year-old woman with a history of liraglutide use and a 68-year-old man with a history of vildagliptin use both presented with nausea. They showed elevated levels of pancreatic enzymes and pancreatic tail swelling on CT. Their symptoms improved after discontinuing the drugs. In the absence of any obvious secondary causes of pancreatitis, we believe that the pancreatitis observed in these cases was associated with the incretin-based therapies. Few reports have been published on the safety and efficacy of incretin-based therapies in ESRD patients, and it remains uncertain whether the changes in the pancreas observed in the present cases are characteristic of ESRD patients.

Key words: pancreatitis, diabetes, end-stage renal disease, incretin-based therapies

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Introduction

Liraglutide and vildagliptin are incretin agents used to control hyperglycemia in type 2 diabetic patients. Liraglutide is a synthetic analog of human glucagon-like peptide-1 (GLP-1). The LEAD trial, which demonstrated the safety and efficacy of liraglutide in controlling hyperglycemia in patients with type 2 diabetes, reported six cases of pancreatitis (1-6). Vildagliptin is a dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor) that is also used to manage type 2 diabetes, and one case of pancreatitis associated with vildagliptin use has been reported (7). However, whether these incretin agents induce pancreatitis remains controversial, as diabetes itself poses a high risk for developing pancreatitis (8, 9). Until recently, few trials have evaluated the safety of incretin-based therapies in type 2 diabetic patients with end-stage renal disease (ESRD) (10-12). We herein report two cases of pancreatitis associated with incretin-based therapies in ESRD patients.

In the following case reports, the values of HbA1c are expressed in line with the National Glycohemoglobin Standardization Program (NGSP) values (13).

Case Reports

Case 1

A 75-year-old woman with type 2 diabetes and ESRD who was undergoing dialysis presented with a 3-month history of nausea. She had been diagnosed with type 2 diabetes mellitus 20 years previously and received drug therapy at that time. Insulin therapy was initiated eight years before the current presentation. Her renal function had gradually deteriorated for approximately seven years before presentation, and she was undergoing hemodialysis. As her renal function decreased, hypoglycemic episodes occurred repeatedly and insulin therapy was discontinued three months before the initiation of dialysis. However, at the time of initiation of dialysis, the patient's laboratory results showed an HbA1c

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Figure 1. Abdominal computed tomography (CT) in Case 1. (A), (B) Abdominal CT obtained two years before presentation. Atrophy of the pancreas is present. (C), (D) Abdominal CT obtained on presentation. A swollen pancreatic tail is seen compared with that observed in (A); (B) however, no peripancreatic fat stranding is noted.

level of 10.3%, and a daily regimen of 40 mg of gliclazide and 50 mg of vildagliptin was initiated. One month later, the vildagliptin regimen was changed to a daily regimen of 0.6 mg of liraglutide in order to control the patient's appetite. Four months later, the patient's glycemic control was observed to have improved and laboratory studies showed an HbA1c level of 6.6%. The daily regimen of 40 mg of gliclazide was reduced to 20 mg of gliclazide. Three months later, the patient reported nausea. Two months later, the patient's glycemic control worsened and the HbA1c level increased to 7.8%. At that time, the patient's fasting blood glucose level was 127 mg/dL and her fasting insulin level was 5.7 μ U/mL. Her blood glucose level two hours after eating was 393 mg/dL and her insulin level two hours after eating was 17.7 μ U/mL.

A diagnosis of pancreatitis was considered based on the presence of elevated levels of pancreatic enzymes (amylase: 1,649 IU/L [reference range: 40-120 IU/L]; pancreatic amylase: 1,627 IU/L [reference range: 18-53 IU/L]) and the results of abdominal computed tomography (CT) (Fig. 1), which showed swelling of the pancreatic tail without peripancreatic fat stranding. Magnetic resonance imaging (MRI) showed no inflammatory changes and no edematous changes (Fig. 2). Magnetic resonance cholangiopancreatography (MRCP) showed no abnormal changes, including in the pancreatic duct. Liraglutide was discontinued and insulin therapy

was resumed. After terminating the use of liraglutide, the patient's nausea improved and the level of pancreatic enzymes decreased on hospital day five (amylase: 248 IU/L; pancreatic amylase: 169 IU/L; lipase: 306 IU/L [reference range: 13-60 IU/L]).

The patient had no history of pancreatitis, cholelithiasis or surgery. The patient also reported no alcohol consumption or smoking and had no family history of pancreatitis. At the time of admission, her other medications included 100 mg per day of cilostazol and 1,500 mg per day of calcium carbonate. Her body mass index was 20.2 kg/m². Relevant laboratory data were normal: corrected calcium concentration: 9.0 mg/dL (reference range: 8.8-10.2 mg/dL), triglyceride concentration: 111 mg/dL (reference range: 45-150 mg/dL) and CA19-9 concentration: 18.1 U/mL (reference range: <3.4 U/mL). The patient's usual amylase concentration before the development of pancreatitis was approximately 120 IU/L. Her IgG4 concentration was 71.2 mg/dL (reference range: 4.8-105 mg/dL). Since obvious secondary causes of pancreatitis were absent in this case, our findings suggest the presence of a relationship between the use of liraglutide and pancreatitis.

Case 2

A 68-year-old man with type 2 diabetes and ESRD who was undergoing dialysis presented with a 1-month history of

Figure 2. Abdominal MRI in Case 1. (A) T1-weighted imaging shows a low intensity area in the pancreas. (B) T2-weighted imaging shows a low intensity area in the pancreas. (C) Diffusion-weighted imaging does not show a high intensity area in the pancreas.

nausea. He had been treated for diabetes with 10 units daily of neutral protamine hagedorn and 30 mg daily of pioglitazone for many years. However, after suffering occasional heart failure due to continued overhydration and worsening of glycemic control to an HbA1c level of approximately 7.6%, his medication regimen was changed to 0.6 mg daily of liraglutide. Soon after changing medications, the patient started to complain of nausea, and his medication regimen was again changed to 50 mg daily of vildagliptin. His HbA1c level improved to 5.6% over four months. One month after changing to vildagliptin, the patient's swallowing function deteriorated. Upper gastrointestinal endoscopy revealed esophageal cancer, and chemoradiation therapy was initiated. The patient's swallowing function and appetite quickly improved; however, six months later he again presented with nausea. His laboratory results showed hyperamylasemia (amylase: 392 IU/dL) and an HbA1c level of 6.3%. CT showed swelling of the pancreatic tail and gallstones without peripancreatic fat stranding and no biliary or pancreatic duct dilatation (Fig. 3A-D). Vildagliptin was discontinued, and the patient's diabetes was treated with insulin. His symptoms improved and his serum amylase levels decreased (amylase: 157 IU/dL). CT performed after five months showed a decrease in the size of the pancreatic tail (Fig. 3E, F). The patient's past medical history included lung tuberculosis; however, no history of pancreatitis or surgery was found. The patient reported being a social drinker, occasionally consuming beer at less than 350 mL per day. He had no family history of pancreatitis. His body mass in-

dex was 20.5 kg/m². His laboratory data were as follows: corrected calcium concentration: 10.2 mg/dL, triglyceride concentration: 232 mg/dL and CA19-9 concentration: 5.9 U/mL. The laboratory data of hepatobiliary enzymes were normal. The patient's medications at the time of admission included 120 µg daily of beraprost, 15 mg daily of nicolandil, 1,500 mg daily of calcium carbonate, 10 mg daily of rabeprazole and 0.25 mg daily of brotizolam. His usual amylase concentration before the development of pancreatitis was approximately 140 IU/L.

Discussion

Incretin-based therapies are widely used for the management of type 2 diabetes, and their efficacy and safety have been demonstrated in trials. However, few studies have examined the efficacy and safety of these medications in ESRD patients. Jacobsen et al. showed the pharmacokinetics of liraglutide to be essentially independent of renal function (14); therefore, the efficacy and safety of liraglutide has been inferred to be similar in patients with ESRD and those with a normal renal function. Lukashevich et al. demonstrated the safety and efficacy of vildagliptin in patients with type 2 diabetes with moderate and severe renal impairment (12). In patients without renal impairment, a small number of cases of incretin-associated pancreatitis have been reported (7, 15); however, no studies have described pancreatitis associated with incretin-based therapies in ESRD patients.

Figure 3. Abdominal CT in Case 2. (A), (B) Abdominal CT obtained four months before presentation. Atrophy of the pancreas is present. (C), (D) Abdominal CT obtained on presentation. A swollen pancreatic tail is seen compared with that observed in (A) and (B) without peripancreatic fat stranding. (E), (F) Abdominal CT obtained two months after presentation. Repeated atrophy of the pancreas is observed.

One study concluded that patients with type 2 diabetes have a 2.83-fold greater risk of developing pancreatitis compared with nondiabetic patients (8); however, another study demonstrated a reduced risk of acute pancreatitis in patients with type 2 diabetes taking anti-diabetic drugs (9). Therefore, the two patients discussed herein, who had been receiving incretin-based therapies, were at a higher risk of developing pancreatitis. In Case 2, gallstones were observed on CT and the patient reported moderate alcohol consumption. However, the levels of hepatobiliary enzymes were normal and CT showed no biliary or pancreatic duct dilatation, which reduces the possibility of gallstone pancreatitis. The risk of pancreatitis associated with the patient's quantity and frequency of drinking is not high (16). Other common causes of pancreatitis such as smoking, past history of pancreatitis and family history of pancreatitis were ruled out in both of our patients. Our two cases did not show high triglyceride or calcium concentrations. In both cases, the patients had good histories of glycemic control; however, they presented with nausea, worsened HbA1c levels and high

amylase concentrations. After discontinuation of the incretin-based therapies, the patients' symptoms improved and their concentrations of amylase decreased. We therefore concluded that incretin agents had induced pancreatitis in these cases.

Our two cases of pancreatitis with type 2 diabetes in ESRD patients share a number of common characteristics. In both cases, the pancreatic diseases were not considered serious, as symptoms of nausea occurred subacutely and CT showed only swelling of the pancreatic tail without peripancreatic fat stranding. In Case 1, MRI showed no evidence of inflammation. In Case 2, the swelling of the pancreatic tail decreased after discontinuation of vildagliptin. Therefore, the pancreatitis observed in these cases is suggested to have been caused by incretin-based therapies. Girgis et al. also reported a case of vildagliptin-induced pancreatitis with diffuse pancreatic swelling on CT (7). Pancreatitis with diffuse pancreatic swelling is characteristic of IgG4-related pancreatitis (17, 18). However, the level of serum IgG4 was low in Case 1, and neither case showed any signs of IgG4-related

diseases, including cholangitis, sialadenitis, retroperitoneal fibrosis or lymphadenopathy, or inflammatory signs of pancreatitis other than swelling of the pancreas on CT and MRI. In both cases, the pancreatitis improved soon after the discontinuation of the incretin-based therapies, which suggests that IgG4-related disease are not applicable in these cases.

Another common characteristic of these cases is that the incretin-based therapies dramatically improved glycemic control despite the patients' past histories of insulin therapy. The HbA1c level was reduced from 10.3% to 6.6% in Case 1 and from 7.6% to 5.6% in Case 2 in spite of the administration of insulin therapy. When both patients experienced nausea, their glycemic control worsened and swelling of the pancreatic tail was shown on CT. It is not clear whether these dramatic glycemic changes and the swelling of the pancreatic tail in each case are related.

Such changes in the pancreas resulting from incretin-based therapies have not yet been reported, and it is not known whether these changes are characteristic of ESRD patients. Few reports have so far been published on the safety of incretin-based therapies in ESRD patients. Tatarkiewicz et al. reported that exenatide does not evoke pancreatitis in rodents; therefore, the possibility is low that the GLP-1 analogue itself directly affects pancreatitis in patients with a normal renal function (19). The possibility remains that some metabolites of incretin-based drugs that accumulate due to renal insufficiency might induce pancreatitis; however, there is no evidence for such substances at this time.

We herein report unique cases of pancreatitis in ESRD patients receiving incretin-based therapies. The current number of ESRD patients receiving these drugs is small. In cases of liraglutide use in particular, there is a possibility that symptoms of nausea could indicate a drug reaction; therefore, we recommend routine measurement of the amylase levels in patients receiving incretin-based therapies in order to distinguish pancreatitis from drug reactions. It remains uncertain whether the changes in the pancreas observed in the present cases are characteristic of ESRD patients, and further research into the experiences of ESRD patients receiving incretin-based therapies should be conducted to evaluate this link.

The authors state that they have no Conflict of Interest (COI).

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