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Case Report

Cystic Fibrosis and Hemochromatosis Carriers May Be Prone to Glucagon-like Peptide-1 Agonist Pancreatitis: 3 Cases

Guy Itzhak Sydney,[1] Tammy Do,[2] William Austin West,[3] and Gabriel Ikponmosa Uwaifo[4]

[1]Section of Endocrinology, Yale School of Medicine, New Haven, CT 06510, USA
[2]Dept of Medicine, Ochsner Medical Center, New Orleans, LA 70121, USA
[3]Section of Pulmonology and Critical Care, University of Southern California Medical Center, Los Angeles, CA 90333, USA
[4]Division of Endocrinology, Department of Medicine, Southern Illinois University School of Medicine, Springfield, IL 62702, USA

Correspondence: Gabriel I. Uwaifo, MD, FACE, FTOS, FACP, Division of Endocrinology, Department of Medicine, Southern Illinois University School of Medicine, 751 North Rutledge Street, Moy Building, Suite 1700, Springfield, IL 62702, USA. Email: guwaifo93@siumed.edu.

Abstract

Glucagon-like peptide-1 (GLP-1) agonists are widely used in the management of type 2 diabetes and obesity, with their therapeutic scope expanding to address cardiometabolic and cardiorenal conditions. However, their increasing use has been associated with potential adverse effects, including acute pancreatitis (AP). The exact prevalence of GLP-1 agonist-induced AP remains uncertain and reliable predictors for its onset have yet to be identified. We present 3 cases of class-associated predilection for GLP-1 analog-associated AP in patients with carrier states for hemochromatosis (HC) and cystic fibrosis. Case 1 is a heterozygous carrier for the *C282Y* HC pathogenic variant. Case 2 is a heterozygous carrier of the *Delta F508* deletion of the cystic fibrosis transmembrane regulator (*CFTR)* gene. Case 3 is compound heterozygous carrier of a single *CFTR* intron 9 poly T allele pathogenic variant (5T/7T/8T), as well as a single pathogenic variant of the *C282Y* HC gene. Our observation suggests that carrier states for cystic fibrosis and HC may predispose individuals to GLP-1 agonist-associated AP. Genetic testing for these carrier states should be considered among patients with GLP-1 agonist-associated AP to provide more support and data for this as a potential true risk factor.

Key Words: GLP-1 agonists, acute pancreatitis, chronic pancreatitis, heterozygous carrier, hemochromatosis, cystic fibrosis

Abbreviations: AP, Acute pancreatitis; BID, twice daily; BMI, body mass index; CF, cystic fibrosis; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; GLP1AP, glucagon-like peptide-1 associated pancreatitis; HC, hemochromatosis; TID, 3 times per day; T2DM, type 2 diabetes mellitus.

Introduction

The pancreas functions as both an exocrine and endocrine gland, essential for digestion, absorption, and metabolism. Impaired exocrine pancreatic function and enzyme activity are often caused by diseases that disrupt the pancreatic parenchyma, including genetic conditions such as cystic fibrosis (CF) and hemochromatosis (HC) [1]. Although HC and CF are autosomal recessive disorders, these conditions are not uncommon, especially among individuals of European ancestry, with even higher carrier rates for both conditions [2-4]. CF affects approximately 1 in 2500 to 3000 Caucasian newborns in the United States, with carrier rates as high as 1 in 30. HC is even more prevalent, with a prevalence of 1 in 300 to 500 individuals and a carrier rate of ~1:10 among those of northern European ancestry. In CF, biallelic mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene impair water secretion from exocrine glands, leading to dense, obstructive pancreatic secretions that damage ducts and parenchyma [4-6].

Heterozygosity for *CFTR* pathogenic variants was previously thought to preserve normal pancreatic function. However, advances in genetic screening and pathophysiology now link *CFTR* carrier states to various CF-related conditions [7-9]. Similarly, HC results from biallelic pathogenic variants in the *HFE* gene, leading to excess iron absorption and deposition in organs, including the pancreas [2, 10, 11]. Iron overload damages the pancreatic parenchyma, potentially impairing both exocrine and endocrine functions [2, 10, 12]. Emerging evidence also implicates HC carrier states in contributing to clinical morbidity [2, 10, 12].

Glucagon-like peptide-1 (GLP-1) receptor agonists, are widely used antidiabetic and weight reduction agents, mimic the effects of the hormone GLP-1, enhancing insulin secretion, decreasing glucagon release, prompting satiety, and slowing gastric emptying [13]. Their therapeutic application now extends to cardiometabolic and cardiorenal conditions, as well as comorbidities like metabolic-associated steatotic liver disease and obstructive sleep apnea [14-16]. However, there have been reports of GLP-1 agonist-associated acute pancreatitis (AP) in both animals and humans, though exact prevalence and predictors remain uncertain [17, 18]. This distinct form of AP, termed GLP-1 receptor agonist-associated pancreatitis (GLP1AP), is characterized by rapid symptom resolution upon drug withdrawal and recurrence upon rechallenge. We present 3 cases suggesting that carrier states for CF

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and/or HC may predispose individuals to GLP1AP, highlighting a potential avenue for identifying at-risk patients.

Case Presentations

Case 1

A 39-year-old Caucasian female was referred to the endocrinology clinic for evaluation of type 2 diabetes mellitus (T2DM). Her medical history included essential hypertension, obesity, obstructive sleep apnea, nonalcoholic fatty liver disease, postsurgical hypothyroidism, and chronic Epstein-Barr virus infection, with reported hyperglycemia during Epstein-Barr virus flares. Diagnosed with T2DM at age 35 years, her treatment regimen included insulin glargine 26 U nightly (before bedtime) and metformin 750 mg twice daily (BID). Previous use of dulaglutide, sitagliptin, and short-acting exenatide (Byetta) resulted in AP. Her hemoglobin A1c (HbA1c) improved from 8.3% (reference range, 4.0%-5.6%) to 6.5%. Autoimmune testing for pancreatic disease was negative. Metformin was increased to 1000 mg BID, and liraglutide was introduced. However, she developed abdominal pain, nausea, and vomiting shortly after starting liraglutide, with serum lipase elevated to 325 U/L (normal: 1-160 U/L). A pancreatic computed tomography scan was unremarkable, yet clinical findings were consistent with AP, triggered by multiple exposures to GLP-1 receptor agonists and a dipeptidyl peptidase 4 (DPP-4) inhibitor.

Case 2

A 62-year-old Caucasian female was referred to endocrinology clinic for optimization of care for her T2DM. Her medical history included essential hypertension, hyperlipidemia, chronic atrial fibrillation, obesity, depression, and obstructive sleep apnea. Despite treatment with insulin detemir (40 U before bedtime), insulin aspart (10 U with meals), metformin (1000 mg BID), and liraglutide, her HbA1c remained elevated at 9.4%. At the initial consultation, she reported postprandial abdominal discomfort since starting liraglutide. Investigation revealed an elevated serum lipase level; 367 U/L (reference range, 1-160 U/L), prompting discontinuation of liraglutide. Her regimen was adjusted to metformin 2.5 g daily, repaglinide 4 mg 3 times daily (TID), canagliflozin 100 mg daily, insulin detemir 40 U BID, and insulin aspart 10 U TID. Dulaglutide 0.75 mg weekly was later introduced following resolution of AP. However, within a few months, she again developed persistent abdominal pain and nausea with intermittent emesis. Laboratory evaluation revealed lipase elevation to 300 U/L, and dulaglutide was discontinued.

Case 3

A 65-year-old Caucasian male had been under endocrine care for 4 years because of hypogonadism, erectile dysfunction, and prediabetes. He had been treated with topical testosterone and lisinopril for hypertension. Despite lifestyle changes and metformin, after 22 years he progressed to T2DM. He also had mixed dyslipidemia and was started on atorvastatin. A cardiology consultation revealed coronary artery disease, leading to an increase in atorvastatin to 80 mg daily and addition of low-dose aspirin. Following diagnosis of T2DM, he lost 40 pounds, reducing his body mass index (BMI) from 31 to 26 kg/m^2. His initial diabetes treatment included metformin 1 g BID and repaglinide 0.5 mg before meals, achieving consistent HbA1c levels below 7.0%. After an acute coronary syndrome and coronary artery bypass grafting, liraglutide was started, with dose escalation to 1.8 mg once daily, for cardiovascular protection and weight loss. However, after 6 weeks, liraglutide was discontinued because of severe epigastric pain and elevated lipase (305 U/L), indicative of AP. Four months later, with only metformin and repaglinide, his HbA1c rose to 7.8%. Dulaglutide 0.75 mg weekly was introduced, resulting in improved glycemic control (HbA1c 5.8%) and weight loss (BMI 24.5 kg/m^2). However, after 7 months, he developed persistent epigastric pain and elevated lipase (487 U/L), indicative of AP and prompting discontinuation of dulaglutide. A year later, the patient requested to be placed on a GLP-1 agent because of their effectiveness in glycemic control, weight management, and heart protection. Instead of injectable semaglutide, he was prescribed oral semaglutide as a precaution, starting at 3 mg daily, which he tolerated well. After 3 months, the dosage was increased to 7 mg daily. However, within 6 weeks of this, he experienced upper abdominal discomfort once again, accompanied by elevated serum lipase levels (peak, 306 U/L), along with clinical symptoms and signs of AP, prompting discontinuation of the medication.

Diagnostic Assessment

Case 1

The patient underwent genetic testing for CF and HC, which revealed that she is a heterozygous carrier of the *C282Y* HC pathogenic variant.

Case 2

Given her family history, notable for 2 grandchildren with CF, and intolerance to GLP-1 agonists, genetic testing was performed that revealed that she is a heterozygous carrier of the delta F5 deletion of the *CFTR* gene.

Case 3

Further investigation revealed a family history of pancreas-related conditions: 2 paternal uncles had pancreatitis, 1 was linked to heavy alcohol use, whereas a maternal aunt died from pancreatic cancer. Genetic testing for familial pancreatitis and pancreatic cancer predisposition identified a single *CFTR* intron 9 poly T allele pathogenic variant (5T/7T/8T), associated with chronic pancreatitis, congenital absence of the vas deferens, and, in some cases, CF when homozygous. The patient also reported a nephew with CF on the paternal side. No pathogenic variants or variants of unknown significance were found in the *CTC*, *PRSS1*, or *SPINK1* genes. Additionally, testing for HC revealed a single *C282Y* pathogenic variant. The patient denied any family history of HC or other iron storage disorders.

Treatment

Case 1

Liraglutide was discontinued, and the patient's symptoms resolved following its cessation. Her glycemic management now excludes the use of GLP-1 analogs and DPP-4 inhibitors.

Case 2

Patient instructed to discontinue GLP-1 analogs. Her current antidiabetic regimen includes metformin 2.5 g total daily dose, repaglinide 4 mg TID, canagliflozin 100 mg daily, insulin detemir 50 U BID, and insulin aspart 10 U TID.

Table 1. Summary and genetic findings of the heterozygous CF/HC GLPAP cases

Category	Case 1	Case 2	Case 3
Age and demographics	39-year-old Caucasian female	62-year-old Caucasian female	65-year-old Caucasian male
Family history	No notable family history of pancreatitis or genetic disorders	Two grandchildren with cystic fibrosis	Two paternal uncles with pancreatitis (1 linked to heavy alcohol use), maternal aunt died from pancreatic cancer. Nephew with cystic fibrosis on the paternal side
GLP-1 history	Liraglutide, dulaglutide, exenatide	Liraglutide, dulaglutide	Liraglutide, dulaglutide, oral semaglutide
Lipase levels (normal: 1-160 U/L)	325 U/L	367 U/L after liraglutide 300 u/L after dulaglutide	305 U/L after liraglutide 487 U/L after dulaglutide
Timeline	Within weeks of starting dulaglutide (previous GLP-1A and DPP-4 inhibitors led to similar episodes)	Within weeks initiating liraglutide. Within months of initiation of dulaglutide	After 6 weeks of liraglutide use After 7 months of dulaglutide use Within 6 weeks of higher dose of oral semaglutide
Genetic findings	Heterozygous C282Y HC mutation	Heterozygous delta F508 CFTR mutation	Single CFTR intron 9 poly T allele mutation (5T/7T/8T); C282Y mutation
Treatment adjustments	Discontinuation of GLP-1A. Insulin degludec, repaglinide, metformin, PRN insulin lispro	Discontinuation of GLP-1A. Metformin, repaglinide, canagliflozin, basal and prandial insulin	Discontinuation of GLP-1RA. Metformin, repaglinide, and empagliflozin
Outcomes	No recurrence of AP; HbA1c 6.5%	No recurrence of AP; HbA1c 7.7% (noted noncompliance with therapy)	No recurrence of AP. Stable BMI (27 kg/m^2); HbA1c 6.2%

Abbreviations: AP, acute pancreatitis; BMI, body mass index; CFTR, cystic fibrosis transmembrane regulator; DPP-4, dipeptidyl peptidase 4; GLP-1A, glucagon-like peptide-1 receptor agonist; HC, hemochromatosis; HbA1c, hemoglobin A1c; PRN, as needed.

Case 3

Chart records were updated to reflect intolerance to GLP-1 agonists. Consequently, the patient was switched to empagliflozin with dose escalation to 25 mg daily with salutary effect.

Outcome and Follow-Up

Case 1

The patient is currently managed with insulin degludec, repaglinide, metformin, and as needed insulin lispro, with a current HbA1c of 6.5%. Since the genetic testing, she has not been treated with any GLP-1 agonists and has not experienced any further episodes of AP.

Case 2

The patient has not experienced a recurrence of AP since discontinuing GLP-1 analogs. Her most recent HbA1c was 7.7%, and she acknowledged being less compliant with her treatment. Her ongoing glycemic management now excludes the use of GLP-1 analogs.

Case 3

The patient's latest HbA1c was 6.2% with weight stable at a BMI of 27 kg/m^2. Current care excludes GLP-1 analogs.

Discussion

GLP-1 agonists provide benefits beyond glycemic control, including β-cell preservation and improvements in comorbidities such as obesity, hypertension, and hyperlipidemia [13-15, 19]. There is growing evidence also indicating their utility for cardiometabolic, cardiorenal, and other obesity-associated comorbid disease amelioration [13-16, 19, 20]. However, gastrointestinal side effects such as nausea, vomiting, and diarrhea are common [13, 18]. Reports of AP associated with GLP-1 agonists have been documented in both animal and human studies, though the prevalence and risk factors remain unclear [20-27]. The cases presented suggest a potential link between carrier states for *CFTR* and *HFE* pathogenic variants (associated with CF and HC, respectively) and GLP1AP susceptibility (Table 1).

Although *CFTR* pathogenic variants carriers were traditionally considered asymptomatic, studies have shown a correlation between carrier states and pancreatitis [4, 28, 29]. In a study published by Cohn et al, researchers demonstrated a 4-fold increased risk of idiopathic chronic pancreatitis in CF carriers with 1 normal *CFTR* allele [29]. Similarly, Ooi and colleagues found that ~40% of patients with recurrent acute or chronic pancreatitis carrying *CFTR* pathogenic variants, predominantly on only 1 allele [30]. As in the 3 cases presented in our study, being a carrier of CF and/or HC might in fact lead to the destruction of healthy pancreatic acinar or ductal cells especially in the setting of other clinical risk factors. This destruction could occur due to concentrated pancreatic secretions or excessive iron deposition, particularly when exacerbated by irritants such as ambient GLP-1 agonist use. Interestingly, GLP-1 receptors, once thought to only be expressed on β cells, were more recently found to be expressed on exocrine cells as well. Of note, studies have been performed evaluating the use of GLP-1 receptor agonist in population with phenotypical CF and HC, yet these have been small with limited follow-up periods to assess true risk for GLP1AP. Furthermore, although our cohort of heterozygotes retains functional exocrine capacity, it is plausible that progressive exocrine dysfunction in individuals with phenotypic cystic fibrosis may impair their ability to express AP.

Although AP is uncommon with GLP-1 agonist use, their rising use in diabetes, weight management, and other therapeutic

vistas demands careful safety measures, ongoing clinical surveillance, and prudent patient selection. Our clinical series suggests that carriers of *CFTR* or *HFE* pathogenic variants, even in the heterozygous state, may have compromised exocrine pancreatic function, increasing their susceptibility to injury from GLP-1 agonists. Therefore, a detailed patient history and consideration of genetic screening for these pathogenic variants may be prudent in those who have developed GLP1AP to solidify evidence of these phenomenon. If found to be true, genetic assessment before treatment initiation in at-risk populations could improve safety and reduce the risk of adverse events associated with GLP-1 agonists.

Learning Points

- Reports of acute pancreatitis in both animals and humans treated with GLP-1 agonists exist, but the precise prevalence and predictors remain uncertain.
- Carriers of CF or HC may increase the risk for GLP1AP.
- In cases of GLP1AP, identification of carrier state of CF and/or HC may prohibit further utilization of other GLP-1 agonists.
- Genetic screening for CF and/or HC gene carrier states should be considered among patients with GLP1AP to provide more support and data for this as a potential true risk factor.

Contributors

All authors made individual contributions to authorship. T.D. and W.A.W. were directly involved in data collection. G.I.S. and G.I.U. were directly involved in drafting the manuscript and editing for submission. All authors reviewed and approved the final version of the manuscript.

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Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patients or a proxy but has been approved by the treating institution.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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