Empagliflozin-Associated Pancreatitis in the Setting of Hyperglycemic Hyperosmolar Syndrome

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Abstract

Acute pancreatitis is the leading cause of gastrointestinal hospital admissions in the United States [1]. While there are a variety of presentations, the majority do not require stay in the intensive care unit. Medication side effect is one large cause of pancreatitis. More recently diabetic agents have been linked to pancreatitis. Here we describe a case of pancreatitis caused by a SGLT-2 Inhibitor, Empagliozin, and the acceleration into hyperosmolar hypoglycemic syndrome and ICU admission. We hope to provide more information for clinicians detailing the link and outlining the management in cases such as this which do significantly increase inpatient morbidity and mortality.

Introduction

Acute pancreatitis is the leading cause of gastrointestinal hospital admissions in the United States [1]. Presentations could range from mild, such as edematous pancreas, to severe, such as necrotizing pancreatitis, and may even involve multi-organ disease and require intensive care unit admission. In the United States, there are approximately 130,000 new cases of acute pancreatitis annually and the incidence is increasing over time likely due to obesity and predisposition to gallstones. [2]. Although only 20% of cases progress to an ICU admission, these severe cases are associated with increased hospital length of stay, procedures and management, with an increase in mortality up to 30% [3].

There are many known causes of acute pancreatitis, the most common being gallstones and chronic alcohol use disorder. Several medications also have pancreatitis listed as a documented side effect. These medications include angiotensin-converting enzyme (ACE) inhibitors, statins, hormone-replacement therapies, diuretics, hypoglycemic agents, and steroids [4]. Concerning the hypoglycemic agents, glucagon-like peptide-1 (GLP-1) mimetics have primarily caused exacerbations of acute pancreatitis [4]. However, recent case reports have identified another possible hypoglycemic agent associated with pancreatitis, that being empagliozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor [8]. The presumed mechanism of drug-induced pancreatitis is through the cytotoxic effects of either the drug itself or its metabolites [6]. This case not only recognizes the recently identified link between SGLT-2 inhibitors and pancreatitis, but it also depicts the accelerated sequela into hyperglycemic hyperosmolar syndrome (HHS) caused by pancreatitis. Hyperglycemic hyperosmolar syndrome encompasses uncontrolled blood glucose levels, commonly seen in type 2 diabetics. Pancreatitis can lead to hyperglycemic hyperosmolar syndrome by damaging the exocrine pancreatic function and decreasing insulin levels [7]. If left untreated, HHS can rapidly progress from lethargy to coma, due to the severe dehydration and hyperglycemic effects. This study discusses the effects of drug-induced pancreatitis on plasma glucose levels and its subsequent complications.

Case Presentation

A 57-year-old man presented with worsening epigastric pain, intermittent nausea, and several episodes of non-bloody, non-bilious emesis for the past five days. His past medical history is significant for
decompensated heart failure (ejection fraction of 30%) requiring a temporary left ventricular assist device, cardiac arrest, newly diagnosed type 2 diabetes mellitus, and hypertension. In the emergency department, the patient was normotensive, and normothermic, with a normal pulse rate, regular respirations, and saturating appropriately. Physical exam was notable for tenderness in the epigastric region and mild abdominal distention.

On admission, labs were notable for plasma glucose of 1261 mg/dL, beta-hydroxybutyrate > 30 mg/dL, lactic acid 4.6 mmol/L, anion gap of 23 mmol/L, serum lipase of 1006 U/L, triglyceride level mildly elevated at 406 mg/dL. Urinalysis demonstrated 3+ glucose and trace ketones, leading to a diagnosis of hyperglycemic hyperosmolar syndrome (see Fig. 2).

Further history revealed the patient's type 2 diabetes was being managed exclusively with empagliozin for one year and confirmed that he was compliant with his medications. The patient denied a history of alcohol use disorder or any recent alcohol intake. Abdominal ultrasound showed a normal gallbladder, no gallstones, no gallbladder wall thickening, and a negative sonographic Murphy's sign. Abdominal CT demonstrated an enlarged pancreas, significant peripancreatic edema/stranding, and peripancreatic fluid extending to the left pararenal space and paracolic gutter (Fig. 1). In the emergency department, the patient was started on a weight-based insulin regimen, lactated ringers for rehydration, and was admitted to the intensive care unit for management of acute pancreatitis with hyperglycemic hyperosmolar syndrome. The patient's symptoms improved within eleven days and his laboratory values normalized. The patient was discharged home on an insulin regimen and Empagliozin was discontinued.

Discussion

The SGLT2 inhibitors, canagliflozin, dapagliflozin, and empagliozin, are FDA-approved oral hypoglycemic agents. The mechanism of these relatively new medications acts by inhibiting the sodium-glucose co-transporter 2 in the proximal tubule, causing glucosuria and leading to lower blood glucose levels [5]. The SGLT2 expressed in the proximal tubule mediates reabsorption of 90% of the filtered glucose. By inhibiting this cotransporter, the drug reduces blood glucose by increasing urinary glucose excretion. The American Diabetes Association recommends that this medication be used after healthy lifestyle changes, diet modification and medical intervention with metformin prove to be insufficient in controlling the patient's hyperglycemia [5]. There are numerous advantages of using an SGLT2 inhibitor compared to other diabetes medications, most of which stem from its mechanism of being independent of insulin levels and sensitivity. By bypassing insulin, patients are at lower risk of hypoglycemia, weight gain, and hepatic injury compared to other diabetic medications. Their well-studied adverse effects include genitourinary infections, diabetic ketoacidosis, and acute kidney injury.

Though pancreatitis is common among other diabetes medications, such as GLP-1 mimetics and Dipeptidyl Peptidase-4 (DPP-4) inhibitors, it is not recognized by the FDA as an adverse effect of SGLT2 inhibitor use. Over the last decade, there have been rare reported cases of pancreatitis linked to canagliflozin, dapagliflozin, and empagliozin [8]. However, this case is interesting because the
Empagliflozin-induced pancreatitis led to the complication of hyperglycemic hyperosmolar syndrome. The pathophysiology behind this is that acute pancreatitis leads to stress hyperglycemia. This phenomenon occurs due to the overactivation of the sympathetic nervous system, causing elevated glucagon [7]. The extensive edema and ischemia also cause decreased insulin production. In a patient without diabetes, the body may either compensate properly or potentially lead to a diabetic state. However, in a patient with preexisting diabetes, pancreatitis may accelerate severe complications.

This report depicts another case of empagliflozin-associated pancreatitis, except with a sequela of hyperglycemic hyperosmolar syndrome, which has not been previously documented. It is imperative that healthcare professionals possess the ability to promptly discern any culpable agents, allowing for their cessation, and ultimately allowing prevention of any further detrimental effects.

Conclusion

Acute pancreatitis often leads to systemic inflammatory disease, potentially complicated by multi-organ system involvement if left untreated [1]. While this disease typically has a classic presentation, there are various etiologies contributing to the onset of disease. It is vital that medical providers are able to identify offending agents as early as possible for prompt discontinuation to prevent further damage or subsequent episodes.

This case impacts the future management of diabetes by highlighting the importance of medication reconciliation. By reviewing medications and their potential side effects at each visit, complications can be identified earlier or potentially avoided, leading to better healthcare management. While the FDA is investigating the possible link between acute pancreatitis and SGLT2 inhibitors, clinicians should be aware of this interrelation to enhance the management of their diabetic patients [8].

Declarations

- **Ethics approval and consent to participate**
  - Not required by our institution
- **Consent for publication**
  - Informed consent obtained from the patient
- **Availability of data and material**
  - Yes
- **Competing interests**
  - None to disclose
- **Funding**
  - None to disclose
- **Authors' contributions**
All listed authors partook in writing and editing of the manuscript

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References


Figures
Figure 1

Abdominal CT depicting an enlarged pancreas, significant peripancreatic edema/stranding (yellow arrow), and peripancreatic fluid extending to the left pararenal space and paracolic gutter.

<table>
<thead>
<tr>
<th>Labs</th>
<th>Admission</th>
<th>Peak</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose</td>
<td>1261 mg/dL</td>
<td>–</td>
<td>196 mg/dL</td>
</tr>
<tr>
<td>Beta-hydroxybutyrate</td>
<td>33.5 mg/dL</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lactic Acid</td>
<td>4.6 mmol/L</td>
<td>–</td>
<td>2.3 mmol/L</td>
</tr>
<tr>
<td>Anion Gap</td>
<td>23 mmol/L</td>
<td>–</td>
<td>9 mmol/L</td>
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<td>Serum Lipase</td>
<td>1006 U/L</td>
<td>7534 U/L</td>
<td>917 U/L</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>406 mg/dL</td>
<td>–</td>
<td>234 mg/dL</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>3+ glucose, trace ketones</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hemoglobin A1c%</td>
<td>12.3 %</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Figure 2

Displayed lab values from admission to discharge, with significant peaks.