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Adverse Effects of Multi-drug Diabetes Regimens: Case Report of Acute Pancreatitis and Diabetic Ketoacidosis

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Abstract Options for treating type 2 diabetes mellitus have evolved in the last few decades with the introduction of glucagon-like-peptide 1 (GLP-1) agonists and dipeptidyl peptidase (DPP-4) inhibitors. These medications are known to slow gastric emptying and have proven to be an effective alternative to insulin in the treatment of diabetes. Newer drugs such as SGLT-2 inhibitors and cardioprotective drugs contribute additional benefit in the management of diabetes. While there have been reports of the side effects associated with individual medications, there is less research on the combined effects of a complete medication regimen. This case describes a patient who developed acute pancreatitis and subsequent diabetic ketoacidosis following major changes to her diabetes medications, including the addition of a DPP-4 inhibitor and dosage increase of a GLP-1 agonist to her existing regimen of an SGLT-2 inhibitor. Therefore, we propose the need for further research into the consequences of prescribing a combination of medications for the treatment of type 2 diabetes.

Keywords: *case report, diabetes, multi-drug, adverse effects, pancreatitis, diabetic ketoacidosis*

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1. Introduction

Diabetes mellitus management has undergone significant evolution since the discovery of insulin in the 1920s, which became a life-saving medication for people with type 1 diabetes [1]. Afterwards, the widespread use of oral medication followed, and options included sulfonylureas, which act by increasing insulin production from the pancreas, and metformin [2]. The most groundbreaking breakthrough in diabetes management, however, has been the development of GLP-1 and DPP-4 inhibitors. These medications have been proven to improve glycemic control and lower the risk of hypoglycemia, making them preferable [3,4]. Additionally, SGLT-2 inhibitors, introduced in the 2010s, have not only shown benefit in the treatment of diabetes but have also proven to be cardioprotective with an established mortality benefit [5]. The simultaneous usage of a GLP-1 agonist, DPP-4 inhibitor, and SGLT-2 inhibitor in the management of type 2 diabetes may increase the risk of diabetic ketoacidosis (DKA) crisis. We describe a case of DKA in the setting of combined GLP-1, DPP-4 and SGLT-2 use, portraying the need for caution and further research when prescribing a combination treatment regimen for diabetes.

2. Case Report

A 40-year-old female with a history of type 2 diabetes and hypertriglyceridemia presented to the emergency department (ED) with symptoms of altered mental status, nausea, and vomiting. The symptoms began 2 nights before her arrival at the ED. On presentation, her vitals were as follows: temperature (36.8°C), heart rate (110 bpm), respiratory rate (25 bpm), blood pressure (92/71 mmHg), and oxygen saturation (99%). Initial pertinent laboratory values showed hyperglycemia (glucose level of 436 mg/dL), an anion gap (34 mmol/L), metabolic acidosis (serum bicarbonate of 6 mmol/L), elevated lipase (2220 U/L), elevated creatinine (1.96mg/dL), a leukocytosis (WBC of 22.6 x 10^3/mcL) and a urinalysis positive for ketones. The patient's vital signs and the rest of her laboratory parameters are also summarized in Table 1.

The patient was admitted to the intensive care unit (ICU) for diabetic ketoacidosis (DKA). She was started on the DKA protocol, which included the use of intravenous fluids and high dose sliding-scale insulin. Computed tomography of the abdomen/pelvis (CTA/P) without contrast did not reveal any pancreatitis or acute abdominal process. On physical exam, abdomen was non-tender, even with deep palpation, therefore no abdominal ultrasound (US) was obtained. Additionally, no infection source was identified, as her work-up included a negative urinalysis, clear chest x-ray, and unremarkable procalcitonin level. The patient was discharged 3 days later. Her acute pancreatitis, encephalopathy, and DKA had resolved. She was discharged home on Lantus (long-acting insulin) with sliding scale coverage. On discharge,

the GLP-1 agonist (Tirzepatide) and DPP-4 inhibitor (Sitagliptin-metformin) were discontinued. It was recommended she follow up with her primary care doctor and endocrinologist.

Table 1. Patient vitals and laboratory parameters in the emergency department

Vitals											
T 36.8 C	HR 110	RR 25	BP 92/71	SPO2 99% RA							
Labs											
CBC		BMP		LFT		Urinalysis		Toxicology screen		Others	
WBC	22.6	Na	144	ALT	27	Urine color	yellow	Amphetamine	NEG	Ethanol	<0.003
RBC	6.3	K	3.9	AST	24	Ur app	clear	Barbituates	NEG	Lipase	>2250
HGB	15.8	Cl	116	Alk Phos	84	Ur s.g	1.02	Opiates	NEG	Mg	3
HCT	49.5	BUN	18	ALB	4	Ur pH	5	Benzo	NEG	Beta HCG	NEG
MCV	78.6	Cr	1.2	T Bili	0.5	Ur protein	100	Cannabinoids	NEG	TSH	2.6
PLT	454	Ca	8.3	T Prot	8.5	Ur glucose	500	PCP	NEG	Trig	241
		Anion gap	18			Ur Ketones	>160	Covid-19	NEG	Lactic acid	2.4
		CO2	10			Ur Bilirubin	small				
						Ur Blood	moderate				
						Ur Nit	NEG				
						Ur Leu	NEG				

T: Temperature, HR: Heart Rate, RR: Respiratory Rate, BP: Blood Pressure, spO2 RA: Oxygen Saturation on Room Air, CBC: Complete Blood Count, WBC: White Blood Cell Count, RBC: Red Blood Cell Count, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean Corpuscular Volume, PLT: Platelet Count, Na: Blood Sodium Level, K: Blood Potassium Level, Cl: Blood Chloride Level, BUN: Blood Urea Nitrogen, Cr: Creatinine, Ca: Blood Calcium Level, CO2: Blood Carbon Dioxide, ALT: Alanine Transaminase, AST: Aspartate Aminotransferase, Alk Phos: Alkaline Phosphatase, ALB: Albumin, T Bili: Total Bilirubin, T prot: Total Protein, Ur app: Urine appearance, Ur S.G: Urine Specific Gravity, Ur Nit: Urine Nitrites, Ur Leu: Urine Leukocyte Esterase, NEG: Negative, Mg: Magnesium, Beta HCG: Beta Human Chorionic Gonadotropin TSH: Thyroid Stimulating Hormone, Trig: Triglycerides.

Prior to admission, at her last visit with her PCP, her hemoglobin A1c was 10.1 and her serum blood glucose was 340. She had never had a previous episode of DKA. Before presenting to the ED, she had been on the GLP-1 agonist (Tirzepatide) 10mg and SGLT-2 inhibitor (Empagliflozin) 25mg for the past 4 months. A DDP-4 inhibitor combination drug (Sitagliptin/Metformin) HCL 50-1000 MG was added to her medication regimen 10 days before she presented to the ED. Additionally, her dose of GLP-1 agonist had just been increased from 10mg to 12.5mg, 10 days before.

When she presented to her primary care doctor's office 5 days after discharge, the SGLT-2 inhibitor was also discontinued. The patient's other home medications included: Atorvastatin 10mg, Fluoxetine 20mg, Norgestimate-eth estradiol (28 PO), Sumatriptan 10mg as needed and Izatriptan 10mg as needed.

3. Discussion

This case report demonstrates a clinically adverse event experienced by a patient after the recent change to a multi-drug regimen of a GLP-1 agonist, DPP-4 inhibitor, and SGLT-2 inhibitor for diabetes management, any of which could have precipitated the development of acute pancreatitis and DKA.

Pancreatitis is characterized by inflammation of the pancreas, a gland located in the retroperitoneum that is of vital importance in the digestion of ingested food and in the reduction of blood glucose levels. There are several causes of pancreatitis, with the two most common being gallstones and alcohol consumption. However, other causes of pancreatitis include genetic factors and hypertriglyceridemia, which is common in patients with type 2 diabetes [6]. DKA, on the other hand, is an urgent complication of diabetes marked by the presence of ketones in the serum that is usually due to a severe lack of insulin. Other causes include any acute trauma or infections, such as in the case of acute pancreatitis.

There has been previous evidence in the literature suggesting an association between acute pancreatitis and the use of newer type 2 diabetes medications. DPP-4-inhibitors primarily act by inhibiting the action of dipeptidyl peptidase-4 (DPP-4), an enzyme present in the kidneys, intestines and bone marrow that is responsible for the activation of glucagon-like peptide-1 (GLP-1). GLP-1 is an incretin hormone involved in the stimulation of insulin synthesis and inhibition of glucagon release. It also serves to improve satiety and slow gastric emptying. Considering how the mechanisms of action of both GLP-1 agonists and DPP-4 inhibitors are interrelated, their physiologic effects may be compounded [7]. DPP-4 inhibitors have been associated with headaches, upper respiratory tract infections and acute pancreatitis [8]. A meta-analysis that assessed the risk of both pancreatic cancer and acute pancreatitis in association with DPP-4 inhibitors showed that there were 64 events of acute pancreatitis in the DPP-4 group compared to 39 events in the control group [9]. Additionally, a recent Cochrane review that only included placebo-controlled trials found that DPP-4 inhibitors significantly increased the risk of pancreatitis compared to placebo [10]. Some of the common side effects of GLP-1 agonists include nausea, vomiting and diarrhea [7]. However, GLP-1 agonists have also been known to have an association with pancreatitis. A recent study that used the FDA adverse event reporting system database found that 70.2 % of pancreatitis reports

were linked to GLP-1 agonists compared to other hypoglycemic agents [11]. Additionally, several case reports continue to demonstrate a causal relationship between GLP-1 agonists and pancreatitis [12,13]. On the other hand, SGLT-2 inhibitors are a class of medication that work by inhibiting the action of sodium/glucose cotransporter-2 (SGLT-2), a protein responsible for the reabsorption of glucose in the kidneys [5]. Likewise, there are several reports of acute pancreatitis associated with the recent addition of SGLT-2 inhibitors to a patient's medication regimen [14,15,16].

The literature illustrates that there has long been data showing a potential association between these medications (DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors) and pancreatitis. However, to our knowledge, there has been much less research into the combined effects of these medications, and whether they significantly increase the risk of developing acute pancreatitis and subsequently, diabetic ketoacidosis.

After the recent addition of a DPP-4 inhibitor to the treatment regimen and an increase in dose of the GLP-1 agonist, our patient was on all three diabetes medications before developing acute pancreatitis and subsequent diabetic ketoacidosis. There has been previous documentation in the literature of acute pancreatitis as a cause of DKA. Recent studies have found that severe episodes of DKA with significant acidosis and hyperlipidemia are more likely to be linked with acute pancreatitis [17,18]. In another case, a patient was recently diagnosed with hyperlipidemia and diabetes before subsequently developing acute pancreatitis and DKA [19]. There are also cases that have highlighted diabetic coma as a result of acute pancreatitis while observing that several of these patients did not have underlying diabetes [17]. While in this case report, no challenge or rechallenge test was performed, considering the temporal relationship of her symptoms to the recent change in her medications, this case strongly suggests a possible correlational link between the combination of these drugs and the etiology of pancreatitis, leading to her serious complications of hospitalization.

Although the adverse effects of DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors have been studied individually, it is crucial to consider the composite consequences of these side effects in a combination drug regimen. Thus, further research is needed to guide clinical management on any contraindications to the combined use of these medications, and at what specific doses these medications can simultaneously be prescribed.

References

[1] De Leiva-Hidalgo, A. & De Leiva-Pérez, A. Experiences of First Insulin-Treated Patients (1922–1923). *American Journal of Therapeutics* 27, e13–e23 (2020).

[2] White, J. R. A Brief History of the Development of Diabetes Medications. *Diabetes Spectrum* 27, 82–86 (2014).

[3] Du, Z., Lu, T., Gao, M. & Tian, L. Reporting and methodological quality of systematic reviews of DPP-4 inhibitors for patients with type 2 diabetes mellitus: an evidence-based mapping. *Acta Diabetol* 59, 1539–1549 (2022).

[4] Yao, H. *et al.* Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. *BMJ* e076410 (2024).

[5] Zinman, B. *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 373, 2117–2128 (2015).

[6] Tenner, S. *et al.* American College of Gastroenterology Guidelines: Management of Acute Pancreatitis. *Am J Gastroenterol* 119, 419–437 (2024).

[7] Gilbert, M. P. & Pratley, R. E. GLP-1 Analogs and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials. *Front. Endocrinol.* 11, 178 (2020).

[8] Huang, J., Jia, Y., Sun, S. & Meng, L. Adverse event profiles of dipeptidyl peptidase-4 inhibitors: data mining of the public version of the FDA adverse event reporting system. *BMC Pharmacol Toxicol* 21, 68 (2020).

[9] Pinto, L. C., Rados, D. V., Barkan, S. S., Leitão, C. B. & Gross, J. L. Dipeptidyl peptidase-4 inhibitors, pancreatic cancer and acute pancreatitis: A meta-analysis with trial sequential analysis. *Sci Rep* 8, 782 (2018).

[10] Sonoda, K. & Saguil, A. DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT-2 Inhibitors for People With Cardiovascular Disease. *Am Fam Physician* 106, 24–25 (2022).

[11] Alenzi, K. A., Alsuhaibani, D., Batarfi, B. & Alshammari, T. M. Pancreatitis with use of new diabetic medications: a real-world data study using the post-marketing FDA adverse event reporting system (FAERS) database. *Front. Pharmacol.* 15, 1364110 (2024).

[12] AlSaadoun, A. R., AlSaadoun, T. R. & Al Ghumlas, A. K. Liraglutide Overdose-Induced Acute Pancreatitis. *Cureus* (2022).

[13] Khan, A. B., Shah, A., Ahmad, S., Khan, M. I. & Amir, A. Dulaglutide (Trulicity)-Induced Acute Pancreatitis: A Case Report. *Cureus* (2023).

[14] Andreea, M. M. *et al.* Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors: Harms or Unexpected Benefits? *Medicina* 59, 742 (2023).

[15] Poloju, A., Majety, P. & Groysman, A. Y. THU371 Empagliflozin Associated Pancreatitis: A Case Report. *Journal of the Endocrine Society* 7, bvad114.804 (2023).

[16] Wu, G., Wu, S., Tang, J. & Wu, H. Delayed euDKA Associated With Dapagliflozin After Pancreatitis. *Clinical Therapeutics* 45, e167–e170 (2023).

[17] Ma, L. P. *et al.* Diabetic Ketoacidosis With Acute Pancreatitis in Patients With Type 2 Diabetes in the Emergency Department: A Retrospective Study. *Front. Med.* 9, 813083 (2022).

[18] Kong, M. T., Nunes, M. P. & Leong, K. F. Diabetic ketoacidosis with acute severe hypertriglyceridaemia-induced pancreatitis as first presentation of type 2 diabetes. *BMJ Case Rep* 14, e239727 (2021).

[19] Mathuram Thiyagarajan, U., Ponnuswamy, A. & Chung, A. An enigmatic triad of acute pancreatitis, diabetic ketoacidosis and hypertriglyceridaemia: who is the culprit? *BMJ Case Rep* 12, e217272 (2019).