EJCRIM
European Journal
of Case Reports
in Internal Medicine

TIRZEPATIDE-INDUCED KETOACIDOSIS IN NON-DIABETIC PATIENTS

Pathan Mohamad Rafe Iqbal[1], Ossama Sajeh Maadarani[2], Zouheir Ibrahim Bitar[2]

[1] Internal Medicine Department, New Ahamdi Hospital, Kuwait Oil Company, Fahahil, Kuwait
[2] Internal Medicine Department, Ahmadi Hospital, Kuwait Oil Company, Fahahil, Kuwait
[3] Critical Care Unit, Internal Medicine Department, Ahmadi Hospital, Kuwait Oil Company, Fahahil, Kuwait

Corresponding author: Zouheir Ibrahim Bitar **e-mail:** zbitar2@hotmail.com

Received: 06/02/2024 **Accepted:** 19/02/2024 **Published:** 11/03/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: The authors declare that patient's written informed consent was obtained prior to the submission of the manuscript.

How to cite this article: Iqbal PMR, Maadarani OS, Bitar ZI. Tirzepatide-induced ketoacidosis in non-diabetic patients. *EJCRIM* 2024;**11**:doi:10.12890/2024_004357.

ABSTRACT

Background: Tirzepatide is a novel glucagon-like peptide 1/glucose-dependent insulinotropic peptide (GLP-1/GIP) receptor agonist. It was recently approved for diabetes control and weight reduction in non-diabetic patients.

Case description: We report the first case of ketoacidosis after the use of tirzepatide in an obese non-diabetic patient, secondary to the possibility of starvation ketoacidosis and insulin resistance.

Conclusion: The dual-acting GLP-1 and GIP receptor agonists, tirzepatide, can induce ketoacidosis in obese non-diabetic patients.

KEYWORDS

Ketoacidosis, tirzepatide, obesity

LEARNING POINTS

- The dual-acting GLP-1 and GIP receptor agonists can cause ketoacidosis in obese non-diabetic patients.
- Ketoacidosis induced by tirzepatide is serious, and physicians should be aware of this complication and be alert to early symptoms, check serum and urine ketone levels, and stop medication.

INTRODUCTION

Ketoacidosis is usually diagnosed by the presence of elevated ketoacids (acetoacetate and beta-hydroxybutyrate) and anion gap metabolic acidosis[1]. The liver produces keto acids – acetoacetic acid and beta-hydroxybutyric acid – and is fuelled by free fatty acids (FFAs) metabolised by extrahepatic tissues, mainly the brain. Increased production requires a significant concentration of FFAs, so the liver converts these FFAs into keto acids. This conversion is commonly observed in diabetic patients due to insulin deficiency and excess glucagon. Tirzepatide is a novel glucagon-like peptide 1/glucose-dependent insulinotropic peptide (GLP-1/GIP) receptor agonist administered by once-weekly subcutaneous injection[2]. It is an approved and effective treatment for obesity in patients with and without diabetes mellitus[3]. We present the case of a non-diabetic patient with obesity who developed ketoacidosis after three weeks of tirzepatide treatment.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

CASE DESCRIPTION

A twenty-one-year-old woman who was not known to have diabetes mellitus or hypertension and had no significant past medical history was admitted to the ICU from the ER with the chief complaints of abdominal pain, two episodes of vomiting and diarrhoea for 2 days. There was no history of fever, cough, dysuria, headache, or chest pain.

Tirzepatide (5 mg) had been subcutaneously administered once a week for weight reduction for the previous three weeks (taken three times until admission) over the counter. The patient developed diarrhoea (3–4 times/day) after she started the tirzepatide. She reported a loss of 5 kg in 3 weeks. She denied having a ketogenic diet. At home, she took pantoprazole whenever she felt epigastric discomfort.

On admission, she was dehydrated with tachyponea due to air hunger, with a heart rate of 110 beats per minute, a blood pressure of 130/80 mmHg, an oxygen saturation of 99% on room air and a BMI of 28.2 kg/m^2. The laboratory test results are shown in *Table 1*. Blood gas analysis revealed a pH of 7.22 (normal value 7.38 to 7.42), a partial pressure of carbon dioxide of 33 mmHg (normal 38 to 42 mmHg), a partial pressure of oxygen of 70 mmHg (75 to 100 mmHg), and a bicarbonate concentration of 13.8 mmHg (normal 21–28 mmol/l). The anion gap was 25 (normal value <12). Her blood ketone concentration was 5.2 mmol/l (normal <0.2 mmol/L). Blood glucose levels were normal (4.9 mmol); there was no osmolar difference. Paracetamol and salicylate levels were undetectable.

She was admitted to the hospital for management of high anion gap metabolic ketoacidosis and normal lactate. Her blood glucose level was not elevated, and her ketosis was initially thought to be caused solely by vomiting and starvation. As an inpatient, she was treated with 0.9 saline (1 l) for 30 min, followed by dextrose 10% (125 ml/hour) with 0.9 saline (125 ml/hour) in two separate lines. Blood glucose levels were between 7 and 8 mmol/l during treatment with dextrose infusion, and the patient did not require insulin. Ondansetron was given every six hours orally for vomiting, and pantoprazole IV.

The anion gap was closed, acidosis was corrected, and the patient was advised against taking tarazepide. The Naranjo adverse drug reaction probability scale was 6, indicating probable adverse events[4]. Follow-up after four weeks showed resolution of all symptoms, and the patient gained one kg.

DISCUSSION

Insulin deficiency or resistance plays an important role in the transfer of free fatty acids (FFAs) from the body's adipose tissue. The presence of excess glucagon and lack of insulin stimulate the transformation of FFAs to keto acids in the liver. Excess glucagon stimulates keto acid production from FFAs by transferring FFAs into the mitochondria, which requires acylcarnitine transferase. Transferring FFAs into mitochondria is followed by the metabolism of FFAs to acetyl coenzyme A (acetyl-CoA) and ultimately to keto acids. The diversification of acetyl-CoA to fatty acid resynthesis requires the enzyme acetyl-CoA carboxylase. Insulin deficiency, excess glucagon and excess catecholamines further inhibit the acetyl-CoA carboxylase enzyme and lead to increased keto acid production[5].

Glucagon-like peptide 1 (GLP-1)-based therapies (GLP-1 receptor agonists [GLP-1RA], dual-acting GLP-1 and glucose-dependent insulinotropic polypeptide [GIP] receptor agonists) affect glucose control through several mechanisms, including enhancement of glucose-dependent insulin secretion, reduction of gastric emptying, enhancement of satiety and reduction of inappropriate glucagon secretion[6].

The dual-acting GLP-1 and GIP receptor agonist tirzepatide has remarkable glycemic and weight-reducing efficacy compared with either agent alone[7]. Its use as a monotherapy has been studied in patients inadequately treated with diet and exercise[8] and in combination with other agents, including metformin, sulfonylureas and insulin[8].

The side effects of GLP-1-based therapies are predominantly gastrointestinal, particularly nausea, vomiting and diarrhoea, which are frequent[9]. These infections occur consistently in 10% to 50% of patients in trials[10]. In a trial comparing tirzepatide with semaglutide, gastrointestinal adverse

Item	Value	Reference range
White blood count (× 109/l)	8.5	4–10
Haemoglobin (g/dl)	13.7	12–15
Platelet count (× 109/l)	351	140–400
Sodium (mmol/l)	137	136–145
Serum potassium (mmol/l)	4.0	3.5–5.1
Blood urea nitrogen (mmol/l)	1.6	2.14–7.14
Corrected calcium (mmol/l)	2.28	2.2–2.6
Phosphorus (mmol/l)	1.1	0.81–1.45
Magnesium (mmol/l)	0.75	0.66–1.07
Total bilirubin (mmol/l)	8	2–17
Gamma glutamyl Transpeptidase (U/l)	13	3–40
Aspartate amino transferase (AST/SGOT) (U/l)	18	5–32
Creatinine (µmol/l)	54	62–106
Glucose (mmol/l)	4.9	
HbA1c	5.1	<5.7
Amylase (U/l)	44	28–100
Lipase (U/l)	35	13–60
C-reactive protein (mg/l)	14	0–5
Lactate (mmol/l)	0.9	<1
Salicylates (mg/dl)	3	50–300

Table 1. Laboratory results.

effects were similar between the two groups (nausea 17.4 to 22.1%, diarrhoea 11.5% to 16.4% and decreased appetite 5.3 to 8.9%)[11]. Adverse events occurred in ≥0.2% of the overall population, leading to discontinuation of tirzepatide or semaglutide; the study did not report any ketoacidosis cases[11]. In the Tirzepatide Once Weekly for the Treatment of Obesity study, adverse events occurred in at least 5% of participants; these adverse events were mainly related to the gastrointestinal tract, and there was no reported case of ketoacidosis[3].

One study aimed to assess the association between GLP-1RA and diabetic ketoacidosis/ketosis in the FDA Adverse Event Reporting System (FAERS) database. From the first quarter (Q1) of 2004 to the fourth quarter (Q4) of 2019, there were 1,382 diabetic ketoacidosis cases (1,491 ketosis cases) associated with GLP-1RA in the FAERS database. There was a slight disproportionate reporting of diabetic ketoacidosis associated with overall GLP-1RA (PRR 1.49, 95% CI 1.24–1.79, $p < 0.001$) after excluding the impact of SGLT2i and insulin. This disproportionality disappeared after GLP-1RA was combined with insulin for comparison. When GLP-1RA was not combined with insulin, the disproportionate reporting of diabetic ketoacidosis associated with GLP-1RA was observed[12].

Ketoacidosis was not reported in obese non-diabetic patients receiving dual-acting GLP-1 agonists aimed at weight reduction. This is the first case report of ketoacidosis being induced by tirzepatide. The most likely mechanism underlying ketoacidosis is starvation ketoacidosis. The main mechanisms causing starvation ketoacidosis are vomiting, nausea, diarrhoea and poor caloric intake induced by dual-acting GLP-1 agonists. In addition, dual-acting GLP-1 agonists can suppress appetite, prolong gastric emptying and decrease calorie intake. Obese patients with limited calorie intake, sometimes less than 500 calories, are at risk of ketosis[13].

Another possible cause is the association between insulin resistance and metabolic unhealthy obesity[14]. An excessive accumulation of free fatty acids in insulin-sensitive non-adipose tissues causes increased insulin resistance[15]. Insulin resistance status could indicate relative insulin deficiency status in obese patients with diabetes, as insulin withdrawal or dose reduction was determined to be an important turning point in the development of diabetic ketoacidosis in patients treated with GLP-1RA[12].

CONCLUSION

We report the first dual-acting GLP-1 and GIP receptor agonist, tirzepatide, that induces ketoacidosis in obese non-diabetic patients. The most likely cause is starvation ketosis in patients with insulin resistance. The complication is serious, and physicians should be aware of this complication, be aware of early symptoms, check serum and urine ketone levels and be ready to stop medication. Tirzepatide should be prescribed only under medical supervision, not over the counter.

REFERENCES

1. Halperin ML, Hammeke M, Josse RG, Jungas RL. Metabolic acidosis in the alcoholic: a pathophysiologic approach. *Metabolism* 1983;**32**:308–305.
2. Willard FS, Douros JD, Gabe MB, Showalter AD, Wainscott DB, Suter TM, et al. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight* 2020;**5**:e140532.
3. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. SURMOUNT-1 Investigators. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;**387**:205–216.
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–245
5. Davids MR, Segal AS, Brunengraber H, Halperin ML. An unusual cause for ketoacidosis. *QJM* 2004;**97**:365–376.
6. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: a pathophysiological update. *Diabetes Obes Metab* 2021;**23**:5–29.
7. Frías JP. Tirzepatide: a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) dual agonist in development for the treatment of type 2 diabetes. *Expert Rev Endocrinol Metab* 2020;**15**:379–394.
8. Del Prato S, Kahn SE, Pavo I, Weerakkody GJ, Yang Z, Doupis J, et al. SURPASS-4 Investigators. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet* 2021;**398**:1811–1824.
9. Trujillo J. Safety and tolerability of once-weekly GLP-1 receptor agonists in type 2 diabetes. *J Clin Pharm Ther* 2020;**45**:43–60.
10. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2011;**2011**:CD006423
11. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;**385**:503–515.
12. Yang Z, Yu M, Mei M, Chen C, Lv Y, Xiang L, et al. The association between GLP-1 receptor agonist and diabetic ketoacidosis in the FDA adverse event reporting system. *Nutr Metab Cardiovasc Dis* 2022;**32**:504–510.
13. Cahill GF Jr. Fuel metabolism in starvation. *Annu Rev Nutr* 2006;**26**:1–22.
14. Samocha-Bonet D, Dixit VD, Kahn CR, Leibel RL, Lin X, Nieuwdorp M, et al. Metabolically healthy and unhealthy obese – the 2013 Stock Conference report. *Obes Rev* 2014;**15**: 697–708.
15. Tong Y, Xu S, Huang L, Chen C. Obesity and insulin resistance: pathophysiology and treatment. *Drug Discov Today* 2022;**27**:822–830.