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Severe Euglycemic Ketoacidosis Following Unsupervised Tirzepatide Dose Escalation in a Non-Obese, Non-Diabetic Woman

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Female, 45-year-old
Final Diagnosis: Euglycemic diabetic ketoacidosis • metabolic acidosis
Symptoms: SOB • vomiting
Clinical Procedure: —
Specialty: Critical Care Medicine

Objective: Unusual clinical course

Background: Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist approved for type 2 diabetes and chronic weight management in adults meeting clinical criteria. Appetite suppression and gastrointestinal intolerance can markedly reduce intake. This report describes a 30-year-old woman with tirzepatide-associated euglycemic ketoacidosis after unsupervised use of tirzepatide obtained without a prescription for weight loss, despite having no history of obesity or diabetes.

Case Report: A 30-year-old woman with a body mass index of 24.8 kg/m^2 and no known diabetes presented with 4 days of severe nausea, approximately 10 vomiting episodes daily, poor intake, and periumbilical abdominal pain. She had self-administered tirzepatide 2.5 mg once weekly and increased the dose to 5 mg 1 week before presentation. Initial testing showed high anion gap metabolic acidosis with a pH of 7.15, bicarbonate level of 10.5 mEq/L, and an anion gap of 24. Lactate was in the normal range. Urine ketones were positive, serum ketones measured 4.5 mmol/L, and glucose level was 4.2 mmol/L. Acidosis persisted after administration of 1.5 L crystalloid, prompting intensive care unit admission. Tirzepatide was stopped. She received 10% dextrose, lactated Ringer's solution, thiamine, antiemetics, electrolyte monitoring and replacement, and gradual refeeding. The anion gap closed and ketones normalized within 36 hours, without bicarbonate therapy or insulin infusion.

Conclusions: Tirzepatide-related nausea, vomiting, and caloric deprivation can be associated with significant euglycemic ketoacidosis even without diabetes or obesity. Clinicians should consider starvation ketoacidosis in tirzepatide users with vomiting, poor intake, abdominal pain, and high anion gap metabolic acidosis.

Keywords: Case Reports • Endocrinology • Ketoacidosis • Tirzepatide

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Introduction

Tirzepatide is a once-weekly injectable dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors [1]. It is used for glycemic control in adults with type 2 diabetes mellitus and is approved in the United States as tirzepatide for chronic weight management in adults with obesity or overweight with at least 1 weight-related condition [1,2]. In clinical trials, once-weekly tirzepatide produced substantial and sustained weight reduction in adults with obesity [3]. Common adverse reactions include nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain [4].

Euglycemic ketoacidosis is ketoacidosis with normal or only mildly elevated blood glucose, and evaluation includes acid-base status, anion gap, glucose, serum or urine ketones, lactate, renal function, medications, diabetes status, and precipitating illnesses [5]. Starvation ketoacidosis occurs when reduced caloric or carbohydrate intake depletes glycogen and shifts metabolism toward lipolysis and hepatic ketogenesis; it can present as high anion gap metabolic acidosis with normal or low glucose and can improve with carbohydrate replacement, fluid therapy, electrolyte monitoring, and treatment of the precipitating cause [6,7].

Recent case reports have described tirzepatide-associated ketoacidosis in non-diabetic patients or patients not taking sodium-glucose cotransporter-2 (SGLT2) inhibitors, often after gastrointestinal symptoms, reduced caloric intake, rapid weight loss, or unsupervised prescribing pathways [8-13]. This report describes the case of a 30-year-old woman who developed tirzepatide-associated euglycemic ketoacidosis after using tirzepatide obtained without a prescription for weight loss, despite having no history of obesity or diabetes mellitus.

Case Report

A 30-year-old woman with a body mass index of 24.8 kg/m^2 was admitted to the intensive care unit (ICU) from the emergency department (ED) after 4 days of severe nausea, repeated vomiting of approximately 10 episodes per day, markedly reduced oral intake, and dull periumbilical, non-radiating abdominal pain. She had no known diabetes mellitus, no obesity, and no significant past medical or surgical history. She reported obtaining tirzepatide without a prescription for weight reduction despite a non-obese body mass index. She started tirzepatide 2.5 mg subcutaneously once weekly and increased the dose to 5 mg once weekly 1 week before presentation. She reported no fever, headache, cough, chest pain, palpitations, dysuria, or respiratory symptoms.

On arrival to the ED, her heart rate was 77 beats/min, temperature was 37 °C, respiratory rate was 19 breaths/min, blood pressure was 116/77 mmHg, and oxygen saturation was 98% on room air. Initial laboratory testing showed high anion gap metabolic acidosis, with a pH of 7.15, bicarbonate level of 10.5 mEq/L, anion gap of 24, normal lactate level of 1.5 mmol/L, serum ketone level of 4.5 mmol/L, positive urine ketones, and normal random glucose of 4.2 mmol/L. The creatinine level was 55.4 micromol/L, C-reactive protein level was 4.2 mg/dL, procalcitonin level was 0.02 ng/mL, and amylase and lipase levels were within reference ranges (**Table 1**).

She received 1.5 L of crystalloid in the ED, but the acidosis persisted and the ICU team was consulted. The diagnostic impression was starvation ketoacidosis associated with tirzepatide-related gastrointestinal intolerance and reduced caloric intake. Diabetic ketoacidosis was considered less likely because she had no known diabetes, no documented use of insulin or SGLT2 inhibitors, and normal glucose. Alcoholic ketoacidosis, lactic acidosis, renal failure, sepsis, and pancreatitis were also considered less likely based on the history, normal lactate level, normal renal function test results, low inflammatory markers, and normal pancreatic enzyme test results.

In the ICU, tirzepatide was discontinued. Treatment focused on reversing starvation, correcting dehydration, preventing thiamine deficiency, and monitoring for electrolyte shifts during refeeding. Intravenous thiamine was administered, and 10% dextrose was started at 60 mL/h with lactated Ringer's solution at 100 mL/h. Electrolytes were checked every 6 hours and replaced as required. Ondansetron 4 mg was administered twice daily. Oral liquid feeding was started within hours and was advanced gradually to a regular diet as nausea improved.

The metabolic acidosis and ketosis improved steadily after dextrose-containing fluids and refeeding. At 36 hours, pH was 7.41, bicarbonate level was 22.2 mEq/L, anion gap was 9, and serum ketone level was 0.1 mmol/L (**Table 2, Figure 1**). Potassium reached a nadir of 3.2 mEq/L at 30 hours and improved to 4.0 mEq/L after replacement. She did not require bicarbonate therapy, insulin infusion, vasopressors, or renal replacement therapy. Her symptoms resolved, oral intake was resumed, and no recurrent ketosis was documented during hospitalization.

Discussion

The main lesson from this case is that clinically significant euglycemic ketoacidosis can occur in a non-obese, non-diabetic patient using tirzepatide without medical indication or monitoring when gastrointestinal intolerance causes prolonged caloric deprivation. The temporal relationship with dose escalation, 4 days of vomiting and poor intake, high anion gap metabolic

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Table 1. Initial laboratory test results at presentation.

Test	Result	Unit	Reference range
WBC	4.82	$\times 10^9$/L	4-11
HGB	14.3	g/dL	12-16
PLT	342	$\times 10^9$/L	140-450
BUN	1.2	mmol/L	2.5-6.7
Creatinine	55.4	µmol/L	50-98
Sodium	136	mmol/L	136-145
Potassium	4.3	mmol/L	3.5-5
Magnesium	0.76	mmol/L	0.66-1.07
Chloride	111	mmol/L	98-107
CRP	4.2	mg/dL	<5
Procalcitonin	0.02	ng/mL	<0.05
Calcium	2.3	mmol/L	2.1-2.55
ALT	12	U/L	7-40
AST	15	U/L	5-34
ALP	95	U/L	40-150
Amylase	38	U/L	25-125
Lipase	27	U/L	12-53
Random glucose	4.2	mmol/L	3.6-11

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; HGB, hemoglobin; PLT, platelet count; WBC, white blood cell count.

Table 2. Serial acid-base, ketone, lactate, and electrolyte trend during the first 36 hours.

Variable	0 h	6 h	12 h	18 h	24 h	30 h	36 h
pH	7.15	7.11	7.23	7.28	7.33	7.40	7.41
PCO_2 (mmHg)	30	31	25	33	34	31	35
Sodium (mEq/L)	134	139	137	135	133	134	133
Potassium (mEq/L)	4.6	4.2	3.5	3.3	3.5	3.2	4.0
Lactate (mmol/L)	1.5	1.0	1.1	1.0	0.7	0.6	1.1
BE (mEq/L)	-17	-18.8	-4.2	-10	-7.2	-4.7	-1.1
Bicarbonate (mEq/L)	10.5	9.8	10.5	15.5	17.9	19.2	22.2
Anion gap (mEq/L)	24	20	14	13	9	10	9
Ketones (mmol/L)	4.5	3.2	2.3	1.1	0.2	0.1	0.1

Abbreviations: BE, base excess; PCO_2, partial pressure of carbon dioxide.

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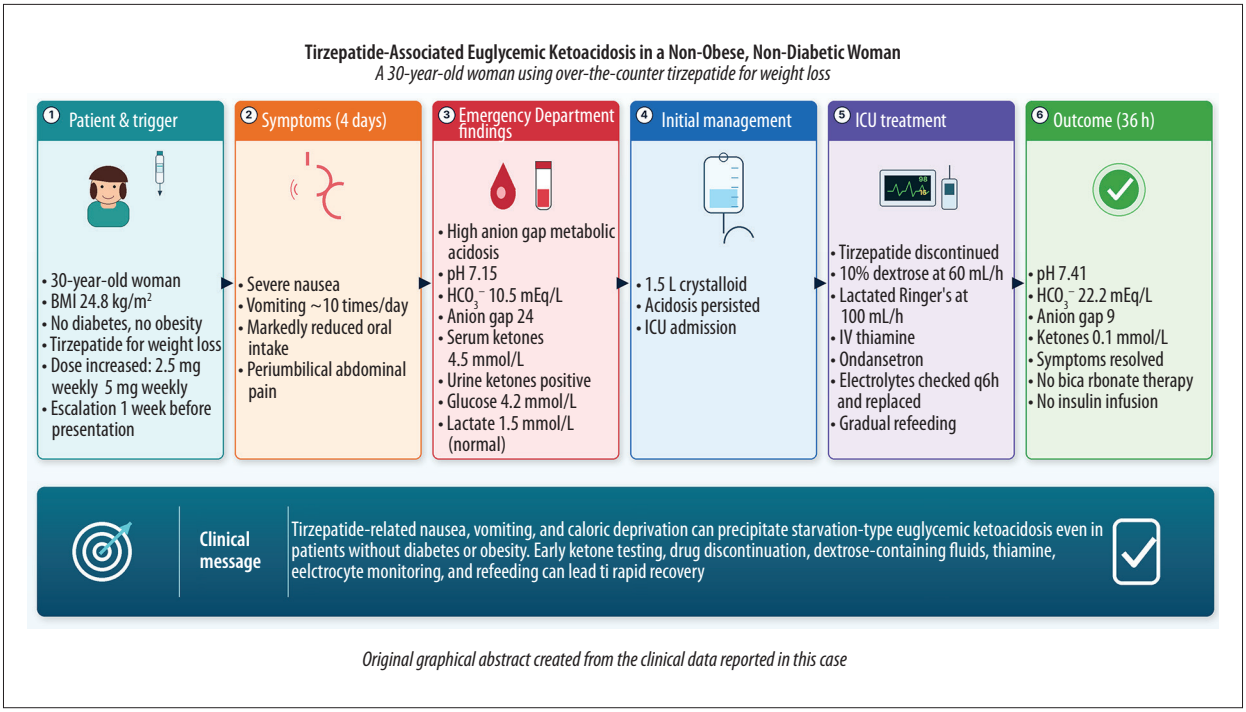

Figure 1. Clinical course of tirzepatide-associated euglycemic ketoacidosis. Original schematic created from the clinical timeline and laboratory values in this case report. The figure summarizes tirzepatide dose escalation from 2.5 mg to 5 mg weekly, 4 days of vomiting and poor oral intake, emergency department findings of high anion gap metabolic acidosis with ketonemia and normal lactate levels, initial crystalloid resuscitation with persistent acidosis, intensive care unit management with 10% dextrose, lactated Ringer's solution, thiamine, electrolyte monitoring, ondansetron, discontinuation of tirzepatide, and recovery by 36 hours with closure of the anion gap without bicarbonate therapy. Abbreviations: D10, 10% dextrose; ED, emergency department; HCO3-, bicarbonate; ICU, intensive care unit; q6h, every 6 hours.

acidosis, ketonemia, normal lactate, normal glucose, and recovery after dextrose-containing fluids and refeeding support starvation ketoacidosis rather than diabetic ketoacidosis.

Tirzepatide can reduce appetite and delay gastric emptying, and nausea, vomiting, dyspepsia, abdominal pain, and clinically significant decreased appetite are recognized adverse reactions [1,4]. When carbohydrate intake falls sharply, glycogen stores become depleted, insulin secretion decreases, counterregulatory hormones increase, and free fatty acids are converted to ketone bodies in the liver [6,7]. In this setting, glucose may remain normal or low, so checking serum or urine ketones is important when a patient taking tirzepatide presents with abdominal symptoms and high anion gap metabolic acidosis [5-7].

Published reports provide context for this case. Iqbal et al reported ketoacidosis after tirzepatide use in a non-diabetic patient with obesity and proposed starvation ketosis with insulin resistance as a mechanism [8]. Bitar et al described hypoglycemic ketoacidosis in non-diabetic patients on tirzepatide and emphasized ketone testing and medical supervision when gastrointestinal symptoms occur [9]. Singh reported euglycemic ketoacidosis in a non-diabetic patient after tirzepatide for weight loss [10]. Sathambihai et al described a 61-year-old woman who developed euglycemic ketoacidosis after an online tirzepatide prescription, highlighting risks related to less-monitored prescribing pathways [11].

Campana et al reported tirzepatide-associated euglycemic diabetic ketoacidosis in the absence of SGLT2 inhibitor use, with nausea, vomiting, abdominal pain, pH of 7.1, anion gap of 28, ketonuria, and mild hyperglycemia; the patient was treated with intravenous fluids, dextrose, and insulin infusion [12]. Minoda et al reported starvation ketoacidosis in a 21-year-old non-diabetic East Asian woman using tirzepatide for weight loss with carbohydrate restriction, vomiting, hypoglycemia, pH of 7.22, and bicarbonate of 10 mmol/L. Improvement occurred within 12 hours after glucose-containing fluids, without insulin therapy [13]. Compared with these reports, our patient had no obesity, had a normal glucose level at presentation, used tirzepatide obtained without a prescription for aesthetic weight reduction, had persistent acidosis after initial crystalloid resuscitation, and recovered without bicarbonate therapy or insulin infusion.

Management in this case was consistent with the suspected starvation mechanism. Dextrose-containing fluids provided

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carbohydrate substrate to suppress ketogenesis, thiamine was given before or with carbohydrate replacement to reduce risk during refeeding, and serial electrolyte monitoring allowed correction of potassium depletion. Because the patient had preserved hemodynamics, normal lactate levels, normal renal function, normal glucose levels, and improving acid-base status after carbohydrate replacement, bicarbonate therapy and insulin infusion were not required.

This case report has limitations. Pretreatment hemoglobin A1c, C-peptide, insulin levels, and pancreatic autoantibodies were not available for inclusion; therefore, occult dysglycemia cannot be fully excluded. Causality cannot be proven from a single case report. However, the close timing after tirzepatide dose escalation, the severe reduction in oral intake, objective ketonemia and high anion gap metabolic acidosis, exclusion of common alternative explanations from available data, and rapid improvement after dextrose and refeeding support a clinically important association.

Conclusions

Tirzepatide-associated gastrointestinal adverse effects and reduced caloric intake can precipitate starvation-type euglycemic ketoacidosis even in patients without diabetes or obesity. Clinicians should consider this diagnosis in tirzepatide users who present with vomiting, poor intake, abdominal pain, normal or low-normal glucose levels, and high anion gap metabolic acidosis. Early ketone testing, discontinuation of tirzepatide, dextrose-containing fluids, thiamine, careful electrolyte monitoring, antiemetics, and gradual refeeding can lead to resolution without bicarbonate therapy when clinically appropriate. This case also underscores the need for medical supervision and patient counseling as access to incretin-based weight-loss drugs increases.

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Department and Institution Where Work Was Done

Critical Care Department, King Fahad Military Medical Complex, Dhahran, Saudi Arabia.

Patient Permission/Consent Declarations

The patient provided written informed consent for the publication of this case report.

Use of AI-Assisted Language Editing

OpenAI was used to assist with language editing. The authors reviewed and approved all AI-assisted edits and take responsibility for the clinical content, data accuracy, interpretation, references, tables, figure content, and final manuscript.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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