CASE REPORT

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A Liraglutide Injection Superimposing a Starvation Acidosis: a Case Report

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ABSTRACT

Background: Metabolic acidosis is defined by reduced serum bicarbonate level; this reduction can be from the addition of acid, reduced acid excretion, or loss of alkali. Starvation acidosis is one of the differential diagnoses of high anion gap metabolic acidosis (HAGMA). **Objective:** We report a rare case presentation of HAGMA associated with Liraglutide and low carbohydrates diet. **Case presentation:** A 27-year-old female patient presented to the Emergency Department (ED) with a complaint of nausea and vomiting for two days. She was following a strict low carbohydrate diet for three months to reduce her weight as her body mass index (BMI) was 30 kg/m3. Her bedside investigations were significant for HAGMA. The patient was seen by the endocrine service and was admitted as a case of starvation ketoacidosis (SKA) vs. euglycemic diabetic ketoacidosis (DKA). The patient was treated with D10W 250 cc/hr with insulin infusion, her the anion gap was closed after 5 hours. She was discharged home as SKA secondary to diet with the possibility of drug superimposing the starvation state. She was given a follow-up clinic regularly to monitor her clinical status. **Conclusion:** This case highlights the possibility of a HAGMA as a rare complication of a low carbohydrate diet with the possibility of Liraglutide injection attribution in developing such critical complication. Further studies are needed to evaluate the safety of a low carbohydrate diet and the effect of Liraglutide injection on these patients following this diet.

Keywords: Liraglutide, Acid-Base Equilibrium, acidosis, diet, Diabetes Mellitus.

1. BACKGROUND

Metabolic acidosis is defined by reduced serum bicarbonate level. This reduction can be from the addition of acid, reduced acid excretion, or loss of alkali. Metabolic acidosis can be further classified into two main types, each with a list of differential diagnoses, HAGMA and non-anion gap metabolic acidosis (1). Starvation acidosis is one of the differential diagnoses of HAGMA. In cases of prolonged fasting and low carbohydrate intake, the hepatocytes will generate another source of fuel for the body (e.g., ketone bodies). As a result of low carbohydrate levels, serum insulin levels will fall, causing lipolysis, which will lead to increased free fatty acid (FFA) production from the fat cells. FFA will then be transported to the hepatocytes, where FFA oxidation occurs, leading to acetyl-CoA production. When acetyl-CoA is produced in large amounts, a ketogenic pathway will be stimulated, leading to ketone bodies production and acidosis (2). Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 is a gut hormone secreted in response to food ingestion. GLP-1 secretion stimulates insulin production and decreases glucagon secretion, leading to better glycaemic control (3, 4). Liraglutide binds reversibly to albumin and stimulates GLP-1 secretion, affecting insulin and glucagon levels (5). It also causes delayed gastric emptying, contributing to better glycaemic control and weight loss (6).

2. OBJECTIVE

We report a rare case presentation of HAGMA associated with Liraglutide and low carbohydrates diet.

3. CASE PRESENTATION

This case is about a 27 years old female patient who presented to the ED with a complaint of nausea and vomiting for two days. The patient is not known to have any medical illness. Her past surgical history is significant

for appendectomy and right arm internal fixation during her childhood years. She was following a strict low carbohydrate diet for three months, trying to reduce her weight as her BMI was 30 kg/m3. Ten days back, for further weight reduction, she started Liraglutide 0.6 mg subcutaneous (SC) once daily (OD) without prescription, which later increased to 1.2 mg SC OD two days before her ED visit. She has been vomiting more than ten times per day for two days. It was food in content initially, then became gastric fluid only. She also complained of heartburn and decreased oral intake. She denied illicit drug use, alcohol consumption, or smoking. On examination, she looks well, not dehydrated, not in any form of distress, not pale nor jaundiced. She was alert, conscious, and oriented to time, place, and person. Her height: 167cm, Weight: > 85 kg. Vital signs temperature of 37 C, SpO2:100% on room air, respiratory rate: 20, heart rate: 107, blood pressure (lying: 117/70, standing 123/80). The head-to-toe exam was unremarkable. Her bedside investigations were significant for HAGMA, and her random blood sugar (RBS) level was 95 mg/dl (Table 1). She was treated as acute gastritis with dehydration secondary to multiple vomiting. For symptomatic relief, 1 L 0.9 NaCl IV fluid bolus was given with metoclopramide and pantoprazole. Blood sample was sent for investigations which was significant for BUN 6 mg/dl (7-18.7), Creat 0.68 mg/dl (0.6-1.3), CO2 9 mEq/L (20-31), Anion gap: 20. The rest of the blood investigations, including complete blood count, liver function test, electrolytes, lactic acid, serum osmolality, lipase, beta HCG, HgbA1c, fasting blood sugar, insulin level, C peptide, and lipid profile, were all unremarkable.Her urinalysis was significant for positive ketones and negative glucose. (Table 2).

In the ED, she received 2 L 0.9 NaCl IV over 2 hours, with a repeated RBS level of 77 mg/dl and VBG showed pH of 7.195, pCO2 of 39.6 mmHg, HCO3 14.2 mmol/L, Base deficit -12.9. Then, she was referred for admission.

The endocrine service admitted her as a case of starvation ketoacidosis (SKA) vs. euglycemic DKA. The endocrine consultant started her on D10W 250 cc/hr with insulin infusion. After five hours, the anion gap was closed, and the patient remained euglycemic for two days during the admission without further insulin doses. She was discharged home as SKA secondary to diet with the possibility of drug superimposing the starvation state.

She was given an outpatient clinic follow-up one week after discharge and instructed to stop the medication and follow another diet for weight reduction. She was not given any prescription upon discharge, and she didn't require any further insulin doses on discharge. Three months follow-up with the patient was done by phone. She is following up with her primary physician with a normal level of HgbA1c and normal fasting, and random blood sugar without requiring any doses of insulin or other forms of antidiabetic medications.

Test	value	Reference range
pH	7.20	7.35–7.45
Pco2 (mmHg)	33.7	35–45
Po2 (mmHg)	25.8	83 – 108
HCO3 (mmol/L)	13.1	22 – 26
BBE	-14.8	-2 – 2

Table 1. Results of laboratory investigations

Test	value	Reference range
Color UA	Pale yellow	-
SPEC GRV	1.014	1.00-1.030
BILIRUBIN	Negative	Negative
UROBILIRUBIN	Negative	Negative
URINE KETONE	+++	Negative
GLUCOSE UA	Negative	Negative
PROTIN UA	Negative	Negative
BLOOD UA	++	Negative
pH	5.0	5.5 – 6.0
nitrate	Negative	Negative
Leukocyte	+	Negative
WBC	5 – 10	0 – 2
UA RBC	10 – 20	0–3

Table 2. Results of laboratory investigations

4. DISCUSSION

HAGMA is a common metabolic abnormality faced in ED with a broad differential diagnosis, each with a different management plan and a different prognosis. This article presents a rare case of HAGMA in a non-diabetic patient without toxicological exposure. In this case, HAGMA was associated with liraglutide injections for weight reduction and starvation secondary to a low carbohydrate diet strictly followed by the patient. A similar case of SKA was published by Chalasani and Fischer of a 30 years old patient who was on a strict low carbohydrate diet and not on any medications (7). In their case, the patient presented with vomiting and abdominal pain, and his laboratory investigations showed HAGMA with mild hyperglycemia and ketonemia, which responded to fluid and insulin therapy. Later on, his HgA1c was normal, and the patient didn't require further insulin doses after anion gap closure. The patient was followed for two years without the requirement of any doses of insulin, and he remained euglycemic.

In conclusion, this prolonged period of euglycemia and a normal level of HgA1c excluded the possibility of diabetes mellitus (DM). Like in our case, this patient was on a strict low carbohydrate diet which was attributed as the cause of the acidosis. However, the toxicological causes are probable since a toxicological screen and osmolality were not requested. Another critical cause of HAGMA that they did not exclude in their case is lactic acidosis, as it was not measured. Another case was published by Blanco et al. (8) as SKA. They reported a case of a 60 years male patient with a known history of type II DM on metformin who follows a strict low carbohydrate diet for better glycemic control. He decided to stop eating for days to fasten the diet response on his Hgb A1c. Five days after fasting, he had vomiting followed by a syncopal attack. After investigations, he was found to have euglycemic HAGMA with ketonuria, for which he received the diagnosis and treatment of SKA. Unlike our patient, this

patient is a known case of DM on metformin which can precipitate the state of dehydration and starvation.

Gall et al. have reported two cases of SKA (9). The first patient was a 28 years old male patient with a known history of depression with a history of self-harm who presented to ED after being found in his room with a decreased level of consciousness. He has stopped eating for five days intentionally for self-harm and had taken 100 tablets of modafinil ten days before presentation in a suicidal attempt. In ED, RBS was normal; VBG revealed HAGMA, lactate of 1.4 mmol/L, and ketones of 3.3 mmol/L. He was diagnosed with SKA and received IV dextrose with potassium replacement. He showed improvement after 10 hours and then cleared for psychiatry admission. The second patient was a 43 years old female patient with a known history of alcohol consumption, depression, and anxiety. She had a history of intentional ingestion of 80 tablets of Co-codamol four days back. She presented to ED with vomiting since the ingestion. She also abstained from alcohol ingestion for four days. In ED, physical examination was unremarkable. Her VBG revealed RBS of 6.7 mmol/LHAGMA, lactate of <1 mmol/L, and ketones of 4.3 mmol/L. She was treated first as DKA and received insulin with IV dextrose until the next day when she was diagnosed with SKA with suspicion of alcohol ketoacidosis (AKA). At that time, insulin was discontinued, and she was kept on IV dextrose with IV thiamine till improvement (9). Unlike our patient, these two patients had different causes of their HAGMA. Both had a history of psychiatric disease with suicidal attempts, and both had a recent history of overdose, keeping the toxicological causes of their acidosis possible. For the second patient with a significant history of alcohol abuse, the sudden stop of alcohol consumption raises the suspicion of AKA.

On the other hand, our patient did not have any psychiatric disorders. She did not have a history of self-harm, drug ingestion, or alcohol consumption. Furthermore, physical examination and laboratory investigations didn't reveal any toxicological clues for the acidosis.

Liraglutide is a food and drug administration (FDA) approved drug in the United States to treat patients with type II DM for better glycemic control. It also has been demonstrated that it causes significant weight reduction in diabetic obese patients (10). It also showed a decrease in weight and obesity-related risk factors in non-diabetic patients (11). For that reason, the use of Liraglutide injections is increasing worldwide. However, the use of Liraglutide is not without downsides. Nausea and vomiting are considered the most common side effects (6), precipitating dangerous metabolic abnormalities. Hooda et al have published a case report of severe metformin-associated metabolic acidosis (MALA) of a diabetic patient soon after introducing Liraglutide to his regimen (12). He was a 70 years old male, an obese diabetic patient with poor glycemic control who was on a maximum daily dose of metformin and had started on Liraglutide three weeks before his presentation to ED. He presented to ED with a history of continuous vomiting since starting Liraglutide. In ED, he was tachypneic, tachycardic, and hypotensive. The VBG revealed severe metabolic acidosis, and other laboratory investigations showed lactic acid of 28 mmol/L (normal < 2.2 mmol/L) and acute kidney injury. Shortly after that, the patient was arrested. Ten min after cardiopulmonary resuscitation (CPR), he achieved the return of spontaneous circulation (ROSC). He was transferred to the intensive care unit (ICU), where he was diagnosed with MALA precipitated by the state of dehydration secondary to continuous vomiting. This case highlights the significance of vomiting associated with Liraglutide and the possible contribution to the development of lactic acidosis in association with metformin therapy. However, in our patient, the lactic acid level and kidney functions were within normal ranges. She was not on metformin and was not diagnosed with DM.

5. CONCLUSION

This case highlights the possibility of a HAGMA as a rare complication of a low carbohydrate diet with the possibility of Liraglutide injection attribution in developing such critical complication. Further studies are needed to evaluate the safety of a low carbohydrate diet and the effect of Liraglutide injection on these patients following this diet.

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