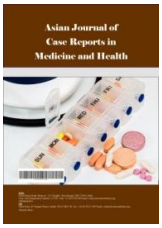

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Starvation Induced Euglycaemic Diabetic Ketoacidosis in a Postoperative Diabetic Patient

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Peri-operative euglycaemic diabetic ketoacidosis is under-recognized and difficult to diagnose due to variable triggers and absence of hyperglycaemia. We report a case of a 58 years old type -2 diabetic female who developed refractory post-operative metabolic acidosis caused by starvation and euglycaemic diabetic ketoacidosis. Recent surgery, major illness, carbohydrate restriction, and a relative insulin deficiency were the contributing factors leading to it. This report highlights the importance of nutrition and appropriate insulin usage in sick peri-operative diabetic patients presenting with unexplained keto acidosis.

Keywords: Euglycaemia; ketoacidosis; diabetic; insulin; starvation.

1. INTRODUCTION

Euglycaemic diabetic ketoacidosis (EDKA) is a clinical triad comprising of increased anion gap metabolic acidosis, ketonemia or ketonuria and near normal or milder degree of hyperglycaemia with blood glucose (BG) levels <200-250 mg/dL, reported in about 10% of patients presenting with

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diabetic ketoacidosis (DKA) [1]. The absence of marked hyperglycaemia and low awareness amongst perioperative physicians can delay diagnosis and treatment, resulting in potential serious adverse outcomes [1]. The pathophysiology involves a decrease in insulin action or secretion with a decrease in total glucose uptake at a cellular level, an increase in the production of counter-regulatory hormones, and a decrease in glucose production by the liver or an increase in the urinary excretion [2]. Episodes can be triggered by surgery, infection, trauma, major illness, reduced food intake, persistent vomiting, gastroparesis, dehydration, and reduced insulin dosage in diabetic patients [1,3]. We present a case of postoperative metabolic acidosis precipitated by poor nutrition, depletion of carbohydrate reserves, surgery and major illness producing starvation induced and associated EDKA in a diabetic patient. This case highlights importance of feeding and adequate insulin therapy in sick diabetic patients presenting with ketosis/ketonuria despite relative normoglycaemia.

2. PRESENTATION OF CASE

A 58 years female, known case of hypothyroidism and type 2 diabetes mellitus for three years (on oral glimepiride 2mg od and metformin 850 mg bd), presented as outpatient with complaints of fatigue, loss of weight and anorexia of six months duration. On further evaluation she was diagnosed with gastric antral adenocarcinoma and advised surgery. Due to covid pandemic and lockdown she discontinued her hospital follow up and further management.

Two months later she presented in the emergency department with complaints of persistent vomiting, loose stools and poor oral intake for last four days. Clinically she was alert, afebrile, moderately hypovolemic with diffuse abdominal pain. Suspecting acute gastric outlet obstruction, she was admitted in intensive care unit and planned for emergency laparotomy. Her laboratory workup revealed mild hypokalemia, low normal bicarbonate and BG (Table 1) with urinalysis positive for glucose (++) and ketones (+). Overnight she was adequately rehydrated with 2 litres plasmalyte A and hypokalemia corrected intravenously.

Next morning, she underwent palliative loop gastro-jejunostomy with jejuno-jejunostomy under general-epidural anaesthesia. Random intraoperative arterial blood gas revealed metabolic acidosis (anion gap 17.4), following which she was resuscitated with additional intravenous fluids, blood products, sodium bicarbonate and electrolytes. She remained haemodynamically stable throughout the surgical procedure and was extubated uneventfully without any vasopressors. In spite of two days of intravenous positive balance fluid therapy (3-2.5 litres/day plasmalyte A) and bicarbonate correction, metabolic acidosis persisted with normal lactate, acceptable urine output and normal haemodynamics [Table2]. Since BG remained less than 250mg/dl minimal insulin was administered (4 U subcutaneous per day) as per correctional sliding scale. She also required repeated intravenous potassium corrections daily to correct chronic hypokalemia along with magnesium and calcium based on serum levels.

Suspecting possible starvation ketoacidosis due to diminished pre-operative and post-operative carbohydrate intake, tube jejunostomy feeding was commenced. Responsively her serum bicarbonate normalized the next day of feeding with stable vital parameters. Surprisingly, in spite of clinically adequate fluid and enteral caloric intake, no signs of systemic hypoperfusion, and normal serum lactate levels; metabolic acidosis again recurred after two days. Patient became lethargic with tachycardia (heart rate 100-120/min) and tachypnea (respiratory rate 25-30/min) with normal blood pressure. The clinical presentation was interpreted as EDKA with BG < 250 mg/dl, serum bicarbonate of 8 Meq/L and aggravating urinary ketones (now 3+). Intravenous 10 % dextrose with insulin bolus (0.1U/kg) followed by infusion (0.1U/kg/hr) was initiated adjusted to BG (150-200 mg/dl) alongside jejunostomy feeding and fluid therapy. Following day her serum bicarbonate started normalizing and clinically tachycardia and tachypnoea started resolving. After two days she was put on basal-bolus subcutaneous insulin regimen and transferred to ward. Her urine ketones remained positive till another 4 days with no relapse of metabolic acidosis occurring for the remainder of her hospital stay.

3. DISCUSSION

EDKA is an acute life-threatening metabolic emergency and a diagnostic challenge due to the absence of hyperglycaemia and varied triggers. The overall mechanism is based on a general state of starvation, resulting in ketosis while maintaining normoglycaemia. The three common causes of EDKA are sodium-glucose

cotransporter-2 (SGLT2) inhibitors, pregnancy and prolonged fasting. The other causes include bariatric surgery, insulin pump failure, cocaine intoxication, pancreatitis, sepsis, chronic liver disease, liver cirrhosis and glycogen storage disease [4]. Our case's initial ketonemia was considered mainly starvation induced as acidosis corrected with feeding. However perioperative stress, low caloric intake, persistent vomiting, gastroparesis, minimal insulin usage and glycosuria contributed simultaneously leading to insidious development on EDKA when acidosis recurred in spite of continued feeding and responded to EDKA management.

Diagnosis of EDKA is difficult as it is primarily a diagnosis of exclusion. Like DKA patients can present with nausea, vomiting, shortness of breath, generalized malaise, lethargy, loss of appetite, fatigue, or abdominal pain. A detailed history of risk factors like pregnancy, surgery, fasting, infections and SGLT-2 inhibitors should be evaluated. Apart from routine work up, laboratory assessment must include blood gas for serum pH, bicarbonate and ketones, and exclusion of other causes of high anion gap metabolic acidosis [1,4]. Major factor for developing hyperketonaemia, defined as serum levels in excess of 3.0mM (normal less than 0.5mM) is rate of production and not impaired uptake [5,6].

Serum and capillary ketones levels are recommended over urine ketones tests for diagnosis and monitoring treatment. Urine ketones measurements are not reliable as they do not detect β-hydroxybutyrate (the predominant metabolite) and does not equate to the plasma ketone concentration. Moreover because of unpredictable degree of resorption in the kidneys, it may be detected long after blood ketones have normalized giving false impression that EDKA or DKA is failing to respond to therapy [6]. Due to non-availability of serum ketone assay in our centre, we relied on urine ketones for diagnosis. However, despite these limitations urine ketones are still commonly used in resource limited countries or regions specially in ruling out DKA [7].

Once diagnosed, management of EDKA is almost similar to DKA and includes rapid correction of dehydration, restoring electrolyte abnormalities, identify and treat underlying cause, and use of dextrose-insulin drip until the anion gap and bicarbonate levels normalize [1,8]. Simultaneously great attention should be paid to correction of hypokalemia, as total body potassium is usually depleted. Hypomagnesemia and hypophosphatemia are also commonly seen in the starvation state due to decreased total intake and increased losses [1].

Metabolic acidosis is common in elective major surgical patients admitted to intensive care unit with reported incidence up to 78 percent post-operatively [9]. Consequently, we also overlooked the possibility of EDKA/starvation acidosis and treated with intravenous bicarbonates and fluid therapy on daily basis post operatively. Because of which anion gap became difficult to assess, which delayed the diagnosis and treatment. In EDKA bicarbonate therapy is not justified, even though it might be frequently administered (like in our case) and may instead be harmful [10]. Acidosis usually improves without the need for intravenous bicarbonate administration [1].

Table 1. Pre-operative laboratory data (day 0)

Investigations	Values	Units	Biological reference
Haemoglobin	12.2	gm/dl	12-15
Total leucocyte count	11210	cell/cumm	4,400-11,000
Calculated anion Gap	15		
S. Urea	14	mg/dl	20-40
S.Creatinine	0.4	mg/dl	0.6-1.2
S.Sodium	139	mEq/L	136-142
S.Potassium	2.9	mEq/L	3.5-5.1
S.Chloride	104	mEq/L	95-105
S.Bicarbonate	20	mEq/L	21-28
HbA1C	8.1	%	5.6 - 7.0
Blood Glucose	119	mg / dl	< 140
Urinalysis	Glucose 2+ Ketones 1+		

Table 2. Clinical data during hospital course

DAY [time]	PH (7.35-7.45)	PCO_2 (32-48 mmHg)	HCO3 (24-28 mmol / L)	Lactate (0.2 - 1.8 mmol / L)	Serum Glucose (73.9 - 100.9 mg/ dl)	Na^+ (136 - 145 mmol / L)	K^+ (3.5 - 5.1 mmol/ L)	Cl^- (98-107 mmol/L)	S. Creatinine (0.6 - 1.2mg/dl)	Urine output (ml/day)
Day 1 - (Surgery)	7.29	21.4_a	13.7	1.22	157	140	3.24	108.9	0.3	1870
Day 2	7.30	22.7_a	12.8	0.99	197	141.9	3.15	106.5	0.4	1470
Day 3 – [05:47] (Feeding started 0600)	7.29	20.3_a	10.6	1.27	201	143.5	3.35	105.9	0.4	2775
- **[20:21]**	7.42	35.3_v	22.9	0.9	228	144.9	3.87	103.5		
Day 4	7.45	28.3_v	25.2	0.92	208	139.7	3.21	100.0	0.3	3390
Day 5	7.42	26.5_v	20	1.09	206	131.7	3.31	95.5	0.4	3435
Day 6 (Insulin started)	7.27	22_v	8	0.73	211	136	3.9	96	0.3	2387
- **[11:00]**										
23:46	7.46	22.9_v	16.2	0.77	234	136.6	4.1	97		
Day 7	7.43	34.1_v	23.3	1.51	215	136.6	3.26	95.6	0.3	2245
Day 8	7.43	33.8_v	23.1	1.22	202	131.8	3.78	94	0.3	1900

a- Arterial blood gas
v- Venous blood gas

As she was relatively stable in the immediate preoperative phase, blood gas was not deemed relevant as part of her anaesthetic assessment. She was kept fasting and received only non-dextrose based intravenous fluid supplementation. Retrospectively we should have paid attention to appropriate nutritional and carbohydrate intake, and simultaneous use of basal-bolus insulin regimen instead of correctional sliding scale right from the beginning. EDKA can be considered a "partially treated DKA" when insulin is under- dosed resulting in euglycaemia in this setting. This is apparently a common error in surgical units which needs to be highlighted. Carbohydrate deficit has a pivotal role in the pathophysiology of euglycaemic DKA while insulin deficit or insulin resistance is relatively minor and secondary [4].

In healthy individuals, mild ketosis generally develops after 12-14 hours fast although pH usually remains above 7.3 [11]. Although rare, when combined with physiologic stress and poor nutritional intake, starvation may cause a severe acid-base disturbances commonly described in pregnant patients, in the elderly, and in young infants [12]. In cases of prolonged fasting, near total glycogen depletion contributes to the normoglycaemia. In a manner very similar to DKA, a lack of insulin is to blame in the case of prolonged starvation even though unlike DKA, patients with starvation ketosis release insulin when carbohydrate is administered, resolving the ketosis [13]. Insulin is less effective at suppressing lipolysis, free fatty acid production and ketogenesis during a fast, exacerbating the development of acidosis. In practice there may be a considerable degree of overlap between starvation ketoacidosis and EDKA as the relative normoglycaemia in EDKA occurs as a result of prolonged fasting [14].

4. CONCLUSION

In summary, a high index of suspicion is required for sick diabetic patients presenting with metabolic acidosis and normoglycaemia with more focus on ketosis and resultant acidosis rather than BG [7]. Health care professionals should be aware of EDKA, as delayed diagnosis and treatment can result in adverse metabolic consequences. They should also recognize starvation ketosis as a peri-operative entity specially with surgical stress, prolonged fasting, poor intake and malnutrition. Clinicians should be encouraged to educate patients about the signs and symptoms of EDKA when discharging post-operatively, as this can occur further after surgery [15]. Remember to check ketones in patients with an unexplained metabolic acidosis. Clinician knowledge of this condition can improve the evaluation and management of patients with EDKA specially in surgical units.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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