Case Report
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Euglycemic Ketoacidosis: An Overlap of Diabetic and Non-diabetic Causes

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Abstract

Objective. Ketoacidosis is the most common cause of high anion gap metabolic acidosis in acute medical settings. Although bedside detection is straightforward, identifying the underlying aetiology may be challenging, particularly in patients with diabetes, in whom multiple mechanisms may coexist. **Case Report.** We report a case of a middle-aged woman with type 1 diabetes who presented with vomiting and reduced oral intake. Initial investigations demonstrated high anion gap metabolic acidosis with severe ketoacidosis (ketones 4.8 mmol/L), hypoglycaemia (glucose 3.3 mmol/L), and profound acute kidney injury (eGFR 5 ml/min/1.73 m² from a baseline of 47 ml/min/1.73 m²). She was initially managed for diabetic ketoacidosis (DKA) with hypoglycaemia using a fixed-rate insulin infusion; however, no clinical or biochemical improvement was observed. Re-evaluation of her clinical presentation and investigations by the multidisciplinary team prompted consideration of other differential diagnoses, such as euglycemic DKA, starvation ketosis, and metabolic acidosis secondary to acute tubular necrosis. Targeted treatment for these causes of metabolic acidosis was initiated, and remarkable clinical and biochemical improvements were noted within 48 hours, suggesting an overlapping metabolic pathophysiology. The patient made a full recovery and was discharged after 10 days. **Conclusion.** This case highlights the diagnostic complexities that may be encountered in managing ketoacidosis, especially in patients with diabetes, and underscores the importance of correctly identifying the different causes of ketoacidosis. It draws the attention of acute and general physicians to the possibility of overlapping metabolic processes in the aetiology of ketoacidosis and that successful treatment often targets all identified causes, rather than a single cause. Additionally, other causes of metabolic acidosis, such as lactic acidosis and acute kidney injury, should be identified and treated.

Key Words: Ketoacidosis ▪ Euglycemic Diabetic Ketoacidosis ▪ Starvation Ketosis ▪ High Anion Gap Metabolic Acidosis ▪ Acute Kidney Injury.

Introduction

Ketoacidosis is the most common cause of high anion gap metabolic acidosis in clinical practice and is often precipitated by diabetes mellitus, starvation, and alcoholism, either in isolation or in combination (1, 2).

In the last two decades following the introduction of sodium-glucose transporter type 2 (SGLT-2) inhibitors in the management of type-2 diabetes, the occurrence of diabetic ketoacidosis (DKA) with normoglycemia, termed euglycemic DKA, has seen an uptick in its reportage in the medical literature. The absence of hyperglycaemia in this condition poses a diagnostic dilemma with starvation ketoacidosis in patients with diabetes presenting with ketoacidosis (3, 4). Other nonketotic contributors to metabolic acidosis - such as renal failure and lactic acidosis - may coexist with ketoacidosis, further confounding the clinical picture. Failure to identify the overlapping causes of acidosis may delay appropriate therapy and adversely affect patient outcomes.

We describe a diagnostically challenging case of multifactorial metabolic acidosis and highlight the key considerations in differentiating overlapping aetiologies, alongside a focused review of the

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literature to enhance clinical reasoning in acute care settings.

Case Description

A middle-aged woman with a medical history of type 1 diabetes mellitus, hypertension, and chronic kidney disease presented to the Emergency Department with a 48-hour history of vomiting, reduced oral intake, and oliguria. Her diabetes was managed with subcutaneous insulin (long-acting (Lantus®) 20 units at night and short-acting (Novorapid®) 8-15 units with meals) and oral metformin 850 mg thrice daily. Importantly, she was not taking any SGLT-2 inhibitors and had never been admitted to the hospital with a diabetes emergency. Due to vomiting and poor oral intake during the intercurrent illness, she omitted her insulin doses and reported home blood glucose readings ranging from 3.0 to 3.9 mmol/L.

On initial assessment, there were signs of clinical dehydration, supported by the findings of a dry buccal mucosa, delayed capillary refill time, and reduced skin turgor. Examinations of the cardiovascular, respiratory, and neurological systems were normal. Her vital signs were also normal (full volume, regular, radial pulse at 80 beats/minute, blood pressure 154/83 mmHg, oxygen saturation 100% inspiring room air, and respiratory rate 18 cycles/minute).

Laboratory investigations revealed severe acute kidney injury (urea 25 mmol/L [baseline 8.3], creatinine 712 µmol/L [baseline 105], eGFR 5 mL/min/1.73 m^2 [baseline 47]) and electrolyte derangement (sodium 130 mmol/L, potassium 6.8 mmol/L). Venous blood gas analysis showed severe high anion gap metabolic acidosis (pH 7.14, bicarbonate 12.2 mmol/L, calculated anion gap 30.6 mEq/L), with ketonemia (4.8 mmol/L), hyperlactataemia (2.5 mmol/L), and hypoglycaemia (3.3 mmol/L). Other blood results on admission are presented in box 1. Bedside urine analysis was positive for ketones and leucocytes, and a sample was sent for culture and sensitivity. Her $HbA1_C$ on admission was 81 mmol/mol, reflecting poor glycaemic control. The previous result from a year earlier was 80 mmol/mol.

Complete blood count:
Haemoglobin – 86 g/L
White cell count – 6.7×10^9/L
Platelet – 240×10^9/L

Liver function tests:
Total bilirubin - 5 umol/L
Aspartate transaminase – 22 IU/L
Alanine transaminase – 15 IU/L
Gamma-glutamyl transaminase – 25 IU/L
Lactate dehydrogenase - 249 IU/L
Alkaline phosphatase - 118 IU/L
Albumin - 34 g/L

Clotting profile:
Prothrombin time - 10.0 s
Activated partial thromboplastin time – 27.0 s
International normalised ratio - 0.9
Activated partial thromboplastin time ratio - 1.1

Electrolytes:
Magnesium - 0.73 mmol/L
Adjusted Calcium - 2.26 mmol/L
Phosphate - 2.50 mmol/L

Others:
Total Protein 60 g/L
C-Reactive protein - 11 mg/L
Procalcitonin - 0.27 ng/mL

Box 1: Blood results on admission.

An initial diagnosis of 'diabetic ketoacidosis (DKA) with hypoglycaemia' was made, and she was commenced on a standard regimen of fixed-dose insulin infusion at 7 units/hour (0.1 units/kg/hour) and 10% dextrose infusion at 125 mls/hour. She was also fluid-resuscitated with a litre of 0.9% sodium chloride intravenously and maintained on 125 mL/hr thereafter. Her clinical diagnosis was later revised to 'euglycemic DKA with acute kidney injury' following further review by the Acute Medical team on call, and her insulin infusion was reduced to 3.5 units/hour (0.05 units/kg/hr) with continuation of 10% dextrose infusion at 100 mls/hr. She was monitored for the next eight

Table 1. Trend of blood gas results (HCO3- - bicarbonate, BE – base excess)

Day	Time	pH	pCO2 (kPa)	pO_2 (kPa)	HCO_3^- (mmol/L)	BE (mmol/L)	Glucose (mmol/L)	Ketones (mmol/L)	Lactate (mmol/L)
0*	23:46	7.14	-	-	12.2	-	3.3	4.8	2.5
1	07:45	7.16	-	-	12.6	-	6.1	2.9	4.9
1	08:38	7.20	-	-	14	–12.7	12.5	-	4.9
1	15:20	7.13	2.47	13.9	-	– 21.0	25	4.4	6.7
1	20:00	7.28	4.23	9.23	16	-	12.3	-	2.9
2	00:00	7.30	-	-	-	-	6.3	0.6	-
2	03:41	7.31	-	-	16	-	9	0.3	-
2	18:30	7.27	4.27	-	15.3	-	12.3	-	2.5
2	22:30	7.32	-	-	-	-	5.5	-	2.0
2	22:37	7.37	3.36	17	16.9	– 9.4	6.0	<0.3	1.7

*Admission.

hours but did not show any appreciable biochemical or clinical improvement (pH 7.16, bicarbonate 12.6 mmol/L, ketone 2.9 mmol/L, lactate 4.9 mmol/L) (See Table 1). She later developed profound hypoglycaemia (1.0 mmol/L), necessitating urgent correction.

Her clinical course remained variable over the next 24-36 hours with labile blood glucose fluctuating between hypo-and hyperglycaemia depending on the treatment strategy (insulin versus glucose infusion) (see Table 1). Maintaining her glucose level within the normal range proved challenging, even with a combination of reduced-dose insulin and dextrose infusion. She was reviewed by the multidisciplinary team (acute medicine, endocrinology, intensive care medicine, nephrology) at various stages during her hospital stay, but a clear diagnosis remained elusive. Several diagnoses were considered, including euglycemic DKA, starvation ketoacidosis, and acute tubular necrosis. Renal biopsy was considered at some point. Her pH remained static, and metabolic acidosis persisted. Meanwhile, her urine sample tested positive for Escherichia coli, suggesting that a urinary tract infection triggered her illness. She was commenced on oral antibiotics (pivmecillinam).

Given the lack of adequate response to insulin therapy and the clinical context of prolonged fasting, an overlapping aetiology was considered. Fixed-dose insulin infusion was permanently discontinued, and her management was revised to maintenance intravenous fluids with Hartmann's solution, reintroduction of her regular subcutaneous insulin at a reduced dose (18 units of Lantus® at night) with the advice to skip her short-acting mealtime doses if hypoglycaemic, and nutritional replenishment orally (vomiting had settled by this time).

This approach resulted in rapid clinical and biochemical improvement by the second and third days of admission, with resolution of acidosis and ketonemia, normalisation of anion gap (18.1mEq/L (calculated)), and gradual recovery of her renal function (Tables 1&2).

She was discharged after 10 days with significantly improved renal function and subsequently demonstrated complete renal recovery to her baseline at follow-up a week after discharge from the hospital (Table 2).

Discussion

The index case reflects the nuances and diagnostic dilemmas faced by clinicians while managing cases of ketoacidosis. Starvation is central to the pathogenesis of ketoacidosis as it lowers the insulin-glucagon ratio in the presence of calorie depletion (3). It induces a catabolic state characterised by increased lipolysis and hepatic ketogenesis to provide ketones as an alternate source of energy for the brain (3). This physiological adaptation may be exaggerated during intercurrent illness,

Table 2. Trend of blood test results (Hb – Haemoglobin, WCC – White cell count, CRP – C-Reactive Protein, Na^+ - Sodium, K^+- Potassium, $HOC3^-$ - Bicarbonate, Cl^- - Chloride, eGFR – estimated glomerular filtration rate)

Day	Hb (g/L)	WCC ($\times 10^9$/L)	CRP (mg/L)	Na^+ (mmol/L)	K^+ (mmol/L)	$HCO3^-$ (mmol/L)	Cl^- (mmol/L)	Urea (mmol/L)	Creatinine (µmol/L)	eGFR (mL/min/1.73 m^2)
0*	86	6.7	11	130	6.8	12.2	94	25	712	5
1	-	-	9	128	6.6	12	-	24.1	734	5
2	-	-	-	126	5.7	-	-	22.4	680	5
4	-	-	-	132	4.1	21	97	21.1	623	6
6	85	6.9	-	-	-	-	-	16.2	446	9
8	87	6.9	7	-	-	-	-	10.4	311	13
9	-	-	-	-	-	-	-	9.5	240	18
10†	89	6.6	5	142	4.0	-	-	7.4	226	19
17‡	106	6.2	-	-	3.0	-	-	3.7	103	47

*Admission; †Discharge; ‡Follow-up.

sepsis, malignancy, pregnancy, or vomiting, causing clinically significant ketoacidosis (3).

The most common causes of ketoacidosis in clinical practice are diabetes (including euglycemic DKA), starvation, and alcoholism (1). All three conditions share similar pathophysiological mechanisms, as described above, and may overlap concomitantly in a patient, confounding the clinical diagnosis and delaying appropriate treatment. In the index case, ketoacidosis in a patient with diabetes and missed insulin doses and a clear history of starvation worsened by vomiting convincingly makes the argument for an overlapping pathophysiologic process between euglycemic DKA and starvation ketoacidosis. Therefore, a sound knowledge of the biochemistry of metabolism during starvation is crucial for the Acute and General Physician managing these cases.

While DKA has been extensively studied and reported in the medical literature, the relatively new concept of euglycemic DKA has only gained traction in the last two decades following the introduction of SGLT-2 inhibitors in the management of Type-2 diabetes (4). These medications cause euglycemic DKA through their glucosuric effect, which lowers blood glucose and simulates carbohydrate deficiency, reducing the insulin-glucagon ratio and triggering ketogenesis. They also inhibit ketonuria and directly stimulate pancreatic alpha cells to secrete glucagon (5, 6). Other reported mechanisms for euglycemic DKA include continued use of insulin at the onset of DKA in patients who are fasting and pre-hospital administration of insulin in suspected DKA (4).

The clinical presentation of ketoacidosis (from any cause) is similar: nausea, vomiting, lethargy, and dehydration, which may cause acute kidney injury and metabolic acidosis (7). The latter results from impaired excretion and accumulation of organic acids, such as urea and lactic acid (4, 8). This clinical picture of mixed metabolic acidosis was well portrayed in our patient, who had ketoacidosis, lactic acidosis, and metabolic acidosis due to acute kidney injury (AKI).

There are slight differences in the management of ketoacidosis, depending on the cause. Successful treatment hinges on correctly identifying the underlying pathophysiological processes and aiming to reverse the reduced insulin-glucagon ratio. In starvation ketoacidosis, this is achieved by oral or intravenous carbohydrate replenishment with dextrose-containing fluids. This stimulates endogenous insulin release, which is sufficient to shut down lipolysis and ketogenesis. The management of euglycemic DKA, on the other hand, is a balancing act between calorie replenishment and exogenous insulin supplementation. While these patients are not profoundly insulin deficient

and/or resistant as in classical DKA, they still require some exogenous insulin at a reduced dose of 0.05 units/kg/hour to reverse ketogenesis (9). Metabolic acidosis with pre-renal AKI is treated with isotonic fluid rehydration.

The absence of hyperglycaemia in patients with diabetes presenting with ketoacidosis may distract clinicians from correctly diagnosing and treating euglycemic DKA. This warrants a high index of suspicion when they present to the acute medical take. Misdiagnosing starvation ketoacidosis as euglycemic DKA, on the other hand, and administering insulin risks worsening hypoglycaemia and putting the patient to harm (10). A careful clinical assessment, correct interpretation of biochemical data, and understanding of overlapping metabolic processes will help distinguish between the two and/or reveal an overlap.

In the case of overlap, a combined management strategy targeting both metabolic processes should be deployed. We suggest managing such patients in a high-monitoring unit, initially with isotonic fluid resuscitation, followed by calorie replenishment (orally or intravenously). In patients with diabetes, low-dose insulin infusion should be initiated with close monitoring for glucose derangements. Urine output and fluid balance should be carefully monitored, and electrolytes and vitamins appropriately replaced.

Conclusion

This case underscores the diagnostic complexity that clinicians may encounter in some presentations of ketoacidosis, especially in patients with diabetes, where multiple causes may be at play. It also highlights the importance of a sound knowledge of the pathophysiology of ketoacidosis, biochemistry in starvation, and their application in clinical practice. This will enable the clinician to promptly make the correct diagnosis, including identifying when overlapping processes are in effect, and institute appropriate treatment to improve outcomes.

What Is Already Known on This Topic:

Ketoacidosis is the most common cause of high anion gap metabolic acidosis in clinical practice, often triggered by diabetes, starvation, or alcoholism. There has been increased reporting of euglycemic DKA since the introduction of SGLT-2 inhibitors for the management of diabetes.

What This Study Adds:

Although the detection of ketoacidosis using simple bedside investigations is straightforward, identifying the underlying cause(s) may pose diagnostic challenges. This case draws the attention of clinicians (especially in Acute and General Internal medicine) to the possibility of a mixed aetiology (overlap) of ketoacidosis, including in patients with diabetes, as well as the co-occurrence of other causes of metabolic acidosis. It emphasizes the need to correctly diagnose these patients early and commence appropriate, individualised treatment targeting the different causes, under close monitoring.

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Patient Consent: Written informed consent was obtained from the patient prior to the preparation of this case report.

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