Euglycaemic ketoacidosis in patients with and without diabetes

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Abstract
Ketoacidosis in individuals with diabetes is usually associated with a raised plasma glucose concentration. However, ketoacidosis in diabetes can occur with normal (≤11mmol/l) plasma glucose levels. Ketoacidosis is also seen in patients who do not have diabetes, most commonly in pregnancy or following alcoholic binges, rarely with starvation, anorexia nervosa or inborn errors of metabolism. The aim of this review is to compare the clinical features, pathophysiology and management of these conditions.

Common clinical features due to a raised anion gap metabolic acidosis are seen. Reduced carbohydrate intake is a usual contributor to ketogenesis. Treatment is primarily with intravenous glucose, insulin if there is insulin deficiency and potassium as needed. The value of using bedside monitors to measure β-hydroxybutyrate levels both for diagnosis and monitoring of response to treatment is emphasised. Early recognition of ketoacidosis and treatment with glucose rather than saline is important for optimum outcome. Copyright © 2013 John Wiley & Sons.


Key words
euglycaemic ketoacidosis; diabetes; pregnancy ketoacidosis; alcoholic ketoacidosis

Introduction
There are a variety of potential causes of a metabolic acidosis. The most common is diabetic ketoacidosis (DKA), typically seen in type 1 diabetes and due to either absolute insulin deficiency (at diagnosis or caused by missed injections) or relative insulin deficiency (in intercurrent illness). It is not always appreciated that DKA can occur in the presence of only mildly-elevated plasma glucose levels or even normal glucose levels (euglycaemic DKA). The absence of hyperglycaemia can lead to diagnostic difficulty.

In this article we briefly review euglycaemic ketoacidosis as it has been reported in patients both with and without diabetes. The potential causes are listed in Table 1.

Diagnosis
Identifying metabolic acidosis cause: use of the anion gap
The cause of a metabolic acidosis is not always clear. Calculation of the anion gap can be informative. Measured as the sum of the measured cations Na⁺ and K⁺ minus the sum of the measured anions Cl⁻ and HCO₃⁻, the normal value is 14mmol/L (range 10–18). The difference is due to negatively charged proteins, organic acids, phosphate and sulphate ions. Metabolic acidosis with normal anion gap is seen in bicarbonate losses via the gut (diarrhoea, pancreatic fistula, ureterosigmoidostomy) or kidney (renal tubular acidosis, treatment with acetazolamide), ingestion of hydrochloric acid or substances that generate it (ammonium chloride, arginine hydrochloride). Bicarbonate losses are replaced by increased renal reabsorption of chloride, maintainingionic balance but with acidity. Metabolic acidosis with high anion gap is caused by ingestion or endogenous synthesis of acids, particularly organic, where the anions are not normally measured. Ketoacidosis is the most common cause. Metabolic acidosis with positive anion gap is also seen in lactic acidosis, uraemic acidosis, poisoning with salicylate, methanol or ethylene glycol and in D-lactic acidosis due to lactobacillus overgrowth.

Definition of euglycaemic diabetic ketoacidosis
The term ‘euglycaemic diabetic ketoacidosis’ was first used in 1973 to describe a group of patients at the ‘extreme of metabolic decompensation’.¹ The use of the term has been challenged on the basis that the condition is not a separate entity from...
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DKA but simply a different presentation of the same process. The definition has changed over the years. In 1973 Munro et al. defined euglycaemic DKA as blood glucose <16.7mmol/L (300mg/dl) and plasma bicarbonate <10mmol/L. More recent American Diabetes Association consensus statements have suggested a definition of <13.9mmol/L in association with ketoacidosis. Current UK statements have recommended diagnostic criteria for DKA of glucose >11mmol/L with acidosi (venous bicarbonate <15mmol/L and/or venous pH <7.3) due to ketonaemia. The International Society for Pediatric and Adolescent Diabetes uses the same definition of DKA. Thus, glucose values ≤11mmol/L in this setting may be regarded as indicating euglycaemic ketoacidosis.

**Pseudo-euglycaemia**

The term pseudo-euglycaemia refers to a measurement artefact in which the plasma glucose is erroneously measured as being in the normal range. It occurs in patients with severe hypertriglyceridaemia. This can lead to late diagnosis of DKA.

**Clinical syndromes and their management**

**Euglycaemic diabetic ketoacidosis**

Munro et al. reported 37 cases of young (age 10–28 years) type 1 diabetic patients as having euglycaemic ketoacidosis. Sixteen of these cases presented with a plasma glucose <11.1mmol/L thus fulfilling current criteria. In the Munro series, 32 of the cases reported vomiting over the two previous days. The remainder reported a reduced carbohydrate intake (nausea or other reason). Twenty-seven patients had continued to take or increased their insulin dosage.

Jenkins and colleagues studied a total of 722 consecutive cases of DKA. Of these, 14 episodes were euglycaemic with blood glucose concentration <10mmol/L and bicarbonate <15mmol/L at presentation. In the Jenkins series, the factors which precipitated euglycaemic ketoacidosis were similar to those in hyperglycaemic DKA except that euglycaemia was seen only once with a new diagnosis of diabetes. As in Munro’s series, most patients with euglycaemic ketoacidosis had taken their normal insulin dose or more in the 12 hours before admission. Reports of euglycaemic ketoacidosis indicate vomiting and reduced calorie intake result in levels of glycaemia closer to normal. For example, in a 52-year-old diabetic man reported by Davies et al., who presented with vomiting and was dehydrated and pyrexial with a background of chronic renal failure, blood glucose was 5.6mmol/L, pH 7.19, bicarbonate 12.4mmol/L. In another case, a 35-year-old patient with type 1 diabetes had not eaten for two to three weeks due to severe depression. He presented with a four-day history of nausea and vomiting, with pH 7.3, bicarbonate 10mmol/L, anion gap +29, ketonuria and blood glucose 5.8mmol/L.

Studies have been undertaken to elucidate the metabolic changes underlying euglycaemic ketoacidosis. In subjects with type 1 diabetes, Burge et al. were able to show that fasting in the presence of insulin deficiency is associated with decreased hepatic glucose production compared with the post-prandial state. Lipolysis and ketogenesis progressed more rapidly in the fasted state. This was associated with, and is probably the result of, elevated levels of glucagon and catecholamines.

The treatment of euglycaemic ketoacidosis in diabetic individuals is similar to that of patients who are initially hyperglycaemic and consists of fixed-rate intravenous (IV) insulin infusion, 10% glucose (when blood glucose is <14mmol/L), potassium and monitoring of plasma ketones, aiming for a reduction of at least 0.5mmol/L per hour.

**Starvation euglycaemic ketoacidosis**

Thus, there is some overlap with starvation ketoacidosis since starvation is a major contributory factor in the development of euglycaemic ketoacidosis in diabetes. In the non-diabetic individual, reduced dietary carbohydrate also leads to the use of alternative energy sources. Free fatty acid (FFA) release from adipose tissue triglyceride stores is increased. The increased availability of FFA and an elevated glucagon/insulin ratio results in generation of ketones by the liver as starvation continues. Although ketosis is common in starvation, acidosis is rare. After a few days, ketone body levels may reach 4–6mmol/L but usually do not exceed this since utilisation (by many tissues) equals production. Ketone bodies are a major fuel for muscle during starvation and there are urinary losses also. However, Owen et al. reported a 24-year-old male who had not eaten for three days prior to presentation with 24 hours of vomiting followed by persistent nausea. Arterial pH was 7.09, bicarbonate 7.2mmol/L and glucose 6mmol/L. His condition only improved when transfused with glucose rather than the initial fluid resuscitation using Hartmann’s solution. Thus it is possible for ketone production to generate severe acidosis in starvation. This phenomenon has been seen in anorexia nervosa also.

**Pregnancy-related euglycaemic ketoacidosis**

The most common presentation of true euglycaemic DKA is in association with pregnancy. The presentation is similar to hyperglycaemic cases with a history of dyspnoea, nausea and vomiting sometimes preceded by infection. Patients usually have gestational diabetes mellitus (GDM) or the development of ketoacidosis leads to the diagnosis of GDM. Ketoacidosis is rare in insulin-treated diabetic pregnancy. Physiological changes that occur in pregnancy may contribute to the development of ketoacidosis in GDM (see below).

Cases of euglycaemic ketoacidosis have been reported in pregnant patients who have no history of

**Table 1. Causes of ketoacidosis**

- Diabetic euglycaemic ketoacidosis
- Non-diabetic euglycaemic ketoacidosis
- Starvation
- Pregnancy related
- Alcohol
- Inborn errors of metabolism
diabetes, nor fit the diagnostic criteria for GDM.18,19 As in the other situations, the euglycaemic ketoacidosis is usually secondary to nausea and vomiting and a period of starvation/fasting which here is either directly related to the pregnancy or supplementary to it. There may be additional precipitating factors as illustrated by the following example from our own practice.

A healthy 33-year-old, who was 30 weeks’ pregnant with her second child, presented with a week-long history of flu-like symptoms, productive cough and rigors. On examination, her blood pressure was 105/53, respiratory rate 30 and temperature 39.1°C, with lobar pneumonia and subsequent empyema. She required inotropic support on the intensive therapy unit. She had had urinary ketones since admission and her plasma β-hydroxybutyrate concentration was 5.3 mmol/L (normal: <0.42 mmol/L). Glucose levels were normal throughout. Arterial pH was 7.32, base excess -12 with a compensated metabolic acidosis, lactate 0.8 mmol/L (normal: <2.1 mmol/L), and eGFR >60 ml/min. Her non-diabetic ketoacidosis was successfully treated with IV insulin 6 units/hour and 10% glucose IV with potassium. On day nine of admission, a 31-week gestation infant was successfully delivered.

Pregnancy results in significant alterations in fuel metabolism. Glucose is transported to the fetus by facilitated diffusion. Amino acids, particularly alanine, cross the placenta by active transport. Maternal fasting glucose concentration is lower than in the non-pregnant state, whereas plasma ketone concentrations are higher and FFAs elevated after an overnight fast. This has been referred to as ‘accelerated starvation’ such that glucose is preferentially available to the fetus and alternative fuels are available for maternal consumption. The physiological response to fasting in the third trimester is very different from the non-pregnant state with reductions in plasma glucose, insulin and alanine and a greater and more rapid rise in FFAs and ketones.20 In Metzger et al.’s study there was a strong correlation between fasting plasma FFA and β-hydroxybutyrate, indicating the potential for patients in the later stages of pregnancy to develop ketoacidosis after starvation in the absence of diabetes.20

The mainstay of treatment of ketoacidosis in non-diabetic pregnancy has been IV fluid resuscitation including 10% glucose. Insulin, bicarbonate and phosphate have sometimes been used in addition.18,19 Glucose infusion has been shown to reduce β-hydroxybutyrate levels during ketonuric labour.21

**Alcohol-related euglycaemic ketoacidosis**

Euglycaemic ketoacidosis occurs in association with alcohol consumption. Typically, there has been heavy drinking followed by prolonged vomiting – for example, the 48-year-old female non-diabetic patient described by Piya et al. who presented with dyspnoea, vomiting and malaise for three days having abruptly stopped drinking alcohol prior to admission.22 The blood glucose concentration was 9.8 mmol/L with a high anion gap metabolic acidosis, pH 7.17, lactate 1.5 mmol/L and capillary ketones 5.2 mmol/L.

Alcohol has also been seen as a contributory cause in diabetic patients presenting with euglycaemic ketoacidosis. Alcoholic ketoacidosis may be more common in diabetes. Navaravong et al. reported a female patient with type 2 diabetes who presented with dyspnoea and was found to have a blood glucose of 4.8 mmol/L, anion gap 37, pH 7.24, urinary ketones present with plasma β-hydroxybutyrate elevated at 17.85 mmol/L. The ketosis was thought to be due to depleted hepatic glycogen stores and increased sympathetic activity.23

The primary ketone present in alcoholic ketoacidosis is β-hydroxybutyrate. In a series of 25 cases of metabolic acidosis in alcoholic patients, Fulop et al. found levels up to 7.68 mmol/L.24 In alcoholic ketoacidosis β-hydroxybutyrate is generated in preference to acetocetate so the diagnosis is facilitated by modern meters that measure this metabolite. The classical nitroprusside test detects acetocetate rather than β-hydroxybutyrate.

Lactic acidosis occurs in patients with liver disease and in acute intercurrent illness, so may be seen in the same patient population at risk of alcoholic ketoacidosis and sometimes in conjunction with it.24 Alcoholic ketoacidosis may be associated with hypoglycaemia as a result of consumption of NAD by the metabolism of alcohol to acetate. The resulting excess of NAD causes the conversion of pyruvate to lactate such that pyruvate is not available for gluconeogenesis. The generation of excess ketones is mainly due to starvation but conversion of acetate to ketone bodies may also contribute. Lipolysis is augmented by increased catecholamines and low insulin levels providing more FAA substrate.

Alcoholic ketoacidosis responds well to glucose infusion. If there is no response, then lactate and β-hydroxybutyrate concentrations should be monitored.

**Inborn errors of metabolism**

Ketoacidosis is a feature of a number of inherited metabolic conditions seen in childhood. The combination of ketoacidosis and hyperglycaemia suggests type 1 diabetes, but organic acidurias (propionic acidemia, methyl malonic acidemia, isovaleric acidemia) and ketolytic defects (e.g. thiolase deficiencies) can also exhibit ketoacidosis in combination with hyperglycaemia and glycosuria. Measurement of lactate and ammonia levels helps to distinguish these. The combination of ketoacidosis and hyperglycaemia suggests defects of gluconeogenesis or glycogen degradation (glycogen storage disease), maple syrup urine disease or adrenal insufficiency. The congenital lactic acidoses also cause ketoacidosis. A diagnosis of fasting ketoacidosis or ketotic hypoglycaemia should be questioned if there is associated metabolic acidosis.

Approximately 50% of patients with inborn errors of intermediary metabolism will present late: in late childhood, adolescence or adulthood. Symptoms are often intermittent and may include episodes of coma, focal neurological signs, seizures, apparently behavioural symptoms, vomiting, abdominal pain and liver dysfunction. It seems
likely that some chronic neurologic disorders currently labelled as degenerative will in time be identified as variant forms of inborn errors of metabolism.²⁵

Discussion

Euglycaemic ketoacidosis is an uncommon occurrence. Although ketones are regularly measured in diabetic patients, they may not be in other clinical situations or their significance may not be appreciated such that the diagnosis can be easily missed in individuals who do not have diabetes. Patients with diabetes can develop other forms of metabolic acidosis or have acidosis due to multiple causes (respiratory acidosis, uraemic acidosis, lactic acidosis most commonly). Of patients with DKA, 10–15% also have lactic acidosis by definition (lactate >5mmol/L, pH <7.2). Thus, measurement of plasma ketone concentration can have significant diagnostic value. Modern bedside plasma ketone monitors are now readily available (Optium, Abbott Labs; GlucoMen LX Plus, Menarini Diagnostics) such that ketosis and ketoacidosis can be quantified. These meters detect β-hydroxybutyrate rather than the acetone/acetoacetate detected by standard urine testing.

There are similarities between the above syndromes of euglycaemic ketoacidosis. In the non-diabetic state, starvation or poor intake due to vomiting is primarily responsible for lack of glucose and suppression of insulin secretion. In diabetic individuals, there is a deficiency of insulin or insulin action in addition. Thus treatment is similar also, being based on IV glucose combined with insulin if there is insulin deficiency. The common pathophysiology is shown in Figure 1.

In diabetic patients, the key difference in initial treatment is the use of glucose rather than the emphasis on saline in hyperglycaemic DKA. This is analogous to

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**Table 2.** Diagnosis and treatment learning points

<table>
<thead>
<tr>
<th>Learning points</th>
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<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td>• Diabetic ketoacidosis (DKA) can occur in the absence of hyperglycaemia thus measurement of ketones on a capillary sample is of value</td>
</tr>
<tr>
<td>• Euglycaemic ketoacidosis occurs in the absence of diabetes, most commonly in association with pregnancy or alcoholism</td>
</tr>
<tr>
<td>• In non-diabetic patients, consider ketones as the unmeasured acid in high anion gap acidosis</td>
</tr>
<tr>
<td>• Modern bedside meters to measure plasma ketones are a valuable tool for diagnosis and monitoring progress. They need to be more widely used</td>
</tr>
<tr>
<td>• Other causes of metabolic acidosis are common and can occur simultaneously with ketoacidosis. The anion gap calculation and direct measurement of ketones are useful here</td>
</tr>
<tr>
<td>• In infants and young children, ketoacidosis is seen with some rare inborn errors of metabolism</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>• Early recognition and treatment with dextrose is important (in adults). Insulin is not necessarily required in the absence of diabetes</td>
</tr>
<tr>
<td>• In hyperglycaemic DKA glucose is required when the plasma glucose falls below 14mmol/L</td>
</tr>
<tr>
<td>• Frequent monitoring of these patients is required</td>
</tr>
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**Figure 1.** Ketoacidosis: pathophysiology common to the clinical syndromes and additional factors
the situation in the management of hyperglycaemic DKA where 10% glucose 125ml/hour is now recommended when the blood glucose falls below 14mmol/L. The most common cause of adverse outcome in euglycaemic ketoacidosis is initial treatment with saline without glucose. In patients not known to have diabetes, glucose concentrations should also be monitored and if an increase is seen with glucose treatment the patient has uncontrolled diabetes and insulin is required in addition.

The lessons in diagnosis and management for practitioners are listed in Table 2.

In summary, there are issues of diagnostic difficulty and diagnosis is sometimes delayed in these situations where ketoacidosis occurs outside the classical hyperglycaemic situation. The aim of this report has been to bring together some of the published case reports and to briefly summarise similarities in metabolic derangement, diagnosis and treatment.

**Declaration of interests**

There are no conflicts of interest declared.

**References**


**Book review**

**Critical care management of the obese patient**

Edited by Ali El Solh
Published by Wiley-Blackwell, 2012
254 pages, price £84.50 (hardback)
ISBN: 978 0 470 655900
Website: www.wiley.com

Obese patients requiring intensive care therapy are multiplying exponentially with the growing worldwide obesity epidemic.

Organised logically and evidence based, this book is packed with information. It covers most aspects of the care of obese patients in a critical care setting such as the specific effects of obesity on physiology, management challenges in positive pressure ventilation, nutrition, organ dysfunction and haemodynamic instabilities.

Importantly, this book also includes a section that focuses on bariatric surgery that is increasingly performed on morbidly obese patients, and another section that addresses ethical dilemmas facing intensivists dealing with obese patients.

The chapters have been organised such that the reader can peruse each chapter/topic independently without reading the entire book, making it useful for quick reference. This book mainly concentrates on clinically-relevant aspects of care, and is quite exhaustive. However, the key points and best practice tips summarised – at the beginning and end of each chapter, respectively – make it easy for reference during routine practice.

There is also a section on multiple choice questions at the end of the book that would serve to self-score the reader’s comprehension of each chapter.

Overall, the book is a significant addition to the obesity minefield. It will be a handy resource for all health professionals caring for obese patients in intensive therapy units, and is a useful addition to the reference shelf/library.

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