Starvation-induced True Diabetic Euglycemic Ketoacidosis in Severe Depression

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True euglycemic diabetic ketoacidosis [blood glucose <200 mg/dl (11.1 mmol/l)] is relatively uncommon and in type 1 diabetes can be caused by starvation of any cause in conjunction with an intercurrent illness. We report a case of euglycemic diabetic ketoacidosis precipitated by starvation resulting from severe depression in a patient with type 1 diabetes. He was acidotic with ketonuria, but his blood glucose was only 105 mg/dl (5.8 mmol/l). He was rehydrated, the acidosis was corrected, and his depression was later treated. This case involves the complex interplay among type 1 diabetes, depression, ketoacidosis, and starvation physiology resulting in glucose concentrations in keeping with euglycemic diabetic ketoacidosis. The case also highlights that even in the absence of hyperglycemia, acid/base status should be assessed in an ill patient with diabetes, and in cases of euglycemic diabetic ketoacidosis, the diagnosis of depression should be considered as a cause for suppressed appetite and anorexia.

KEY WORDS: type 1 diabetes; depression; ketoacidosis; starvation.
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INTRODUCTION

Diabetic ketoacidosis (DKA) is a state of absolute or relative insulin deficiency and is defined by the American Diabetes Association's (ADA) diagnostic criteria of hyperglycemia [blood glucose >250 mg/dl (13.9 mmol/l)], acidosis (arterial pH<7.3 and serum bicarbonate <15 mEq/l), and ketosis (moderate ketonuria or ketonemia)[1]. Although normally associated with significantly elevated blood glucose levels, in 1973 Munro et al. reported a series of 211 episodes of DKA, of which 37 episodes were described as euglycemic [defined as blood glucose of 300 mg/dl (16.7 mmol/l) or less with plasma bicarbonate of 10 mEq/l or less][2]. In a larger analysis, Jenkins et al. (1993) reported 23 episodes of euglycemic DKA (in a series of 722 episodes), based on the same diagnostic criteria[3]. It has since been argued that glucose readings above 200 mg/dl (11.1 mmol/l) cannot be considered to represent euglycemia, and therefore a blood glucose level of 200 mg/dl (11.1 mmol/l) or less should be used as the cutoff for defining true euglycemic diabetic ketoacidosis[4]. Based on this criterion, only 16 of the 37 episodes in the study by Munro et al. and 6 of the 23 episodes in the study by Jenkins et al. could be described as true euglycemic DKA[2,3]. The suggested etiology for the relatively low blood glucose seen in this condition is the low caloric intake precipitated by starvation and persistent vomiting together with continuation of insulin treatment[2,3,5]. We report a case of true euglycemic ketoacidosis that highlights firstly the need for assessment of acid/base status in patients with type 1 diabetes presenting with nausea, vomiting, and decreased oral intake, even when the circulating glucose concentration is in the normal range, and secondly that in such patients severe depression may be a cause of the anorexia and starvation.

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CASE REPORT

A 34-year-old man with a 19-year history of type 1 diabetes presented as an emergency with a 4-day history of nausea, vomiting, and flu-like symptoms. He was on a basal bolus insulin regime comprising 8 units of bolus insulin lispro injected at mealtimes and 12 units of basal isophane insulin at bedtime, but did not monitor capillary blood glucose levels. He did however empirically increase his insulin doses during times of illness and had increased his isophane insulin to 15 units during the 3 days prior to presentation. He had only one prior hospital admission, which occurred 6 years previously and was due to an episode of DKA precipitated by gastroenteritis. He was single, unemployed, did not drink alcohol, had no previous psychiatric history, no family history of diabetes or other medical conditions, and lived in a hostel. He had a record of poor clinic attendances and a history of long-term cannabis use. He denied any salicylate consumption, but admitted to some weight loss; however, he was unable to quantify this. His body mass index (BMI) was 19 kg/m^2, and he looked unkempt. Physical examination revealed a temperature of 36.4°C (97.5°F), heart rate of 106 beats per minute, supine blood pressure of 131/85 mmHg, and sitting blood pressure of 122/80 mmHg. He had a respiratory rate of 30 breaths per minute, and his oxygen saturation using a pulsoximeter was 99% on room air. He appeared clinically dehydrated with dry oral mucosa, but cardiovascular, respiratory, abdominal, and neurological examinations were otherwise normal. Diabetic ketoacidosis (DKA) was suspected; metabolic acidosis was confirmed with a pH of 7.3, bicarbonate concentration of 10 mEq/l, and an elevated anion gap of 29 mEq/l [sodium=134 mEq/l, potassium=5.7 mEq/l, chloride=101 mEq/l, blood urea nitrogen (BUN)=9.5 mg/dl (3.4 mmol/l), and creatinine=0.98 mg/dl (87 mmol/l)]. Urinaly-

sis confirmed heavy (4+) ketonuria (Bayer- Uro-diastix®), but no glycosuria, and his venous blood glucose concentration was only 105 mg/dl (5.8 mmol/l). Further biochemical investigations revealed an amylase of 104 IU/l (normal range: <150 IU/l) and lactate of 9.9 mg/dl (1.1 mmol/l (normal range: 0.5–2.2 mmol/l)). Blood salicylate, alcohol, and methanol levels were all undetectable. A diagnosis of euglycemic ketoacidosis was made with the precipitating factor thought to be a viral gastroenteritis. He was treated with 0.9% saline rehydration, 10% dextrose, and intravenous insulin, and his acidosis gradually improved. Vitamins B including thiamine and vitamin C were also administered intravenously three times a day during the first 72 h of admission.

Later, his HbA1C was found to be 11.5%, suggesting poor control, but the patient himself felt his diabetes was "reasonably controlled" as he had no polyuria or polydipsia. He was later restarted on lower doses of subcutaneous insulin as his oral intake was still poor. Upon further assessment it was noticed that he had anhedonia, and he appeared to have no interest in his food or the management of his diabetes despite having insight into the complications of the disease. He also admitted to not having eaten for nearly 2 to 3 weeks prior to his presentation to the hospital. He was referred to the psychiatrists, who made a diagnosis of severe depression and felt that the starvation was not an attempt at passive suicide, but rather a consequence of appetite suppression caused by the depression. Antidepressant therapy was commenced, and he was scheduled for behavioral therapy sessions. With input from the diabetes specialist nurses and dietician, his diet began to improve and he was discharged to be followed up in the diabetes clinic and also by the psychiatrists.

Following discharge from the hospital, he has continued to attend follow-up psychiatry appointments, but has not returned to the hospital diabetes clinic despite multiple attempts to contact him. He fortunately sees his general practitioner for renewal of his insulin prescription on a regular basis, but appears to have little motivation to monitor and improve his glycemic control.

DISCUSSION

A decrease in caloric intake is frequently associated with the development of DKA, usually due to nausea or vomiting caused by a precipitating illness or by worsening ketoacidosis itself. During these times of decreased caloric intake, patients with diabetes who continue taking sufficient amounts of insulin may maintain euglycemia, but are unable to stop the ketone body formation and can present with DKA with only mild elevations of blood glucose or even relative normoglycemia[2,6,7]. In cases of prolonged fasting, near total glycogen depletion contributes to the normoglycemia as metabolic acidosis continues to develop[8,9]. Also lipolysis and free fatty acid production are accelerated during fasting[10], and insulin is less effective at suppressing lipolysis and ketogenesis during a fast[11], exacerbating the development of acidosis. In addition, situations where there is sufficient circulating fluid volume to maintain glucose excretion near normal circulating glucose concentrations may be observed[12]. Glycogen storage disorders as well as chronic liver disease resulting in decreased glycogen stores can also result in euglycemic ketoacidosis and must be considered in the differential diagnosis[13,14]. In women with diabetes, pregnancy is also a condition that is associated with euglycemic ketoacidosis[15,16] as pregnancy is considered to be a state of accelerated starvation[17] with increased lipolysis and ketone body production in the presence of increased insulin insensitivity[18].

In clinical practice it must be remembered that patients with diabetes may be at risk of developing acidosis from conditions that are also seen in patients without diabetes, and a distinction between non-diabetic euglycemic ketoacidosis and euglycemic DKA is essential. The former includes differential diagnoses, such as prolonged starvation, excess alcohol consumption, salicylate overdose, lactic acidosis, tricyclic antidepressant overdose, and renal tubular acidosis, while the latter is a complex pathophysiological process specific to individuals with severe insulin deficiency[1,2,19]. We would suggest that these conditions should not only be excluded in diabetic patients with normal or mildly elevated glucose concentrations, but should also be considered in situations of overt hyperglycemia where it may be suspected that the diabetic condition may not be the sole contributor to the acidotic state[1,2,19]. Starvation ketoacidosis can be differentiated from euglycemic DKA by clinical assessment (one would usually expect the presence of an intercurrent illness to act as a precipitant for euglycemic DKA, with the starvation possibly occurring as a result of the intercurrent illness rather than as a primary event) and measurement of the serum bicarbonate concentration, which in starvation ketosis is usually not lower than 18 mEq/l[1]. In practice there may be a considerable degree of overlap between starvation ketoacidosis and euglycemic DKA, as the relative normoglycemia in euglycemic DKA occurs as a result of prolonged fasting[2,3,5]. The correct diagnosis of euglycemic DKA is also necessary to tailor therapy accordingly. The initial management should be, as in any case of ketoacidosis, to correct fluid/electrolyte abnormalities and re-establish carbohydrate metabolism[1,2,4,16]. Increased glucose administration using higher percentages of dextrose (10 or 20%) are required to facilitate the concomitant administration of the relatively large amounts of insulin that are needed to correct the severe acidosis in these patients[1,2,4,16]. Acidosis should improve with normalization of serum bicarbonate without the need for intravenous bicarbonate administration[1].

The importance of emotional well-being as part of good diabetes management is clearly recognized by the ADA, which

Table 1. Causes of Euglycaemic Ketoacidosis

As a result of decreased circulating glucose concentration
Starvation
Vomiting (ketoacidosis, gastroparesis)
Intentional dieting
Depression, anhedonia
Pregnancy
Glycogen storage disorders
Cirrhosis
As a result of H^+ excess
Exogenous
Salicylate overdose
Methanol ingestion
Endogenous
Lactic acidosis
Pancreatitis
Sepsis
Renal tubular acidosis

recommends that screening of psychosocial status occur at regular intervals as part of the ongoing medical management of diabetes[20]. Our case is interesting in that the decrease in caloric intake was a result of the previously undiagnosed severe depression with anhedonia. Depression in patients with diabetes is at least twice as common as in non-diabetic populations[21]. It is associated with poorer self-care and can mask the osmotic symptoms of diabetes, making self-management more difficult with resulting loss of metabolic control[20,22,23]. Also lack of appetite, starvation, and anhedonia are all well recognized biological features of severe depression[24]. Our patient did not initially seek medical care and went on to develop starvation physiology in conjunction with insulin deficient diabetes and viral gastroenteritis. He continued to develop ketosis despite continued use of exogenous insulin and eventually sought medical attention when he became symptomatic with nausea and vomiting, but unfortunately by this time he had developed significant metabolic abnormalities. Thus, his anhedonia, suppressed appetite, and prolonged starvation triggered a cascade of events resulting in metabolic decompensation, euglycemic ketoacidosis, and then ultimately the diagnosis of his severe depression.

In summary euglycemic DKA, although uncommon, still continues to be observed in clinical practice. Patients with type 1 diabetes presenting with nausea and vomiting and found to have a normal glucose may still have life-threatening ketoacidosis, and an assessment of their acid/base status is still indicated. In such patients extreme starvation and poor nutritional intake due to various causes may be contributory to the euglycemic DKA. Underlying severe depression and anhedonia comprise one such potential cause of anorexia and decreased oral intake (Table 1).

Conflicts of Interest: *None disclosed.*

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