Diabetic ketoacidosis: not always due to type 1 diabetes

This article discusses how to diagnose and manage patients with ketoacidosis prone type 2 diabetes

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Who gets diabetic ketoacidosis?

Diabetic ketoacidosis (DKA) is not just the hallmark of absolute insulin deficiency in type 1 diabetes—it is increasingly being seen in people presenting with type 2 diabetes. This is at odds with traditional physiological teaching—that clinically significant ketosis does not occur in the presence of insulin concentrations associated with type 2 diabetes because there will always be sufficient insulin to suppress lipolysis (fig 1). Current knowledge suggests that some people with type 2 diabetes may develop acute reductions in insulin production, which, coupled with insulin resistance, can cause DKA, usually without a precipitant. This is particularly so in African-Caribbean and other non-white ethnic groups. This potentially life threatening presentation of type 2 diabetes is referred to as ketosis prone type 2 diabetes (also Flatbush or type 1b diabetes). Clinicians should be aware of this variant of type 2 diabetes because observational studies in African-Caribbean people presenting with ketoacidosis indicate that 20-50% have type 2 diabetes.

What is known about the pathophysiology of ketoacidosis prone type 2 diabetes?

It is unclear why some people with type 2 diabetes are susceptible to DKA. Polymorphisms in key transcription factors involved in islet cell development are common in ethnic groups that are prone to this condition. Other studies have implicated glucose-6-phosphate dehydrogenase deficiency, which may lead to reduced protection of β cell function in the presence of oxidative stress caused by acute hyperglycaemia. At presentation of DKA, people with ketosis prone type 2 diabetes fulfill the same biochemical criteria for ketoacidosis as those with type 1 diabetes. However, unlike people with type 1 diabetes, after initial insulin treatment and improvement in glycaemic control, endogenous insulin production recovers over a relatively short time. This recovery in insulin secretion is usually sufficient to allow these patients to be managed with oral agents alone for many years. In between episodes of DKA, β cell function is preserved but suboptimal, and patients remain insulin resistant.

Why is it important to recognise ketosis prone type 2 diabetes?

It is important to consider whether patients presenting with ketoacidosis have ketosis prone type 2 diabetes or type 1 diabetes because the diagnosis may never subsequently be questioned. Incorrectly diagnosing ketosis prone type 2 diabetes as type 1 diabetes at presentation may lead to unnecessary long term insulin treatment with potential weight gain, hypoglycaemia, and implications for employment and quality of life. Correct recognition of ketosis prone type 2 diabetes enables most cases to be treated successfully with oral agents and insulin to be safely down-titrated and stopped over a period of months. Patients with ketosis prone type 2 diabetes will also need different education and follow-up from those with typical type 2 diabetes. Despite effective treatment with oral hypoglycaemic agents, patients with ketosis prone type 2 diabetes are at risk of further hyperglycaemic episodes or DKA. As with type 1 diabetes, education should focus on capillary blood glucose testing, home ketone testing, and the recognition and avoidance of DKA. Current guidelines advocate testing for urine ketones only in self management of type 1 diabetes, and guidance on self management of type 2 diabetes does not mention ketosis prone type 2 diabetes. Testing for both capillary blood glucose and urine ketones may ensure early self management of
hyperglycaemia associated ketosis, allowing for appropriate early management and avoidance of admission, as is seen for type 1 diabetes.

How do we recognise ketosis prone type 2 diabetes?

Clinical features

Owing to the phenotypic heterogeneity of people with ketosis prone type 2 diabetes, type 1 diabetes, and type 2 diabetes, no reliable specific features can clearly distinguish ketosis prone type 2 diabetes (table 1). However, ketosis prone type 2 diabetes needs to be considered in all non-white patients presenting with DKA, especially those from African-Caribbean, west African, and Hispanic backgrounds, although it has also been reported in white and other minority populations.

In the absence of reliable discriminatory features, patients with ketosis prone type 2 diabetes are generally older, more obese, and more likely to have a family history of type 2 diabetes. Age is a poor discriminator because 20-30% of new diagnoses of type 1 diabetes occur above the age of 20 years and ketosis prone type 2 diabetes has been reported in children. More that half of all emergency admissions to hospital for DKA in patients with ketosis prone type 2 diabetes occur at the time of initial diagnosis of diabetes, after a relatively short history of polyuria, polydipsia, and weight loss with no obvious precipitating causes. The remaining presentations occur in patients with established type 2 diabetes.

Biochemical features

Laboratory tests routinely carried out in emergency departments to establish the diagnosis of DKA (glucose >11 mmol/L, (1 mmol/L=18.02 mg/dL), bicarbonate <15 mmol/L (1 mmol/L=1 mEq/L) or pH <7.3, and ketosis with ketonuria or ketonaemia >3 mmol/L) do not distinguish between ketosis prone type 2 diabetes and type 1 diabetes. However, patients with ketosis prone type 2 diabetes tend to have higher plasma glucose and glycated haemoglobin (HbA₁c) values than those with type 1 diabetes. Ketosis prone type 2 diabetes can be firmly diagnosed only in retrospect, because specialised laboratory testing and the passage of time are needed to show insulin independence. However, the atypical features described should prompt clinicians to consider the diagnosis. All patients with DKA should be managed with insulin as per national DKA protocols and be discharged on insulin, with an early appointment at the diabetes clinic to undertake tests, review the results, and assess insulin requirements. Biochemical tests such as pancreatic autoantibodies and C peptide and antibody measurements may help specialists to make the diagnosis (see below).

How does ketosis prone type 2 diabetes differ from hyperosmolar hyperglycaemic syndrome?

Hyperosmolar hyperglycaemic syndrome is another life threatening metabolic complication of type 2 diabetes, characterised by hyperglycaemia (plasma glucose usually >30 mmol/L), hyperosmolarity (serum osmolality >320 mOsm/kg of water), and hypovolaemia. This syndrome is usually easy to distinguish from DKA. Because it is not associated with acidosis or ketosis, hyperglycaemia develops more insidiously and concentrations of glucose are often higher at presentation. See table 2 for key differences between hyperosmolar hyperglycaemic syndrome and DKA.

There are also important differences in the acute management of hyperosmolar hyperglycaemic syndrome and DKA. Clinical guidelines recommend fixed rate insulin infusions in hyperosmolar hyperglycaemic syndrome only in the presence of severe ketosis, specifying that this is given at half the rate recommended for DKA to minimise the risk of cerebral oedema. Patients with ketosis prone type 2 diabetes, however, should be managed as per the national guidance for DKA, which states a fixed rate insulin infusion.

What is the natural course of ketosis prone type 2 diabetes?

In these patients, ketoacidosis is caused by an acute reduction in insulin secretion and action, on the background of severe insulin resistance. As with type 1 diabetes, exogenous insulin is needed to treat the ketoacidosis. However, once the acute metabolic derangement of hyperglycaemia and accelerated lipolysis (the cause of the ketoacidosis) is reversed with insulin, both β cell function and insulin sensitivity improve. In most cases, good glycaemic control can be maintained with oral agents alone within three to six months.

Data from follow-up studies of patients with ketosis prone type 2 diabetes show that 70% of patients have at least one repeat episode of acute hyperglycaemia or DKA within two years if treated with diet and lifestyle changes alone. These patients also showed a progressive requirement for insulin with time.

Data from randomised controlled trials on the treatment of ketosis prone type 2 diabetes are limited. Recurrence of serious hyperglycaemia was lower after treatment with sulfonylureas than diet alone in one study (20% v 72%). In addition, pioglitazone significantly reduced the risk of further hyperglycaemia in 68% of cases compared with 32% for lifestyle modifications alone. However, neither drug mitigated the risk completely. Metformin, dipeptidyl peptidase-4 inhibitors, and incretin mimetics have not been evaluated, although studies are ongoing.
How should we monitor and follow up patients with suspected ketosis prone type 2 diabetes?

The management challenge in this type of diabetes is not at presentation but at follow-up, when, in addition to considering the diagnosis, the correct distinction between type 1 diabetes and type 2 diabetes also needs to be made. Consensus from specialist centres suggests that, after an acute admission, all patients should be treated with and discharged on insulin.

Biochemical testing

Autoimmunity and β cell function (using fasting or glucagon stimulated C peptide) should be assessed one to three weeks after resolution of ketoacidosis in a specialist diabetes clinic. Such tests are not routinely available at all hospitals but are readily accessible at specialised clinical laboratories. Pancreatic autoimmune markers such as glutamic acid decarboxylase (GAD65) or islet antigen 2 (IA2) antibodies are not present in ketosis prone type 2 diabetes, so their absence distinguishes the condition from type 1 diabetes.

Although the concentration of C peptide, a marker of β cell function, is low at the time of diagnosis of DKA (and therefore of no use at admission), it increases within a few weeks to months, when β cell function recovers. This is the hallmark of ketosis prone type 2 diabetes.

The measurement of glucagon stimulated C peptide is currently the best predictor of long term insulin independence, although fasting serum C peptide values also correlate well. Classification of ketosis prone type 2 diabetes according to C peptide values and autoantibody results had 99% sensitivity and 96% specificity for predicting absence or presence of β cell function 12 months after the initial DKA episode. This was significantly better than criteria relying on body mass index, clinical features, and insulin dependence. If autoantibodies are negative, C peptide concentrations are sufficient, and glycaemic control is maintained, insulin doses can safely be down-titrated, as long as the patient can perform home blood glucose monitoring and ketone testing. Such an approach requires specialist supervision. Once insulin treatment has been stopped and oral agents prescribed, frequent assessment of β cell function reserve, preferably with C peptide measurement, is advised, unlike in the routine follow-up for type 2 diabetes.

The measurement of C peptide will establish whether the patient has recovered sufficient endogenous insulin production to allow insulin treatment to be down-titrated. Follow-up measurements will also predict which patients are likely to require insulin treatment. Conventionally, these decisions have been made clinically—using symptoms, body weight, and glycaemia. However, C peptide measurements are now more widely available and have an emerging evidence base for use in a variety of contexts in the management of people with diabetes. Further studies are needed before robust guidelines for its routine use in assessing β cell function and insulin independency in people with ketosis prone type 2 diabetes can be produced.

Contributors: Each author contributed to this article through conception, research, writing, development, and editing. AD is senior author and guarantor.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: None.

Provenance and peer review: Not commissioned; externally peer reviewed.

References


Accepted: 14 May 2013
### Tables

Table 1  | Clinical and biochemical differences between adult onset type 1 diabetes, type 2 diabetes, and ketosis prone type 2 diabetes

<table>
<thead>
<tr>
<th>Factor</th>
<th>Type 1 diabetes</th>
<th>Ketosis prone type 2 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary abnormality</td>
<td>Insulin deficiency</td>
<td>Acute temporary defect in insulin secretion and sensitivity</td>
<td>Insulin resistance and ( \beta ) cell dysfunction</td>
</tr>
<tr>
<td>Course</td>
<td>Relapsing remitting course</td>
<td>Insulin resistance and progressive insulin secretory defect</td>
<td></td>
</tr>
<tr>
<td>Development of ketosis</td>
<td>Relapsing remitting course</td>
<td>Insulin resistance and progressive insulin secretory defect</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Non-discriminatory</td>
<td>Non-discriminatory</td>
<td>Non-discriminatory</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Mainly African-Caribbean and Hispanic groups</td>
<td>Non-discriminatory</td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td>Hyperglycaemia ± diabetic ketoacidosis</td>
<td>Hyperglycaemia ± diabetic ketoacidosis</td>
<td>Hyperglycaemia ± hyperosmolar hyperglycaemic syndrome</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Weeks</td>
<td>Weeks</td>
<td>Months</td>
</tr>
<tr>
<td>Proportion of patients with a family history</td>
<td>30%</td>
<td>80-100%</td>
<td>30-80%</td>
</tr>
<tr>
<td>Control with oral hypoglycaemic agents</td>
<td>Insulin required</td>
<td>Can be maintained with oral agents for a long duration</td>
<td>First line agent</td>
</tr>
<tr>
<td>Pancreatic autoantibodies</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>C peptide at follow-up</td>
<td>Absent or reduced</td>
<td>Preserved</td>
<td>Preserved</td>
</tr>
</tbody>
</table>
### Table 2: Comparison of diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome\(^*\)^

<table>
<thead>
<tr>
<th>Factor</th>
<th>Diabetic ketoacidosis</th>
<th>Hyperosmolar hyperglycaemic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume status</td>
<td>Usually dehydrated</td>
<td>Hypovolaemic</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>&gt;11 or known diabetes</td>
<td>≥30</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>+++ or more</td>
<td>++ or less</td>
</tr>
<tr>
<td>Capillary blood ketones (mmol/L)</td>
<td>&gt;3</td>
<td>&lt;3</td>
</tr>
<tr>
<td>pH</td>
<td>&lt;7.3</td>
<td>&gt;7.3</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>&lt;15</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Osmolarity (mosmol/kg)</td>
<td>Variable</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Intravenous fluids</td>
<td>Immediately</td>
<td>Immediately</td>
</tr>
<tr>
<td>Insulin</td>
<td>Immediately at fixed rate infusion of 0.1 units/kg/h; otherwise withhold insulin until fluid resuscitated</td>
<td>Immediately only if capillary ketones &gt;1 mmol/L or urine ketones &gt;2+ (at 0.05 units/kg/h); otherwise withhold insulin until fluid resuscitated</td>
</tr>
</tbody>
</table>
Fig 1 Physiological effects of circulating insulin on ketone production. Lipolysis is the process by which triglycerides are hydrolysed to fatty acids. This is controlled by hormone sensitive lipase, which in turn is inhibited by insulin. Fatty acids are oxidised to acetyl CoA, which enters the Krebs cycle to produce cellular energy. In type 1 diabetes, absolute insulin deficiency causes acetyl CoA production to exceed the oxidative capacity of the Krebs cycle, causing the formation of ketone bodies. In type 2 diabetes, endogenous insulin is sufficient to suppress uncontrolled lipolysis and ketone formation. However, in ketosis prone type 2 diabetes, insulin secretion can be acutely reduced, which, on a background of insulin resistance, leads to uncontrolled lipolysis and ketone formation.