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PRACTICE POINTER

Diabetic ketoacidosis: not always due to type 1 diabetes

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- Skin camouflage (*BMJ* 2012;344:d7921)

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

SUMMARY POINTS

Patients presenting with diabetic ketoacidosis may have type 1 or type 2 diabetes
Diabetic ketoacidosis should be treated with insulin in accordance with nationally agreed guidance
After treatment of diabetic ketoacidosis, patients found to have type 2 diabetes may not require lifelong insulin treatment
Consider ketosis prone type 2 diabetes in older, overweight, non-white patients who present with diabetic ketoacidosis at their first presentation of diabetes; this diagnosis is also a possibility in patients with any features that are atypical for type 1 diabetes
Discharge all patients on insulin and arrange for specialist follow-up
Under specialist supervision consider whether insulin can be down-titrated on the basis of clinical progress and, where possible, C peptide and antibody measurements

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.[1 2] 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).[3] 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.[4] This is particularly so in African-Caribbean and other non-white ethnic groups.[5 6] 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.[2]

What is known about the pathophysiology of ketosis 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.[7] 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.[8]

At presentation of DKA, people with ketosis prone type 2 diabetes fulfil 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.[9] This recovery in insulin secretion is usually sufficient to allow these patients to be managed with oral agents alone for many years.[9 10] In between episodes of DKA, β cell function is preserved but suboptimal, and patients remain insulin resistant.[5 9 11]

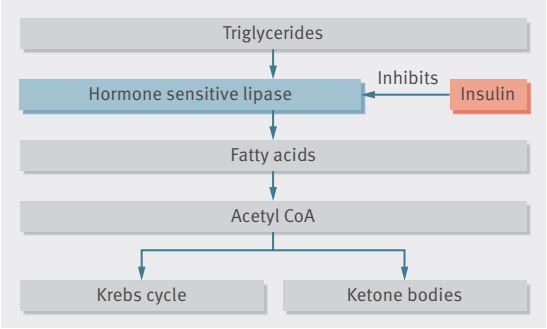

Fig 1 | Physiological effects of circulating insulin on ketone production. Lipolysis is the process by which triglycerides are hydrolysed to fatty acids. This is controlled by hormone sensitive lipase, which in turn is inhibited by insulin. Fatty acids are oxidised to acetyl CoA, which enters the Krebs 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

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.[2 9 12]

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.[9] As with type 1 diabetes, education should focus on capillary blood glucose testing, home ketone testing, and the recognition and avoidance of DKA.[2 12] Current guidelines advocate testing for urine ketones only in self management of type 1 diabetes,[13] and guidance on self management of

Table 1 | Clinical and biochemical differences between adult onset type 1 diabetes, type 2 diabetes, and ketosis prone type 2 diabetes[12]

Factor	Type 1 diabetes	Ketosis prone type 2 diabetes	Type 2 diabetes
Primary abnormality	Insulin deficiency	Acute temporary defect in insulin secretion and sensitivity	Insulin resistance and β cell dysfunction
Course	Progressive decline in insulin secretion	Relapsing remitting course	Insulin resistance and progressive insulin secretory defect
Development of ketosis	Result of absolute insulin deficiency	Acute insulin deficiency that recovers for sustained periods	Relative insulin deficiency sufficient to prevent ketosis
Age	Non-discriminatory	Non-discriminatory	Non-discriminatory
Ethnicity	Non-discriminatory	Mainly African-Caribbean and Hispanic groups	Non-discriminatory
Presentation	Hyperglycaemia ±diabetic ketoacidosis	Hyperglycaemia ±diabetic ketoacidosis	Hyperglycaemia ±hyperosmolar hyperglycaemic syndrome
Duration of symptoms	Weeks	Weeks	Months
Proportion of patients with a family history	30%	80-100%	30-80%
Control with oral hypoglycaemic agents	Insulin required	Can be maintained with oral agents for a long duration	First line agent
Pancreatic autoantibodies	Present	Absent	Absent
C peptide at follow-up	Absent or reduced	Preserved	Preserved

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.[6 12 14]

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.[5 9 12] 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.[12 15]

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.[2 9 14] The remaining presentations occur in patients with established type 2 diabetes.

Table 2 | Comparison of diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome[16 18]

Factor	Diabetic ketoacidosis	Hyperosmolar hyperglycaemic syndrome
Volume status	Usually dehydrated	Hypovolaemic
Glucose (mmol/L)	>11 or known diabetes	>30
Urine ketones	+++ or more	++ or less
Capillary blood ketones (mmol/L)	>3	<3
pH	<7.3	>7.3
Bicarbonate (mmol/L)	<15	>15
Osmolarity (mosmol/kg)	Variable	>320
Intravenous fluids	Immediately	Immediately
Insulin	Immediately at fixed rate infusion of 0.1 units/kg/h	Immediately only if capillary ketones >1 mmol/L or urine ketones >2+ (at 0.05 units/kg/h); otherwise withhold insulin until fluid resuscitated

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.[16] However, patients with ketosis prone type 2 diabetes tend to have higher plasma glucose and glycated haemoglobin (HbA_{1c}) values than those with type 1 diabetes.[2 17]

Thus 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 measurement 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.[18] 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.[18] 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.[16]

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.[11] 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 ketosis) 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.[9]

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.[9]

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%).[19] In addition, pioglitazone significantly reduced the risk of further hyperglycaemia in 68% of cases compared with 32% for lifestyle modifications alone.[20] 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.[2 12] 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.[4]

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.[12] 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.[21]

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.[12] 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.[2 12]

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.[22] 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.

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EASILY MISSED?

Imported malaria

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A 19 year old student phoned an official health service telephone helpline with a 10 day history of aching legs, vomiting, diarrhoea, and abdominal pain. She mentioned a recent trip to Uganda but was reassured and told she had "flu." The next day her boyfriend took her to see her doctor, where she mentioned general malaise, tiredness, and occasional nausea; the doctor diagnosed a viral illness and advised her to keep taking paracetamol. Three days later a friend found her dead in bed in her university halls of residence. The coroner recorded death due to cerebral malaria.[1]

What is malaria?

Malaria is an infection caused by protozoa of the genus *Plasmodium*. Five species infect humans (*P falciparum*, *P vivax*, *P ovale*, *P malariae*, and *P knowlesi*). Most of the fatal cases are caused by *P falciparum*.

Why is malaria missed in non-endemic countries?

As illustrated by the case described here, the symptoms of malaria are non-specific and can easily be mistaken for a viral illness such as influenza, unless clinicians think to ask patients whether they have travelled abroad.

A retrospective observational study of 191 deaths due to malaria in the United Kingdom from 1987 to 2006 found that the case fatality was inversely related to incidence, suggesting that cases were more easily missed by clinicians unaccustomed to seeing this disease.[4] A retrospective series of 39 cases of malaria diagnosed in Sheffield from 2000 to 2005 found that eight of these patients had presented to health professionals with symptoms of malaria but were not immediately referred to hospital or for a diagnostic test, suggesting that the diagnosis of malaria had not been considered.[6] A retrospective case review of 211 children admitted to hospital with malaria in east London found that 114 had initially presented to their doctor, but malaria was suspected at the first visit in only 32% of these, and diagnosis was delayed in 53%, by one to 14 days.[7]

KEY POINTS

If patients have fever, history of fever, or flu-like symptoms, always ask about travel to a malaria endemic country within the past year

If malaria is suspected, request urgent thick and thin malaria films (three negative films results on consecutive days are needed to exclude the diagnosis) and a full blood count (thrombocytopaenia is common in acute malaria)

If there are any signs of severe malaria, admit as an emergency

HOW COMMON IS MALARIA?

- Worldwide over 200 million cases of malaria occur annually and 0.5-1 million deaths, 90% of which are among children in Africa[2]
- *Plasmodium falciparum* accounted for about 70% of the 1677 cases notified in the United Kingdom in 2011, whereas 25% of cases were due to *P vivax*[3]
- Of the 191 deaths from malaria in the United Kingdom from 1987 to 2006, 184 were due to *P falciparum*[4]
- About 20% of imported malaria cases are in children[5]

Why does this matter?

If untreated, malaria can be rapidly fatal, particularly in non-immune patients. Delay in diagnosis is associated with an increased risk of severe malaria and death.[5 8] The overall case fatality rate from malaria in the United Kingdom is 0.73%,[4] but for cases with signs of severe malaria (box) this may reach 10-20%.[9] Severe complications and death may occur within 24-48 hours of onset of symptoms.[10 11] Early diagnosis and appropriate treatment are therefore crucial.

How is malaria diagnosed?

Clinical

Question anyone presenting with a history of fever or flu-like symptoms about travel to malaria endemic countries within the past year. Investigate urgently those returning from a malaria endemic area, regardless of whether they have taken malaria prophylaxis. Intermittent fever may be a feature of malaria, so temperature may be normal at the time of examination. A case series of 482 patients in the United States found that half of adult patients were not febrile when they presented, although most had a history of fever.[12] Other common symptoms include vomiting, diarrhoea, headache, and myalgia.[5 12] Most patients with *P falciparum* present within six months of returning from abroad, although later presentations may occur. The box shows the features of severe disease.

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at easilymissed@bmj.com.

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- Colorectal cancer (*BMJ* 2013;346:f3172)
- Acute leg ischaemia (*BMJ* 2013;346:f2681)
- Delirium in older adults (*BMJ* 2013;346:f2031)

Definition of severe malaria[9]

In patients with *Plasmodium falciparum* asexual parasitaemia and no other obvious cause of symptoms, severe malaria is defined by one or more of the following features:

Clinical features

Impaired consciousness or coma from which patients cannot be roused

Prostration—that is, generalised weakness such that that patients cannot sit up unaided

Failure to feed

Multiple convulsions—more than two episodes in 24 hours

Deep breathing, respiratory distress (acidotic breathing)

Circulatory collapse or shock, systolic blood pressure <70 mm Hg in adults and <50 mm Hg in children

Clinical jaundice plus evidence of other vital organ dysfunction

Haemoglobinuria

Abnormal spontaneous bleeding

Pulmonary oedema (radiological)

Laboratory findings

Haematology

Severe normocytic anaemia (haemoglobin level <50 g/L, packed cell volume <15%)

Hyperparasitaemia (>2% or 100 000/µL in areas of low intensity of transmission; >5% or 250 000/µL in areas of high and stable intensity of transmission)

Biochemistry

Hypoglycaemia (blood glucose level <2.2 mmol/L or <40 mg/dL)

Renal impairment (serum creatinine level >265 µmol/L)

Metabolic acidosis (plasma bicarbonate level <15 mmol/L)

Hyperlactataemia (lactate >5 mmol/L)

Urine

Haemoglobinuria

Investigations

It is preferable to refer all patients with suspected malaria to hospital immediately for further investigation because of the risk of rapid progression of falciparum malaria. However, if the patient is relatively well and it is possible to obtain results rapidly (the same day), it may be reasonable to investigate in a primary care setting. This calls for some clinical judgment. If the risk of malaria is low and the patient is not severely ill, outpatient testing with next day results may be acceptable, but the patient should then be advised to reconsult rapidly if there is any worsening of symptoms.

The clinician should request an urgent full blood count and "malaria thick and thin films" (both on the same EDTA sample). Although microscopy is the standard diagnostic method, low density infection may be missed,[13] particularly if microscopists are inexperienced or if patients have taken an antimalarial or an antibiotic with antimalarial activity. Therefore, if the first slide gives a negative result, films should be repeated after 12-24 hours, and again after another 24 hours. The likelihood of malaria is low if experienced microscopists find three consecutive negative blood film results.[14]

In the United Kingdom some haematology laboratories may also be able to perform a rapid diagnostic test. These tests are based on detection of parasite antigens or enzymes; a recent Cochrane review found that the sensitivity and specificity of the most common rapid diagnostic tests were both 95%, compared with microscopy.[15] Rapid diagnostic tests are useful in increasing speed of diagnosis, even in non-endemic countries[16] and, if available, can be used as an adjunct to microscopy, although they cannot replace it. All positive malaria test results should be telephoned immediately to the requesting doctor and communicated by the doctor to the patient.[14]

Thrombocytopenia is common in acute malaria, and, if otherwise unexplained, may be an important clue even if the blood film has been reported as negative. A prospective study looking at returning travellers with fever found that leucocyte counts $<10\times10^9$/L, platelet counts $<150\times10^9$/L, and haemoglobin levels <120 g/L were all associated with an increased probability of malaria. Thrombocytopenia was the best predictor, with a positive likelihood ratio of 11.[17]

How is malaria managed?

Seek expert advice on treatment, particularly if there are signs of complications. In the primary care setting, if there are any signs of severe malaria, refer the patient to hospital as an emergency and treat any complications (for example, shock, hypoglycaemia, convulsions) while awaiting transfer.

Most patients with falciparum malaria need admission to hospital, although recent evidence has suggested that a small selected group with uncomplicated falciparum malaria can be treated safely as outpatients.[18 19] Those with uncomplicated non-falciparum infections can usually be managed as outpatients provided they are able to take oral drugs. Mixed infections can occur and *P falciparum* may be missed or misdiagnosed. Therefore it is sensible to have a low threshold for admission and to advise all those treated as outpatients to seek further medical attention urgently if they deteriorate. It is also advisable to review all patients with malaria 1-2 weeks after completion of treatment.[18 19]

Because of the risk of increasing drug resistance, the World Health Organization now recommends that uncomplicated *P falciparum* malaria should be treated with artemisinin combination therapies.[9] Recent studies have proved that intravenous artesunate is more effective than quinine for the treatment of severe malaria,[20 21] but UK guidelines still recommend quinine because artesunate is unlicensed in the European Union.[14] These guidelines are, however, currently under review. Chloroquine is usually effective for non-falciparum malarias; however, chloroquine resistant *P vivax* is increasingly prevalent in some areas (for example, Indonesia, Peru, and Oceania).[9] In addition, patients with *P vivax* or *P ovale* infections should have their glucose 6 phosphate dehydrogenase (G6PD) status checked and, unless significantly G6PD deficient, should also be treated with an appropriate course of primaquine to reduce the likelihood of relapses.[22]

UK guidelines for malaria treatment[14] and a useful management algorithm are available at www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Malaria/Guidelines/mala20guidelinesTreatment/.

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