

Diabetic ketoacidosis in type 2 diabetes mellitus

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Abstract

Diabetic ketoacidosis is usually associated with type 1 diabetes; however, it is increasingly being recognised in type 2 diabetes. The three main mechanisms suggested are: insulinopaenia, elevation in counter-regulatory hormones as a stress response, and increase in free fatty acids. This review aims to highlight the mechanism of diabetic ketoacidosis in type 2 diabetes, the difference compared to its occurrence in type 1 diabetes, the main triggers and its management.

The most common mechanism is relative insulin deficiency (insulinopaenia) and usual triggers are non-concordance or infection. Treatment is exactly the same as in type 1 diabetes with intravenous fluid resuscitation and insulin, though the duration of treatment may not be as long. These patients are able to stop insulin following resolution of ketoacidosis and can be managed on oral hypoglycaemic agents. It is important for clinicians to be aware of this condition due to the increasing burden of type 2 diabetes and to avoid unnecessary treatment with insulin in the long term. Copyright © 2014 John Wiley & Sons.

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Key words

DKA; ketoacidosis; type 2 diabetes; ketosis prone

Introduction

Diabetic ketoacidosis (DKA) is a well-known, life-threatening acute complication of type 1 diabetes. For a long time it has been considered the hallmark of type 1 diabetes; however, recently, its presence has been increasingly recognised in patients with type 2 diabetes and a newer entity called ketosis prone diabetes is also commonly recognised.

This paper reviews what is currently known about DKA in patients with type 2 diabetes, and provides an insight into the possible mechanisms and important practical points for the clinician.

There are documented instances of ketosis and acidosis occurring in type 2 diabetes in the setting of excess alcohol intake, pregnancy or anorexia;^{1–3} however, this paper looks at only confirmed diabetic ketoacidosis in patients with type 2 diabetes.

It is important to recognise that DKA can occur in type 2 diabetic patients as this will have implications for acute management as well as planning for further follow up and treatment, especially with the increasing prevalence of diabetes and the longer life expectancy of the population.

Diabetic ketoacidosis

Diabetic ketoacidosis is a condition characterised by ketonaemia,

acidaemia and raised blood glucose levels – i.e. hyperglycaemia,⁴ though hyperglycaemia may not always be present.⁵

It is a life-threatening condition with reported mortality rates in patients with type 1 diabetes of 2% in the United Kingdom⁶ and 2–5% in the USA.^{7,8} However, prompt recognition and management can result in full recovery.

The incidence of DKA (regardless of underlying diabetes type and including first presentation) has been estimated as between 4.6–8 episodes per 1000 patients with diabetes in the USA,⁹ and there is documented incidence of 11% of people with type 1 diabetes experiencing an episode of DKA in England.¹⁰

The mechanism of DKA is due to complete insulin deficiency, or relative insulin deficiency which is inadequate to prevent ketosis and in the presence of excess counter-regulatory hormone.¹¹

The mechanism of the hyperglycaemia in DKA is due to increased glucose production from gluconeogenesis and glycogenolysis, and reduced uptake of glucose by muscle and fat tissue.^{4,11}

Insulin is known to inhibit gluconeogenesis and glycogenolysis; however, in insulin resistant states insulin is unable to effectively control glucogenic enzymes thereby

Authors	DKA cases	Type 2 DM: no. (%)	New diagnosis: no.	Trigger	Ethnicity	BMI (kg/m ²)
Newton, Raskin ²⁶ (USA)	138	30 (21.7)	5	Discontinue insulin/ non-compliance 69.2% Infection 48.4%	White = 3 African = 17 Latino = 9 Other = 1	70% BMI >27
Wilson, <i>et al.</i> ¹⁵ (USA)	17	17 (100)	0	Non-compliance 20% Infection 47% Hx of alcohol abuse in 94%	Apache Indians	24.9±4.4
Balasubramanyam, <i>et al.</i> ²⁵ (USA)	141	55 (39)	26	No trigger 50%	Black = 28 Hispanic = 20 White = 5 Asian = 2	77% BMI >25 51% BMI >30
Pitteloud, Philippe ²¹ (Switzerland)	43	7 (16.3)	Not clear	No trigger 43% Infection 28.5% Pancreatitis 28.5%	Caucasian	Mean BMI 31.6
Rao, <i>et al.</i> ¹⁸ (India)	27	22 (81)	Not clear	Non-compliance 50% Infection 33% No trigger 14%	South Asian	No data
Jabbar, <i>et al.</i> ¹⁷ (Pakistan)	57	57 (100)	8	Infection 63%	South Asian	No data
Chih-Hsun Chu, <i>et al.</i> ¹⁶ (China)	137	98 (71.5)	24	Infection 48% Non-compliance 19.4%	South East Asian (Chinese)	No data

Table 1. Summary of key findings of studies analysing diabetic ketoacidosis (DKA) in type 2 diabetic patients^{15–18,21,25,26}

increasing glucose output from the liver.¹² In insulin resistant states the body still remains sensitive to the anti-lipolytic effects of insulin. This is strengthened by data suggesting that the amount of insulin required to prevent lipolysis is one-tenth of that required for glucose utilisation.¹³

This is the reason why it had been thought that patients with type 2 diabetes did not develop ketoacidosis. Type 2 diabetes is predominantly a disease of inadequate insulin availability or increased insulin resistance – i.e. the body's own insulin is insufficient for its needs. The residual beta-cell function in the pancreas of these individuals could produce insulin in sufficient amounts so as to prevent ketogenesis but inadequate for the body's glucose requirements, thereby preventing build up of ketones in the blood stream.

Various precipitating factors have been acknowledged including intercurrent infection/illness, omission of regular insulin (either due to poor compliance or inadvertent

discontinuation by professionals), initial presentation of diabetes and cardiovascular or cerebrovascular events.⁴

From the above mechanisms it could be assumed that it is possible for DKA to occur in patients with type 2 diabetes when the insulin production is insufficient (or absent) to prevent ketone production with or without precipitating factors – that is, relative insulin deficiency.

DKA in type 2 diabetes

There have been many cases and studies looking at ketoacidosis and its presence in patients with type 2 diabetes.

There have been cases documenting DKA in patients with type 2 diabetes as predominantly found in ethnic minorities and specifically Afro-Caribbean populations or indigenous populations of America.^{14,15}

However, studies have also analysed DKA admissions in Chinese,¹⁶ Pakistani¹⁷ and Indian¹⁸ populations, and further recent

studies have also looked at DKA in Caucasian patients with type 2 diabetes.^{19–21} This indicates that the development of DKA is not just related to ethnic minorities as once was thought.

The above studies were retrospective ranging between one and seven years in duration. All but two^{16,21} classified type 2 diabetes depending on whether the study population had been treated with diet or oral hypoglycaemic agents at some point previously or, if new onset, were controlled without insulin or were glutamic acid decarboxylase (GAD)/islet cell antibody negative. The other two studies used basal C-peptide measurements to categorise patients as type 1 or type 2 diabetes.

The definitions of DKA were based on variations of the American Diabetes Association guidelines. The parameters used were pH, glucose levels, presence of ketones (serum or urine), bicarbonate levels and anion gap.

Table 1 provides a review of the key findings of each of the studies.

While predominantly found in adults with type 2 diabetes, it is interesting to note that DKA has also been described in children and adolescents with type 2 diabetes.²²

Causes

The occurrence of DKA in type 2 diabetes has been thought to be due to the presence of co-existing stressors, predominantly infections. Other reported causes include myocardial infarction, cerebrovascular accidents, antipsychotic usage and malignancy, such as pancreatic adenocarcinoma.^{4,23,24} Sometimes no stressor can be found and it can be the initial mode of presentation.^{25,26} Another well documented cause is poor compliance with medication either due to the patient themselves or inappropriate discontinuation by medical professionals.^{15,16,18,26} The authors could not find any specific documented reports of steroids triggering DKA in patients with pre-existing type 2 diabetes; however, in one of the studies mentioned above, one case of steroid induced DKA in the study population was mentioned.¹⁷

Mechanism in type 2 diabetes

As described earlier, the occurrence of DKA in patients with type 1 diabetes is due to the presence of insulinopaenia. A similar mechanism has been thought to occur in long-standing type 2 diabetes patients due to complete loss of beta-cell function. However, this is not always the case as some patients present within a few years of diagnosis where complete beta-cell dysfunction is unlikely.²⁶

Studies suggest the cause could also be due to relative insulin deficiency arising from constant hyperglycaemia as a result of poor control, and the presence of stressors which cause increased lipolysis due to counter-regulatory hormones (glucagon, cortisol and growth hormone).^{24,27} It is also this hyperglycaemia which further blunts the body's own insulin secretion and reduces glucose removal by down-regulating glucose transporter systems and even reducing insulin gene transcription.²⁸ The term 'glucose toxicity' has often been quoted when describing the above mechanisms.^{14,28}

Differences between DKA in type 1 and type 2 diabetes

Literature shows that DKA in patients with type 2 diabetes tends to present with a less severe acidosis and patients are more likely to have normal potassium levels.^{25,26} Patients with type 2 diabetes and DKA also tend to be older, have a higher body mass index and a shorter duration of diabetes with an older age of onset.²¹

Phenotypically, type 2 diabetes patients with DKA tend to have typical features of insulin resistance such as large body habitus and acanthosis nigricans (though this is not present in all patients) compared to type 1 patients. They also have positive family history and no autoimmune markers of diabetes, and may require larger amounts of insulin to correct the hyperglycaemia.^{14,24}

In keeping with type 1 diabetes, the triggers for DKA development are similar, with infection and omission of insulin being the most common causes.^{16–18,21}

Despite requiring insulin infusions to resolve ketoacidosis, many of these patients are able to stop insulin therapy following resolution of the DKA episode, and can be maintained on oral hypoglycaemic agents or diet alone.^{14,17}

Improvement in C-peptide levels following resolution of the DKA episode indicates improvement in beta-cell function,^{29,30} therefore C-peptide measurement after glucagon administration may be of benefit in differentiating patients as being type 1 or type 2 when presenting for the first time with DKA. This helps to identify whether there is any residual beta-cell function, and can help predict whether or not the patient requires further future insulin therapy.^{21,29,31}

Outcome of patients with DKA and type 2 diabetes

The majority of patients who have an episode of DKA and have newly diagnosed type 2 diabetes are able to discontinue insulin after the acute episode and remain on diet control or on oral hypoglycaemic agents. Studies show that between 50–66.7% of patients admitted are able to remain off

insulin.^{14,17,21} This may be related to the recovery of beta-cell function once the acute hyperglycaemic episode has resolved.

The importance of recognising DKA as a feature of type 2 diabetes lies in this finding. Understanding the nature of the diabetes type ensures that patients are not unnecessarily continued on insulin. This can provide significant cost, economic and emotional benefit to individuals due to the lifestyle restrictions and side effects that occur with insulin use.

Only one study has looked at comparing inpatients with DKA who had either type 1 or type 2 diabetes.³² The authors found that DKA was more likely to be associated with adverse outcomes in patients with type 2 diabetes than in those with type 1 diabetes. They found a 30-day mortality rate of 11.9% in type 2 diabetes versus 2.4% in type 1 diabetes. This could possibly be related to the presence of comorbidities and older age of presentation in the type 2 group.

To date, no studies have looked at whether development of DKA in patients with type 2 diabetes is associated with a poorer outcome in the long term. The risks of DKA remain the same in the acute phase regardless of diabetes type.

Ketosis prone type 2 diabetes

Recently, the notion of ketosis prone diabetes has been put forward as a way of classifying patients with diabetes who are prone to ketone formation.

Study populations of various ethnicities presenting with DKA have been reviewed by Maldonado and Balasubramanyam *et al.* They prospectively assessed patients admitted with DKA with regard to clinical and biochemical profiles. Their findings indicated that patients presenting with DKA could be classified into four main groups depending on their characteristics and presence of beta-cell function or autoimmune antibodies. They classified people into with or without autoimmune markers (A+/A-) or having/not having beta-cell function (β +/ β -). Their

Key points

- Diabetic ketoacidosis is increasingly being reported in patients with type 2 diabetes and can even be the initial mode of presentation in such individuals
- Diagnostic criteria for diabetic ketoacidosis are the same irrespective of the type of diabetes
- There may not always be a trigger factor; however, infection and poor compliance have been the most common reasons for developing diabetic ketoacidosis
- Acidosis and hypokalaemia tend to be mild, but there is often a requirement for higher rates of insulin infusions in type 2 diabetes patients with diabetic ketoacidosis compared to patients with type 1 diabetes
- Intravenous insulin infusion is the mainstay of treatment and results in resolution of the relative beta-cell functional deficit
- Most patients can be managed without insulin after the resolution of diabetic ketoacidosis and may remain off insulin for months to years

classification had a sensitivity of 99.4%, specificity of 95.9% and positive predictive value of 97.1% in predicting preserved beta-cell function in those patients admitted with DKA, and this could help aid long-term management. They argued that old methods of classifying diabetes are inadequate, and the new classification would help divide patients with diabetes into those who are more likely to be at risk of ketosis, and help predict long-term beta-cell function and requirement for insulin.^{30,33,34}

The underlying mechanism in ketosis prone diabetes is not known; however, increased susceptibility to glucose desensitisation has been suggested³⁵ whereby persistently high levels of glucose in the blood stream lead to pancreatic beta-cell desensitisation and lack of function at high glucose levels.

Other studies have suggested the possibility of glucose-6-phosphate dehydrogenase deficiency causing reduced beta-cell function in patients with hyperglycaemia.³⁶

A further study performed in 2005 by Linfoot *et al.*³⁷ looked at the pathophysiology of DKA in ketosis prone type 2 diabetes mellitus by obtaining blood samples from patients presenting with DKA prior to intravenous insulin commencement, and suggested that the mechanism was greater insulinopaenia (i.e. relative insulin deficiency).

The notion of ketosis prone diabetes and its classification is an interesting proposition and recent articles have highlighted this entity, bringing it into more prominence;

however, its use into the medicine community as a whole is still to be accepted.

Declaration of interests

There are no conflicts of interest declared. Source of funding: none.

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