An interesting case of new-onset ketosis-prone diabetes in a Scottish teaching hospital

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Review

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Abstract

Background: Clinical teaching for many years has been to assume that diabetic ketoacidosis is pathognomic of type 1 diabetes. However, this dogma is now increasingly questioned as increasing numbers of people are admitted with diabetic ketoacidosis without the typical features of autoimmune type 1 diabetes. Such individuals are increasingly diagnosed with ketosis-prone diabetes, a heterogenous syndrome where individuals present with diabetic ketoacidosis or unprovoked ketosis but are usually autoantibody negative and have no residual β-cell function. Classification of ketosis-prone diabetes using the Aβ system can aid in diagnosis and treatment decisions.

Case report: An Afro-Caribbean male presented with hyperglycaemic ketosis. Initially diagnosed with type 1 diabetes and treated with a basal-bolus regimen, he was able to stop insulin completely within one month of presentation following rapid improvements in glycaemic control and repeated hypoglycaemia. Clinical investigation revealed he was negative for β-cell autoantibodies and had a stimulated C-peptide of >0.5 pmol/ml, suggesting preserved β-cell function. A diagnosis of ketosis-prone diabetes (A-β+) was made.

Discussion: A high index of suspicion for ketosis-prone diabetes should arise when someone presents with diabetic ketoacidosis, who is obese, middle-aged, male and with a strong family history of type 2 diabetes and from a Black or Hispanic population. There is currently limited evidence on the pathophysiology of this transient β-cell defect, with suggestions that it may be related to glucotoxicity.

Keywords

Ketosis prone; type 2; glucotoxicity; ketoacidosis; Aβ

Case report

A 31-year old marine engineer presented with a three month history of polyuria, polydipsia, blurred vision and lethargy with significant weight loss (6.35 kg over four weeks). He had been taking carbohydrate-heavy carbonated drinks to alleviate his thirst. He was a non-smoker who exercised regularly and drank alcohol only occasionally. He had no past medical history of note. He was of mixed Caribbean origin. His mother was diagnosed with type 2 diabetes at the age of 33 and managed with diet and oral hypoglycaemic agents.

On examination, he was of normal build and his weight was 87 kg (BMI 26 kg m^2). He was haemodynamically stable and systemic examination was unremarkable. His relevant blood chemistry on admission was: laboratory glucose 26 mmol/l (3.3–5.8 mmol/l), bicarbonate 27 mmol/l (18–23 mmol/l). Bedside blood ketones (β-hydroxybutyrate) were 2.1mmol/l (normal being <0.6). He was treated with insulin and fluids overnight for this hyperglycaemic, mildly ketotic episode. A presumptive diagnosis of new type 1 diabetes (T1D) was made and he was subsequently commenced on a basal bolus regime (average total daily insulin dose, 20 units) prior to discharge.

When reviewed in the diabetes clinic one month after discharge, he reported that his blood glucose monitoring had initially shown levels of 15–20mmol/l, with ketones always remaining below 0.6mmol/l, but that during subsequent weeks he rarely noted readings above 5–6 mmol/l. He also reported frequent dizzy spells and hunger, associated with blood glucose levels of <4 mmol/l, indicative of recurrent hypoglycaemia. His total daily

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Abbreviations:

T1D	type 1 diabetes
anti-GAD	anti-glutamic acid decarboxylase
MMT	mixed meal tolerance test
CGM	continuous glucose monitoring
KPD	ketosis-prone diabetes
T2D	type 2 diabetes
DKA	diabetic ketoacidosis
LADA	latent autoimmune diabetes of adulthood

insulin dose was 17 units and HbA1c level was 27mmol/mol (4.5%). Anti-glutamic acid decarboxylase (anti-GAD) and anti-IA-2 antibodies taken on admission were both negative. The decision was made to stop insulin therapy and he was advised to continue monitoring his blood glucose and ketone levels and to report any significant rise immediately to the diabetes team. The patient remained stable over the ensuing three-month period and reported that blood glucose readings nearly all remained <7 mmol/l before meals and <10 mmol/l two hours after meals. Six months after his original admission, and five months after stopping insulin therapy, a mixed meal tolerance test (MMT) was performed and a period of continuous glucose monitoring (CGM) arranged. The MMT stimulated C-peptide is a measure of β cell function that is better tolerated than a glucagon stimulation test and thought to be more reproducible.[1]

As can be seen in Figure 1, CGM demonstrated that overall glucose levels were well maintained. His MMT showed fasting and 90-minute C-peptides of 0.25 and 1.04 pmol/ml, respectively. His HbA1c at this time was 48 mmol/mol. A diagnosis of ketosis-prone diabetes (KPD) autoantibody negative but with adequate β-cell functional reserve (KPD A-β+) was made. He is currently managed according to standard guidelines for the treatment of type 2 diabetes (T2D) (dietary and exercise recommendations) and will undergo annual screening for micro- and macrovascular complications of diabetes. In addition, home glucose and ketone monitoring has been recommended, particularly during inter-current illness.

Discussion

This 31-year old male patient of Caribbean origin presented to hospital for the first time with a hyperglycaemic, mildly ketotic episode. He was initially diagnosed with T1D, but responded very rapidly to insulin therapy and dietary modification, such that he began experiencing periods of recurrent hypoglycaemia and within one month of admission all exogenous insulin therapy was stopped. Subsequent testing revealed he was IA-2 and GAD antibody negative and six months following his admission he was shown to have adequate β-cell reserve with a stimulated C-peptide >0.5 pmol/ml. A diagnosis of KPD A-β+ was made.[2]

KPD is a heterogeneous syndrome characterised by patients presenting with DKA or unprovoked ketosis, but who do not have the typical phenotypic features of T1D. This condition was first reported in the 1960s in African and Caribbean patients, who were noted to have presented with ketosis but after initially requiring insulin therapy later became insulin independent.[3] Initially, this condition was thought to be confined to individuals of African ancestry and the term 'Flatbush' diabetes frequently applied; however, case series now describe KPD in patients from a wide variety of geographic and ethnic backgrounds.[3] The actual term 'ketosis-prone diabetes' was first used by Sobngwi in 2004 in a review of diabetes in West Africans.[4]

There have been a number of attempts to classify individuals who present with KPD. Current WHO and

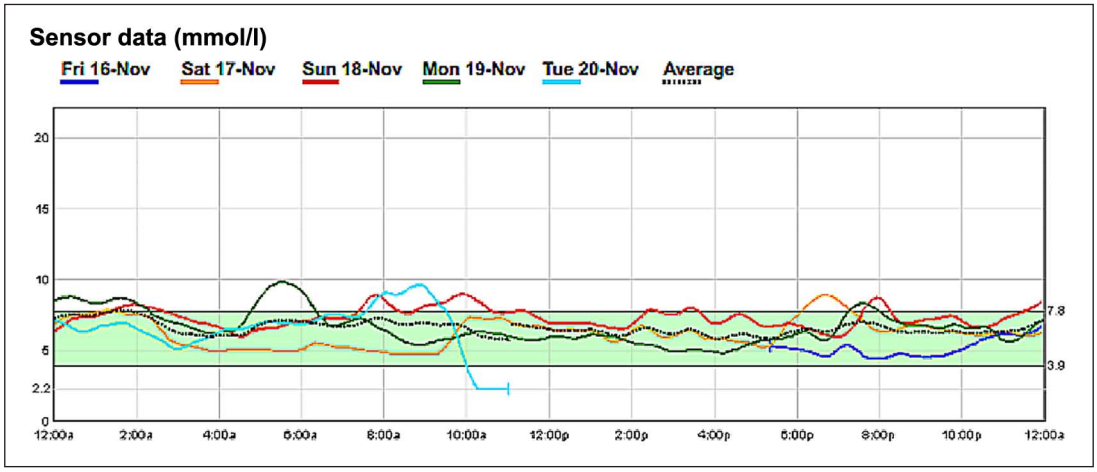

Figure 1. Data from continuous glucose monitoring. Graph showing daily overview of blood glucose for patient. X axis is the hour of the day. Y axis is blood glucose levels in mmol/l.

ADA guidelines both consider KPD as a form of T1D (type 1 idiopathic and type 1b diabetes respectively).[5,6] More recently, investigators from Baylor College of Medicine and the University of Washington have developed a classification system that includes four KPD subtypes based on the presence or absence of autoantibodies (A+/A−) and the presence or absence of β-cell (β +/β−) functional reserve (the Aβ system).[7] The Aβ system most accurately predicts β-cell function 12 months following the index DKA/ketosis. The most common subgroup (approx. 50%) of these KPD patients are those without autoimmunity and preserved β-cell function (A−β+), who, similar to our index case, present with DKA/ketosis, yet show the clinical and biochemical characteristics of T2D. These patients are often obese, middle-aged and with a family history of T2D, and β-cell function usually recovers within two weeks of the initial presentation with DKA, with a continued improvement over the next 6–12 months.[2] This has led to the description of such individuals as having ketosis-prone type 2 diabetes; however, it has been argued that the broader definition of KPD is more useful in that it allows for further investigation into the aetiology and natural history of this condition.[3] Current evidence indicates that for individuals with KPD A−β+, the probability for a further episode of DKA/ketosis is 90% within 10 years, and approximately 50% will become definitively insulin dependent.[4]

The pathophysiology of KPD syndromes remains incompletely understood. A+β− KPD is essentially classical early onset T1D, while A+β+ KPD clearly overlaps with latent autoimmune diabetes of adulthood (LADA), with the exception that individuals with LADA do not usually require insulin at diagnosis whereas the majority (90%) of KPD A+β+ do. In individuals with KPD A−β+, transient β-cell dysfunction may result from significant glucotoxicity.[8] Acute exposure to high glucose levels for 20 h resulted in severe blunting of C-peptide responses to glucose stimulation, as well as impaired insulin-signalling in skeletal muscle in obese African-American males with KPD A+β−, but not in those who were lean (those with and without diabetes).[8] This finding suggested that in some insulin-resistant individuals, glucotoxic blunting of intracellular pathways involved in insulin secretion may contribute to a marked, but reversible, β-cell dysfunction.[8] Others have suggested that G6PD deficiency may increase the susceptibility of the pancreatic β-cells to oxidative stress[9] or that polymorphisms in PAX4, a transcription factor essential for β-cell development,[10] may contribute to β-cell dysfunction.

The initial management of KPD is as per standard inpatient guidelines on the management of an acute hyperglycaemic crisis with intravenous fluids and continuous insulin therapy. In addition all patients should be discharged on the appropriate insulin replacement regimen until the results of autoantibody and further testing are known. Assessment of β-cell reserve is usually performed after full resolution of the presenting DKA (approx. 3–12 weeks) and is most usually assessed with either a glucagon stimulation test or MMT (see Table 1).

Subsequently, A+ or A− individuals with impaired β-cell function (β−) should be managed with insulin replacement therapy as evidence from longitudinal studies indicates recovery of β-cell function is unlikely.[3] For individuals who are A−β+ insulin doses can be gradually reduced providing that frequent blood glucose monitoring shows that glucose targets are being achieved. Many individuals, as in our case, may then no longer require insulin replacement therapy. However, most individuals with KPD

Table 1. Protocols that can be used for conducting a mixed meal tolerance test.

Mixed meal tolerance test	
Protocol	
Stimulus:	
250ml Fortisip liquid drink (18.4g CHO per 100ml) over a period of 2–5 min. A blood sample will be taken immediately prior to the drink (time 0). Samples will then be taken every 30 min post the Fortisip liquid drink up to 150 min.	
Measurements:	
C-peptide every 30 min for 150 min	
Or C-peptide at 90 min[10]	
Adequate β-cell function	Fasting C-peptide >0.1 nmol/l *Or* AUC >23 nmol/l for 150 min (five stim. blood samples) *Or* C-peptide at 90min >0.2 nmol/l (one stim. blood sample)
Glucagon stimulation test	
Protocol	
Stimulus: intravenous glucagon 1mg	
Measurements: glucose, insulin and C-peptide at 5, 10 and 15 min	
Adequate β-cell function	150–300% rise in C-peptide from basal levels

A−β+ will eventually develop T2D[4] and are at increased risk for recurrent DKA/ketosis. Progressive hyperglycaemia precedes and is a strong risk factor for ketotic relapses (hazard ratio 38).[4] Individuals should therefore be managed according to standard guidelines for T2D and screened annually for micro- and macrovascular complications. In addition, patients should ordinarily continue with blood glucose monitoring and be provided with a blood ketone testing meter to assess for ketones when required.

Conclusion

Diabetic ketoacidosis is no longer pathognomic of T1D. In patients presenting with DKA or unprovoked ketosis, especially if obese, middle-aged, male and with a strong family history of T2D, ketosis-prone diabetes should be considered. Testing for autoantibodies and stimulated C-peptide following resolution of DKA may help in deciding on the most appropriate management strategies. Long term follow-up is essential as many will develop T2D and 90% will relapse within 10 years after their initial ketotic episode and therefore patients should be recommended for regular review and advised on the use of blood and ketone monitoring.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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