

Ketosis-prone diabetes: Identification and management

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Article points

1. There are many people who present atypically with a mixed clinical picture of diabetes, demonstrating metabolic features of both type 1 and type 2 diabetes.
2. A significant number will present with ketosis or diabetic ketoacidosis, alongside impaired insulin secretion and action, and an absence of autoimmune markers, with no islet cell or glutamic acid decarboxylase autoantibodies. This is defined as ketosis-prone diabetes (KPD).
3. In the longer term, KPD is characterised by a period of remission followed by relapse. The lynchpin for predicting an individual's clinical course and aiding the decision to stop insulin therapy is an assessment of islet cell autoantibodies and beta-cell function.

Key words

- Ketosis-prone diabetes
- Islet cell autoantibodies

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Ketosis-prone diabetes (KPD) is becoming a more widely recognised form of diabetes, occurring predominantly in the non-white population. Cases present acutely with a mixed clinical picture that has features of both type 1 and type 2 diabetes. The clinical characteristics of ketosis or diabetic ketoacidosis suggest insulinopaenia at presentation, requiring intensive insulin replacement. With intensive exogenous insulin treatment, however, these people can become insulin-independent within a matter of months. This article discusses KPD and its diagnosis, aetiology, clinical course and treatment.

Type 1 diabetes is defined by the World Health Organization (2002) as “autoimmune destruction of islet beta-cells,” resulting in an absolute insulin deficiency requiring life-long treatment with exogenous insulin. Type 2 diabetes is characterised by insulin resistance combined with beta-cell dysfunction, with an absence of autoimmune markers (Williams and Pickup, 2004). Type 1 diabetes can be subdivided into type 1A, in which there is a presence of autoantibodies, and type 1B, also known as “idiopathic diabetes” (American Diabetes Association, 2010). Type 1B diabetes encompasses a group in which the underlying aetiology is not known but individuals are said to be prone to developing diabetic ketoacidosis (DKA). It has been acknowledged for some time that there is a subset of people who present atypically with a mixed clinical picture, demonstrating metabolic features of both type 1 and type 2 diabetes (Umpierrez et al, 2006).

Another autoimmune disorder that presents with mixed clinical features is latent autoimmune diabetes of adults (LADA). People with LADA, however, are autoantibody-positive but have slower deterioration of beta-cell function, which leads to a delay in the requirement of insulin (Dunning, 2009; Levy, 2011). This period of insulin independence is reported to last a minimum of 6 months. In recent years, the

“typical” clinical features of diabetes displayed at diagnosis have become somewhat indistinct.

Ketosis-prone diabetes

At diagnosis, a significant number of people will present with ketosis or DKA and, clinically, impaired insulin secretion and action. There can be a notable absence of autoimmune markers, with no islet cell antibodies or glutamic acid decarboxylase (GAD) autoantibodies (Balasubramanyam et al, 2006; Imran and Ur, 2008). These individuals require insulin replacement; however, over the long term, many will be able to discontinue insulin treatment. The literature describes this unusual type of diabetes as ketosis-prone diabetes (KPD). DKA predominantly occurs in people with type 1 diabetes, although more recently it has been observed in those with type 2 diabetes (Newton and Raskin, 2004). In people with type 2 diabetes, DKA usually develops when there is an intercurrent illness. In people with KPD, the incidence of DKA at diagnosis has been reported to be as high as 75% of cases (Umpierrez et al, 2006; Smiley et al, 2011). KPD cases tend to present with a similar biochemical and acid–base picture that would be expected in type 1 diabetes.

KPD appears to be an underdiagnosed condition, principally because of its heterogeneity at diagnosis

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1. Ketosis-prone diabetes (KPD) can be defined as new-onset diabetes associated with ketosis or diabetic ketoacidosis, in the absence of islet cell or GAD65 autoantibodies.
2. KPD predominantly occurs in people of African-Caribbean origin, although it has also been reported in Hispanic people in the US.
3. Male gender, age 30–50 years, excess weight and a family history of diabetes are also associated with the condition.

and a lack of clinical experience. Another complicating factor is the diversity in the names used to describe the condition, including atypical diabetes and type 1.5 diabetes; in addition, the eponym “Flatbush diabetes” is used, based on a large number of African-American adults from the Flatbush area of New York who have presented with KPD (Sobngwi et al, 2002).

Ethnicity

KPD is observed predominantly in people of African-Caribbean ethnicity, although it has also been reported in Hispanic people in the US (Mauvais-Jarvis, 2004). Umpierrez et al (2006) suggest a prevalence of KPD of 20–50% among newly diagnosed black and Hispanic individuals who present with DKA. Mauvais-Jarvis et al (2004) conducted one of the largest and longest studies in KPD to date, with a 10-year follow-up. They followed the progress of 233 people from sub-Saharan Africa or the Caribbean who were admitted to a French hospital with uncontrolled diabetes between 1990 and 2000. They observed that among the 111 participants with KPD, there was a higher proportion of people from sub-Saharan Africa (83.8%) than from the African-Caribbean population (16.2%).

Gender

A male predominance has been reported in all of the available literature. A two- to three-fold higher prevalence in men was reported by Mauvais-Jarvis et al (2004), Umpierrez et al (2006) and Smiley et al (2011).

Age

Smiley et al (2011) reviewed 14 studies, reporting that, at presentation, people with KPD are usually aged 30–50 years. This supported earlier work by Kitabchi (2003), who reported similar findings from a review of nine studies, with the majority of people presenting with KPD in their forties.

Weight

It is reported that people presenting with KPD are generally overweight or obese (BMI of 28–37 kg/m²), with obesity present in a least 29% of cases (Umpierrez et al, 2006; Smiley et al, 2011).

Family history of diabetes

People presenting with KPD often report a family

history of diabetes. Umpierrez et al (2006) and Smiley et al (2011) suggest that there could be a family history of diabetes (usually type 2 diabetes) in as many as 80% of cases. In a cohort studied in Houston in the US, Maldonado et al (2003) found a family history of type 2 diabetes in 86% of the 103 individuals studied. In a French study by Mauvais-Jarvis et al (2004), 67.6% of the participants with KPD had a family history of diabetes.

Onset of symptoms

In the literature, most cases have a short history of symptoms (polyuria and polydipsia). This is usually less than 4 weeks (Mauvais-Jarvis et al, 2004). Weight loss is reported to be between 4 kg and 12 kg.

Diagnosing KPD

Mauvais-Jarvis et al (2004) define KPD as:

“new-onset diabetes without precipitating illness (infection, stress), with the presence of strong ketosis (urinary ketones >80 mg/dL) or DKA, and in the absence of to islet cell autoantibodies and GAD65 autoantibodies.”

Increasing recognition of people who fit the clinical picture of KPD has resulted in a rising prevalence of KPD globally in recent years, and interest in this emerging syndrome has led to the development of classification schemes.

The A β system

KPD can be classified into four clinical subgroups according to the presence or absence of autoantibodies and the presence or absence of residual beta-cell function (the A β system). Banerji and Dham (2007) report that the A β system is the most accurate of a number of posited classification schemes. The A β system was developed at the Baylor College of Medicine (Houston, US) and the University of Washington (Seattle, US) by Maldonado et al (2003). Balasubramanyam et al (2006) assessed the system in a group of 294 people over a minimum follow-up of 12 months. The participants had their islet cell autoantibody levels and beta-cell function measured in the days immediately following presentation with DKA and were tested regularly throughout the duration of the study. Using the A β system, the authors were able to predict those participants who

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1. KPD can be divided into four subgroups according to autoantibody presence and beta-cell function using the A β classification system.
2. The majority of people with KPD have type 2B (A $^{-}\beta^{+}$) KPD, characterised by a lack of islet cell autoantibodies and preserved beta-cell function.
3. Correct identification of the subtype of KPD is vital in order to optimise treatment.
4. The underlying mechanism of KPD is largely unknown; however, one suggested theory is that it may be caused by transient glucose toxicity, in which the pancreatic beta-cells develop a temporary failure in insulin synthesis.

achieved better glycaemic control. Preserved beta-cell function predicted those who were able to discontinue insulin independently of the presence or absence of antibodies. The system had 99.4% sensitivity and 95.9% specificity.

A β system subgroups.

The A β system classifies people with KPD into four subgroups according to autoantibody presence and beta-cell function (*Table 1*). In turn, Smiley et al (2011) further define these groups as type 1A (A $^{+}\beta^{-}$), 1B (A $^{-}\beta^{-}$), 2A (A $^{+}\beta^{+}$) and 2B (A $^{-}\beta^{+}$).

People with type 1A (A $^{+}\beta^{-}$) KPD have permanent beta-cell failure and positive islet cell autoantibodies; they therefore require life-long treatment with exogenous insulin. Those with type 1A and type 1B (A $^{-}\beta^{-}$) KPD will display some clinical characteristics that are similar to those with type 1 diabetes, namely low or absent beta-cell function. People with type 1B KPD have no islet cell autoantibodies; however, they have permanent beta-cell failure and, therefore, also require life-long exogenous insulin.

People with type 2A (A $^{+}\beta^{+}$) KPD have islet cell autoantibodies at diagnosis but have some preserved beta-cell function. Within this group, some will regain beta-cell function, enabling them to discontinue insulin, whereas others will experience progressive beta-cell failure and will require insulin in the longer term. People with type 2B (A $^{-}\beta^{+}$) KPD share some characteristics with those with type 2 diabetes. They have no islet cell autoantibodies and have preserved beta-cell function; this group has the potential to enter remission phases and, therefore, stop insulin therapy (Smiley et al, 2011). Balasubramanyam and Nalini (2013) suggest that, in

the USA, type 2B (A $^{-}\beta^{+}$) KPD is the most common form of the condition, accounting for approximately 50% of cases.

Aetiology of KPD

Much work has been undertaken in the last decade to establish a cause of KPD and identify the characteristics present in people who develop it. The exact aetiology of KPD remains unknown, but genetic, viral and metabolic causes have been proposed. Some researchers suggest that the condition is related to oxidative stress in the pancreatic beta-cells (Balasubramanyam and Nalini, 2013).

KPD is thought to be a condition of hyperglycaemia-induced transient beta-cell dysfunction (Gosmanov et al, 2010). Choukem et al (2013) suggest that the underlying mechanism may be more due to “a functional disorder of beta-cells rather than to cell destruction.” What is known is that people experience transient beta-cell failure combined with insulin resistance during the acute phase of presentation; these defects in insulin synthesis are thought to be related to glucose toxicity (Imran and Ur, 2008).

Glucose toxicity

Glucose toxicity is defined by Smiley et al (2011) as:

“a metabolic phenomenon that happens when there is desensitisation of beta-cells and impaired insulin secretion in response to sustained elevations of plasma glucose.”

It is known that chronically elevated blood glucose levels in people with type 2 diabetes damage the pancreatic beta-cells and contribute significantly to the progressive decline in their ability to secrete insulin (Brunner et al, 2009).

Hyperglycaemia is also known to have adverse toxic effects on many of the body’s tissues and organs; this is the mechanism that leads to the development of secondary complications, including retinopathy, nephropathy and peripheral vascular disease, in people with diabetes. It does this via numerous complex biochemical pathways that result in high levels of reactive oxygen species (ROS). The pancreatic beta-cells are incredibly sensitive to the effects of ROS, as they have low levels of protective antioxidant enzymes; therefore, high levels of ROS

Table 1. The A β classification system for people with ketosis-prone diabetes (Maldonado et al, 2003; Smiley et al, 2011).

Subgroup	Features
Type 1A (A $^{+}\beta^{-}$)	Positive autoantibodies but no evidence of beta-cell function
Type 1B (A $^{-}\beta^{-}$)	No antibodies and no evidence of beta-cell function
Type 2A (A $^{+}\beta^{+}$)	Positive autoantibodies and evidence of beta-cell function
Type 2B (A $^{-}\beta^{+}$)	No autoantibodies and evidence of beta-cell function; the most common subgroup

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1. KPD typically improves in the months following diagnosis, allowing discontinuation of insulin. Over the longer term (usually within 2 years of diagnosis), the condition may relapse, as beta-cell function gradually deteriorates.
2. The A β classification system can be used to predict patients' clinical course and, in particular, their likelihood of becoming insulin-independent in the long term.

lead to oxidative stress. The development of oxidative stress-induced beta-cell dysfunction is not completely clear, but it is known that chronic oxidative stress leads to defective gene expression, insulin secretion and increased beta-cell death. This deterioration of beta-cell function as a direct result of exposure to elevated blood glucose concentrations is described as glucose toxicity (Robertson, 2004; Poutout and Robertson, 2008; Lee et al, 2011).

Pointers to a diagnosis

Along with an understanding of the clinical pathway, correct identification of people with a potential diagnosis of KPD is vital in order to optimise treatment. For example, performing pathology tests for the presence or absence of islet cell or GAD autoantibodies, along with assessing beta-cell functional reserve, will enable us to determine whether people can be treated with insulin for a short period of time or if they are more likely to need life-long insulin replacement.

In individuals presenting with the "typical" characteristics of KPD (ketosis or DKA without precipitating cause, African-Caribbean ethnicity, male, age 30–50 years), performing the necessary investigations following resolution of metabolic decompensation will aid in identifying those with type 2B (A β ⁺) KPD. As a result, people will have a more predictable, structured management plan in place, clinicians will have more confidence in the management of these individuals and patient satisfaction will have the potential to improve dramatically.

Clinical course of KPD

In the months following diagnosis, there is typically a recovery in beta-cell function that enables people with KPD to discontinue insulin therapy, and over the long term, KPD is characterised by a period of remission followed by relapse (Umpierrez et al, 2006; Imran and Ur, 2008; Sze et al, 2006). Umpierrez et al (2006) suggest that approximately 50% of adults presenting with KPD will be able to discontinue insulin treatment and that initial aggressive management with insulin appears to contribute to improvements in insulin secretion. Mauvais-Jarvis et al (2004) report relapse rates of 90%, with around half of their cohort with KPD

requiring insulin treatment over the longer term. They suggest that people with KPD experience a longer-term deterioration in beta-cell function similar to that seen in people with type 2 diabetes.

Discontinuing insulin

It has become apparent from the A β system classification scheme of KPD that investigations to assess the presence or absence of autoantibodies and residual beta-cell function can be used to predict the likely clinical course of people with the condition and, in particular, their likelihood of becoming insulin-independent.

Remission and relapse

Remission and relapse is largely determined by residual beta-cell function. If a relapse does occur, it appears that it takes place within 2 years of the initial presentation. Many people with KPD will experience irreversible damage to the beta-cells and, therefore, follow a similar path to individuals with type 1 diabetes (Smiley et al, 2011). This would include people with type 1A (A β ⁻) and type 1B (A β ⁻) KPD.

In the French study by Mauvais-Jarvis et al (2004), 10-year follow-up data showed that 76% of 111 people with KPD entered a remission phase and that the mean time to achieve this was 14.3 weeks. The likelihood of relapse in this group was around 90%, with approximately 45% of the original KPD cohort becoming insulin-dependent in the longer term. A total of 34 participants (40% of those who achieved remission) remained insulin-independent at the close of the study. McFarlane et al (2001) studied a much smaller group of 26 individuals; in this cohort, there was a remission rate of 42%, with a mean time to remission of 11.8 weeks (83 days); one patient relapsed after 42 weeks (294 days).

Balasubramanyam and Nalini (2013) suggest that in people who are able to discontinue their insulin but go on to develop a second episode of ketosis or DKA, insulin should not be withdrawn a second time, as this would point to inadequate beta-cell reserve.

Treatment options

This article does not permit in-depth exploration of ongoing treatments. However, there are two crucial studies in which oral hypoglycaemic agents were used in people with KPD post-insulin treatment and may have helped to delay or prevent relapse. Banerji

“With the opportunity to discontinue insulin therapy and with the introduction of oral hypoglycaemic agents, confidence in managing this group of patients is growing.”

et al (1995) carried out a double-blind randomised controlled trial to compare daily low-dose glipizide (2.5 mg) with placebo. A total of 30 people were recruited; of these, 10 elected not to participate in either study arm and were, therefore, monitored as a “no treatment group.” The other 20 participants were assigned in equal numbers to the glipizide or placebo groups and were followed for 3 years. The glipizide group had a significantly lower recurrence rate of hyperglycaemia ($P < 0.05$).

Umpierrez et al (1997) carried out an intention-to-treat trial in 35 people who presented with either DKA ($n=17$) or severe hyperglycaemia ($n=18$). Seven people from each group were assigned to take a daily dose of glyburide (1.25–2.5 mg) in conjunction with a controlled diet, while the remainder were treated with diet alone. The participants were followed for a median of 16 months. As in the previous study, there was a significant reduction in recurrence of hyperglycaemia ($P=0.03$). Among participants treated with diet only, hyperglycaemia recurred in six of 10 people in the DKA group and five of 11 in the severe hyperglycaemia group; conversely, there was one recurrence in seven people in each of the treatment groups. From these studies, it appears that sulphonylureas have a role to play in the ongoing management of KPD following remission.

Conclusion

The prevalence of KPD is rising. Insulinopaenia at presentation requires intensive insulin treatment at diagnosis; however, these individuals present a challenge to healthcare professionals with regard to how their diabetes should be managed over the longer term. With the opportunity to discontinue insulin therapy and with the introduction of oral hypoglycaemic agents, confidence in managing this group of people is growing. The lynchpin for predicting the clinical course of KPD and aiding in the decision to stop insulin is assessment of islet cell autoantibodies and beta-cell function, and the use of the A β system of classification seems to accurately provide clinicians with the biochemical support that, in turn, will make us more confident in managing these individuals. ■

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