

Diabetes 1.5: Ketone-Prone Diabetes

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Ketone-prone diabetes (KPD) is considered one of the atypical diabetes syndromes because its presentation can lead to misdiagnosis of the type of diabetes. Patients with KPD present in diabetic ketoacidosis (DKA), but once the DKA resolves, some patients can discontinue insulin and maintain adequate glycemic control with oral agents (1). Here, we present the case of a patient who was diagnosed with type 1 diabetes because of recurrent DKA. KPD was suspected because of his high insulin requirements and signs of insulin resistance. He was transitioned from insulin to a glucagon-like peptide-1 (GLP-1) receptor agonist and attained ideal glycemic control.

Presentation

D.H., a 23-year-old man, was diagnosed with type 1 diabetes in October 2013, when he presented to the hospital in DKA. He required 125 units of insulin glargine daily and 41 units of insulin lispro three times daily with meals to achieve glycemic control. In the subsequent months, he had recurrent episodes of DKA while taking the prescribed amounts of insulin.

His physical examination was remarkable for a BMI of 39.1 kg/m² and the presence of acanthosis nigricans on the neck (Figure 1) and in the axilla bilaterally. Laboratory studies revealed a glucose level of 336 mg/dL, bicarbonate of 8.4 mmol/L, ketones in urine, and an anion gap of 24. A1C was 9.1%. He was afebrile without leukocytosis, and there was no physical evidence of infection.



FIGURE 1. Acanthosis nigricans present on patient's neck.

At a follow-up visit, his blood glucose was in the range of 180–350 mg/dL on 60 units of glargine daily and 18 units of lispro with meals. Tests for islet cell and glutamic acid decarboxylase (GAD) antibodies were negative, and his C-peptide level was normal. He was started on the GLP-1 receptor agonist liraglutide, 1.8 mg/day, and instructed to discontinue lispro but continue glargine.

At a close follow-up visit, D.H. reported no hyper- or hypoglycemia while on liraglutide and adequate glycemic control. He was instructed to discontinue glargine and only use liraglutide. At the next visit, he had lost 13 lb since starting liraglutide and again reported adequate glycemic control. His A1C was 5.2%, down from 9.1% 3 months earlier. He was kept on the same dose of liraglutide with stable glycemic control.

Questions

1. What is KPD?
2. What are the different classification schemes for KPD?
3. How does treatment and management differ for patients with

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KPD compared to those with type 1 or type 2 diabetes?

Commentary

Three different subgroup classification schemes have emerged in attempts to help clinicians determine which patients might be able to discontinue insulin and which will continue to be insulin dependent. The three schemes are a modified American Diabetes Association (ADA) system, a BMI-based system, and a scheme called the AB system.

The modified ADA system (2) defines KPD as either type 1a, KPD insulin-dependent (ID), or KPD insulin-independent (IID). Type 1a and KPD ID are characterized by poor β -cell function and clinically resemble type 1 diabetes, whereas KPD IID features preserved β -cell function and clinically resembles type 2 diabetes.

The BMI system (3) defines a BMI of 28 kg/m² as the cutoff to separate KPD patients in two categories. If BMI is <28 kg/m², the patient is considered lean and resembles type 1 diabetes with poor β -cell function; if BMI is \geq 28 kg/m², the patient is considered obese with resemblance to type 2 diabetes and preserved β -cell function.

The AB classification system (4) separates KPD patients into four categories based on the presence or absence of autoantibodies and β -cell function, as follows:

- A+B-: autoantibodies present and β -cell function absent
- A+B+: autoantibodies present and β -cell function present
- A-B-: autoantibodies absent and β -cell function absent
- A-B+: autoantibodies absent and β -cell function present

People classified as A+B- or A-B- have decreased β -cell function and clinically resemble type 1 diabetes, as opposed to those classified as A-B+ or A+B+, who have preserved β -cell function and clinically resemble

type 2 diabetes. The patient in this case had negative autoantibodies and preserved β -cell secretory reserve evident with a normal C-peptide level. Hence, according to the AB system, our patient was A-B+.

Treatment for KPD consists of standard treatment with aggressive intravenous fluids and continuous insulin therapy until resolution of DKA. Because the type of diabetes is unclear at presentation, these patients should be continued on insulin therapy when discharged from the hospital, as was the case for this patient (1).

Classification of KPD should be performed at the first outpatient visit 1–3 weeks after discharge from the hospital. Classification of KPD is determined by testing for GAD and anti-islet cell autoantibodies and fasting C-peptide level. A C-peptide >1 ng/mL is consistent with preserved β -cell function.

For patients who are B+, insulin can be discontinued via slow downward titration, and an oral agent can be started if blood glucose values remain at goal (5). The insulin withdrawal process should be performed over a period of weeks or longer (5). Medications such as metformin, an insulin-sensitizing agent, are recommended in patients with A-B+ KPD because most of these patients have metabolic syndrome. Liraglutide is a GLP-1 receptor agonist that increases endogenous insulin production, delays gastric emptying, and suppresses prandial glucagon secretion. It is preferred over other agents because it carries a low risk of hypoglycemia, has the potential to regenerate β -cells, reduces appetite, and lowers triglyceride levels (6).

In patients with KPD, the decompensation of β -cell function is thought to have a metabolic, genetic, or viral etiology in patients with A-B+ KPD. Because of his preserved β -cell function, the patient in this case was able to discontinue insulin and main-

tain adequate glycemic control with liraglutide alone.

Clinical Pearls

- KPD is an atypical diabetes syndrome; its clinical presentation can lead to misdiagnosis of the type of diabetes a patient has.
- Patients with KPD present in DKA, but once the DKA resolves, some are able to discontinue insulin and maintain adequate glycemic control with oral agents.
- Classification of KPD should be performed at the first outpatient visit 1–3 weeks after hospital discharge, and clinicians should use the classification to determine the appropriate treatment plan for patients found to have KPD.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. *Ann Intern Med* 2006;144:1335–1343
2. Umpierrez G. Ketosis-prone type 2 diabetes: time to revise the classification of diabetes. *Diabetes Care* 2006;29:2755–2757
3. Umpierrez GE, Woo W, Hagopian WA, et al. Immunogenetic analysis suggests different pathogenesis for obese and lean African Americans with diabetic ketoacidosis. *Diabetes Care* 1992;22:39–43
4. Maldonado M, Hampe CS, Gaur LK, et al. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis and clinical outcomes. *J Clin Endocrinol Metab* 2003;88:5090–5098
5. Maldonado MR, Otiniano ME, Cheema F, Rodriguez L, Balasubramanyam A. Factors associated with insulin discontinuation in subjects with ketosis-prone diabetes but preserved beta-cell function. *Diabet Med* 2005;22:1744–1750
6. Dungan K, DeSantis A. Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus. UpToDate. Available from http://www.uptodate.com/contents/glucagon-like-peptide-1-receptor-agonists-for-the-treatment-of-type-2-diabetes-mellitus?source=search_result&search=Liraglutide&selectedTitle=4~21#H. Accessed 2 February 2015