An Important Form of Diabetes for Clinicians: Ketosis-Prone Diabetes

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Keywords

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Abstract

Ketosis-prone diabetes (KPD) is defined as a hybrid form of diabetes mellitus, which is predominantly seen in overweight-to-obese men. Although the diagnosis is based on diabetic ketoacidosis (DKA) as a presenting feature, which also is characteristic of type 1 diabetes, the course of the disease differs from type 1. Recognition of this form by the clinicians is important as these patients are negative for autoantibodies and share the characteristics of type 2 diabetes during follow-up. Here we report 2 cases of KPD presenting with DKA and maintaining normoglycemia without insulin after receiving short-term intensive insulin treatment.

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Introduction

Ketosis-prone diabetes (KPD) has been recognized as a clinical entity for the past 30 years. The condition is defined as a syndrome in which diabetes commences with ketoacidosis in individuals who are anti-glutamic acid decarboxylase (anti-GAD) and anti-islet cell (anti-IC) antibody negative and have no known precipitating causes.

Here, we report 2 cases of KPD, presenting with *severe* diabetic ketoacidosis (DKA), one of which was first misdiagnosed as type 1 diabetes. Both were able to be controlled with lifestyle modifications and/or the use of oral antidiabetics after <6 months of treatment with insulin. We aimed to present 2 cases of KPD, a rare form of diabetes.

Case Presentation

Case 1

A 31-year-old male attended an internal medicine outpatient clinic in March 2018 because he had been experiencing malaise and polyuria over the past 2 months. He had no polydipsia or polyphagia and did not complain of nausea, vomiting, or abdominal pain. A comprehensive review did not reveal any other symptoms. He had no history of chronic disease and no family history of diabetes. On examination, the patient was obese, with a BMI of 30 kg/m²; however, his vitals were within normal range. Though a systemic examination was normal, a random blood sugar measurement from a fingerprick was 445 mg/dL. Although patient did not have severe symptoms, acidosis regarding his quite high blood glucose was to be excluded. Thus, an arterial blood gas (ABG) was requested on the same day which showed metabolic acidosis with a pH of 7.26 and bicarbonate (HCO₃) levels were 16.6 mmol/L. On biochemical analysis, random blood sugar was 381 mg/dL, urine analysis showed 2 + ketonuria, and HbA_{1c} was 16%. Fasting c-peptide levels were 3.22 ng/mL, which was again within normal limits. Liver enzymes and renal function studies with electrolytes were all normal, apart from triglyceride and low-density lipoprotein, which were 250 and 188 mg/dL, respectively.

Table 1. HbA1c, c-peptide levels, and autoantibody status of each case; results before and after the slash (/) are for case 1 and 2, respectively

	HbA1c, %	C-peptide, ng/mL (0.78–5.19)	Anti-GAD antibody, IU/mL (<17)	Anti-IC antibody (negative)	Anti-insulin antibody, IU/mL (<0.4)
At time of diagnosis	16/12.3	3.22/na	5/na	Negative/na	<0.4/na
Month 3	7.6/na				
Month 6	6.6/5.7	–/2.03	–/6	–/Negative	–/ <0.4
Month 9	7.5/5.8				
Month 23	6.2/na				

Anti-GAD, anti-glutamic acid decarboxylase; anti-IC, anti-islet cell.

The patient rejected admission to the hospital despite being given detailed counselling; however, he agreed to receive basal-bolus insulin at home followed by glucose 6 times per day. He was prescribed 24 units of insulin glargine, along with 8 units of insulin aspart, for each meal. He returned to the clinic 3 days later and reported no symptoms. His FBS averaged 150 mg/dL, with postprandial glucose (PPG) levels ranging between 175 and 220 mg/dL. Repeat testing for urine showed 2 + ketonuria with relative improvement in ABG, with a pH of 7.35 and HCO₃ at 19 mmol/L. Insulin doses were adjusted according to an FBS target level of <125 mg/dL and PPG target levels not exceeding 150 mg/dL. The patient was asked to follow up with the clinic after a further 5 days. Eight days after the diagnosis, FBS was <120 mg/dL and PPG ranged between 135 and 155 mg/dL. The last ABG reading showed totally normalized pH and HCO₃ levels. Ketonuria had also resolved. Test results for anti-GAD, anti-IC, and anti-insulin antibodies were all negative.

The patient was asked to follow up after 2 weeks but did not attend his appointment. However, he returned to the clinic 3 months later during which time he had adjusted his insulin doses so that he was taking only 12 units of insulin glargine and 4 units of insulin aspart prior to every meal. He had adopted a vigorous exercise program and a low carbohydrate diet and lost 6 kg in 12 weeks. At that visit, his HbA1c was 7.6% with no acidosis or ketonuria. Short-acting insulin was discontinued; basal insulin was prescribed at the same dose but with a metformin/sitagliptin combination at 1,000/50 mg twice daily. At his next appointment, HbA1c levels were 6.6 and the patient had lost a total of 10 kg. Over subsequent visits, the patient's HbA1c levels dropped to 6.2% and, after 1 year, the patient is only taking metformin at a dose of 750 mg twice daily, without insulin (Table 1).

Case 2

A 35-year-old male visited an outpatient clinic in August 2019 to follow up on a diabetes diagnosis that he had received 6 months earlier in abroad. He had no history of chronic disease and there was family history of diabetes. He was thought to have had type 1 diabetes since he had presented with long-standing nausea not explained by any gastrointestinal disorder and that he had, at the time of presentation, acidosis with a pH of 7.2 and HCO₃ levels of 15, 2 + ketonuria with glucose levels of 510 mg/dL, and his HbA1c was 12.3%. However, his BMI was 31.2 kg/m² (Fig. 1) and he had

not been following a healthy diet. He was not tested for either c-peptide or autoantibodies. After recovering from DKA, he was discharged and prescribed mixtard insulin at a dose of 15 units each morning and 10 units each evening, however, he experienced several hypoglycemic attacks on this medication and adjusted the insulin doses himself to a maximum of 10 units per day. During the following 6 months, he lost around 20 kg thanks to a diet and exercise regimen. At the time of his first visit to our clinic, his BMI was 23.9 kg/m² (Fig. 2).

To confirm a diagnosis, anti-GAD, anti-IC, and anti-insulin antibodies, as well as c-peptide levels and routine biochemistry, were tested. HbA1c was 5.7, c-peptide was within normal limits (2.03 ng/mL; range: 0.78–5.19 ng/mL), and all autoimmune antibodies were negative.

After a 1-week trial period during which time he discontinued insulin, the patient's FBS did not exceed 105 mg/dL; however, his PPG reached a maximum of 138 mg/dL. He was asked to continue only with his dietary regimen. Three months after his first visit to our clinic, HbA1c controlled without insulin was at 5.4%. Nine months after his first diagnosis, with diet and regular exercise only, his HbA1c was at 5.7% (Table 1).

Discussion/Conclusion

KPD is defined as a heterogeneous syndrome characterized by patients who present with DKA or unprovoked ketosis but who do not have the typical phenotype of autoimmune type 1 diabetes [1, 2]. These subjects are usually obese and have a low prevalence of autoimmune markers. At presentation, they usually have impairment in both insulin secretion and insulin action. Aggressive diabetes management leads to significant improvement in cell function and insulin sensitivity, sufficient to allow discontinuation of insulin therapy within a few months of treatment [3–5]. Upon discontinuation, the period of near-normoglycemic remission may last from a few months to several years [6, 7]. Patients newly diagnosed

1

2

Fig. 1. Case 2, before weight loss.

Fig. 2. Case 2, after weight loss.

with ketoacidosis, particularly those that are overweight or obese, are more likely to demonstrate clinical and immunologic features of type 2 rather than type 1 diabetes during follow-up appointments. For this reason, the name “type 1B diabetes” was recently updated by the World Health Organization (WHO) classification to “ketosis-prone type 2 diabetes,” a term which distinguishes it as a hybrid form of the disease. The same WHO diabetes classification report of 2019 suggests that the ketotic episodes in patients with KPD may recur in 90% of patients during the upcoming 10 years from the previous episode. This also has to be kept in mind by both the clinicians and the patients to be on a watchful waiting period [8].

Insulin secretion in KPD is impaired in several ways. The beta cells of patients with severe hyperglycemia with or without ketosis lose the ability for exogenous or endogenous glucose to stimulate beta-cell insulin secretion. The ability of glucose to stimulate insulin secretion begins to return after 2 weeks of normoglycemic treatment and maximizes by 8–12 weeks [9].

In terms of alpha- and beta-cell function, a case-control study that took place in France found that glucagon suppression after glucose infusion was impaired in patients with KPD; however, fasting plasma glucagon did not differ between normal subjects and KPD patients [10]. Umpierrez et al. [11] assessed the possibility that patients with KPD might have increased sensitivity to lipotoxicity, finding that there was no difference in beta-cell response in

patients with KPD as compared to obese patients who had presented with severe hyperglycemia or nondiabetic obese controls after 48-h lipid infusion. In another study with newly diagnosed obese diabetics, he also found out that c-peptide response to glucagon infusion after 1 week from the discontinuation of insulin was the same between both DKA and non-DKA diabetics and that sulfonylurea treatment significantly reduced recurrence of hyperglycemia in both obese DKA and obese hyperglycemic patients [12]. Last but not the least, all healthcare professionals should bear in mind that some oral antidiabetics, like SGLT-2 inhibitors, might pose a risk for KPD patients, regarding the fact that those medications, although more commonly prescribed in daily practice nowadays, are known to be associated with euglycemic acidosis and should be avoided if the case is a ketosis-prone diabetic [13].

In summary, the exact causes of the development of severe hyperglycemia in overweight or obese patients with KPD remain unknown. However, the inability of glucose to stimulate insulin secretion appears to be its central mechanism.

Conclusion

Accurate diagnosis of KPD in overweight-to-obese patients who present with DKA is of paramount importance since the symptoms these patients exhibit are more likely to

be similar to type 2 diabetes rather than type 1, thus requiring close monitoring during off-medication periods. Clinicians should also be aware that hybrid forms of diabetes are on the rise. With regards to patient follow-up, it is worth bearing in mind that insulin secretagogues such as sulfonylureas have been shown to prolong the remission period [12] and, if oral antidiabetics are needed, that SGLT-2 inhibitors should be avoided because of the risk of acidosis.

Statement of Ethics

Verbal and written consent was obtained for the article from both of our cases. One of our cases also accepted that we can use the photo for the article.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E.E.: designed the article and wrote the paper; T.C.: contributed to writing and discussion on the paper; and Y.K.: contributed to writing and discussion on the paper.

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