

Bodyweight threshold for sudden onset of ketosis might exist in ketosis-prone type 2 diabetes patients

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ABSTRACT

Ketosis-prone type 2 diabetes is recognized as atypical diabetes. These patients are often male, characterized by obesity, sudden onset of ketosis and a transient decrease in insulin secretion capacity that can be recovered with temporal insulin therapy. Here, we report a male patient with ketosis-prone type 2 diabetes who was followed up for 8 years. During the follow-up period, his bodyweight fluctuated and he experienced four episodes of critical ketosis recurrence in association with bodyweight gain. He discontinued insulin therapy after each ketosis episode within the first 4 years, but thereafter, he had to continue insulin therapy because of decreased insulin secretion capacity. Interestingly, his peak bodyweight just before the repeated ketosis episode gradually decreased, and the insulin secretion capacity after the recovery from repeated ketosis decreased in parallel with his peak bodyweight. This long-term clinical course might be a clue to understand the pathophysiology of ketosis-prone type 2 diabetes.

INTRODUCTION

Type 2 diabetes is considered a heterogeneous disease, and ketosis-prone type 2 diabetes is recognized as atypical diabetes. Reportedly, ketosis-prone type 2 diabetes was considered as a disease mainly observed in African Americans¹, but recently, ketosis-prone type 2 diabetes has also been observed in Asians². The classification system, combining the presence or absence of islet-associated autoantibodies (A+ or A-) and β -cell reserve ($\beta+$ or $\beta-$), for patients who develop diabetic ketosis has been proposed³. Our group is particularly interested in the autoantibody-negative and β -cell function preserved (A- $\beta+$) group of ketosis-prone type 2 diabetes patients. These patients are often male, and are characterized by the onset of disease at a relatively young age, obesity, sudden onset of ketosis and a transient decrease in insulin secretion capacity that can be recovered with temporal insulin therapy. Furthermore, insulin therapy can be discontinued within a few months of treatment in these patients. Despite multiple etiologies of ketosis-prone type 2 diabetes, very few data are available regarding the long-term clinical course of ketosis-prone type 2 diabetes. Here, we report a case of ketosis-prone type 2 diabetes with an 8-year follow-up period with close monitoring of bodyweight and intrinsic insulin secretion capacity.

CASE REPORT

A 21-year-old man (height 168.5 cm) experienced weight loss from 105 to 90 kg within a month, and hyperglycemic symptoms appeared. He was admitted to Saitama Medical University Hospital, Saitama, Japan, with the diagnosis of diabetic ketosis; his blood glucose level was 872 mg/dL, hemoglobin A1c level was 10.9% (96 mmol/mol) and blood total ketone level was $\geq 5,000$ $\mu\text{mol/L}$. His postprandial serum C-peptide level was 0.6 ng/mL, and he tested negative for anti-glutamic acid decarboxylase and anti-insulinoma-associated antigen-2 antibodies by enzyme-linked immunosorbent assay and radioimmunoassay, respectively. After intensive insulin therapy, his postprandial serum C-peptide increased from 0.6 to 4.3 ng/mL; therefore, the insulin therapy could be completely discontinued after discharge. Thereafter, his bodyweight gradually increased; however, 3 years post-discharge, it decreased from 95.3 to 87.8 kg within a month, and similar hyperglycemic symptoms appeared. He was readmitted because of the second episode of diabetic ketosis.

During the follow-up period, his bodyweight fluctuated, and he experienced four episodes of critical ketosis within 8 years after the first episode of ketosis without any precipitating factor, except for increased bodyweight caused by physical inactivity and overeating. The patient reported no change in lifestyle before his change of bodyweight. He had a tendency for

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overeating and physical inactivity throughout the clinical course. He had no history of excessive intake of soft drinks. His endogenous insulin secretion capacity was impaired at the time of ketosis, and improved after ketosis resolved in the first and third episodes of diabetic ketosis (Table S1). His detailed clinical course is described in the Appendix S1. Given that his Δ C-peptide level, defined as the difference in fasting serum C-peptide and postprandial C-peptide levels, was decreased at the time of critical ketosis (Table S1), the decrease in bodyweight before each critical ketosis is believed to be due to depressed endogenous insulin secretion capacity.

The patient could discontinue insulin therapy after each ketosis episode within the first 4 years, but thereafter, he had to continue insulin therapy because of a decrease in insulin secretion capacity over time. Interestingly, his peak bodyweight just before the episode of repeated ketosis gradually decreased, and the intrinsic insulin secretion capacity (postprandial serum C-peptide and Δ C-peptide levels) after the recovery from repeated ketosis decreased in parallel with his peak bodyweight (Figure 1; Table S1). The patient's peak bodyweight and intrinsic insulin secretion capacity might not have been induced by poor glycemic control and glucose toxicity, respectively, at least in the first to fourth episodes of diabetic ketosis, because both hemoglobin A1c levels at the time of peak bodyweight and soon after the disappearance of diabetic ketosis were $\leq 7.2\%$ (Table S1).

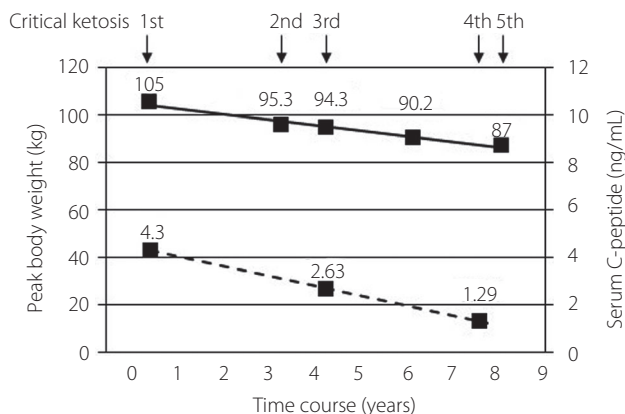


Figure 1 | Time courses of peak bodyweight just before the onset of repeated ketosis and postprandial serum C-peptide levels after recovery from repeated ketosis. After the first episode of ketosis, the patient presented with critical ketosis four times during a follow-up period of nearly 8 years. We believe that each peak bodyweight might reflect a threshold of bodyweight that leads to ketosis in ketosis-prone type 2 diabetes, and that the threshold of bodyweight gradually declines parallel to a decreased intrinsic insulin secretion capacity each time ketosis repeatedly develops. The x-axis shows the time course since the first episode of ketosis. The y-axes on the left and right sides show the peak bodyweight and postprandial serum C-peptide levels, respectively. Solid line, peak body weight; dashed line, serum C-peptide.

The speed of decline in the peak bodyweight over time was evidently higher in the present case (-2.25 kg per year in bodyweight, or -0.79 kg/m² per year in body mass index) than in patients with usual type 2 diabetes ($-0.61 \sim +0.22$ kg/m² per year in body mass index)⁴. Furthermore, the pace of the decrease in β -cell function over time seemed to be faster in the present patient (-14.4% per year in serum C-peptide level) than in participants with usual type 2 diabetes (-4% per year in homeostatic model assessment of percentage β -cell function)⁵, although a direct comparison between the two parameters is unavailable.

Written informed consent was obtained from the patient.

DISCUSSION

We have encountered dozens of hospitalized participants with suspected ketosis-prone type 2 diabetes, who are mostly characterized by younger age, male preponderance, obesity, bodyweight gain before the onset of ketosis followed by bodyweight loss at the onset of ketosis and a transient decrease in insulin secretion capacity, which can be resolved with temporal insulin therapy (data not shown). However, we have not yet encountered ketosis-prone type 2 diabetes patients who could be followed up for long time-periods and who experienced repeated ketosis during their clinical courses. From our experience with the patient in the present case, who was followed up for 8 years, we assume that there might be a threshold of bodyweight that leads to sudden onset of ketosis in ketosis-prone type 2 diabetes, and that typical ketosis-prone type 2 diabetes might be characterized by the clinical course in which the threshold gradually declines parallel to a decreased intrinsic insulin secretion capacity each time ketosis develops (Figure 1); accordingly, continuous insulin therapy might be required within several years after the first episode of ketosis. Because the present patient had DRB1*04:05, which is a susceptible human leukocyte antigen allele in Japanese type 1 diabetes patients, ascertaining whether ketosis-prone type 2 diabetes is a subtype of type 1 diabetes is subject to further discussion, although no islet-associated autoantibodies were detected in the serum of the present patient, as mentioned above. Interestingly, we detected insulin peptide-specific T cells in ketosis-prone type 2 diabetes patients, as presented previously (American Diabetes Association meeting, 2017), which supports the idea that ketosis-prone type 2 diabetes might be a subtype of type 1 diabetes (Appendix S1). It is unclear why the threshold of bodyweight that leads to the sudden onset of ketosis exists in ketosis-prone type 2 diabetes patients; however, we believe that this long-term clinical course observed in the present patient might be one of characteristics of ketosis-prone type 2 diabetes, and that this observation might be a clue to understanding the pathophysiology of this atypical form of diabetes.

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DISCLOSURE

Akira Shimada has received lecture fees from Novo Nordisk Pharma, Inc., Sanofi K.K. and Eli Lilly Japan K.K. Mitsuhiro Noda has received lecture fees from Novo Nordisk Pharma, Inc., and MSD K.K. Ikuo Inoue has received a lecture fee from Sanofi K.K. The other authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Peak body weight, glycemic control, diabetes treatment, and insulin secretion capacity at the time of each episode of critical diabetic ketosis.

Appendix S1 | Detailed clinical course in this case and peripheral frequency in insulin peptide-reactive interferon-γ-producing mononuclear cells in ketosis-prone type 2 diabetes patients we have encountered.