Evaluation of Insulin Secretion and Sensitivity in a Patient with Slowly Progressive Type 1 Diabetes Mellitus

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Abstract

We herein report the case of a patient with slowly progressive type 1 diabetes and insulin independence lasting for >10 years despite the detection of continuously elevated glutamic acid decarboxylase autoantibody titers. We monitored the patient’s clinical course and analyzed his endogenous insulin secretion and sensitivity using an intravenous glucose tolerance test (IVGTT) and oral glucose tolerance test (OGTT). His body mass index remained at approximately 22, while his serum C-peptide immunoreactivity level gradually decreased. The level of insulin secretion was significantly higher on the OGTT than the IVGTT. The patient’s insulin sensitivity was within the normal limits. These results suggest that maintaining a lifestyle sufficient to preserve insulin secretion and/or normal insulin sensitivity is important and that β-cell responsiveness to incretins may, in part, contribute to insulin independence.

Key words: slowly progressive type 1 diabetes mellitus, glutamic acid decarboxylase autoantibodies, insulin secretion, insulin sensitivity, incretin

Introduction

Slowly progressive type 1 diabetes (SPT1D), also known as latent autoimmune diabetes in adults (LADA), is characterized by the absence of insulin dependence at the onset of diabetes and the persistence of islet cell autoantibodies, such as glutamic acid decarboxylase autoantibodies (GADA) and insulinoma-associated antigen-2 autoantibodies [IA-2A (1, 2)]. Most patients with SPT1D experience a gradual decline in the number of pancreatic β-cells and become insulin dependent after a mean period of three years (3, 4).

We herein report a case of SPT1D in which the patient presented with high levels of islet cell autoantibodies and susceptible human leukocyte antigens (HLA) DRB1-DQB1 haplotypes, compatible with a diagnosis of type 1 diabetes, and remained insulin independent over the long term. We evaluated the patient’s insulin secretion and sensitivity and measured the difference in insulin secretion induced by orally and intravenously administered glucose.

Case Report

We evaluated a 60-year-old Japanese man [height: 163 cm; body weight: 57.3 kg; and body mass index (BMI): 21.6]. In 1999, at 46 years of age, hyperglycemia was identified during a regular medical checkup. An oral glucose tolerance test (OGTT) was used to determine the diagnosis of diabetes mellitus, and the patient was counseled to undergo lifestyle modification without any medication. In addition, he was positive for GADA (150 U/mL). During the initial five years of therapy, the HbA1c (NGSP) level was <6.0%. In 2007, the patient visited the Chiba Central Medical Center for further follow-up. He had no family history of diabetes mellitus. His fasting plasma glucose level was 140 mg/dL, and his fasting immunoreactive insulin (IRI) level was 4.0 μU/mL. His GADA titer was 99.9 U/mL (normal range, <1.5 U/mL), and his IA-2A titer was 2.7 U/mL (normal range, <0.399 U/mL). The HLA DR beta 1 and HLA DQ beta 1 alleles were DRB1*04:05/09:01 and DQB1*03:03/04:01, respectively. The haplotypes were DRB1*04:05-DQB1*04:04 and DRB1*09:01-DQB1*03:03, respectively. An asso-
Association between these haplotypes and susceptibility to SPT1D in the Japanese population has been demonstrated (5, 6). Based on these findings, the patient was diagnosed with SPT1D. In 2012, his antithyroid peroxidase antibody (TPOA) level was 22.0 IU/mL (normal range, <16 IU/mL). We recommended the initiation of insulin therapy to prevent or delay progression to an insulin-dependent state. However, the patient chose to continue lifestyle interventional changes alone (dietary prescription of 1,700 kcal/day, including exercise). His BMI remained at approximately 22 (Fig. 1). His GADA titer and fasting C-peptide immunoreactivity (CPR) level gradually decreased. Although the HbA1c level gradually increased (0.14%/year, Fig. 1), the patient remained in an insulin-independent state.

In 2011, a 25-g intravenous glucose tolerance test (IVGTT) with a regular insulin intravenous bolus of 3 U (0.05 U/kg of body weight) added 20 minutes after the glucose load was performed to determine the capacity of insulin secretion from pancreatic β-cells and the level of whole-body insulin sensitivity. The capacity of insulin secretion was estimated according to the response of the peripheral serum insulin and CPR levels and the 2-compartment model analysis of CPR kinetics method (7-9); insulin-modified minimal model parameters were used to estimate insulin sensitivity. A computer program we developed according to the report of Eaton et al. (10) was used to calculate the whole-body insulin sensitivity index (Si) based on the algorithm described by Bergman et al. (normal range, 2.6-7.6 mU/mL/min) (11). The peripheral serum insulin level, CPR level and CS1 markedly decreased (0.445 ng/mL/min). In contrast, the Si was within the normal limits [5.52×10^{-7}/min(μU/mL); Fig. 2]. In addition, we determined the level of insulin secretion in response to oral glucose administration (Fig. 3). Although the insulinogenic index during the first 30 minutes significantly decreased [0.03 (μU/mL)/(mg/dL)], the integrated serum C-peptide (ΣCPR) level determined from the measurements obtained at 0, 30, 60, 90 and 120 minutes was 9.53 ng/mL, which indicated that the early phase of insulin secretion was attenuated, whereas the late phase was relatively preserved. Furthermore, the peak insulin and CPR levels measured using the OGTT were higher than those measured using the IVGTT at similar blood glucose concentrations (IRI: 4.6 vs. 16.2 μU/mL; SCPR: 1.6 vs. 3.12 ng/mL; PG: 278 vs. 276 mg/dL, respectively). In January 2013, the patient remained insulin independent and continued to be treated with lifestyle intervention alone.

**Discussion**

In most patients with SPT1D, insulin secretion gradually decreases over several years and, after a mean period of three years, progresses to a deficient state, which results in the patient becoming insulin dependent (3, 4). In contrast, our patient remained insulin independent, although his gly-
cemic control progressively worsened and his fasting CPR level decreased. According to previous reports, the risk factors for progression to an insulin-dependent state include sulfonylurea therapy, a high GADA titer (>10 U/mL), a low CPR level (ΣSCPR <10 ng/mL on OGTT) (3) and the presence of other islet autoantibodies or TPOA (12, 13). In our patient, the GADA titer was >10 U/mL, the ΣSCPR level was 9.53 ng/mL and IA-2A and TPOA were positive. Despite the presence of these risk factors, the patient was protected from progression to insulin deficiency and remained insulin independent for 13 years.

In this case, acute insulin secretion decreased in response to the elevated blood glucose level during intravenous glucose administration. In contrast, the insulin and CPR levels during the oral glucose load were higher than those observed during the administration of intravenous glucose. A probable reason for the difference in insulin secretion between the two tolerance tests is the so-called “incretin effect.” Yamane et al. evaluated gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) secretion in Japanese patients with normal glucose tolerance after glucose loading (75 g of glucose) (14). In the 75-g OGTT, the GIP levels significantly increased at 30 minutes after the glucose load, peaked at 120 minutes and were maintained up to 180 minutes, whereas the GLP-1 levels peaked at 60 minutes and gradually decreased over time but remained higher than the baseline levels, even at 180 minutes. In our patient, the insulin level was approximately two times the baseline level at 60 minutes and increased to a maximum at 90 minutes. These results suggest the presence of GIP- and GLP-1-stimulated insulin secretion during the OGTT in our patient and that β-cell responsiveness to incretins was preserved 13 years after the diagnosis.

Recently, Takeda et al. reported the ability of a dipeptidyl peptidase-4 (DPP-4) inhibitor to suppress the progression to hyperglycemia with the alleviation of β-cell death and α-cell proliferation in a streptozotocin-induced diabetic mouse model (15). In humans, a recent report indicated that the se-
rum DPP-4 activity is elevated in patients with type 1 diabetes treated with prandial bolus insulin (16). Furthermore, Kamoi et al. indicated that the postprandial GLP-1 levels following the ingestion of test meals in Japanese patients with type 1 diabetes being treated with bolus rapid-acting insulin analogs decreased in proportion to that observed in the controls (17). Therefore, by increasing the GLP-1 level, DPP-4 inhibitor therapy may have been effective in our patient.

Most patients with LADA in Western countries are obese and have hyperinsulinemia (18, 19). It has been reported that the insulin resistance observed in patients with LADA is equivalent to that found in patients with type 2 diabetes mellitus (20). Patients with LADA are at a significant risk of metabolic consequences of insulin resistance other than glucose metabolism, including those associated with metabolic syndrome; however, the insulin sensitivity was within the normal limits in our patient. Therefore, it is unlikely that the exacerbation of glycemic control was caused by an alteration in insulin sensitivity. As the patient’s BMI did not increase in this case, maintaining a lifestyle sufficient to preserve insulin secretion and/or normal insulin sensitivity is important for such cases.

The authors state that they have no Conflict of Interest (COI).

References


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