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Olanzapine-induced severe hyperglycemia was completely reversed by the restoration of insulin secretion after switching to aripiprazole and initiating insulin therapy

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ABSTRACT

A 54-year-old Japanese man who had received a diagnosis of schizophrenia and been treated with olanzapine for nearly 16 months consulted our department because of severe hyperglycemia (535 mg/dL). The use of antipsychotics, switching the patient from olanzapine to aripiprazole, and 7 weeks of insulin therapy resulted in a decrease in the patient's postprandial blood glucose levels and an increase in his postprandial C-peptide levels (442 mg/dL to 106 mg/dL and 1.72 ng/mL to 4.94 ng/mL, respectively) as well as an improvement in his pre-prandial levels (250 mg/dL to 85 mg/dL and 1.00 ng/mL to 1.69 ng/mL, respectively) with almost no change in the 24- hour urinary excretion of C-peptide. These results suggested that an insufficiency of insulin secretion, not insulin resistance, was associated with the patient's severe hyperglycemia, and that olanzapine-induced pancreatic β-cell impairment might be reversible if the hyperglycemia is diagnosed and treated sufficiently early. When prescribing second-generation antipsychotics such as olanzapine, clinicians should take the level of insulin into account in addition to monitoring serum glucose levels.

Keywords: olanzapine, hyperglycemia, schizophrenia, insulin secretion, C-peptide

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INTRODUCTION

Among second-generation antipsychotics (SGAs), the risks of developing hyperglycemia and other metabolic effects are highest for clozapine and olanzapine, followed by quetiapine, risperidone and aripiprazole, according to the large automated database study [1] and the Clinical Antipsychotic Trials of Intervention Effectiveness study [2]. Although the SGA-induced metabolic abnormalities may be temporally associated with weight gain, reports of severe hyperglycemia in the absence of weight gain or shortly after initiation of treatment have suggested that some SGAs may have a rapid and direct effect that impairs insulin secretion or insulin action [3, 4].

We present a non-obese case whose severe olanzapine-induced hyperglycemia was improved with the restoration of insulin secretion after the patient was switched to aripiprazole and insulin therapy was initiated.

CASE PRESENTATION

A 54 year-old Japanese male patient who had been treated for schizophrenia with olanzapine (10 mg daily) for 16 months was referred by a psychiatrist to our department of internal medicine because of

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postprandial severe hyperglycemia (535 mg/dL). Over 14 years he had continuously received several antipsychotic medications for psychotic symptoms. Prior to olanzapine, he had been treated with risperidone at other hospitals and at the department of psychiatry at our hospital for about seven years with lasting autosynnoia and affective blunting. Before using olanzapine his postprandial blood glucose levels in routine testing showed no evidence of abnormal glucose tolerance, although the level at 2 months after the initiation of olanzapine was high (187 mg/dL), suggesting impaired glucose tolerance. No subsequent follow-up checks were performed.

Olanzapine therapy was discontinued because of diabetes mellitus, and aripiprazole (12 mg daily) was introduced for two weeks, with no improvement in the patient's high glucose levels. During the previous 6 months, he had lost 10 kg (body mass index: 20.2 kg/m^2) and complained of thirst, polydipsia, polyuria. He had a family history of type 2 diabetes mellitus in his mother. Laboratory examination on admission revealed high levels of fasting glucose and HbA1c (250 mg/dL, 13.5%), with high levels of fasting triglyceride and LDL-cholesterol. Tests for GAD (glutamic acid decarboxylase) and IA-2 (anti-insulinoma-aassociated protein-2) antibodies were negative.

While continuing the patient's treatment for schizophrenia with aripiprazole, we initiated ultra-short-acting insulin therapy, adjusting the regimen depending on the patient's pre-prandial blood glucose levels. The clinical course is shown in Figure 1. After the initiation of insulin therapy, glycemic control was dramatically improved, although there had been no remarkable change in his lifestyle, diet or exercise. A gradual reduction in the insulin requirement, from 26 U/day to 4 U/day, was observed in seven weeks. We examined fasting and 2-hour postprandial serum C-peptide level and 24-hour urine C-peptide area every two weeks, as shown in Table 1. Endogenous insulin secretion increased as the hyperglycemia improved. The decrease in the average preprandial blood glucose levels resulted in the discontinuation of insulin therapy and a switch to oral therapy with an alpha-glycosidase inhibitor to control the patient's postprandial glucose level. On day 59, the patient was discharged and subsequently treated in our department as an outpatient for four weeks. Afterwards, he was completely taken off of his diabetes medication, and his HbA1c level was normal (5.5%) one year after his hospitalization.

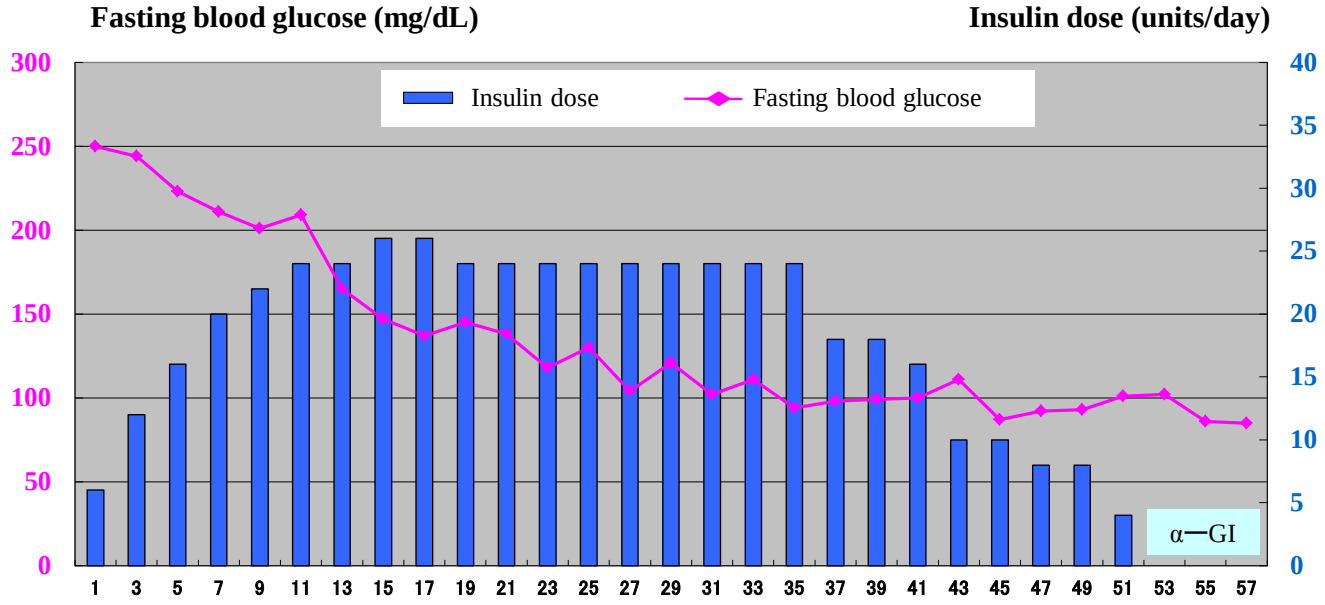

Fig. 1. Clinical course of the changes in fasting blood glucose and insulin dose. A gradual reduction in insulin requirement and pre-prandial blood glucose were observed. In this figure, the data presented are from every other day.

Table 1. Endogenous Insulin Secretory Function

	Pre	Day 15	Day 29	Day 43	Day 55
Fasting blood glucose (mg/dL)	250	152	110	85	98
Blood glucose 2 hours after breakfast (mg/dL)	442	270	169	106	161
Fasting serum C-peptide (ng/mL)	1.00	1.44	1.28	1.69	1.61
Serum C-peptide 2 hours after breakfast (ng/mL)	1.72	5.74	6.30	4.94	7.22
24-hour urinary excretion of C-peptide (μg/day)	54.6	77.6	77.4	51.8	60.4

Day1-Day 51: Insulin therapy; Day 52 on: Alpha-glucosidase inhibitors

DISCUSSION

The changes in the patient's serum and/or urine levels of glucose and C-peptide can be summarized as follows: after being switched to aripiprazole and started on insulin therapy, 1) the patient's 2-hour postprandial serum peptide level rapidly increased as his 2-hour postprandial hyperglycemia improved, 2) the patient's fasting serum peptide level slowly increased as his fasting serum glucose levels recovered, 3) the patient's total 24-hour urinary excretion of C-peptide was largely unchanged, which suggested that the olanzapine-induced hyperglycemia that occurred in the present case may be due to a delayed response, without irreversible impairment of insulin secretion.

Evidence for the direct glucose metabolic effects of olanzapine has been provided by several studies. Newcomer et al. [3] showed that, in comparison to risperidone and other conventional antipsychotics, clozapine and olanzapine resulted in insulin resistance as measured by a homeostasis model assessment (HOMA-IR) after oral glucose tolerance testing, adjusting for BMI and eliminating weight gain as a factor. Henderson et al. [4] found that in non-obese, non-diabetic subjects, HOMR-IR and leptin levels were elevated following treatment with clozapine and olanzapine, again indicating insulin resistance. They concluded that before causing obesity olanzapine induced insulin resistance. Kim et al. [5] have suggested that certain atypical antipsychotics such as olanzapine or clozapine have weight-independent effects on insulin resistance that are above and beyond obesity.

Although insulin resistance may have been present concurrently with hyperglycemia, in this case the use of olanzapine resulted in decreased insulin secretion, and in severe hyperglycemia.

Reports from clinical practice have indicated that olanzapine may directly reduce pancreatic β cell function. Chiu et al. [6] found that in schizophrenic patients treated with olanzapine for 8 weeks, insulin secretion significantly decreased at week 2, returned to baseline at week 4, and significantly increased at week 8, and therefore concluded that olanzapine displayed time-dependent biphasic changes in insulin secretion to a hyperglycemic challenge. We have previously reported the case of an overweight Japanese female patient in which switching from olanzapine to risperidone and one month of insulin therapy resulted in a decrease in the fasting blood glucose level and an increase in the insulin level [7]. A case has also been reported that suggests that even young adults who are judged to not be at any risk of diabetes can develop diabetic ketoacidosis at low plasma concentrations of olanzapine, and can recover from impaired glucose tolerance with the restoration of insulin secretion capacity [8].

At a fundamental level, several mechanisms of olanzapine-induced abnormal glucose metabolism and insulin action have been discussed. The M3 muscarinic receptor is the major receptor that is present on the pancreatic β cell. It plays a key role in maintaining proper insulin release and glucose homeostasis in vitro [9]. Olanzapine has the highest binding affinity with the M3 receptor of all the SGAs [10] and also alters M3 receptor density in discrete

nuclei of the hypothalamus and caudal brainstem regions that regulate glucose homeostasis and insulin secretion through vagal innervation of the pancreas [11]. Recently, Ozasa et al. [12] showed that olanzapine but not risperidone evoked mild endoplasmic reticulum (ER) stress, as evidenced by mild activation of the ER stress sensor molecule PKR-like ER kinase (PERK) on a hamster pancreatic β cell line. However, phosphorylation of the α subunit of eukaryotic initiation factor 2 (elF2α), an event immediately downstream of PERK activation [13], was not observed in cells treated with olanzapine. Thus, protein synthesis continued despite PERK activation, and ER stress was sustained, resulting in marked apoptosis of β cells by olanzapine.

Type 2 diabetes results from the deterioration of both insulin secretion and insulin action, but the contribution of these factors to glucose intolerance varies among ethnic groups [14]. In East Asian countries, including Japan, reduced insulin-secreting capacity appears to play a more important role than impaired insulin resistance during the transition from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT), and then to overt type 2 diabetes [15]. The fact that this patient received relief not only from insulin therapy but also from treatment with oral diabetes drugs suggested that the decrease in insulin secretion caused by olanzapine may be reversible if the hyperglycemia is diagnosed and treated sufficiently early. Therefore, when prescribing an SGA such as olanzapine, especially in high-risk patients (e.g., low body weight, middle-aged or elderly, family history of type 2 diabetes), clinicians should consider monitoring closely the levels of both insulin and serum glucose.

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