Glucose Metabolism in Japanese Schizophrenia Patients Treated With Risperidone or Olanzapine

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Objective: Atypical antipsychotics are increasingly replacing conventional neuroleptic agents, but induction of impaired glucose tolerance and development of type 2 diabetes are of concern as side effects. Risperidone has been suggested to be superior to olanzapine for glucose tolerance in whites, but there is little information on these drugs in Asian populations, even though Asians have a higher risk of type 2 diabetes compared to whites.

Method: A 75-g oral glucose tolerance test (OGTT) was performed in 100 age-matched, sex-matched, and body mass index (BMI)–matched Japanese inpatients with schizophrenia (DSM-IV criteria) who did not suffer from diabetes and had taken risperidone (N = 50) or olanzapine (N = 50) for at least 3 months. Subjects were from 1 university hospital and 3 mental hospitals in Japan; data were collected from April 2005 to March 2006. The same test was performed in 50 age-matched, sex-matched, and BMI-matched healthy Japanese subjects. Plasma glucose and serum insulin concentrations were measured just before loading (0 minutes) and 30, 60, and 120 minutes after oral glucose loading, and sorbitol levels in red blood cells were assayed at 0 and 120 minutes.

Results: The fasting glucose level and insulin concentration did not differ among the risperidone, olanzapine, and control groups, but the areas under the concentration time curves for plasma glucose and serum insulin concentrations from 0 to 120 minutes in patients receiving risperidone or olanzapine were significantly higher ($p < .05$) than those for healthy controls. However, neither the insulinogenic index nor homeostasis model assessment of insulin resistance differed among the 3 groups. Sorbitol in red blood cells was significantly higher ($p < .05$) in both patient groups compared to the control group.

Conclusion: Olanzapine and risperidone may impair glucose tolerance due in part to increased insulin resistance. However, neither drug influenced insulin secretion in Japanese patients, and, therefore, these findings do not necessarily imply that atypical antipsychotics are directly associated with a risk of impairment of glucose tolerance.

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Life expectancy in patients with schizophrenia is approximately 20% shorter than that of the general population due to higher rates of suicide, accidental death, infectious disease, and endocrine disorders.[1,2] A further contributory factor in adverse health outcomes is the side effect profile of antipsychotic drugs,[3,4] and problems of obesity,[5–9] hyperlipidemia,[7–9] and diabetes mellitus[7,9,10] have been reported in patients with schizophrenia exposed to certain atypical antipsychotics.[4,7,11–17] On the basis of U.S. Food and Drug Administration surveillance data, Koller et al.[18,19] showed that both olanzapine and risperidone have a risk for newly diagnosed hyperglycemia and new-onset diabetes. Such cases that were attributable to olanzapine or clozapine were more numerous than those associated with risperidone,[20,21] but more risperidone-associated cases of hyperglycemic diabetes were found compared with haloperidol, a conventional neuroleptic drug.[18]

In direct systematic comparisons of patients treated with major atypical antipsychotics, olanzapine and clozapine have been shown to influence insulin resistance to a significantly greater extent than risperidone or in comparison with healthy controls.[22,23] In addition, Lieberman et al.[24] compared a typical antipsychotic agent, perphenazine, with several atypical antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) in the Clinical Antipsychotic Trials of Intervention Effectiveness study and showed that patients receiving olanzapine gained more weight and had increased glucose levels and higher lipid metabolism compared to those receiving other drugs.

The pathophysiology underlying unbalanced glucose metabolism in Japanese type 2 diabetic patients is impaired insulin secretion due to abnormal pancreatic beta cell function and insulin resistance, which is mediated mainly by obesity. Some type 2 diabetic patients become obese if insulin secretion is compensated in parallel with increased insulin demand, whereas others exhaust their insulin secretory capacity prior to becoming obese. Japanese patients with type 2 diabetes have a genetically based low insulin secretory capacity, which limits their ability to compensate for insulin resistance. Therefore, many nonobese subjects are included among Japanese type 2 diabetic patients. This feature is quite different from the clinical picture of northern European and American diabetic patients with severe obesity, whose main pathophysiology is the deterioration of insulin sensitivity.[25–29]

In Japan, it had been reported until 2002 that 2 and 1 patients who were treated with olanzapine and quetiapine, respectively, died of diabetic ketoacidosis and 7 and 12 patients treated with olanzapine and quetiapine, respectively, suffered from hyperglycemia, diabetic ketoacidosis, and diabetic coma; the cause-and-effect relationship with these medications can scarcely be denied (Pharmaceutical and Medical Devices Agency, Tokyo, Japan;www.info.pmda.go.jp/kinkyu_anzen/file/kinkyu20020416.pdf and www.mhlw.go.jp/houdou/2002/11/h1107-1.html). Based on these reports, olanzapine and quetiapine have been contraindicated in the presence of diabetes in schizophrenia patients in Japan since 1992 under strong recommendation of the Japanese government.

There is little information on the association between atypical antipsychotics and glucose tolerance in Asian populations. Therefore, glucose tolerance in 100 Japanese patients with schizophrenia who did not have diabetes and were taking risperidone or olanzapine was compared with that in 50 matched Japanese healthy subjects.

METHOD

Study Population

One hundred thirty inpatients matched in age, sex, and body mass index (BMI), each of whom received risperidone (N = 65) or olanzapine (N = 65), were recruited for this study (April 2005 to March 2006). Before initiation of the study, the subjects were screened using clinical laboratory tests. Ten patients who had diabetes mellitus (risperidone, N = 7), thyroid disease (olanzapine, N = 1 and risperidone, N = 1), or endocrine metabolic disease (olanzapine, N = 1) were excluded from the study. Five patients being treated with drugs known to affect glucose tolerance, including steroids (olanzapine, N = 1 and risperidone, N = 1), β-blockers (olanzapine, N = 1), thiazide diuretics (olanzapine, N = 1), or diuretic thyroid hormones (N = 1), were also excluded. Five patients receiving olanzapine (N = 3) or risperidone (N = 2) declined to be enrolled in this study.

Table 1. Characteristics of Schizophrenia Patients Treated With Risperidone or Olanzapine and Healthy Control Subjects Matched for Age, Sex, and BMI[a]

Characteristic	Control (N = 50)	Risperidone (N = 50)	Olanzapine (N = 50)
Age, mean ± SD, y	46.0 ± 11.2	46.9 ± 14.8	47.0 ± 13.0
Duration of illness, mean ± SD, y	NA	21.6 ± 8.6	23.2 ± 10.6
Sex, male/female, N	23/27	27/23	25/25
Height, mean ± SD, cm	161.3 ± 9.9	160.1 ± 10.0	159.4 ± 8.8
Body weight, mean ± SD, kg	63.6 ± 13.0	63.2 ± 11.5	63.4 ± 13.1
BMI, mean ± SD, kg/m^2	24.6 ± 6.2	24.7 ± 4.1	25.4 ± 5.25
Dose, mean ± SD, mg/d[b]	NA	5.1 ± 2.1	14.3 ± 6.0
Length of treatment, mean ± SD, mo	NA	12.6 ± 18.2	8.2 ± 14.3

[a]All comparisons were not significant.
[b]Compared chlorpromazine-equivalent doses between risperidone and olanzapine.
Abbreviations: BMI = body mass index, NA = not applicable.

At enrollment, patients diagnosed with schizophrenia according to DSM-IV criteria were included in the study only if they had a history of normal glucose metabolism, a normal physical examination, and a fasting glucose level below 110 mg/dL. As a result, 15 matched pairs (N = 30) were excluded from this study, and final subjects were 100 inpatients in 1 university hospital and 3 mental hospitals. The patients were treated with either risperidone (N = 50) or olanzapine (N = 50) for more than 3 months. The mean ± SD length of medication treatment was 12.6 ± 18.2 months for risperidone and 8.2 ± 14.3 months for olanzapine. Several prior medications including haloperidol, chlorpromazine, levomepromazine, zotepine, and quetiapine were administered to almost all patients before risperidone or olanzapine treatment.

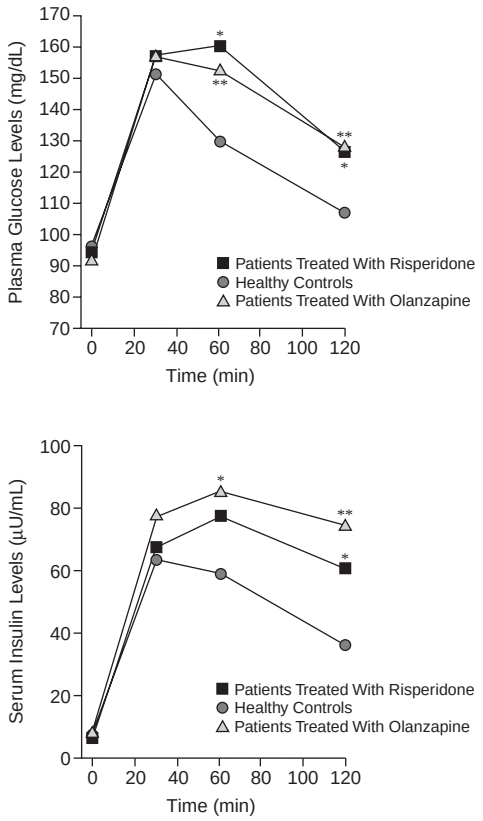
After enrollment of 100 patients, 50 of 62 healthy subjects, whose age, sex, and obesity (BMI) were matched with 50 pairs of the patients, were recruited as controls (Table 1). Twelve healthy subjects were excluded from the study based on unmatched characteristics (N = 8) and fasting glucose levels > 110 mg/dL (N = 4).

The study was approved by the ethics committee of Hirosaki University, Graduate School of Medicine, Hirosaki, Japan, and written informed consent to participate in the study was obtained from the patients and their families.

Intervention

A 75-g oral glucose tolerance test (OGTT) was conducted in all subjects. Blood samples were taken 4 times (just before loading [0 minutes] and 30, 60, and 120 minutes after loading with 75 g of glucose). Plasma glucose and serum insulin levels at 0, 30, 60, and 120 minutes and sorbitol levels in red blood cells at 0 and 120 minutes were determined. The homeostasis model assessment of

Figure 1. Plasma Glucose Concentration and Serum Insulin Concentration Time Curves From 0 to 120 Minutes After Oral Glucose Loading in Schizophrenia Patients Treated With Risperidone and Olanzapine and in Healthy Control Subjects Matched for Age, Sex, and BMI



*p < .05 compared with healthy controls.
**p < .01 compared with healthy controls.
Abbreviation: BMI = body mass index.

insulin resistance (HOMA-IR), which is used to estimate insulin sensitivity (insulin resistance),[30–33] was computed using the formula [(fasting plasma glucose concentration, mg/dL) × (fasting serum insulin concentration, μU/L)]/405. Low HOMA-IR values indicate high insulin sensitivity, and high HOMA-IR values indicate low insulin sensitivity. The insulinogenic index, which is used to estimate insulin secretion,[29] was calculated from the differences in insulin and glucose concentrations 30 minutes after initiation of the OGTT compared to the respective basal levels using the formula (insulin 30 minutes – insulin 0 minutes)/(glucose 30 minutes – glucose 0 minutes).

Statistical Analysis

Differences between chlorpromazine-equivalent doses,[34] duration of illness, and length of medication use during olanzapine and risperidone administration were analyzed using the student t test. Among risperidone olanzapine, and control groups, body weight, fasting plasma glucose levels, fasting serum insulin levels, sorbitol levels in red blood cells, HOMA-IR, insulinogenic index, sigma glucose levels in the OGTT, and sigma insulin levels in the OGTT were compared using 1-way analysis of variance (ANOVA). Post hoc analyses were performed using the Scheffe method. To determine the significance of changes in plasma glucose and serum insulin levels over time, comparisons among patients receiving olanzapine, those receiving risperidone, and healthy subjects were performed using 2-way ANOVA. All calculations were performed using SPSS 15.0J (SPSS Japan, Tokyo, Japan).

RESULTS

The clinical characteristics of the patients with schizophrenia treated with risperidone or olanzapine and the healthy control subjects are shown in Table 1. There were no significant differences in age, gender, height, weight, or BMI among patients treated with risperidone, those treated with olanzapine, and control subjects. Therefore, these 3 groups were regarded as comparable. The mean ± SD doses of risperidone and olanzapine were 5.1 ± 2.1 and 14.3 ± 6.0 mg/day, respectively. For conversion to chlorpromazine-equivalent doses, doses of 2 mg/day for risperidone and 5 mg/day for olanzapine were considered equivalent to chlorpromazine at 100 mg/day.[32] Therefore, the mean ± SD chlorpromazine-equivalent doses were 255 ± 105 mg/day for risperidone and 286 ± 120 for olanzapine, indicating no significant difference in the chlorpromazine-equivalent dosage between risperidone and olanzapine.

Plasma concentration time curves for serum glucose and insulin are shown in Figure 1. The plasma glucose concentrations in patients treated with risperidone or olanzapine were significantly higher than in control subjects at 60 and 120 minutes after glucose loading. Serum insulin concentrations in patients treated with risperidone at 120 minutes and olanzapine at 60 and 120 minutes after glucose loading were significantly higher than the respective values in control subjects. There was a significant difference between the time course of plasma glucose levels in the OGTT between controls and patients receiving risperidone or olanzapine ($p < .05$), and insulin secretion also differed significantly among the 3 groups ($p < .05$).

The OGTT results are summarized in Table 2. Fasting glucose levels, fasting insulin concentrations, and HOMA-IR did not differ among the 3 groups. However, sigma insulin levels and areas under the concentration time curves from 0–120 minutes ($AUC_{0–120}$) for insulin in patients treated with olanzapine were significantly greater than in control subjects. Patients treated with risperidone also showed this tendency, but the data were not significantly different than that of controls. Patients treated with either drug had significantly higher sigma glucose levels

Table 2. Oral Glucose Tolerance Test Parameters in Schizophrenia Patients Treated With Risperidone or Olanzapine and in Healthy Control Subjects[a]

Parameter	Control (N = 50)	Risperidone (N = 50)	Olanzapine (N = 50)	p
Fasting glucose level, mg/dL	96.0 ± 8.8	94.4 ± 10.3	92.1 ± 8.9	.134
Fasting insulin level, μU/L	7.2 ± 3.2	6.7 ± 4.2	8.5 ± 5.4	.102
Insulinogenic index	1.4 ± 1.4	1.1 ± 1.3	1.2 ± 0.8	.432
HOMA-IR	1.7 ± 0.8	1.6 ± 1.0	2.0 ± 1.3	.148
Sigma glucose level (0–120 min), mg/dL	485.2 ± 78.9	538.4 ± 104.9[b]	529.1 ± 99.9[b]	.019
Sigma insulin level (0–120 min), μU/L	166.5 ± 74.5	214.4 ± 108.7	245.9 ± 143.2[b]	.004
AUC glucose level (0–120 min), mg/dL	15071.4 ± 2820.6	16373.2 ± 3231.9	16799.8 ± 3579.0[c]	.031
AUC insulin level (0–120 min), μU/L	5772.4 ± 2742.3	7471.4 ± 3789.5	8554.2 ± 4932.7[c]	.004
Sorbitol level (0 min), nmol/g	28.1 ± 5.5	33.7 ± 9.5[b]	33.7 ± 11.6[c]	.010
Sorbitol level (0–120 min), nmol/g	31.4 ± 4.3	37.4 ± 11.8[b]	38.5 ± 13.7[c]	.006

[a]All values are mean ± SD.
[b]$p < .05$ compared with control subjects.
[c]$p < .01$ compared with control subjects.
Abbreviations: AUC = area under the concentration time curve, HOMA-IR = homeostasis model assessment of insulin resistance.

than control subjects, but only the olanzapine group had a significantly greater $AUC_{0–120}$ for glucose compared to controls. The insulinogenic index did not differ among the 3 groups, and no parameters differed significantly between patients treated with risperidone and olanzapine.

Sorbitol levels at 0 and 120 minutes after glucose loading were significantly higher in both patient groups compared to controls, but there was no difference in the sorbitol level between patients receiving risperidone and those taking olanzapine.

DISCUSSION

Numerous studies have suggested that antipsychotics induce weight gain,[5–9] although it is possible that weight gain results from secondary behavioral changes such as increased sedation associated with medication. Regardless of the causality, obesity is a significant public health concern and is a well-documented risk factor for type 2 diabetes and atherosclerosis.

A risk of diabetes with antipsychotics has also been reported in the absence of significant weight gain,[35,36] and, therefore, we performed a detailed investigation of the effects associated with atypical antipsychotics. The main finding in the current study was that insulin levels in olanzapine treatment are greater than those with risperidone treatment or in control subjects, although HOMA-IR did not differ among schizophrenia patients treated with risperidone or olanzapine and controls. These findings suggest that olanzapine impairs glucose tolerance due to an increase in insulin resistance, which is largely consistent with the findings of Newcomer et al.[3,22] and Henderson et al.[23]

In impaired fasting glucose (IGF), HOMA-IR increases but hyperglycemic clamp–determined insulin sensitivity does not decrease, leading to the postulate that in IGF (defined as a fasting plasma glucose concentration of 100–125 mg/dL), there may be selective or preferential hepatorenal insulin resistance. Conversely, in impaired glucose tolerance (defined as a 2-hour OGTT plasma glucose concentration of 140–199 mg/dL), hyperglycemic clamp–determined insulin sensitivity is reduced but HOMA-IR does not increase, suggesting that there may be preferential insulin resistance in muscle.[28–31] These findings indicate that HOMA-IR largely reflects resistance to insulin suppression of glucose production by the liver and kidneys, whereas hyperglycemic clamp–determined insulin sensitivity largely reflects the sensitivity of muscle glucose uptake to stimulation by insulin.

Thus, we analyzed the sensitivity of muscle glucose uptake to stimulation by insulin using measurement of sigma glucose and sigma insulin concentrations and $AUC_{0–120}$ for glucose and insulin. Our results suggest that olanzapine may induce abnormalities in the sensitivity of muscle glucose uptake to stimulation by insulin but that neither risperidone nor olanzapine induce resistance to insulin suppression of glucose production by the liver and kidneys.

No OGTT parameters differed between patients treated with risperidone and olanzapine, although some significant differences were found between the patient groups and healthy subjects. These findings suggest that the risk of impaired glucose tolerance with risperidone and olanzapine is unlikely to differ.

However, comparative studies[37] suggest that risperidone may have been administered preferentially because it is regarded as safer for patients with risk factors for diabetes (for example, obesity, family history of diabetes, physical inactivity) even in the absence of differences in BMI and patient background among groups. Therefore, the possibility of a difference between the 2 drugs cannot be entirely excluded, and a direct analysis of which drug has greater risk for impaired glucose tolerance, hyperglycemia, and new-onset diabetes will require investigation of metabolic changes in the same patient before and after switching from 1 drug to another.

There were no differences in insulinogenic index among the 3 groups in the current study, suggesting that neither risperidone nor olanzapine have an inhibitory effect on insulin secretion. These findings are in accordance with previous clinical studies.[38–40] However, several animal studies suggest that insulin secretion is inhibited by atypical antipsychotics,[41–44] but this discrepancy may be explained by high experimental doses in animal or in vitro studies compared with the low dose in clinical settings.

Several cases of patients suffering from new-onset diabetic ketoacidosis during treatments with atypical antipsychotics were reported in Japan.[45,46] These cases may be explained by the fact that Asians are more likely to develop diabetes than non-Hispanic whites probably because of different skeletal frame and body composition[47,48] and impaired beta cell function in Asians compared with other groups.[49] Frequent monitoring of hemoglobin A_{1c} is recommended in schizophrenia patients receiving atypical antipsychotics because observed elevated hemoglobin A_{1c} levels suggest that patients had undiagnosed diabetes mellitus for at least several weeks before the diabetic ketoacidosis episode.[50]

There were also no differences in fasting glucose and insulin concentrations among the groups, but glucose and insulin concentrations at 2 hours after the start of the OGTT were significantly higher in patients than in healthy subjects. This finding implies that the postprandial glucose or insulin concentration is a more sensitive parameter to determine the risk of insulin resistance compared to fasting glucose or insulin levels and hence HOMA-IR. However, it is evident that antipsychotics induce weight gain in close association with metabolic changes such as hyperlipidemia and hypertension, in addition to changes associated with diabetes mellitus. Therefore, general food loading containing some fat, rather than glucose loading, may be a more accurate approach to assess the metabolic tolerance of the whole body.[51–54]

Peripheral neuropathy is a major complication of diabetes with a prevalence rate > 50%,[55,56] and the polyol pathway has been suggested as an intrinsic element in development of peripheral neuropathy.[57] In response to elevated blood glucose, the enzymatic activity of aldose reductase is increased, leading to increased conversion of glucose to sorbitol, which is one of the alcohol sugars. This increased conversion results in accumulation of sorbitol in erythrocytes and nerves, and several studies in diabetic model animals have shown that an increased sorbitol level is associated with nerve damage.[58] Abnormal activity of the polyol pathway has also been associated with multiple pathophysiologic changes in peripheral nerves,[57,58] and inhibition of aldose reductase has been related to improvement of peripheral neuropathy.

In the current study, the sorbitol concentrations in patients treated with risperidone and olanzapine were significantly higher than in control subjects. We do not have a clear explanation for the significant difference in the sorbitol concentration in red blood cells, but it is possible that these drugs have effects on the polyol pathway, although the pathophysiology remains unclear. We did not evaluate diabetic peripheral sensorimotor polyneuropathy in patients or healthy controls, but our results suggest that long-term administration of atypical antipsychotics may be associated with peripheral neuropathy.

The limitation of this study should be noted. The protocol of this study was not randomized. Although age and BMI were intentionally matched, gender and duration of illness or severity of illness were not controlled. Therefore, existing selection bias that prescribers involuntarily avoided administration of olanzapine to those patients at high risk of diabetes (e.g., family history or adiposity) cannot be excluded entirely.

In conclusion, the study suggests that atypical antipsychotics might impair glucose tolerance due to an increase in insulin resistance. However, these findings do not necessarily imply that atypical antipsychotics are directly associated with a risk of impairment of glucose tolerance, and further studies are required to investigate the direct influence of atypical antipsychotics on development of type 2 diabetes.

Drug names: chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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