Glucose Metabolism in Patients With Schizophrenia Treated With Olanzapine or Quetiapine: A Frequently Sampled Intravenous Glucose Tolerance Test and Minimal Model Analysis

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Objective: Clozapine and olanzapine treatment has been associated with insulin resistance in nonobese schizophrenia patients. Much less is known regarding other agents such as quetiapine. The objective of this study was to compare matched olanzapine- and quetiapine-treated schizophrenia patients and normal controls on measures of glucose metabolism.

Method: A cross-sectional comparison of quetiapine-treated and olanzapine-treated nonobese (body mass index < 30.0 kg/m^2) schizophrenia subjects (DSM-IV) with matched normal controls using a frequently sampled intravenous glucose tolerance test and nutritional assessment was conducted from April 2002 to October 2004. Data from 24 subjects were included in the analysis (7 quetiapine, 8 olanzapine, 9 normal controls).

Results: There was a significant difference among groups for fasting baseline plasma glucose concentrations (p = .02), with olanzapine greater than normal controls (p = .01). The insulin sensitivity index (SI) differed significantly among groups (p = .039); olanzapine subjects exhibited significant insulin resistance compared to normal controls (p = .01), but there was no significant difference for quetiapine versus olanzapine (p = .1) or quetiapine versus normal controls (p = .40). SI inversely correlated with quetiapine dose (p = .0001) and waist circumference (p = .03) in quetiapine-treated subjects. Insulin resistance calculated by the homeostasis model assessment of insulin resistance (HOMA-IR) also differed significantly among groups (p = .03). The olanzapine group had a higher HOMA-IR level than normal controls (p = .01). There was a significant difference in glucose effectiveness (SG) among the groups (p = .049). SG was lower in the olanzapine group than in the quetiapine group (p = .03) and in the olanzapine group compared to normal controls (p = .049).

Conclusions: Our findings are consistent with our previous report that nonobese olanzapine-treated subjects showed insulin resistance, measured by both HOMA-IR and SI, and reduction in SG. Studies that include larger samples, unmedicated patients, and varying durations of antipsychotic exposure are necessary to confirm these results.

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Several reports have suggested higher rates of type 2 diabetes mellitus (DM) in patients with schizophrenia compared to the general population, even before the introduction of atypical antipsychotics.[1] Ryan and colleagues[2] found evidence of insulin resistance and impaired glucose tolerance in 15% of 26 medication-naive first-episode schizophrenia patients using an oral glucose tolerance test. Case reports filed with the U.S. Food and Drug Administration have implicated clozapine, olanzapine, and, to a lesser degree, risperidone and quetiapine in cases of DM and diabetic ketoacidosis.[3–6] Aripiprazole and ziprasidone appear to be the agents least likely to impair glucose tolerance and increase the risk of DM.[7–9]

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Several cases of DM developing in the absence of weight gain and resolving after discontinuation of the antipsychotic have been reported in the literature.[3,4] In a review of 45 published cases of new-onset DM or exacerbation of existing cases, Jin and associates[10] noted that 50% of patients had gained no weight and 42% of new-onset cases presented with diabetic ketoacidosis, an unusually high incidence. A possible relationship between DM and antipsychotic medication has been examined in several pharmacoepidemiologic studies utilizing 6 large databases,[11–17] with clozapine and olanzapine being the drugs most often implicated. Few reports suggest an association between quetiapine and new-onset type 2 DM.[18–20] However, Reinstein et al.[21] reported a study in which quetiapine was added to clozapine patients and resulted in reduced weight and an improvement in glucose metabolism in the 20% of patients who developed DM on clozapine treatment alone.

Clozapine and olanzapine treatment has also been associated with insulin resistance in nonobese schizophrenia patients.[22,23] Consistent with this impression, Newcomer and colleagues[22] found evidence for increased insulin resistance with olanzapine and clozapine compared to haloperidol and untreated healthy controls in a nonrandomized cross-sectional study, whereas risperidone exhibited a smaller effect that did not differ from the effect of haloperidol.[22]

We[24] confirmed Newcomer's results using frequently sampled intravenous glucose tolerance tests (FSIVGTTs) in 36 relatively lean patients (mean body mass index [BMI] = 25 kg/m^2), demonstrating that patients taking clozapine or olanzapine had a significantly greater homeostasis model assessment of insulin resistance (HOMA-IR) score and lower insulin sensitivity index (SI) suggesting significant insulin resistance than those taking risperidone.

As a follow-up study, we conducted a cross-sectional comparison of quetiapine- and olanzapine-treated schizophrenia subjects with matched normal controls using an FSIVGTT and minimal model analysis.

METHOD

The study was conducted from April 2002 to October 2004. Subjects were recruited from a community mental health clinic and were studied at the Mallinckrodt General Clinical Research Center (GCRC) at Massachusetts General Hospital. The study was approved by the Institutional Review Boards (IRBs) of the Massachusetts General Hospital and the Massachusetts Department of Mental Health. Outpatients from the ages of 18 to 65 years with the diagnosis of schizophrenia or schizoaffective disorder and a BMI less than 30.0 kg/m^2 were eligible for the study along with normal controls. Normal controls were recruited through IRB-approved announcements for research subjects.

Subjects were excluded on the basis of current substance abuse; DM; thyroid disease; pregnancy; significant medical illness including severe cardiovascular, hepatic, or renal disease; or unstable psychiatric illness. Eligibility was determined by interview and a chart review for history and recent laboratory values. No screening laboratory tests were performed prior to the procedure. Patients treated with medications known to affect glucose tolerance such as birth control pills containing norgestrel, steroids, β-blockers, anti-inflammatory drugs (including daily aspirin and ibuprofen), thiazide diuretics, agents that induce weight loss, and valproate were excluded from the study. Potential normal controls taking any psychotropic medication were also excluded. A urine pregnancy test was performed prior to the study for female subjects of childbearing potential. Additionally, as the luteal phase is associated with a reduction in insulin sensitivity,[25] menstruating women (N = 6) were interviewed regarding their menstrual history and date of last menses, were instructed to keep a log, and underwent the procedure during the early follicular phase of their menstrual cycle (days 1–7).

All subjects provided written informed consent. After providing consent, schizophrenia subjects underwent a diagnostic evaluation by a research psychiatrist using the Structured Clinical Interview for DSM-IV (SCID).[26] Assessments for psychopathology were not performed on normal controls.

Subjects were given a diet plan calculated to maintain body weight and to provide a minimum of 250 g of carbohydrate for each of the 3 days prior to the FSIVGTT. Residential program staff, outreach workers, and family members assisted subjects to maintain a high carbohydrate intake and to guarantee a 12-hour overnight fast prior to the FSIVGTT. Additionally, research staff had daily contact with subjects and staff to reinforce the recording of the subjects' dietary intake and the fasting state required for the procedure. Subjects were admitted to the GCRC at 7:00 a.m. on the morning of the test. A complete nutritional assessment was conducted prior to the initiation of the FSIVGTT.

Nutritional Assessment

Height was measured using a Harpenden stadiometer (Holtain, Crymmych, U.K.), which was calibrated on a weekly basis. Subjects were weighed on a digital electronic scale, and weight was recorded to the nearest 0.1 kg. The percent ideal body weight was determined using Metropolitan Life Insurance Tables[27] using elbow breadth for frame size determination and actual measured height. Circumferences were measured at the narrowest waist, umbilicus waist, iliac waist, and broadest hip (buttocks). Waist-hip ratio was calculated as iliac waist measure relative to the widest hip circumference. Percent body fat was calculated from biceps, triceps, suprailiac, and subscapular skinfold measurements.[28,29]

A 4-day food record was obtained from each participant prior to the 3-day high-carbohydrate diet and procedure. Assessment of food intake is important when examining glucose metabolism, energy expenditure, activity level, and anthropometric measurements. Energy and nutrient intake were analyzed using an extensive nutrient database (NDS-R; Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minn.).[30] Bioelectrical impedance was used to estimate body composition; the total conductive volume of the body is equivalent to total body water. Predictive equations were used to estimate total body water and percent body cell mass as a function of impedance, height, weight, age, and gender.[31,32] Indirect calorimetry measures were obtained with subjects in an alert, fasting state, resting with a canopy placed over their heads for collection of gases. Using a standardized equation involving respiratory quotient measured through indirect calorimetry, resting energy expenditure was calculated.[33] A quantitative activity questionnaire (Modifiable Activity Questionnaire [MAQ]) was used to assess both leisure and occupational activity components.[34]

Frequently Sampled Intravenous Glucose Tolerance Test

One intravenous line was placed in an antecubital vein in each arm. Baseline fasting blood samples were drawn for glucose and insulin, complete blood count, basic chemistry profiles, serum cortisol, lipid profile, and serum leptin. Glucose at 0.3 g/kg in normal saline was administered intravenously over 30 seconds at time 0. Approximately 2-cc blood samples were withdrawn at –10, –5, 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 27, 30, 35, 40, 45, 50, 55, 60, 65, 70, 80, 90, 100, 110, 120, 140, 160, and 180 minutes for measurement of glucose and insulin concentration.[35–37] Twenty minutes after the glucose infusion, regular human insulin at 0.05 units/kg was administered intravenously over 45 seconds. Plasma glucose concentrations and vital signs were monitored throughout the procedure. Samples for glucose were collected in a gray-top tube containing sodium fluoride and potassium oxalate and analyzed immediately in the Massachusetts General Hospital Chemistry Laboratory. Samples for insulin were collected in a red-top tube (no additives). The samples were allowed to clot at room temperature, spun, separated, and immediately stored in cloudy Falcon tubes at –80°C.

Laboratory Assays

Laboratory assays were performed by the GCRC Core Laboratory and the Chemistry Laboratory of the Massachusetts General Hospital. Duplicate fasting plasma glucose was measured with a hexokinase reagent kit (A-gent glucose test, Abbott Laboratories, South Pasadena, Calif.) with an intra-assay coefficient of variation (CV) ranging from 2% to 3%. Insulin immunometric assays were performed using an Immulite analyzer (Diagnostic Products Corporation, Los Angeles, Calif.) with an intra-assay CV of 4.2% to 7.6%. Fasting triglyceride and total plasma cholesterol levels were measured enzymatically[38] with an intra-assay CV of 0.9% to 1.2% and 1.7% to 2.7%, respectively. The high-density lipoprotein (HDL) cholesterol fraction was measured after precipitation of low-density and very low–density lipoproteins with dextran sulfate-magnesium[39] with an intra-assay CV of 0.89% to 1.82%. Low-density lipoprotein (LDL) cholesterol values were estimated indirectly for participants with plasma triglyceride levels less than 4.52 mmol/L.[40] Leptin was measured by a radioimmunoassay with a CV of 3.4% to 8.3% (Human Leptin, Linco Research, Inc, St. Charles, Mo.). Cortisol was measured by competitive immunoassay with an intra-assay CV of 6.8% to 9.0% (Immulite Cortisol, Diagnostic Products Corporation, Los Angeles, Calif.).

Minimal Model Calculations

Insulin sensitivity index, glucose effectiveness (SG), and the acute insulin response to glucose (AIRg) were calculated from glucose and insulin values using the Minimal Model (MINMOD) version 3.0 computer program developed by Bergman.[36,37,41] SI represents the increase in net fractional glucose clearance rate per unit change in serum insulin concentration after the intravenous glucose load. SG represents the net fractional glucose clearance rate due to the increase in glucose independent of any increase in circulating insulin concentrations above baseline. AIRg measures the acute (0–10 minutes) β-cell response to a glucose load calculated by the area under the curve (AUC) above basal insulin values. AIRg was assessed as the incremental AUC (calculated by the trapezoid rule) from 0 to 10 min of the FSIVGTT. The disposition index (= SI × AIRg), an index of β-cell function that takes account of prevailing insulin sensitivity and exploits the hyperbolic relationship between the two,[35,42] was calculated by the method described by Kahn et al.[43] HOMA-IR was calculated by the following formula: fasting insulin (μU/mL) × fasting glucose (mg/dL)/22.5.[44,45]

Statistical Methods

The primary outcome variables were fasting glucose and insulin, HOMA-IR, SI, SG, and AIRg levels. Covariates included lipid concentrations, waist-hip ratios, and MAQ scores. Descriptive statistics are represented as mean ± SD. Within-group correlation coefficients were determined between indices of medication dose and blood levels, glucose, insulin, HOMA-IR, SI, SG, and AIRg. Analysis of variance was used to compare the 3 antipsychotic agent groups for the following variables: fasting plasma glucose concentration, fasting insulin concentration, SI level, HOMA-IR level, SG level, cortisol level, serum lipid level, leptin level, BMI, skinfold measure-

Table 1. Demographics and Blood Pressure of Study Participants[a]

Variable	Quetiapine (N = 7)	Olanzapine (N = 8)	Normal Controls (N = 9)	p Value
Gender				.83
Male	5 (71)	7 (88)	7 (78)	
Female	2 (29)	1 (13)	2 (22)	
Age (years), mean ± SD	43 ± 12	46 ± 8	35 ± 12	.56
Race				.48
Asian	0	0	1 (11)	
Hispanic	0	0	1 (11)	
African American	2 (29)	2 (25)	0	
White	5 (71)	6 (75)	7 (78)	
Family history of diabetes mellitus (first degree)?				.36
Yes	4 (57)	2 (25)	2 (22)	
No	3 (43)	6 (75)	7 (78)	
Diagnosis				.0001
Schizoaffective disorder	2 (29)	0	0	
Schizophrenia	5 (71)	8 (100)	0	
SSRI used?				.05
Yes	3 (43)	1 (13)	0	
No	4 (57)	7 (88)	9 (100)	
Cigarette smoker?				.06
Yes	3 (43)	5 (63)	3 (33)	
No	4 (57)	3 (38)	6 (67)	
Metabolic syndrome	2 (29)	3 (38)	0 (0)	.20
Duration of illness (years), mean ± SD	15 ± 9	20 ± 9		.28
Dose of antipsychotic agent (mg), mean ± SD	607 ± 217	18 ± 8		.20
Duration of medication treatment (months), mean ± SD	24 ± 19	34 ± 26		.48
Systolic blood pressure (mm Hg), mean ± SD	124 ± 10	120 ± 12	115 ± 10	.22
Diastolic blood pressure (mm Hg), mean ± SD	74 ± 9	80 ± 11	71 ± 6	.24

[a]Values are expressed as N (%) unless otherwise noted.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

ments (triceps, biceps, suprailiac, subscapular, percent body fat), bioimpedance analysis of body fat, waist-hip ratio, widest hip circumference, MAQ score, resting energy expenditure, dietary assessment variables, duration of illness, and duration of medication treatment. A correction for multiplicity was not performed. However, a closed testing procedure was used so that pairwise comparisons were made only if the overall group effect F test p value was < .05.

Categorical demographic variables were compared between groups using Fisher exact test and included gender, race, diagnosis, use of selective serotonin reuptake inhibitors (SSRIs), and family history of DM. Continuous demographic variables were compared using Kruskal-Wallis test or Wilcoxon test and included age, fasting plasma glucose concentration, fasting insulin concentration, SI level, HOMA-IR level, SG level, cortisol level, serum lipid level, leptin level, BMI, skinfold measurements (triceps, biceps, suprailiac, subscapular, percent body fat), bioimpedance analysis of body fat, waist-hip ratio, widest hip circumference, MAQ score, resting energy expenditure, dietary assessment variables, duration of illness, and systolic and diastolic blood pressure. The longitudinal data (3 fasting time points: minute –10, minute –5, minute 0) HOMA-IR was compared between groups by analyzing the variance with repeated measures. A p value < .05 was used to test for statistical significance, and all statistical tests were 2-tailed.

RESULTS

Thirty subjects signed informed consent, but 5 withdrew consent (1 normal control, 2 olanzapine, 2 quetiapine) prior to participation in the study. Additionally, 1 subject's procedure was cancelled on the day of the procedure because of inability to fast. Data from 24 subjects were included in the analysis (7 quetiapine, 8 olanzapine, 9 normal controls). Overall, the procedure was well tolerated and all subjects were able to complete all aspects of the study.

Demographics

For the entire sample (N = 24), the mean ± SD age was 41.3 ± 11.5 years with a mean BMI of 24.4 ± 3.3 kg/m^2. Eighteen participants (75%) were white, 4 (17%) were African American, 1 (4%) was Asian, and 1 (4%) was Hispanic; 19 participants (79%) were male. The 3 treatment groups were similar in age, gender, race, BMI, systolic and diastolic blood pressure, and family histories of DM and cardiovascular disease. The quetiapine and olanzapine groups did not differ for the age at onset, the use of SSRIs, duration of illness, or duration of medication treatment (Table 1).

Glucose Metabolism

There was a significant difference among groups for fasting baseline plasma glucose concentrations (p = .02; Table 2), with olanzapine larger than normal controls (p = .01), but no significant difference was found between olanzapine and quetiapine (p = .4) or quetiapine and normal controls (p = .1) (Figure 1). Fasting serum insulin concentrations did not differ among groups (p = .1).

The SI differed significantly among groups (p = .039); olanzapine subjects exhibited significant insulin resistance compared to normal controls (p = .01), but there was no significant difference for quetiapine versus olanzapine (p = .1) or quetiapine versus normal controls (p = .40) (Figure 2). SI is inversely proportional to insulin resistance (lower SI indicates greater insulin resistance or less insulin sensitivity).[36]

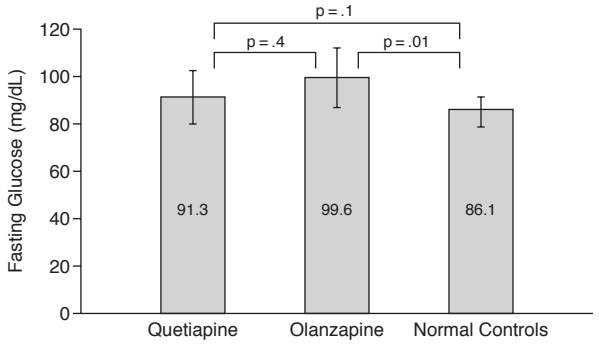
Insulin resistance calculated by the HOMA-IR also differed significantly among groups (F = 3.69, df = 46, p = .03), with olanzapine effect larger than that of normal controls (t = 2.67, df = 46, p = .01), but no significant difference between olanzapine and quetiapine (t = 1.76, df = 46, p = .09) or quetiapine and normal controls

Table 2. Baseline Glucose, Metabolism, Hormone, and Lipid Measurements in Participants[a]

Measurement	Quetiapine (N = 7)	Olanzapine (N = 8)	Normal Controls (N = 9)	p Value	Within-Group p Values[b] Quetiapine vs Control	Olanzapine vs Control	Quetiapine vs Olanzapine
Fasting glucose (mg/dL)	91.3 ± 11.2	99.6 ± 12.5	86.1 ± 5.3	.02	.1	.01	.4
Fasting insulin (μU/mL)	6.4 ± 4.0	10.5 ± 6.9	5.2 ± 4.1	.1			
Insulin sensitivity index ($\times 10^{-4} \cdot min^{-1} \cdot /\mu U/mL$)	9.1 ± 6.1	4.0 ± 2.2	12.6 ± 7.7	.039	.4	.01	.1
HOMA-IR	1.5 ± 1.0	2.7 ± 1.9	1.0 ± 0.9	.03	.45	.01	.09
Glucose effectiveness (min^{-1})	0.023 ± 0.007	0.014 ± 0.007	0.022 ± 0.008	.049	.67	.049	.03
AIRg (AUC 0–10) (μU/mL/10 min)	371.4 ± 228.8	808.4 ± 703.0	299.6 ± 181.2	.22			
Disposition index ($\times 10^{-4}$ min^{-1})	2240 ± 1904	3379 ± 3588	4082 ± 3295	.52			
Cortisol (μg/dL)	13.7 ± 4.0	12.0 ± 4.0	10.6 ± 4.1	.3			
Total cholesterol (mg/dL)	179.9 ± 49.6	195.1 ± 61.9	172.4 ± 27.9	.83			
High-density lipoprotein (mg/dL)	35.7 ± 3.3	38.7 ± 15.3	52.9 ± 12.0	.048	.03	.06	.7
Low-density lipoprotein (mg/dL)	112.6 ± 49.0	103.7 ± 48.2	97.4 ± 22.8	.96			
Triglycerides (mg/dL)	157.9 ± 104.7	199.0 ± 160.6	109.3 ± 76.0	.28			
Alkaline phosphate (mg/dL)	77.4 ± 12.2	84.3 ± 13.6	57.6 ± 9.9	.002	.005	.004	.15
AST (SGOT) ($min \cdot mL^{-1}$)	25.9 ± 6.6	27.8 ± 8.2	25.8 ± 7.5	.4			
Leptin (ng/mL)	13.7 ± 15.1	10.2 ± 13.6	5.9 ± 4.6	.47			

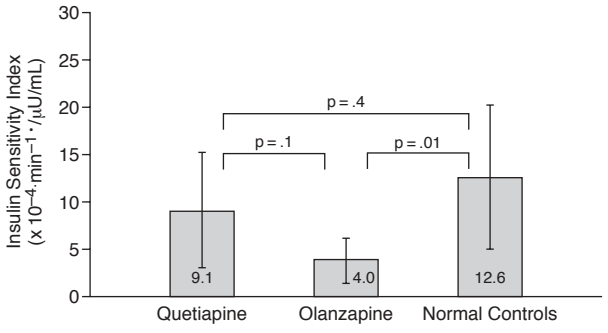
[a]Values reported as mean ± SD.
[b]Pairwise comparisons were made only if the overall group effect F test p value was < .05.
Abbreviations: AIRg = acute insulin response to glucose; AST (SGOT) = aspartate aminotransferase, formerly serum glutamic-oxaloacetic transaminase; AUC = area under the curve; HOMA-IR = homeostasis model assessment of insulin resistance.

Figure 1. Fasting Glucose in Nonobese Schizophrenia Subjects Treated With Olanzapine (N = 8) or Quetiapine (N = 7) and Normal Controls (N = 9)[a]



[a]Values expressed as mean ± SD.

Figure 2. Insulin Sensitivity Index in Nonobese Schizophrenia Subjects Treated With Olanzapine (N = 8) or Quetiapine (N = 7) and Normal Controls (N = 9)[a]



[a]Values expressed as mean ± SD.

(t = 0.76, df = 46, p = .45) (Figure 3). The olanzapine group displayed elevations in HOMA-IR (greater insulin resistance) compared to normal controls. Although there was no significant difference among groups for AIRg (p = .22) or disposition index (p = .52), there was a significant among-group difference for SG (p = .049), with olanzapine less than quetiapine (p = .03) and olanzapine less than normal controls (p = .049), but no difference between quetiapine and normal controls (p = .67) (Figure 4).

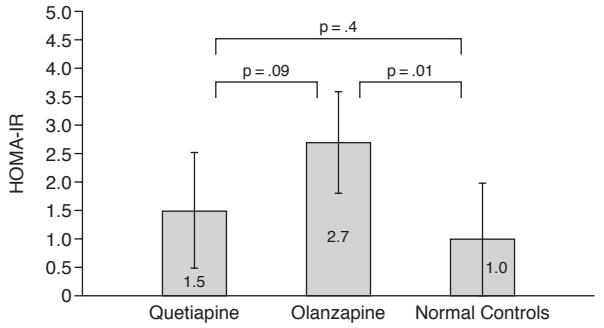
Lipids

There were no significant differences comparing total cholesterol (p = .83), LDL cholesterol (p = .96), and serum triglyceride (p = .28) levels among groups. However, HDL cholesterol levels significantly differed among groups (p = .048), with the quetiapine group lower than normal controls (p = .03), but there was no significant difference between the olanzapine group and normal controls (p = .06) or between the quetiapine and olanzapine groups (p = .70) (Table 2).

Nutritional Assessment and Physical Activity

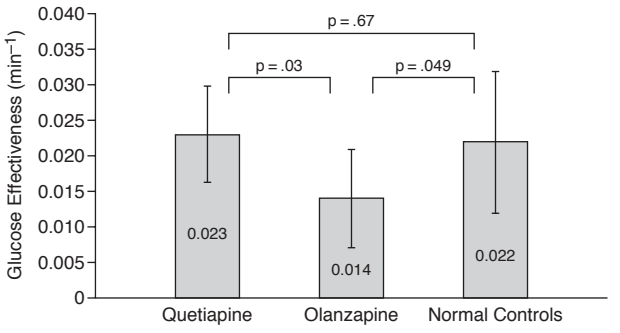
There were no significant differences among groups for measurements of percent body cell mass; biceps, triceps, and subscapular skinfold measurements; ideal body weight; percent ideal body weight; total body fat and total body water measured by bioelectric impedance; widest hip measurements; and waist-hip ratio. MAQ total scores significantly differed among groups (p = .02), with the

Figure 3. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in Nonobese Schizophrenia Subjects Treated With Olanzapine (N = 8) or Quetiapine (N = 7) and Normal Controls (N = 9)[a]



[a]Values expressed as mean ± SE.

Figure 4. Glucose Effectiveness in Nonobese Schizophrenia Subjects Treated With Olanzapine (N = 8) or Quetiapine (N = 7) and Normal Controls (N = 9)[a]



[a]Values expressed as mean ± SD.

Table 3. Anthropometric Measurements of Study Participants[a]

Measurement	Quetiapine (N = 7)	Olanzapine (N = 8)	Normal Controls (N = 9)	p Value	Within-Group p Values[b]		
					Quetiapine vs Control	Olanzapine vs Control	Quetiapine vs Olanzapine
Body mass index (kg/m^2)	25.5 ± 4.0	23.7 ± 3.7	24.1 ± 2.3	.7			
Bicep skinfold (mm)	8.5 ± 8.3	6.8 ± 5.2	6.0 ± 2.0	.8			
Tricep skinfold (mm)	9.0 ± 3.4	15.1 ± 7.1	13.4 ± 6.4	.6			
Subscapular skinfold (mm)	15.9 ± 8.5	18.0 ± 6.8	14.7 ± 7.0	.6			
Suprailiac skinfold (mm)	18.8 ± 10.5	21.7 ± 10.2	8.7 ± 2.9	.6			
Body cell mass (%)	41.3 ± 9.8	42.7 ± 8.2	40.4 ± 4.6	.9			
Bioimpedance analysis (% body fat)	24.1 ± 14.6	26.6 ± 7.1	19.1 ± 6.4	.3			
Waist (iliac crest) (cm)	94.7 ± 11.5	92.1 ± 9.3	87.7 ± 11.1	.5			
Waist/hip ratio	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	.15			
Widest hip (cm)	101.5 ± 9.4	99.1 ± 7.4	99.6 ± 5.2	1.0			
MAQ total[c]	5.5 ± 5.3	15.5 ± 18.4	21.4 ± 11.4	.02	.003	.19	.49
Occupational[c]	0.1 ± 0.3	5.7 ± 11.9	4.7 ± 6.7	.15			
Leisure[c]	5.4 ± 5.4	9.9 ± 14.7	16.7 ± 6.9	.02	.004	.06	.91
Resting energy expenditure (kcal/day)	1615.0 ± 311.0	1648.0 ± 358.1	1614.4 ± 481.1	.97			
Respiratory quotient	.93 ± .09	.82 ± .15	.91 ± .10	.46			
Reactance	59.1 ± 6.5	155.8 ± 259.2	54.2 ± 6.6	.06			
Resistance	525.0 ± 77.7	523.5 ± 85.6	406.5 ± 163.1	.07			

[a]Values reported as mean ± SD.
[b]Pairwise comparisons were made only if the overall group effect F test p value was < .05.
[c]Average hours of activity/week.
Abbreviation: MAQ = Modifiable Activity Questionnaire.

quetiapine group lower than normal controls (p = .003); there was no significant difference between the olanzapine group and normal controls (p = .19), or between the quetiapine and olanzapine groups (p = .49). There was also a significant difference among groups for leisure activity level (p = .02), with a significant difference between the quetiapine group and normal controls (p = .004) but no significant difference between the olanzapine group and normal controls (p = .06) or the quetiapine and olanzapine groups (p = .91). Occupational activity level (p = .15) did not differ among groups (Table 3). Additionally, the groups did not differ on measures of energy expenditure including resting energy expenditure or respiratory quotient.

Food Intake Assessment

There were few statistically significant differences among groups on food intake calculated on the basis of a 4-day food record (Table 4). The groups did not differ in total fat level, polyunsaturated fat level, saturated fat level, total energy (kcal), or total kcal/kg body weight. Only folate (p = .007) and galactose intake (p = .04) differed significantly between groups.

Cortisol and Leptin and Correlations of Antipsychotic Dose and Anthropometric Measurements With Measures of Glucose Metabolism

There were no significant differences among groups for fasting serum cortisol and leptin levels. Alkaline

Table 4. Nutrient Intake in Study Participants Based on a 4-Day Food Record[a,b]

Measurement	Quetiapine (N = 7)	Olanzapine (N = 8)	Normal Controls (N = 9)	p Value	Within-Group p Values[b] Quetiapine vs Control	Olanzapine vs Control	Quetiapine vs Olanzapine
Total energy (kcal)	1982.0 ± 443.7	2260.0 ± 837.3	2319.2 ± 734.5	.6			
Total body weight (kcal/kg)	90.6 ± 44.3	76.1 ± 12.4	76.0 ± 15.1	1.0			
Protein (% total energy)	15.3 ± 4.4	14.6 ± 3.0	14.1 ± 2.2	.7			
Total fat (g)	71.4 ± 15.2	90.4 ± 45.9	86.9 ± 34.8	.9			
Fat (% total energy)	32.6 ± 3.2	36.4 ± 10.3	33.8 ± 7.1	.6			
Cholesterol (mg)	286.3 ± 138.8	313.9 ± 214.6	280.7 ± 103.0	1.0			
Polyunsaturated fat (g)	13.6 ± 5.9	19.6 ± 15.5	17.0 ± 7.3	.8			
Saturated fat (g)	27.0 ± 6.4	29.5 ± 12.7	31.4 ± 13.6	.9			
Polyunsaturated to saturated fat ratio (g)	0.5 ± 0.2	0.7 ± 0.4	0.6 ± 0.2	.5			
Starch (g)	121.2 ± 34.7	109.9 ± 56.0	131.7 ± 38.7	.8			
Glucose (g)	26.7 ± 13.2	32.6 ± 30.8	32.7 ± 16.5	.4			
Fructose (g)	22.2 ± 11.8	28.9 ± 30.7	30.8 ± 14.1	.3			
Galactose (g)	0.4 ± 0.4	0.0 ± 0.1	0.7 ± 0.6	.04	.5	.02	.07
Lactose (g)	14.2 ± 10.3	15.6 ± 6.0	20.4 ± 10.7	.4			
Maltose (g)	3.8 ± 2.8	1.2 ± 1.0	3.8 ± 3.1	.2			
Sucrose (g)	50.6 ± 45.6	55.3 ± 28.4	53.8 ± 26.1	.7			
Alcohol (g)	1.0 ± 2.4	2.9 ± 7.0	7.0 ± 16.3	.3			
Folate (mcg)	433 ± 111	263 ± 123	589 ± 223	.007	.11	.01	.03

[a]Values reported as mean ± SD.
[b]Pairwise comparisons were made only if the overall group effect F test p value was < .05.

phosphate significantly differed among groups (p = .002), with differences between olanzapine and normal controls (p = .004) and quetiapine and normal controls (p = .005). However, the mean values were all within normal limits and not clinically relevant.

Within treatment groups, fasting glucose and insulin levels and SG did not correlate with dose of antipsychotic concentrations. SI significantly inversely correlated with quetiapine dose (t = –5.98, SE = 0.004, p = .0001) but not olanzapine dose. Higher doses of quetiapine were associated with greater insulin resistance. SI also inversely correlated with BMI for the entire sample (t = –2.39, SE = 0.37, p = .03) and for normal controls (t = –2.21, SE = 0.81, p = .04). Waist circumference (cm) inversely correlated with SI for the entire sample (t = –2.53, SE = 0.11, p = .02) and for the quetiapine group (t = –2.38, SE = 0.18, p = .03) but not the olanzapine group or normal controls. Greater BMI and waist measurements were associated with greater insulin resistance. Waist-hip ratio inversely correlated with SI for the entire sample (t = –2.31, SE = 17.9, p = .04) but was nonsignificant for the quetiapine group (t = –2.08, SE = 37.6, p = .054), olanzapine group (t = 0.19, SE = 29.2, p = .85), and normal controls (t = –2.05, SE = 25.1, p = .057). AIRg inversely correlated with age for the entire sample (t = –2.21, SE = 7.9, p = .04) and for the olanzapine-treated subjects (t = –3.53, SE = 17.3, p = .002). The older the subject, the less β-cell response to the glucose load. HOMA-IR did not correlate with gender or family history of DM.

Fasting HDL cholesterol levels correlated with olanzapine dose (t = 3.35, SE = 0.38, p = .007). HDL also correlated with age among the entire sample (t = 2.36, SE = 0.22, p = .03) and among olanzapine-treated subjects (t = 2.79, SE = 0.49, p = .01). HDL inversely correlated with BMI (t = –2.26, SE = 0.79, p = .04). Gender, family history of DM, race, and smoking status did not correlate with any of the major outcome measures.

DISCUSSION

Our findings are consistent with our previous report[24] that nonobese olanzapine-treated subjects showed significant insulin resistance measured by both HOMA-IR and SI compared to normal controls. Olanzapine-treated subjects also had significantly higher fasting glucose concentrations than normal controls, which also reflects impairment in glucose metabolism. Additionally, quetiapine-treated patients did not exhibit insulin resistance compared to normal controls. In this sample, the mean BMI for olanzapine-treated subjects was 23.7 kg/m^2, and, though not statistically significant, it was less than the mean BMI for both quetiapine-treated subjects and normal controls.

Insulin resistance is a potential precursor of type 2 DM and is pathogenetically linked to an increased risk of cardiovascular events.[46] The insulin resistance syndrome originally included hyperinsulinemia, impaired glucose tolerance, hypertension, increased plasma triglycerides, and decreased HDL cholesterol.[47] Other features were observed such as visceral adiposity, small dense LDL, exaggerated postprandial lipids, increased plasma plasminogen activator inhibitor-1, and decreased sex hormone–binding globulin levels.[48] These metabolic abnormalities have, in turn, been associated with cardiovascular disease individually and together have been found to greatly increase cardiovascular mortality.[49] Metabolic syndrome is a

high-risk constellation of lipid waist measurements, blood pressure, and fasting glucose risk factors to be targeted for intensified therapy.[50] The diagnosis of metabolic syndrome can be made when 3 or more of the risk determinants are present. In this study, despite the normal mean BMI, 29% of quetiapine-treated patients and 38% of olanzapine-treated patients met the criteria for metabolic syndrome, while none of the normal controls met this criteria.

We replicated our findings[24] of reduced SG in olanzapine-treated subjects compared to normal controls and quetiapine-treated subjects. Possible mechanisms of reduced SG may be the blocking of glucose transporters.[51] Roughly two thirds of SG, in humans, represents a disposal effect and one third a suppression of glucose production in the liver.[52,53] Olanzapine has been found to impair the insulin-mediated suppression of hepatic glucose production in dogs,[54] but this has not been well studied in humans. Additionally, a reduction in β-cell functioning, measured by AIRg and disposition index, was not observed in this study.

Quetiapine subjects showed significantly lower activity levels measured by MAQ compared to normal controls. Schizophrenia patients may be less likely to work and exercise than the general population. Exercise expends calories and promotes leanness, while lowering blood glucose and improving insulin sensitivity.[55] As measures of physical activity were lower in the quetiapine group than normal controls in our sample, one might expect a reduction in SI or elevations in HOMA in the quetiapine group since exercise and physical activity are known to increase SI and improve insulin resistance. However, this was not evident in this study and quetiapine subjects did not differ from normal controls on any measure of glucose metabolism.

The inverse correlation SI and quetiapine dose must be interpreted with caution. SI also inversely correlated with waist circumference in quetiapine-treated subjects. As the sample size was small, the degree of impact of each factor could not be determined. It also appeared that, in quetiapine-treated subjects, doses below 600 mg were not associated with insulin resistance. A further study of glucose metabolism in subjects treated with higher doses of quetiapine is warranted.

There are a number of limitations to this study. The small sample size may limit the interpretation of our findings. However, the addition of normal controls greatly strengthens our findings in olanzapine-treated subjects. Nevertheless, normal controls may be quite different from medication-free schizophrenia patients, as schizophrenia patients may be at greater risk for a number of medical disorders including DM.[56] The exclusion of nonobese subjects may also limit the generalizability of this study. Obese schizophrenia patients should have a greater degree of insulin resistance than the subjects in this study. Previous treatment with other antipsychotic agents may have had an undetermined impact on the results. The impact of duration of exposure to antipsychotic drugs and treatment with other antipsychotic agents, as well as possible differences in vulnerability in schizophrenia patients compared to normal subjects, requires further study. Studies that include larger samples, unmedicated patients, and varying durations of antipsychotic exposure will help to address these limitations.

Finally, this study confirms the association of treatment with olanzapine and impairment of glucose metabolism in patients with schizophrenia. Guidelines for patient education, risks assessments, and monitoring of weight, fasting glucose, and lipids are currently in place for atypical antipsychotic agents.[7–9] It has been recommended that considerations in the choice of antipsychotic agents include patients' individual risk for type 2 DM, hyperlipidemia, and weight gain along with individual drugs' association with these medical disorders.[7–9]

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), ibuprofen (Motrin, Ibu-tab, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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