ORIGINAL ARTICLE

Glucose Metabolism in Patients With Schizophrenia Treated With Atypical Antipsychotic Agents

A Frequently Sampled Intravenous Glucose Tolerance Test and Minimal Model Analysis

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Background: While the incidence of new-onset diabetes mellitus may be increasing in patients with schizophrenia treated with certain atypical antipsychotic agents, it remains unclear whether atypical agents are directly affecting glucose metabolism or simply increasing known risk factors for diabetes.

Objective: To study the 2 drugs most clearly implicated (clozapine and olanzapine) and risperidone using a frequently sampled intravenous glucose tolerance test.

Design: A cross-sectional design in stable, treated patients with schizophrenia evaluated using a frequently sampled intravenous glucose tolerance test and the Bergman minimal model analysis.

Setting: Subjects were recruited from an urban community mental health clinic and were studied at a general clinical research center.

Patients: Fifty subjects signed informed consent and 41 underwent the frequently sampled intravenous glucose tolerance test. Thirty-six nonobese subjects with schizophrenia or schizoaffective disorder, matched by body mass index and treated with either clozapine, olanzapine, or risperidone, were included in the analysis.

Main Outcome Measures: Fasting plasma glucose and fasting serum insulin levels, insulin sensitivity index, homeostasis model assessment of insulin resistance, and glucose effectiveness.

Results: The mean±SD duration of treatment with the identified atypical antipsychotic agent was 68.3±28.9 months (clozapine), 29.5±17.5 months (olanzapine), and 40.9±33.7 (risperidone). Fasting serum insulin concentrations differed among groups ($F_{33}=3.35$; $P=.047$) (clozapine>olanzapine>risperidone) with significant differences between clozapine and risperidone ($t_{33}=2.32$; $P=.03$) and olanzapine and risperidone ($t_{33}=2.15$; $P=.04$). There was a significant difference in insulin sensitivity index among groups ($F_{33}=10.66$; $P<.001$) (clozapine<olanzapine<risperidone), with subjects who received clozapine and olanzapine exhibiting significant insulin resistance compared with subjects who were treated with risperidone (clozapine vs risperidone, $t_{33}=-4.29$; $P<.001$; olanzapine vs risperidone, $t_{33}=-3.62$; $P=.001$ [$P<.001$]). The homeostasis model assessment of insulin resistance also differed significantly among groups ($F_{33}=4.92$; $P=.01$) (clozapine>olanzapine>risperidone) (clozapine vs risperidone, $t_{33}=2.94$; $P=.006$; olanzapine vs risperidone, $t_{33}=2.42$; $P=.02$). There was a significant difference among groups in glucose effectiveness ($F_{30}=4.18$; $P=.02$) (clozapine<olanzapine<risperidone) with significant differences between clozapine and risperidone ($t_{30}=-2.59$; $P=.02$) and olanzapine and risperidone ($t_{30}=-2.34$, $P=.03$).

Conclusions: Both nonobese clozapine- and olanzapine-treated groups displayed significant insulin resistance and impairment of glucose effectiveness compared with risperidone-treated subjects. Patients taking clozapine and olanzapine must be examined for insulin resistance and its consequences.

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COMPARED WITH THE GENeral population, life expectancy in patients with schizophrenia is shorter by as much as 20%, attributable to higher rates of suicide, accidental deaths, and natural causes such as cardiovascular disease, infectious disease, and endocrine disorders.[1,2] Recently, the newer "atypical" antipsychotic agents have been linked to several forms of morbidity, including obesity; hyperlipidemia; type 2 diabetes mellitus; and diabetic ketoacidosis.[3-5] While impaired glucose metabolism has been frequently reported, the mechanisms responsible for such an association remain unclear, as does the relative risk for individual atypical antipsychotic agents.

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In a nonrandomized, cross-sectional study, Melkersson et al[6] found elevated fasting serum insulin levels and reduced growth hormone–dependent insulin-like growth factor I in 13 patients with schizophrenia treated with clozapine compared with 28 patients treated with conventional antipsychotic agents, which is suggestive of insulin resistance despite no significant difference between groups in body mass index (BMI). Olanzapine treatment similarly resulted in elevated serum levels of insulin, in addition to weight gain and elevations of serum leptin and lipid concentrations compared with baseline in a naturalistic 5-month follow-up study of 14 patients with schizophrenia.[7] Newcomer et al[8] reported elevated serum glucose levels at baseline and following a modified oral glucose tolerance test in patients with schizophrenia treated with clozapine and olanzapine compared with age- and weight-matched subjects treated with typical antipsychotic agents and untreated healthy controls. Elevations in fasting and postload serum glucose levels in patients treated with risperidone differed only in comparison with untreated healthy control subjects. Insulin resistance, calculated by the homeostasis model assessment of insulin resistance (HOMA-IR), was significantly greater in subjects treated with olanzapine and clozapine compared with patients treated with haloperidol and untreated normal controls, but this measure of insulin resistance did not differentiate the risperidone group from the haloperidol-treated group. Finally, in a naturalistic study of 82 patients with schizophrenia who switched from taking conventional antipsychotic agents to clozapine at a mean age of 27 years, 37% developed new-onset diabetes mellitus during a 5-year follow-up period.[9] Weight significantly increased over time and correlated with an increase in total serum cholesterol and serum triglyceride levels. There also was a significant increase in serum triglyceride level.[9]

Pharmacoepidemiological studies have yielded mixed results. Of 8 published studies examining large, independent databases, 5 found clozapine and/or olanzapine use associated with higher rates of diabetes mellitus compared with conventional antipsychotic agents or risperidone[10-14]; 1 suggested atypical antipsychotic agents as a class were associated with greater risk compared with conventional antipsychotic agents[15]; 1 found the conventional agents chlorpromazine and thioridazine associated with greater risk compared with clozapine[16]; and 1 suggested that both conventional and atypical antipsychotic agents were associated with increased risk for diabetes compared with a general medical patient population.[17] Although methodological issues related to nonrandom prescribing patterns and insensitive or nonuniform ascertainment of diabetes mellitus make these results difficult to interpret, clozapine and olanzapine have been most strongly implicated in pharmacoepidemiological studies.

Additionally, a group from the Food and Drug Administration research program compiled MedWatch reports of exacerbation of existing diabetes mellitus, new-onset diabetes mellitus, diabetic ketoacidosis, and hyperosmolar nonketotic diabetic coma in patients treated with clozapine and olanzapine.[18,19] The clinical characteristics of the diabetic ketoacidosis cases were more consistent with type 2 rather than type 1 diabetes mellitus. The number of cases, temporal relation to initiation of treatment, and observation that diabetes mellitus resolved completely in several cases when the atypical antipsychotic agent was discontinued, only to return on rechallenge, suggested a plausible association between treatment with these 2 drugs and impaired glycemic control. However, the reports also highlighted cases where the diabetes mellitus did not resolve on discontinuation of the antipsychotic agent. Risperidone also has been linked more recently to reports of new-onset diabetes mellitus and diabetic ketoacidosis by the Food and Drug Administration research and MedWatch surveillance program, although the reports are fewer in number compared with clozapine and olanzapine despite a substantially greater exposure in terms of patient-years.[20]

While the incidence of new-onset diabetes mellitus appears to be increasing in patients with schizophrenia treated with certain atypical antipsychotic agents, it remains unclear whether atypical antipsychotic agents are directly affecting glucose metabolism or simply increasing known risk factors for diabetes, such as obesity, lipid abnormalities, and decreased activity secondary to sedative effects.[3,5,9,21] Identification of mechanisms contributing to a putative increased risk of diabetes with atypical agents may help explain apparent inconsistencies in results between pharmacoepidemiological studies and allow identification of patients at risk.

Finally, effects of atypical antipsychotic agents on glucose metabolism may be complicated by impairments of glucose metabolism possibly associated with schizophrenia and with the stress of acutely untreated psychosis.[22] As a first approach to the examination of drug effects on glucose metabolism, we chose to study the 2 drugs most clearly implicated (clozapine and olanzapine) and risperidone using a frequently sampled intravenous glucose tolerance test (FSIVGTT) and minimal model analysis. The FSIVGTT is a well-established, standardized method for assessing glucose metabolism and has been widely used in the medical fields of diabetes and obesity research in both small-scale and large population-based studies. A cross-sectional design in stable, treated patients with schizophrenia or schizoaffective disorder was chosen to allow comparison of nonobese patient groups matched by BMI. This design also minimizes the confounding effect of differential weight gain between antipsychotic agents, which would be expected in a prospective treatment study, and eliminates the stress effects of untreated illness on glucose metabolism.

METHODS

Subjects were recruited from an urban community mental health clinic and were studied at the Mallinckrodt General Clinical Research Center at Massachusetts General Hospital, Boston. The study was approved by the institutional review boards of Massachusetts General Hospital and the Massachusetts Department of Mental Health. Outpatients between the ages of 18 and 65 years with the diagnosis of schizophrenia or schizoaffective disorder and a BMI less than 30 kg/m^2 were eligible for the study. Patients were excluded on the basis of current substance abuse; diabetes mellitus; thyroid disease; pregnancy; significant medical illness

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including severe cardiovascular, hepatic, or renal disease; or unstable psychiatric illness. Eligibility was determined by interview and a medical record review for history and recent laboratory values. No screening laboratory tests were performed prior to the procedure. Patients treated with the following medications known to affect glucose tolerance were also excluded: birth control pills containing norgestrel, steroids, β blockers, antiinflammatory drugs (including aspirin and ibuprofen), thiazide diuretics, agents that induce weight loss, and valproate sodium. 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,[23] menstruating women (n=6) were interviewed on their menstrual history and date of last menses, instructed to keep a log, and underwent the procedure during the early follicular phase of their menstrual cycle (days 1-7).

After providing written informed consent, subjects underwent a diagnostic evaluation by a research psychiatrist using the Structured Clinical Interview for *DSM-IV*.[24] 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. Subjects were also instructed to fast for 12 hours preceding the FSIVGTT and to hold their morning medications the day of the test. Family, residential program staff, and outreach workers assisted subjects to maintain a high-carbohydrate intake and to guarantee fasting. Subjects were admitted to the Mallinckrodt General Clinical Research Center at 6:45 AM on the morning of the test. A complete nutritional assessment was conducted on admission and immediately prior to the initiation of the FSIVGTT.

NUTRITIONAL ASSESSMENT

Height was measured using a Harpenden stadiometer, 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 ideal body weight percentage was determined using Metropolitan Life Insurance tables[25] 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. Body fat percentage was calculated from skinfold measurements of the biceps, triceps, suprailiac, and subscapular.[26,27]

A 4-day food record was obtained from each participant. Energy and nutrient intake were analyzed using an extensive nutrient database (Minnesota Nutrient Data System).[28] 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 body cell mass percentage as a function of impedance, height, weight, age, and sex.[29,30] 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.[31] A quantitative activity questionnaire (Modifiable Activity Questionnaire) was used to assess both leisure and occupational activity components.[32]

FREQUENTLY SAMPLED INTRAVENOUS GLUCOSE TOLERANCE TEST

Two intravenous catheters were placed in antecubital veins (1 in each arm). Baseline blood samples were drawn for fasting plasma glucose and serum insulin levels, basic chemistry profiles, serum cortisol level, lipid profile, complete blood count, serum leptin level, and serum risperidone, clozapine, or olanzapine concentrations 10 minutes prior to the glucose infusion (time, 10 minutes). Subjects with possible diabetes mellitus (fasting plasma glucose level ≥126 mg/dL [6.99 mmol/L]) at baseline were dropped from study. Glucose 0.3 g/kg in normal saline was administered intravenously for 30 seconds at time 0. Approximately 2-mL[3] 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 plasma glucose and serum insulin concentrations.[33-35] Twenty minutes after the glucose infusion, 500 mg of tolbutamide (Upjohn Co, Kalamazoo, Mich) was administered intravenously for 45 seconds. Vital signs and plasma glucose concentrations 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 chemistry laboratory and the Mallinckrodt General Clinical Research Center Core Laboratory of Massachusetts General Hospital. Insulin immunometric assays were performed using an Immulite Analyzer (Diagnostic Product Corp; Los Angeles, Calif) with an intra-assay coefficient of variation of 4.2% to 7.6%. Fasting plasma glucose level was measured with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, Calif). Glucose assays were run in duplicate, and the intra-assay coefficient of variation ranged from 2% to 3%. Fasting total plasma cholesterol and triglyceride levels were measured enzymatically[36] with an intra-assay coefficient of variation of 1.7% to 2.7% and 0.9% to 1.2%, respectively. The high-density lipoprotein cholesterol fraction was measured after precipitation of low-density and very low–density lipoproteins with dextran sulfate-magnesium[37] with an intra-assay coefficient of variation of 0.89% to 1.82%. Low-density lipoprotein cholesterol values were estimated indirectly for participants with plasma triglyceride levels less than 400 mg/dL (4.52 mmol/L).[38] Leptin level was measured by a radioimmunoassay with a coefficient of variation of 3.4% to 8.3% (Linco Human RIA kit [DSL-53100]; Linco Research, Inc, St Charles, Mo). Cortisol level was measured by competitive immunoassay with an intra-assay coefficient of variation of 6.8% to 9.0% (Immulite Cortisol; Diagnostic Products Corp, Los Angeles, Calif). Growth hormone level was measured using immunoradiometric assay (Nichols Institute Diagnostics, San Clemente, Calif) with an intra-assay coefficient of variation of 1.6% to 8.1%.

MINIMAL MODEL CALCULATIONS

Insulin sensitivity index (SI), glucose effectiveness (SG), and the acute insulin response to glucose (AIRG) were calculated from plasma glucose and serum insulin values using the MINMOD version 3.0 computer program developed by Richard Bergman, PhD.[34,35,39] The SI represents the increase in net fractional glucose clearance rate per unit change in serum insulin concentration after the intravenous glucose load. The SG represents the net fractional glucose clearance rate due to the increase in glucose independent of any increase in circulating insulin concentrations above baseline. The AIRG measures the acute (0-10 minutes) β-cell response to a glucose load calculated by the areas under the curve higher than basal insulin val-

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ues. The AIRG was assessed as the incremental area under the curve (calculated by the trapezoid rule) from 0 to 10 minutes of the FSIVGTT. The disposition index (which equals SI × AIRG), an index of β-cell function that takes account of prevailing insulin sensitivity and exploits the hyperbolic relationship between the 2, [33,40] was calculated by the method described by Kahn et al.[40]

HOMEOSTASIS MODEL OF ASSESSMENT OF INSULIN RESISTANCE

The HOMA-IR is an alternative method to assess insulin resistance and β-cell function on the basis of known relationships with fasting plasma glucose and serum insulin concentrations. The HOMA-IR was calculated by the following formula: fasting serum insulin concentration × fasting plasma glucose concentration/22.5.[41,42] The HOMA-IR was calculated by taking the mean of 3 fasting values (times, –10, –5, and 0).

STATISTICAL METHODS

The primary outcome variables were fasting plasma glucose and serum insulin levels, HOMA-IR, SI, SG, and AIRG. Covariates included lipid concentrations, waist-hip ratios, and the Modifiable Activity Questionnaire. Descriptive statistics are represented as mean ± SD. Within-group correlation coefficients were determined between indices of medication dose and blood levels, plasma glucose level, serum insulin level, 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 level, fasting serum insulin level, SI, HOMA-IR, SG, growth hormone level, cortisol level, serum lipid level, leptin level, BMI, skinfold (triceps, biceps, suprailiac, subscapular, body fat percentage), bioimpedance analysis of body fat, waist-hip ratios, widest hip circumference, Modifiable Activity Questionnaire, resting energy expenditure, dietary assessment variables, duration of illness, and duration of medication treatment. A closed testing procedure was used so that pairwise comparisons were only made if the overall group effect F test *P* value was less than .05. Categorical demographic variables were compared between groups using the Fisher exact test and included sex, race, diagnosis, use of selective serotonin reuptake inhibitors, and family history of diabetes mellitus. Continuous demographic variables were compared using analysis of variance and included age, duration of illness, and systolic and diastolic blood pressure. A *P* value less than .05 was used to test for statistical significance, and all statistical tests were 2-tailed.

RESULTS

Fifty subjects signed informed consent, but 6 withdrew consent prior to participation in the study. Additionally, 3 subjects' procedures were canceled the day of the procedure; 1 patient had not previously disclosed a history of diabetes mellitus, 1 patient was unable to fast, and 1 patient exhibited significant elevation in blood pressure prior to initiating the procedure. Another subject's procedure was terminated early secondary to symptomatic hypoglycemia (mild restlessness and sweating with stable vital signs) at time 90 minutes with a plasma glucose level of 34 mg/dL (1.89 mmol/L). Four subjects were eliminated because their BMI had increased to greater than 30 kg/m^2 at the time of the procedure. Data from 36 subjects were included in the analysis (12 clozapine, 12 olanzapine, 12 risperidone). Overall, the procedure was well tolerated, and all but 1 subject were able to complete all aspects of the study.

DEMOGRAPHICS

For the entire sample (N = 36), the mean ± SD age was 41.7 ± 10.6 years with a mean ± SD BMI of 25.4 ± 2.6 kg/m^2. Twenty-eight (78%) were white, 8 (22%) were African American, and 30 (83%) were male. The 3 treatment groups did not differ in age, sex, race, BMI, systolic or diastolic blood pressure, family history of diabetes mellitus, use of selective serotonin reuptake inhibitors, or duration of illness or medication treatment (**Table 1**).

BASELINE GLUCOSE METABOLISM

There was a nonsignificant difference among groups for fasting baseline plasma glucose concentrations (F_{33} = 2.63; *P* = .09) (**Table 2**). Fasting serum insulin concentrations differed among groups (F_{33} = 3.35; *P* = .047) (clozapine > olanzapine > risperidone) with significant differences between both clozapine and risperidone (t_{33} = 2.32; *P* = .03) and olanzapine and risperidone (t_{33} = 2.15; *P* = .04) but not clozapine and olanzapine (t_{33} = 0.17; *P* = .87).

GLUCOSE METABOLISM

The SI differed significantly among groups (F_{33} = 10.66; *P* < .001) (clozapine < olanzapine < risperidone), with subjects treated with clozapine and olanzapine exhibiting significant insulin resistance compared with subjects treated with risperidone (clozapine vs risperidone, t_{33} = –4.29; *P* < .001; olanzapine vs risperidone, t_{33} = –3.62; *P* = .001) but not clozapine and olanzapine (t_{33} = –0.67; *P* = .51). While SI varies across studies and ethnic groups, we rely on data from the general population to understand the direction of insulin resistance.[34,43-45] The SI is inversely proportional to insulin resistance (lower SI indicates greater insulin resistance or less insulin sensitivity).

Insulin resistance calculated by the HOMA-IR also differed significantly among groups (F_{33} = 4.92; *P* = .01) (clozapine > olanzapine > risperidone) treated with clozapine vs risperidone (t_{33} = 2.94; *P* = .006) and olanzapine vs risperidone (t_{33} = 2.42; *P* = .02) but not clozapine and olanzapine (t_{33} = 0.52; *P* = .61). Both the clozapine and olanzapine groups displayed elevations in HOMA-IR compared with the risperidone group. The HOMA-IR and SI were significantly inversely correlated for patients treated with olanzapine (*r* = –0.72; *P* = .01) and risperidone (*r* = –0.67; *P* = .02) but not clozapine (*r* = –0.41; *P* = .18). **Figure 1** and **Figure 2** show the distribution of the primary outcome measures of the 3 groups, plotted by age (Figure 1) and BMI (Figure 2).

Although there was no significant difference among groups for AIRG (F_{30} = 1.58; *P* = .22) or disposition index (F_{30} = 0.90; *P* = .42), there was a significant group effect difference in SG (F_{30} = 4.18; *P* = .02) (clozapine < olanzapine < risperidone) and significant differences between groups comparing clozapine with risperidone (t_{30} = –2.59; *P* = .02) and comparing olanzapine with risperidone (t_{30} = –2.34; *P* = .03) but not clozapine with olanzapine (t_{33} = –0.42; *P* = .68). The SG values could

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Table 1. Demographics of Participants Receiving Antipsychotic Agents*

Demographic	Clozapine (n = 12)	Olanzapine (n = 12)	Risperidone (n = 12)	*P* Value
Sex, No. (%) of patients				.85
Male	10 (83)	11 (92)	9 (75)	
Female	2 (17)	1 (8)	3 (25)	
Age, y	37.5 ± 11.2	44 ± 10.1	43.6 ± 10.1	.25
Race, No. (%) of patients				.95
African American	2 (17)	3 (25)	3 (25)	
White	10 (83)	9 (75)	9 (75)	
Family history of diabetes mellitus, No. (%) of patients				.89
Yes	5 (42)	4 (33)	4 (33)	
No	7 (58)	8 (67)	8 (67)	
Diagnosis, No. (%) of patients				.88
Schizoaffective disorder	1 (8)	1 (8)	3 (25)	
Schizophrenia	11 (92)	11 (92)	9 (75)	
Use of SSRI				.90
Yes	2 (17)	2 (17)	3 (25)	
No	10 (83)	10 (83)	9 (75)	
Duration of illness, y, 25th, 75th %	3, 19; 14.0 ± 11.1	11, 29; 21.4 ± 12.1	10, 30; 20.0 ± 12.1	.31
Dose of AA, mg	361 ± 130	17.7 ± 8.2	4.5 ± 2.0	
Total serum level of AA, ng/mL	596 ± 351	27.8 ± 15.2	43.0 ± 36.7	
Duration of medication administration, mo, 25th, 75th %	48, 91; 68.3 ± 28.9	12, 48; 29.5 ± 17.5	12, 60; 40.9 ± 33.7	.17
Systolic blood pressure, mm Hg	131 ± 15	122 ± 8	123 ± 9	.83
Diastolic blood pressure, mm Hg	81 ± 11	77 ± 14	72 ± 11	.34

Abbreviations: AA, antipsychotic agent; SSRI, selective serotonin reuptake inhibitor.
*Values are expressed as mean ± SD unless otherwise indicated.

Table 2. Glucose, Metabolism, Hormone, and Lipid Measurements in Participants*

Measurement	Clozapine (n = 12)	Olanzapine (n = 12)	Risperidone (n = 12)	*P* Value	Within-Group *P* Value: Clozapine-Risperidone	Clozapine-Olanzapine	Olanzapine-Risperidone
Fasting plasma glucose, mg/dL	97.8 ± 7.8	95.3 ± 13.8	88.9 ± 5.5	.09			
Fasting serum insulin, μIU/L	11.1 ± 8.1	10.6 ± 8.8	4.3 ± 3.2	.047	.03	.87	.04
Insulin sensitivity index, $\times 10 - 4$ min^{-1} per μU/mL	3.2 ± 4.1	4.5 ± 2.7	11.7 ± 6.9	<.001	<.001	.51	.001
HOMA-IR	2.7 ± 1.8	2.4 ± 1.9	0.9 ± 0.5	.01	.006	.61	.02
Glucose effectiveness, min^{-1}	0.0157 ± 0.005	0.0167 ± 0.01	0.0218 ± 0.01	.03	.02	.68	.03
AIRG (AUC, 0-10), μU/mL per 10 min	619 ± 428	801 ± 610	446 ± 389	.22			
Disposition index	2240 ± 1904	3379 ± 3588	4082 ± 3295	.42			
Growth hormone, ng/mL	0.059 ± 0.019	0.0122 ± 0.171	0.144 ± 0.115	.20			
Cortisol, μg/dL	12.8 ± 5.7	11.9 ± 2.8	11.6 ± 2.9	.75			
Total cholesterol, mg/dL	155.6 ± 31.2	182.6 ± 62.5	129.1 ± 26.7	.054			
HDL cholesterol, mg/dL	28.0 ± 9.4	35.8 ± 13.0	37.3 ± 10.1	.15			
LDL cholesterol, mg/dL	89.0 ± 39.6	94.4 ± 46.5	77.9 ± 23.3	.68			
Triglycerides, mg/dL	193.5 ± 145.4	205.9 ± 147.1	73.6 ± 17.4	.07			
Alkaline phosphate, mg/dL	91.8 ± 23.7	78.0 ± 24.3	66.3 ± 10.8	.02	.005	.11	.17
AST, min per mL^{-1}	28.2 ± 17.8	24.7 ± 8.5	23.2 ± 6.9	.59			
Leptin, ng/mL (controlling for sex)	11.4 ± 6.1	9.9 ± 11.2	6.9 ± 5.0	<.001	.02	.91	.03

Abbreviations: AIRG, acute insulin response to glucose; AST, aspartate aminotransferase; AUC, area under the curve; HDL, high-density lipoprotein. HOMA-IR, homeostasis model of assessment of insulin resistance; LDL, low-density lipoprotein.
SI conversions: To convert plasma glucose to micromoles per liter, multiply by 0.0555; serum insulin to picomoles per liter, 6.945; growth hormone to picomoles per liter, 44; cortisol to nanomoles per liter, 27.59; total cholesterol to micromoles per liter, 0.0259; HDL cholesterol to micromoles per liter, 0.0259; LDL cholesterol to micromoles per liter, 0.0259; triglycerides to micromoles per liter, 0.0113.
*Values are expressed as mean ± SD.

not be calculated for 3 subjects treated with clozapine because of a "floating point error."[34] The floating point error occurs in the face of severe insulin resistance, where SI is not distinguishable from zero and SG cannot be calculated.[46]

LIPIDS

There were no significant differences comparing total cholesterol (F_{25}=3.30; P=.054), high-density lipoprotein cho-

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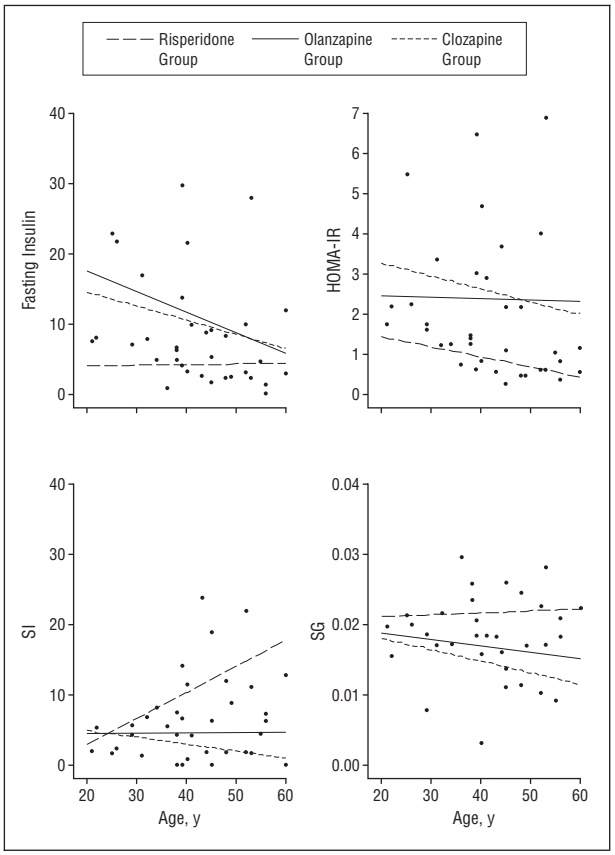

Figure 1. The results of primary outcome measures on glucose metabolism, plotted by age, in nonobese subjects with chronic schizophrenia treated with clozapine, olanzapine, or risperidone. HOMA-IR indicates homeostasis model of assessment of insulin resistance; SI, insulin sensitivity index; and SG, glucose effectiveness.

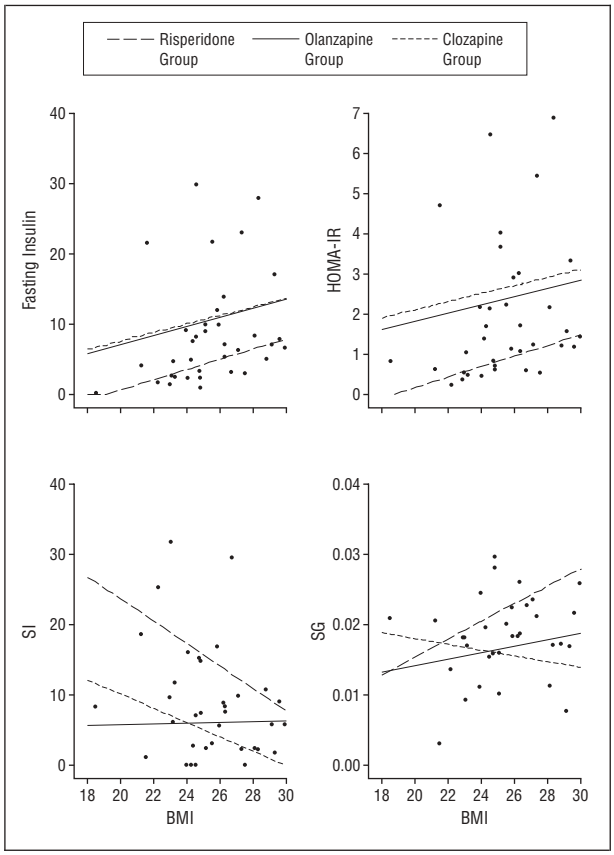

Figure 2. The results of primary outcome measures on glucose metabolism, plotted by body mass index (BMI), in nonobese subjects with chronic schizophrenia treated with clozapine, olanzapine, or risperidone. HOMA-IR indicates homeostasis model of assessment of insulin resistance; SI, insulin sensitivity index; and SG, glucose effectiveness.

lesterol (F_{25}=2.07; P=.15), low-density lipoprotein cholesterol (F_{23}=0.39; P=.68), and serum triglyceride levels (F_{24}=2.92; P=.07) among groups (Table 2).

NUTRITIONAL ASSESSMENT AND PHYSICAL ACTIVITY

There were no significant differences among groups for measurements of body cell mass percentage, biceps and triceps skinfold measurements, ideal body weight, ideal body weight percentage, total body fat measured by bioelectric impedance, widest hip measurements, Modifiable Activity Questionnaire total score, leisure activity level, and occupational activity level (**Table 3**). Additionally, the groups did not differ on measures of energy expenditure including resting energy expenditure.

However, subscapular skinfold measurements differed significantly among groups (F_{33}=3.30; P=.049) (clozapine>olanzapine>risperidone) (clozapine vs olanzapine, t_{33}=1.20; P=.24; clozapine vs risperidone, t_{33}=2.57; P=.02; and olanzapine vs risperidone, t_{33}=1.37; P=.18). Additionally, the waist-hip ratio significantly differed among groups (F_{33}=3.62; P=.038) (clozapine>olanzapine>risperidone), with differences between clozapine and risperidone (t_{33}=2.69; P=.01) but not between olanzapine and either the risperidone (t_{33}=1.47; P=.15) or clozapine groups (t_{33}=1.22; P=.23).

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, polyunsaturated fat, saturated fat, or total daily caloric intake or total kilocalories (kilojoules) per kilogram of body weight. Only percentage of protein (F_{33}=4.46; P=.02) and lactose (F_{33}=4.08; P=.03) intake differed significantly between groups.

CORTISOL, GROWTH HORMONE, AND LEPTIN LEVELS AND CORRELATIONS OF SERUM ANTIPSYCHOTIC AGENT LEVELS WITH MEASURES OF GLUCOSE METABOLISM

There were no significant among-group differences in fasting serum cortisol and growth hormone levels. However, as leptin concentrations differ between men and women, controlling for sex, there was a significant difference among groups (F_{32}=30.86; P<.001) (clozapine>olanzapine>risperidone) and between clozapine and risperidone (t_{32}=2.44; P=.02) and olanzapine and risperidone (t_{32}=2.30; P=.03) but not clozapine and olanzapine (t_{32}=0.11; P=.91). Within treatment groups, fasting plasma glucose and serum insulin levels, SI, and SG did not correlate with dose or serum antipsychotic

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Table 3. Anthropometric Measurements of Test Subjects*

Measurement	Clozapine (n = 12)	Olanzapine (n = 12)	Risperidone (n = 12)	*P* Value	Within-Group *P* Value		
					Clozapine-Risperidone	Clozapine-Olanzapine	Olanzapine-Risperidone
Body mass index, kg/m^2	25.7 ± 2.3	25.3 ± 3.3	25.0 ± 2.1	.81			
Bicep skinfold, mm	8.6 ± 3.2	6.8 ± 5.0	6.3 ± 3.6	.32			
Triceps skinfold, mm	18.1 ± 4.4	15.0 ± 6.3	14.2 ± 6.3	.23			
Subscapular skinfold, mm	19.2 ± 5.5	16.4 ± 6.7	13.1 ± 5.1	.049	.02	.24	.18
Suprailiac skinfold, mm	20.4 ± 6.4	21.7 ± 8.9	15.3 ± 6.2	.09			
Body cell mass, %	39.7 ± 3.1	41.5 ± 4.7	41.7 ± 5.6	.50			
Bioimpedance analysis, % body fat	25.3 ± 3.9	24.7 ± 7.0	23.3 ± 6.8	.69			
Waist circumference (iliac crest), cm	97.8 ± 9.4	95.7 ± 9.6	90.4 ± 7.6	.12			
Waist-hip ratio	0.99 ± 0.09	0.95 ± 0.07	0.91 ± 0.06	.04	.01	.23	.15
Widest hip circumference, cm	99.1 ± 9.2	100.6 ± 6.2	99.6 ± 6.3	.86			
Ideal body weight, %	117.0 ± 12.2	113.9 ± 13.6	104.3 ± 13.0	.06			
MAQ total score	16.0 ± 11.2	12.6 ± 15.5	8.5 ± 9.8	.34			
Occupational†	7.2 ± 9.0	5.1 ± 10.0	2.7 ± 4.3	.48			
Leisure†	8.8 ± 7.5	7.9 ± 12.5	6.4 ± 6.4	.82			
Resting energy expenditure, kcal/d	1804 ± 426	1747 ± 432	1613 ± 381	.52			

Abbreviation: MAQ, Modifiable Activity Questionnaire (average hours of activity per week).
SI conversion: To convert kilocalories to kilojoules, multiply by 4.2.
*Values are expressed as mean ± SD.
†Average hours of activity per week.

agent concentrations. Olanzapine serum levels correlated with AIRG at a trend level (r=0.55; P=.06), but olanzapine doses did not correlate with AIRG values. Insulin resistance calculated by HOMA-IR analysis correlated (positively) with olanzapine serum concentrations (r=0.66; P=.02) and, at a trend level, with clozapine doses (r=0.53; P=.09). Norclozapine serum concentrations did not correlate with measures of glucose metabolism, whereas 9-hydroxy-risperidone concentrations correlated with SG at a trend level (r=0.53; P=.07).

COMMENT

Our finding that nonobese subjects treated with clozapine and olanzapine displayed significant insulin resistance measured by both SI and HOMA-IR compared with subjects treated with risperidone is consistent with the findings reported by Newcomer et al[8] using a modified oral glucose tolerance test. While data from normal populations are informative in the direction of SI and glucose effectiveness, comparisons across studies are difficult secondary to minor differences in procedures as well as laboratory techniques. Insulin resistance, a major but not a necessary risk factor for diabetes mellitus, represents a potential pathway to type 2 diabetes mellitus over time. We would expect that patients who experience greater weight gain or BMI with these antipsychotic agents than the nonobese subjects in our study would exhibit even greater degrees of insulin resistance than we observed.[34]

Sowell et al[47] studied insulin secretion using a hyperglycemic-clamp technique, primarily used to assess insulin secretion and not insulin sensitivity, in normal subjects following a 15- to 17-day single-blind trial of olanzapine (n=17), risperidone (n=13), and placebo (n=18). There was a significant change in insulin sensitivity in the olanzapine group and not the risperidone group, consistent with our findings. The authors ascribed this change to weight gain, based on the regression analysis. As insulin response must be considered in the context of insulin sensitivity, which was not accurately measured in the study using a hyperglycemic clamp, the study did not adequately assess whether olanzapine or risperidone impaired insulin-secretion functioning. Additionally, the study may not have been adequate to detect differences because of the small sample size, brief exposure to antipsychotic drugs, and the possible difference in vulnerability in patients with schizophrenia compared with normal subjects.

Our finding of reduced glucose effectiveness in patients taking clozapine and olanzapine compared with risperidone is also consistent with findings reported in patients with type 2 diabetes mellitus. Whereas a reduced SG is characteristic of type 2 diabetes mellitus, and rarely has been reported in women treated with norgestrel, a reduction in SG is not found in obese subjects.[34,48] The lower SG values observed in patients treated with clozapine and olanzapine could result from several mechanisms, including reduced functioning of glucose transporters[49] or an impairment in the suppression of hepatic glucose production.[50]

A reduction in β-cell function was not observed in any of the treatment groups; however, considerable variability in AIRG and disposition index was apparent. Five of 36 subjects (all in the olanzapine or clozapine groups) exhibited markedly reduced AIRG in addition to reduced SI and SG. In fact, 2 of these individuals (1 treated with clozapine and 1 treated with olanzapine) developed type 2 diabetes mellitus within 2 years after the procedure was performed. While not statistically significant, the lower mean values for disposition index in subjects treated with clozapine and olanzapine suggests

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Table 4. Nutrient Intake in Subjects Treated With Atypical Antipsychotic Agents*

Measurement	Clozapine (n = 12)	Olanzapine (n = 12)	Risperidone (n = 12)	*P* Value
Total energy, kcal	2199 ± 1094	2583.6 ± 1386	1921 ± 585	.33
Total kcal/kg body weight	28.1 ± 12.8	31.9 ± 15.0	26.5 ± 8.6	.56
Carbohydrate, % total energy	49.8 ± 5.1	51.0 ± 9.4	57.4 ± 9.1	.06
Protein, % total energy	16.7 ± 3.5	14.8 ± 3.1	12.9 ± 2.7	.02
Total fat, g	85.0 ± 45.6	98.7 ± 60.1	64.1 ± 20.7	.18
Fat, % total energy	34.3 ± 5.6	33.8 ± 8.4	29.7 ± 5.4	.18
Cholesterol, mg	335 ± 231	326.6 ± 229.1	272.7 ± 129.0	.72
Polyunsaturated fat–saturated fat ratio	0.5 ± 0.2	0.8 ± 0.7	0.6 ± 0.3	.26
Saturated fat, g	33.4 ± 20.3	35.0 ± 26.0	21.2 ± 4.7	.17
Starch, g	113.2 ± 71.0	124.9 ± 94.5	108.3 ± 39.0	.25
Fiber, g	15.3 ± 7.2	14.7 ± 7.3	13.5 ± 4.8	.50
Glucose, g	28.7 ± 18.1	34.6 ± 26.0	38.7 ± 19.5	.56
Fructose, g	27.9 ± 19.3	33.4 ± 29.0	34.2 ± 18.1	.78
Galactose, g	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	.33
Lactose, g	22.7 ± 17.5	14.0 ± 8.2	8.5 ± 7.0	.03
Maltose, g	1.6 ± 1.5	2.2 ± 1.8	2.9 ± 2.7	.42
Sucrose, g	40.1 ± 25.0	66.4 ± 40.2	58.4 ± 38.4	.25
Alcohol, g	0.1 ± 0.2	3.1 ± 7.1	3.4 ± 5.7	.25

SI conversion: To convert kilocalories to kilojoules, multiply by 4.2.
*Values are expressed as mean ± SD.

that these drugs may restrict the normal β-cell response to the development of insulin resistance.

Although treatment groups were matched for weight, both clozapine and olanzapine are associated with greater mean weight gain than other atypical antipsychotic agents,[51] and our sample significantly differed on waist-hip ratio and subscapular skinfold measurements. Waist measures may thus be a better predictor of insulin resistance and risk for type 2 diabetes mellitus than weight gain in patients treated with atypical antipsychotic agents. Visceral adiposity has been associated with hyperinsulinemia, dyslipidemia, impaired glucose tolerance, and increased risk for cardiovascular disease.[52-54] A study of 2964 elderly men and women found that approximately one third of men and less than half of women with type 2 diabetes were obese.[55] Despite similar amounts of subcutaneous thigh fat, intermuscular and visceral abdominal fat were higher in subjects with type 2 diabetes and impaired glucose tolerance than in subjects with normal glucose tolerance.[55] Finally, there was a significant difference in leptin levels, controlling for sex, in our study. Leptin is important for the control of body weight and has been proposed to be a link between obesity, insulin resistance syndrome, and treatment with some antipsychotic agents.[56,57] Differences observed may be related to differences in body fat distribution.

It is possible that schizophrenia is associated with insulin resistance and diabetes mellitus independent of pharmacological treatment.[58] First-episode, drug-naive patients with schizophrenia (n = 26) were found to have higher fasting plasma glucose, insulin, and cortisol levels compared with age-matched healthy subjects.[22] Elevations of serum cortisol levels have previously been linked to the acute stress of psychosis[59,60] and could contribute to impaired glycemic control. In our sample of psychiatrically stable subjects with schizophrenia, serum cortisol levels were not elevated, which may reflect the tendency of antipsychotic agents to decrease plasma cortisol levels.[61]

There are a number of limitations to this study. Because drug treatment was not randomized and assessment was cross-sectional, the finding of an association between olanzapine and clozapine treatment and impairment of glucose metabolism cannot be conclusively established as a causal relationship. In addition, the exclusion of obese subjects may limit the generalizability of our findings. Nevertheless, the cross-sectional assessment of psychiatrically stable, nonobese patients well-matched for type 2 diabetes mellitus risk factors does overcome other important methodological considerations as discussed earlier, and our findings, which are consistent with other reports in the literature, raise potentially important clinical concerns. Future studies that include larger samples, unmedicated patients, and varying durations of prospective antipsychotic agent exposure can address some of the limitations of this study design. Finally, because the mean SI in subjects treated with risperidone was greater than reported in the general population, the potential for type 1 error exists; therefore, replication of these findings are necessary.

CONCLUSIONS

Psychiatrists and primary care professionals should be aware that patients treated with clozapine and olanzapine may be at increased risk for insulin resistance, even if not obese. Insulin resistance is associated with hyperlipidemia, hypertension, and cardiovascular disease and over time may increase the risk for diabetes mellitus in vulnerable individuals. Patients treated with these agents should be routinely screened, counseled to reduce risk, and provided early interventions.[3,62] Established guidelines for monitoring and assessing patients' risk for dia-

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betes and cardiovascular disease exist.[63,64] Waist and hip measurements, along with monitoring lipid levels, may be a useful tool for patient follow-up and assessing the change in risk for insulin resistance and type 2 diabetes mellitus, consistent with recent guidelines.[64]

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REFERENCES

1. Harris E, Barraclough B. Excess mortality of mental disorder. *Br J Psychiatry*. 1998;173:11-53.
2. Newman SC, Bland RC. Mortality in a cohort of patients with schizophrenia: a record linkage study. *Can J Psychiatry*. 1991;36:239-245.
3. Henderson DC. Atypical antipsychotic-induced diabetes mellitus: how strong is the evidence? *CNS Drugs*. 2002;16:77-89.
4. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry*. 2001;62(suppl 7):22-31.
5. Mir S, Taylor D. Atypical antipsychotics and hyperglycaemia. *Int Clin Psychopharmacol*. 2001;16:63-73.
6. Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. *J Clin Psychiatry*. 1999;60:783-791.
7. Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *J Clin Psychiatry*. 2000;61:742-749.
8. Newcomer JW, Haupt DW, Fucetola R, Melson AK, Schweiger JA, Cooper BP, Selke G. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry*. 2002;59:337-345.
9. Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, Goff DC. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry*. 2000;157:975-981.
10. Caro JJ, Ward A, Levinton C, Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry*. 2002;63:1135-1139.
11. Sernyak MJ, Leslie DL, Alarcon RD, Losonczy MF, Rosenheck R. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. *Am J Psychiatry*. 2002;159:561-566.
12. Koro CE, Fedder DO, L'Italien GJ, Weiss SS, Magder LS, Kreyenbuhl J, Revicki DA, Buchanan RW. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ*. 2002;325:243.
13. Lund BC, Perry PJ, Brooks JM, Arndt S. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. *Arch Gen Psychiatry*. 2001;58:1172-1176.
14. Gianfrancesco FD, Grogg AL, Mahmoud RA, Wang RH, Nasrallah HA. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. *J Clin Psychiatry*. 2002;63:920-930.
15. Kornegay CJ, Vasilakis-Scaramozza C, Jick H. Incident diabetes associated with antipsychotic use in the United Kingdom general practice research database. *J Clin Psychiatry*. 2002;63:758-762.
16. Wang PS, Glynn RJ, Ganz DA, Schneeweiss S, Levin R, Avorn J. Clozapine use and risk of diabetes mellitus. *J Clin Psychopharmacol*. 2002;22:236-243.
17. Buse JB, Cavazzoni P, Hornbuckle K, Hutchins D, Breier A, Jovanovic L. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. *J Clin Epidemiol*. 2003;56:164-170.
18. Koller E, Schneider B, Bennett K, Dubitsky G. Clozapine associated diabetes. *Am J Med*. 2001;111:716-723.
19. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. *Pharmacotherapy*. 2002;22:841-852.
20. Koller EA, Cross JT, Doraiswamy PM, Schneider BS. Risperidone-associated diabetes mellitus: a pharmacovigilance study. *Pharmacotherapy*. 2003;23:735-744.
21. Henderson DC. Clinical experience with insulin resistance, diabetic ketoacidosis, and type 2 diabetes mellitus in patients treated with atypical antipsychotic agents. *J Clin Psychiatry*. 2001;62(suppl 27):10-14; discussion 40-41.
22. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psychiatry*. 2003;160:284-289.
23. Valdes CT, Elkind-Hirsch KE. Intravenous glucose tolerance test-derived insulin sensitivity changes during the menstrual cycle. *J Clin Endocrinol Metab*. 1991;72:642-646.
24. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for *DSM-III-R* (SCID), I: history, rationale, and description. *Arch Gen Psychiatry*. 1992;49:624-629.
25. 1983 Metropolitan height and weight tables. *Stat Bull Metropol Life Insur Co*. 1983;64:3-9.
26. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr*. 1974;32:77-97.
27. Lange TG, Roche AF, Martorell R. *Anthropometric Standardization Reference Manual*. Champaign, Ill: Human Kinetics Books; 1988.
28. Schakel SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nutrient database. *J Am Diet Assoc*. 1988;88:1268-1271.
29. Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. *J Appl Physiol*. 1986;60:1327-1332.
30. Kushner RF. Bioelectrical impedance analysis: a review of principles and applications. *J Am Coll Nutr*. 1992;11:199-209.
31. Ritz RCJ. *Indirect Calorimetry: Monitoring in Respiratory Care*. St Louis, Mo: Mosby-Yearbook, Inc; 1993.
32. Pereira MA, FitzerGerald SJ, Gregg EW, Joswiak ML, Ryan WJ, Suminski RR, Utter AC, Zmuda JM. A collection of physical activity questionnaires for health-related research. *Med Sci Sports Exerc*. 1997;29(suppl 6):S1-S205.
33. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest*. 1981;68:1456-1467.
34. Bergman RN. Lilly lecture 1989: toward physiological understanding of glucose tolerance: minimal-model approach. *Diabetes*. 1989;38:1512-1527.
35. Bergman RN, Watanabe R, Rebrin K, Ader M, Steil G. Toward an integrated phenotype in pre-NIDDM. *Diabet Med*. 1996;13:S67-S77.
36. McNamara J, Schaefer E. Automated enzymatic standardized lipid analyses for plasma lipoprotein fractions. *Clin Chim Acta*. 1987;166:1-8.
37. Warnick G, Benderson J, Albers J. Dextran sulfate-Mg2+ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. *Clin Chem*. 1982;28:1379-1388.
38. Friedewald W, Levy R, Fredrickson D. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499-502.

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39. Bergman RN, Prager R, Volund A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J Clin Invest*. 1987;79:790-800.
40. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects: evidence for a hyperbolic function. *Diabetes*. 1993;42:1663-1672.
41. Perez-Martin A, Raynaud E, Hentgen C, Bringer J, Mercier J, Brun JF. Simplified measurement of insulin sensitivity with the minimal model procedure in type 2 diabetic patients without measurement of insulinemia. *Horm Metab Res*. 2002; 34:102-106.
42. Hermans MP, Levy JC, Morris RJ, Turner RC. Comparison of insulin sensitivity tests across a range of glucose tolerance from normal to diabetes. *Diabetologia*. 1999;42:678-687.
43. Haffner SM, Howard G, Mayer E, Bergman RN, Savage PJ, Rewers M, Mykkanen L, Karter AJ, Hamman R, Saad MF. Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM: the Insulin Resistance Atherosclerosis Study. *Diabetes*. 1997;46:63-69.
44. Watanabe RM, Azen CG, Roy S, Perlman JA, Bergman RN. Defects in carbohydrate metabolism in oral contraceptive users without apparent metabolic risk factors. *J Clin Endocrinol Metab*. 1994;79:1277-1283.
45. Haffner SM, D'Agostino R Jr, Festa A, Bergman RN, Mykkanen L, Karter A, Saad MF, Wagenknecht LE. Low insulin sensitivity (S(i) = 0) in diabetic and nondiabetic subjects in the Insulin Resistance Atherosclerosis Study: is it associated with components of the metabolic syndrome and nontraditional risk factors? *Diabetes Care*. 2003;26:2796-2803.
46. Sowell MO, Mukhopadhyay N, Cavazzoni P, Shankar S, Steinberg HO, Breier A, Beasley CM Jr, Dananberg J. Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone, or placebo. *J Clin Endocrinol Metab*. 2002;87:2918-2923.
47. Best J, Kahn S, Ader M, Watanabe R, Ni T, Bergman R. Role of glucose effectiveness in the determination of glucose tolerance. *Diabetes Care*. 1996;19: 1018-1030.
48. Dwyer DS, Pinkofsky HR, Lin Y, Bradley RJ. Antipsychotic drugs affect glucose uptake and the expression of glucose transporters in PC 12 cells. *Prog Neuropsychopharmacol Biol Psychiatry*. 1999;23:69-80.
49. Ader M, Catalano K, Ionut V, Kim S, Huecking K, Richey J, Bergman RN. Differential metabolic effects between atypical antipsychotics in normal dogs. Poster presented at: the 63rd Scientific Sessions of the American Diabetes Association Meeting; June 15, 2003; New Orleans, La.
50. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156:1686-1696.
51. Macor C, Ruggeri A, Mazzonetto P, Federspil G, Cobelli C, Vettor R. Visceral adipose tissue impairs insulin secretion and insulin sensitivity but not energy expenditure in obesity. *Metabolism*. 1997;46:123-129.
52. Pi-Sunyer FX. The medical risks of obesity. *Obes Surg*. 2002;12(suppl 1):6S-11S.
53. Pi-Sunyer F. Medical hazards of obesity. *Ann Intern Med*. 1993;119:655-660.
54. Goodpaster BH, Krishnaswami S, Resnick H, Kelley DE, Haggerty C, Harris TB, Schwartz AV, Kritchevsky S, Newman AB. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes Care*. 2003;26:372-379.
55. Hagg S, Soderberg S, Ahren B, Olsson T, Mjorndal T. Leptin concentrations are increased in subjects treated with clozapine or conventional antipsychotics. *J Clin Psychiatry*. 2001;62:843-848.
56. Herran A, Garcia-Unzueta MT, Amado JA, de La Maza MT, Alvarez C, Vazquez-Barquero JL. Effects of long-term treatment with antipsychotics on serum leptin levels. *Br J Psychiatry*. 2001;179:59-62.
57. Mukherjee S, Decina P, Bocola V, Saracini F, Scapicchio PL. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry*. 1996;37:68-73.
58. Christie JE, Whalley LJ, Dick H, Blackwood DH, Blackburn IM, Fink G. Raised plasma cortisol concentrations a feature of drug-free psychotics and not specific for depression. *Br J Psychiatry*. 1986;148:58-65.
59. Whalley LJ, Christie JE, Blackwood DH, Bennie J, Dick H, Blackburn IM, Fink G. Disturbed endocrine function in the psychoses, I: disordered homeostasis or disease process? *Br J Psychiatry*. 1989;155:455-461.
60. Wik G. Effects of neuroleptic treatment on cortisol and 3-methoxy-4-hydroxyphenylethyl glycol levels in blood. *J Endocrinol*. 1995;144:425-429.
61. Henderson DC. Diabetes mellitus and other metabolic disturbances induced by atypical antipsychotic agents. *Curr Diab Rep*. 2002;2:135-140.
62. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry*. 2004;65:267-272.
63. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-3421.
64. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596-601.

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