Abnormalities in Glucose Regulation During Antipsychotic Treatment of Schizophrenia

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Background: Hyperglycemia and type 2 diabetes mellitus are more common in schizophrenia than in the general population. Glucoregulatory abnormalities have also been associated with the use of antipsychotic medications themselves. While antipsychotics may increase adiposity, which can decrease insulin sensitivity, disease- and medication-related differences in glucose regulation might also occur independent of differences in adiposity.

Methods: Modified oral glucose tolerance tests were performed in schizophrenic patients (n=48) receiving clozapine, olanzapine, risperidone, or typical antipsychotics, and untreated healthy control subjects (n=31), excluding subjects with diabetes and matching groups for adiposity and age. Plasma was sampled at 0 (fasting), 15, 45, and 75 minutes after glucose load.

Results: Significant time × treatment group interactions were detected for plasma glucose (F_{12,222}=4.89, P<.001) and insulin (F_{12,171}=2.10, P=.02) levels, with significant treatment group interactions in adiposity.

Conclusion: Antipsychotic treatment of nondiabetic patients with schizophrenia can be associated with adverse effects on glucose regulation, which can vary in severity independent of adiposity and potentially increase long-term cardiovascular risk.
SUBJECTS AND METHODS

SUBJECTS

Forty-eight patients with schizophrenia and 31 healthy adult control subjects participated after giving written informed consent. Subjects included individuals who had participated in modified OGGTs conducted over several years, studying the cognitive effects of glucose and insulin.7,8 Studies were approved by the institutional review boards for Washington University School of Medicine, St Louis, Mo, and the Department of Mental Health, Jefferson City, Mo. Patients with schizophrenia were recruited through outpatient clinics, as well as a single inpatient unit, associated with Washington University School of Medicine. Patients who had participated in a similar research project were excluded. Patients were matched for body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), an indicator of adiposity that is strongly predictive of changes in glucose regulation,7,13 and age, another predictor of glucoregulatory status,14 and balanced for ethnicity. No previously recruited study subjects were included in this study.

Baseline clinical data as well as mean doses of the primary antipsychotic treatments for each patient group are listed in Table 1. Seventeen of the 48 patients were receiving typical antipsychotic therapy. Of these 17 subjects, 11 were receiving oral agents only (haloperidol decanoate, trifluoperazin hydrochloride, and perphenazine), 1 was receiving oral agents in combination with depot preparations (haloperidol decanoate, 200 mg/4 wk, plus haloperidol in 1 patient and fluphenazine decanoate, 12.5 mg/2 wk, plus fluphenazine in 1 patient), and 4 patients were receiving haloperidol decanoate as their only antipsychotic treatment (mean±SD, 91.67±14.43 mg/4 wk). Mean antipsychotic dose for typical oral agents (n=13; haloperidol equivalents) is listed in Table 1. Eleven of the 17 subjects taking typical agents were receiving anticholinergics (benztropine mesylate [mean daily dose, 2.21±1.35 mg] in 7 and trifluproperazine hydrochloride [mean daily dose, 4.30±3.38 mg] in 4), 3 of 17 were receiving antidepressants (sertraline hydrochloride, 150 mg/d; sertraline, 50 mg/d, plus buspirone hydrochloride, 10 mg/d; and amitriptyline hydrochloride, 10 mg/d, in 1 each), 2 were receiving benzodiazepines (temazepam, 30 mg/d, and lorazepam, 1.5 mg/d, in 1 each), and 1 patient was receiving citalopram (400 mg/d). Ten of 48 patients were receiving risperidone (Table 1). Of those 10, 2 were receiving anticholinergics (benztropine mesylate, 2 mg/d, and diphenhydramine, 50 mg/d, in 1 each), and 4 were receiving antidepressants (buspirone hydrochloride, 5 mg/d, in 3 each and sertraline, 50 mg/d, in 1 each).

whether the limited number of reports for risperidone, despite extensive use, reflects less frequent or smaller glucoregulatory effects similar to haloperidol, or a reporting bias. Other currently published reports concerning risperidone describe uncomplicated use in patients with preexisting diabetes.9,60,61

Increased abdominal adiposity can decrease skeletal muscle insulin sensitivity and contribute to hyperglycemia.62,63 Antipsychotic treatments produce weight gain of varying magnitude,64-68 with larger effects for agents like clozapine66-69 and olanzapine.69-71 Therefore, reported changes in glucose regulation during antipsychotic treatment have been assumed to be entirely secondary to increased adiposity. However, clinical reports suggest that changes in glucose regulation can also be observed without differences in weight,4,27,35,56,67,70 suggesting the potential for additional adverse effects that may not require drug-induced increases in adiposity.

Studies from this laboratory concerning glucose and insulin effects on cognitive function7,8,72 provided glucoregulatory data concerning different antipsychotics. The
ride, 40 mg/d, plus sertraline, 30 mg/d; clomipramine hydrochloride, 75 mg/d; fluoxetine, 20 mg/d; and bupropion, 300 mg/d, in 1 each). In addition, 1 subject was receiving adjunctive haloperidol decanoate (100 mg/4 wk).

Twelve of the 48 patients were receiving olanzapine (Table 1). Of these, 2 were being treated with benzotropine mesylate (mean daily dose, 1.25 ± 1.06 mg), 2 were receiving antidepressants, (citalopram, 20 mg/d, and bupropion, 250 mg/d, in 1 each), 1 was receiving clonazepam (3 mg/d), and 4 were receiving other psychotropic agents (valproic acid [mean daily dose, 833.33 ± 381.88 mg] in 3 and lithium carbonate, 600 mg/d, in 1). In addition, 2 subjects were receiving adjunctive haloperidol (decanoate, 75 mg/4 wk, and hydrochloride, 10 mg/d, in 1 each).

Nine of the 48 patients were receiving clozapine (Table 1). Within the clozapine group, 2 patients were receiving benzotropine mesylate (mean [SD] daily dose, 5.00 ± 1.41 mg), and 2 were receiving antidepressants (sertraline, 50 mg/d, and paroxetine, 10 mg/d, in 1 each).

PROCEDURE
Study protocols were approved and conducted through the General Clinical Research Center at Washington University School of Medicine. A modified OGTT was used. Standard clinical OGTTs do not require a fasting baseline and only measure plasma glucose level at 120 minutes after load. For this study, subjects had fasting (baseline) and multiple postload (15, 45, and 75 minutes) plasma samples for glucose, insulin, C-peptide, glucagon, and cortisol, originally intended to characterize glucose regulation during administration of a cognitive battery of similar length. Although the standard 120-minute duration used for diagnostic testing may offer additional sensitivity to separate diabetic and nondiabetic subjects, this study excluded diabetic subjects. After at least a 9-hour overnight fast, subjects came to the laboratory between approximately 8 and 9 AM and had an intravenous catheter placed in the nondominant upper extremity for blood sampling. After baseline sampling, subjects consumed a 453.5-g (16-oz) orange-flavored beverage containing 50 g of anhydrous dextrose powder. Sixty-four milligrams of sodium saccharin was added to the dextrose beverage to make taste comparable with that of a placebo (saccharin) control used for the cognitive studies. Plasma glucose level was acutely monitored during the OGTT with a blood glucose meter (SureStep; LifeScan, Milpitas, Calif) or a glucose analyzer (Beckman Instruments). Plasma insulin and C-peptide, glucagon, and cortisol concentrations were measured by radioimmunoassay.

DATA ANALYSIS
Data for plasma glucose level, BMI, and age within each treatment group approximated normal distributions, without evidence of significant heteroscedasticity for plasma glucose (Table 2). Analysis of variance (ANOVA) was used to test the primary study hypothesis that different antipsychotic treatments would be associated with alterations in plasma glucose level independent of differences in adiposity. For the main models, mixed-design ANOVAs were constructed with 1 within-subjects repeated measure (time), 1 between-subject factor (treatment group), and either plasma glucose or insulin values as dependent variables. Significant time × treatment condition interactions were further analyzed with factorial ANOVA to test the effect of treatment group at each time point, with Bonferroni-Dunn post hoc tests used to compare individual treatment conditions. The overall significance level was set at P = .05. In the Bonferroni-Dunn post hoc tests, this corresponds to the assignment of statistical significance for P values less than .005.

To ensure group comparability, ANOVA was used to test for an effect of treatment group on either BMI or age. In addition to effects of BMI and age, variables such as race and sex may also be associated with differences in glucose regulation. As an additional precaution against founders to the interpretation of the results, each of these variables was individually added as either a covariate term (analysis of covariance) or factor to the main model for glucose. The relationship of symptom severity (BPRS total) to glucose and insulin levels was explored by means of Spearman rank-order correlations. Data were analyzed with Statview/SuperANOVA software (SAS Institute Inc, Cary, NC).

Insulin resistance (IR) and decreased insulin secretion due to decreased beta-cell function can be involved in type 2 diabetes mellitus. Homeostasis model assessment (HOMA) has been used by Haffner et al and others to assess IR and beta-cell function on the basis of the known relationship between fasting glucose and insulin concentrations. The HOMA measures of IR have been well validated for characterizing diabetes and impaired glucose tolerance in population-based studies. Differences in HOMA IR were tested across specific treatment groups, indicated by significant group comparisons for plasma glucose level in the main analysis, calculating HOMA IR by means of a previously described formula: HOMA IR = [fasting insulin (µU/mL) × fasting glucose (mmol/L)]/22.5.

GROUP-RELATED DIFFERENCES IN FASTING AND POSTLOAD PLASMA GLUCOSE LEVEL
Significant differences in plasma glucose levels across treatment groups were observed at all time points, beginning at the fasting baseline measurement (Figure 1 and Table 2). In the primary ANOVA model, a significant time × treatment group interaction was detected for plasma glucose level (F12,222 = 4.89, P < .001), with signifi-

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cant main effects of time (F3,222 = 166.52, P < .001) and treatment group (F4,74 = 12.94, P < .001). In separate ANOVAs for each time point, the effect of treatment group on plasma glucose concentration was significant at 0 minutes (fasting; F4,74 = 11.20, P < .001), 15 minutes (F4,74 = 6.79, P < .001), 45 minutes (F4,74 = 9.66, P < .001), and 75 minutes after glucose load (F4,74 = 10.34, P < .001). Bonferroni-Dunn post hoc comparisons indicate that olanzapine-treated patients had significant (approximately 1.0-1.5 SDs) elevations in fasting and postload plasma glucose level at all measured time points, in comparison with untreated healthy control subjects and patients receiving typical antipsychotic treatment (Figure 1 and Table 2; P < .005 for both comparisons at all time points). Clozapine-treated patients had significant (approximately 1.0-1.5 SDs) elevations in fasting and 75-minute postload plasma glucose levels, again in comparison with both untreated healthy controls and patients taking typical antipsychotics (Figure 1; P < .005 for both comparisons at both time points). Mean plasma glucose level for clozapine-treated subjects was still rising at the final measurement time point. Risperidone-treated subjects had significant (approximately 1.0-1.5 SDs) elevations in fasting as well as 45- and 75-minute postload plasma glucose

Table 1. Descriptive Statistics for Treated Patients With Schizophrenia and Untreated Healthy Control Subjects Receiving Modified Oral Glucose Tolerance Tests*

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>Age, y</th>
<th>BMI</th>
<th>Ethnicity, No.</th>
<th>Sex, No.</th>
<th>BPRS Total Score</th>
<th>Dose†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 31)</td>
<td>39.61 ± 12.26</td>
<td>26.26 ± 5.82</td>
<td>White/African/Asian</td>
<td>12/19</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Typical (n = 17)</td>
<td>42.65 ± 13.17</td>
<td>24.70 ± 3.85</td>
<td></td>
<td>9/8/0</td>
<td>30.30 ± 9.97</td>
<td>9.77 ± 6.35</td>
</tr>
<tr>
<td>Clozapine (n = 9)</td>
<td>36.67 ± 6.42</td>
<td>27.81 ± 4.11</td>
<td>3/5/1</td>
<td>6/3</td>
<td>34.78 ± 12.96</td>
<td>480.56 ± 234.43</td>
</tr>
<tr>
<td>Olanzapine (n = 12)</td>
<td>37.42 ± 7.67</td>
<td>28.57 ± 5.95</td>
<td>2/19/0</td>
<td>11/1</td>
<td>26.00 ± 4.03</td>
<td>17.09 ± 5.42</td>
</tr>
<tr>
<td>Risperidone (n = 10)</td>
<td>38.10 ± 6.72</td>
<td>28.84 ± 4.44</td>
<td>5/5/0</td>
<td>10/0</td>
<td>29.11 ± 9.71</td>
<td>5.80 ± 1.55</td>
</tr>
</tbody>
</table>

*Data are mean ± SD or frequency distribution. BMI indicates body mass index; BPRS, Brief Psychiatric Rating Scale.
†See “Subjects and Methods” section; dosages for subjects who were taking other typical drugs were converted to haloperidol equivalents.

Table 2. Additional Plasma Measurements During Modified Oral Glucose Tolerance Tests in Treated Patients With Schizophrenia and Healthy Control Subjects*

<table>
<thead>
<tr>
<th>Measurement and Subject Group</th>
<th>Time Points, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>Glucose, mg/dL</td>
<td>74.94 ± 10.13</td>
</tr>
<tr>
<td>Typical (n = 17)</td>
<td>77.94 ± 9.81</td>
</tr>
<tr>
<td>Clozapine (n = 9)</td>
<td>90.89 ± 11.30</td>
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<tr>
<td>Olanzapine (n = 12)</td>
<td>93.47 ± 8.50</td>
</tr>
<tr>
<td>Risperidone (n = 10)</td>
<td>86.60 ± 8.80</td>
</tr>
<tr>
<td>Insulin, mg/dL</td>
<td>10.14 ± 9.92</td>
</tr>
<tr>
<td>Clozapine (n = 6)</td>
<td>18.1 ± 18.51</td>
</tr>
<tr>
<td>Olanzapine (n = 12)</td>
<td>12.42 ± 12.11</td>
</tr>
<tr>
<td>Risperidone (n = 9)</td>
<td>8.41 ± 4.30</td>
</tr>
<tr>
<td>Glucagon, pg/mL</td>
<td>17.34 ± 11.77</td>
</tr>
<tr>
<td>Typical (n = 12)</td>
<td>14.18 ± 6.46</td>
</tr>
<tr>
<td>Clozapine (n = 6)</td>
<td>14.92 ± 4.21</td>
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<tr>
<td>Olanzapine (n = 11)</td>
<td>10.95 ± 6.10</td>
</tr>
<tr>
<td>Risperidone (n = 10)</td>
<td>11.96 ± 5.46</td>
</tr>
<tr>
<td>Cortisol, mg/dL</td>
<td>74.71 ± 18.51</td>
</tr>
<tr>
<td>Typical (n = 7)</td>
<td>64.53 ± 13.19</td>
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<tr>
<td>Clozapine (n = 3)</td>
<td>74.83 ± 19.46</td>
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<tr>
<td>Olanzapine (n = 6)</td>
<td>69.28 ± 21.77</td>
</tr>
<tr>
<td>Risperidone (n = 9)</td>
<td>83.04 ± 46.24</td>
</tr>
<tr>
<td>C-peptide, ng/mL</td>
<td>0.52 ± 0.25</td>
</tr>
<tr>
<td>Typical (n = 7)</td>
<td>1.14 ± 0.74</td>
</tr>
<tr>
<td>Clozapine (n = 2)</td>
<td>2.45 ± 0.78</td>
</tr>
<tr>
<td>Olanzapine (n = 7)</td>
<td>1.86 ± 0.79</td>
</tr>
<tr>
<td>Risperidone (n = 8)</td>
<td>1.89 ± 1.12</td>
</tr>
</tbody>
</table>

*Data are mean ± SD. To convert glucose values to millimoles per liter, multiply by 0.0555.
EVALUATING ADDITIONAL CLINICAL AND TREATMENT EFFECTS ON PLASMA GLUCOSE LEVEL

Increases in BMI and age, the latter related to increased adiposity, are associated with hyperglycemia, and both variables were well matched across treatment groups (Table 1); no significant effect of treatment group was detected for BMI (F_{4,74}=1.64, P=.18) or age (F_{4,74}=0.67, P=.62). As an additional precaution, however, BMI was separately added as a covariate term in a reanalysis of the main model for plasma glucose. This addition did not alter the level of significance of the time \times treatment group interaction (F_{12,207}=1.93, P=.03), or the main effect of time (F_{12,207}=4.11, P=.007), while reducing the main effect of treatment group (F_{4,68}=1.88, P=.12). No 2-way interaction between group and BMI (F_{4,69}=1.33, P=.27) and no 3-way interaction between time, treatment group, and BMI (F_{12,207}=1.51, P=.12) was detected. We also explored interactions with ethnicity and sex, which might complicate the interpretation of results. The significant additional effect of ethnicity or sex to the main ANOVA model for plasma glucose did not alter the significance level of the time \times treatment group interaction (F_{12,207}=3.71, P<.001, and F_{12,210}=3.76, P<.001, respectively), or the main effects of time (F_{12,207}=117.51, P<.001, and F_{12,210}=43.67, P<.001, respectively), or treatment group (F_{4,68}=10.40, P<.001, and F_{4,69}=6.09, P<.001, respectively). No 2-way interactions between treatment group and either ethnicity or sex (F_{4,68}=1.53, P=.20, and F_{4,69}=0.40, P=.76, respectively) and no 3-way interactions between time, treatment group, and either race or sex (F_{12,207}=1.27, P=.24, and F_{12,210}=0.64, P=.76, respectively) were detected.

Additional reanalyses concerning plasma glucose level were performed to address a variety of possible confounders to the interpretation of the results of the main ANOVA model. Restricting the typical control group to treatment with haloperidol (n=10), previously associated with minimal changes in glucose control, and excluding subjects (n=3) treated with atypical antipsychotics plus typical decanoate preparations, could provide a typical control group with the smallest risk of glucose regulatory effects and avoid modulating any effects associated with atypical agents. The significant time \times treatment group interaction for plasma glucose level was not altered in this reanalysis by restricting the typical antipsychotic treatment group to haloperidol (F_{12,102}=4.90, P<.001), with persistent main effects of time (F_{3,102}=135.59, P<.001) and treatment condition (F_{3,64}=11.99, P<.001). Significant main effects of time condition were still observed at 0 minutes (F_{3,64}=10.62, P<.001), 15 minutes (F_{3,64}=5.73, P<.001), 45 minutes (F_{3,64}=9.70, P<.001), and 75 minutes (F_{3,64}=9.78, P<.001) after load, with no changes in significant Bonferroni-Dunn comparisons except the detection of a single additional significant comparison between risperidone and haloperidol treatment at 45 minutes only. Excluding subjects receiving concomitant treatment with antidepressants and/or mood stabilizers (n=15) could reduce concerns that drug-drug interactions contributed to effects observed in the main analysis. In this reanalysis, the significant time \times treatment group interaction for plasma glucose was retained (F_{3,177}=3.86, P<.001), with persistent main effects of time (F_{3,177}=118.07, P<.001) and treatment condition (F_{3,177}=8.73, P<.001). Significant main effects of time condition were still observed at 0 minutes (F_{3,59}=7.22, P<.001), 15 minutes (F_{3,59}=4.19, P=.005), 45 minutes (F_{3,59}=6.56, P<.001), and 75 minutes (F_{3,59}=7.33, P<.001) after load. Significant Bonferroni-Dunn comparisons present in the original analysis were retained with the exception of (1) risperidone vs typical antipsychotics at 0 and 75 minutes (comparison with healthy controls still significant at both time points), (2) typical agent vs olanzapine at 45 and 75 minutes (all other comparisons between olanzapine and typical agents or control subjects still significant), and (3) healthy control subjects vs risperidone at 0 and 75 minutes.

GROUP-RELATED DIFFERENCES IN FASTING AND POSTLOAD PLASMA INSULIN LEVEL

Modest differences in plasma insulin levels across the treatment groups were observed (Table 2). In the main ANOVA model, a significant time \times treatment group interaction was detected for plasma insulin level...
(F_{12,17}=2.10, P=.02), with a significant main effect of time (F_{1,17}=50.42, P<.001) and no main effect of treatment group (F_{5,2}=1.40, P=.25). In separate ANOVAs for each time point, the effect of treatment group on plasma insulin concentration only approached significance at 75 minutes after glucose load (F_{5,2}=2.39, P=.06) (Figure 1; Bonferroni-Dunn post hoc test, P=.007; threshold for significance, P<.005). The effect of treatment group at 75 minutes (F_{5,2}=2.95, P=.03), as well as the post hoc comparison of olanzapine-treated and healthy subjects (Bonferroni-Dunn post hoc test, P<.005), were significant when subjects receiving typical antipsychotic deca-noate preparations in addition to treatment with olanzapine or risperidone were excluded and the typical treatment group was restricted to haloperidol.

**HOMA IR ANALYSIS**

The HOMA IR values were calculated for all subject groups by means of the formula listed in the “Subjects and Methods” section. Unpaired t tests were performed to explore differences in HOMA IR across specific treatment groups, targeting group comparisons associated with significant differences in plasma glucose level in the main analysis. Modest increases in HOMA IR values were detected for patients treated with olanzapine (r=−2.07, P<.05) and clozapine (r=−2.03, P=.06), in comparison with patients taking typical antipsychotics only (Figure 2). No significant alterations in HOMA IR were detected for patients treated with risperidone or typical antipsychotics, as compared with control subjects.

**ADDITIONAL PLASMA VARIABLES AND CLINICAL MEASURES**

Spearman correlations indicated no significant association in patients between BPRS total scores and either fasting (r=−0.24, corrected for ties, P=.12, n=45) or 75-minute postload plasma glucose level (r=−0.19, corrected for ties, P=.21, n=45). Modest correlations were detected between BPRS total scores and fasting (r=−0.40, corrected for ties, P=.01, n=38) and 75-minute postload plasma insulin level (r=−0.31, corrected for ties, P=.06, n=37). Mean plasma C-peptide, cortisol, and glucagon values for all treatment groups are provided in Table 2 and may be useful for hypothesis generation. While reduced sample sizes argue against formal analysis, C-peptide values were numerically higher in certain treatment groups (eg, olanzapine group values approximately 2 SDs higher than those of typical treatment group, and approximately 3 SDs higher than those of healthy controls). No treatment-related effects were apparent for cortisol and glucagon levels.

The results of this study measuring fasting plasma glucose and modified OGTTs indicate that newer antipsychotic treatments such as clozapine and olanzapine, in comparison with typical agents, are associated with adverse effects on plasma glucose regulation, which can vary in severity independent of adiposity and age. The HOMA calculations suggest that at least some of this effect may involve group-related differences in insulin resistance. This is consistent with the observation that patients taking clozapine and olanzapine had mean plasma insulin values that were still rising at the final sample time point, in comparison with falling insulin levels in the other treatment groups. These results extend previous case reports suggesting that clinically significant hyperglycemia, and diabetic complications, can occur during antipsychotic treatment with and without changes in weight.24,27,36,47,58 Although this study used nondiabetic subjects, limiting the magnitude of glucose excursions, differences in plasma glucose values approximating 1.0 to 1.5 SDs (eg, olanzapine vs typical antipsychotics or control subjects) were still observed. Differences in fasting, postglucose load, and postprandial glucose level of this magnitude have been associated with long-term increases in cardiovascular morbidity and mortality (eg, myocardial infarction), even when plasma glucose values remain below diabetic and impaired thresholds.88-93 Antipsychotic treatments, particularly clozapine and olanzapine,66-71 can induce clinically significant gains in weight and adiposity,94 with insulin resistance and the risk of diabetes mellitus increasing with abdominal adiposity.95 Differences in plasma glucose level were observed in this study with subjects matched for adiposity. In clinical practice, where there is no matching for adiposity and some treatments produce more weight gain than others, additional adiposity-related differences in insulin resistance and plasma glucose level may occur.

There were several limitations to this study. The comparison of plasma glucose levels between antipsychotic-treated subjects and untreated healthy controls did not disassociate glucoregulatory effects associated with antipsychotic treatment from any glucoregulatory changes associated with schizophrenia itself. In contrast, the comparison between groups receiving newer and typical antipsychotic treatments tested potential differences between the glucoregulatory effects associated with one
antipsychotic treatment vs the other, with both groups vulnerable to disease effects. Conclusions regarding relative differences in glucoregulatory effects between specific antipsychotic treatments may be limited by the sample size in this study, and a type II error cannot be excluded (eg, additional treatment groups might show differences in larger samples). However, the large effect sizes observed in this study with this sample size produced power of 0.99 or greater to detect the effect of treatment group on plasma glucose level at all time points. Random treatment assignments in this study would eliminate concerns about nonrandom sampling bias that could, for example, preferentially assign patients to one group or another on the basis of glucoregulatory status or risk (eg, preferentially assigning patients with risk factors like obesity away from treatment with olanzapine). The time course for developing glucoregulatory changes was not addressed by this study. In addition, this report did not address the glucoregulatory effects of quetiapine, and clinical reports suggest that treatment with this agent, like other antipsychotics, may be associated with adverse glucoregulatory effects.

Subjects taking adjunctive agents, such as valproic acid, lithium, and antidepressants, which may themselves contribute to changes in weight and glucose regulation, were included in the different patient groups, along with subjects taking decanoate preparations of typical antipsychotics within the olanzapine and risperidone treatment groups. This approach increases the generalizability of results but could potentially contribute to increases or decreases in observed glucoregulatory changes. When patients receiving concomitant mood stabilizers and/or antidepressants were removed from the main analysis, there was still a significant time × treatment group interaction, effects of treatment condition at each time point, and still significant differences between individual groups. In the case of valproic acid, an adjunctive agent in 3 of the olanzapine-treated subjects, the package insert warns of hyperglycemia as a possible adverse effect, but other reports describe hypoglycemia with valproic acid. This study used a plasma sampling schedule that ended at 75 minutes after glucose load (along with cognitive batteries related to original experimental aims) rather than the single conventional 120-minute end point used in World Health Organization and American Diabetes Association criteria for the diagnosis of diabetes mellitus. In contrast, research evaluations routinely use fasting as well as various, preferably frequent, postglucose plasma time points less than 120 minutes, with briefer times (eg, 60 minutes) remaining clinically predictive and longer periods potentially allowing better rather than worse separation of diabetic, impaired, and normoglycemic subjects. Future studies might consider the use of dual-energy x-ray absorptiometry or magnetic resonance imaging to measure and match for adiposity, rather than BMI. While BMI is strongly associated with insulin resistance and hyperglycemia, abdominal adiposity acting at least in part through the hormone resistance plays a critical role in increasing insulin resistance. Future studies should also consider standardizing carbohydrate intake before measurements.

Hyperglycemia in type 2 diabetes is related to impaired pancreatic beta-cell function, which decreases insulin secretion, along with insulin resistance in skeletal muscle (causing decreased glucose uptake) and liver (causing increased glucose production). The results of this study suggest hyperglycemia-related increases in plasma insulin levels, numeric increases in C-peptide levels, and HOMA IR. Results for the postload insulin values, suggesting treatment-related hyperinsulinemia and insulin resistance, are consistent with the HOMA calculations we performed on fasting glucose and insulin values in the same subjects, which also suggested treatment-related differences in insulin sensitivity. These results do not exclude defects in beta-cell function. From the standpoint of hypothesis generation, measures of counter-regulatory hormones like glucagon and cortisol in this study did not suggest a contribution to treatment effects on plasma glucose or insulin. Serotonin receptor activity has been hypothesized to be involved in glucose regulation, with both 5-HT₁A and 5-HT₂ receptors implicated; however, their exact roles appear complex. Earlier studies have suggested that phenothiazines decrease insulin secretion or release catecholamines that inhibit insulin secretion, or that chlorpromazine has some other anti-insulin action. The results of the present study suggest treatment effects on IR, and Dwyer et al recently reported effects of antipsychotic medications on glucose transporters.

Hyperglycemia is an underrecognized comorbid complication of schizophrenia. Diabetes mellitus has well-defined acute (eg, diabetic ketoacidosis) and chronic complications associated with increased morbidity and mortality. Diabetic ketoacidosis, more typical of type 1 but increasingly observed in type 2 diabetes, has been reported during antipsychotic treatment, including a fatality. Hyperglycemia can cause or contribute to long-term medical complications including peripheral neuropathy, retinopathy, and nephropathy, as well as cardiovascular and cerebrovascular disease. Recent reports indicate a progressive relationship between hyperglycemia and cardiovascular event risk (eg, myocardial infarction, stroke) beginning with glucose levels well below diabetic thresholds. Hyperglycemia can interact with treatment-induced increases in adiposity, treatment-related triglyceride elevations, and factors such as smoking, sedentary lifestyle, and reduced access to care, to increase the risk of adverse cardiovascular outcomes in patients with schizophrenia. The results of this study provide additional motivation to clinically monitor plasma glucose, on the basis of the risk that changes in glucose control could occur without easily observed increases in weight or adiposity.

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