Glucometabolic Hormones and Cardiovascular Risk Markers in Antipsychotic-Treated Patients

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ABSTRACT

Objective: Treatment with antipsychotic drugs is widely associated with metabolic side effects such as weight gain and disturbed glucose metabolism, but the pathophysiologic mechanisms are unclear.

Method: Fifty nondiabetic (fasting plasma glucose ≤ 7.0 mmol/L), antipsychotic-treated male patients (ICD-10 diagnosis code F20, F21, F22, F25, F28, or F60; mean ± SD age = 33.0 ± 6.7 years; body mass index [BMI; kg/m²] = 26.0 ± 4.7; waist circumference = 95.9 ± 13.3 cm; glycated hemoglobin A1c [HbA1c] = 5.7% ± 0.3%) and 93 age- and waist circumference–matched healthy male controls (age = 33 ± 7.3 years; BMI = 26.1 ± 3.9; waist circumference = 94.6 ± 11.9 cm; HbA1c = 5.7% ± 0.3%) participated in this cross-sectional study. Blood was sampled in the fasting state and 90 minutes after ingestion of a standardized liquid meal (2,268 kJ). The primary outcomes were glucometabolic hormones and cardiovascular risk markers. Data were collected between March 2008 and February 2010.

Results: Compared to healthy controls, patients were characterized by elevated fasting levels of proinsulin, C-peptide, and glucose-dependent insulino tropic polypeptide (GIP) (P < .05) and higher postprandial levels of insulin, proinsulin, C-peptide, and GIP (P ≤ .02). Also, patients exhibited elevated plasma levels of C-reactive protein and signs of dyslipidemia. Fasting plasma levels of insulin, glucagon, glucagon-like peptide-1 (GLP-1), ghrelin, leptin, adiponectin, tumor necrosis factor-α, plasminogen activator inhibitor-1, and interleukin-6 and postprandial levels of glucagon, GLP-1, ghrelin, leptin, and adiponectin did not differ between groups.

Conclusions: Presenting with an insulin resistant–like pattern, including beta cell hypersecretion and elevated GIP levels, nondiabetic antipsychotic-treated patients display emerging signs of dysmetabolism and a compromised cardiovascular risk profile. The appetite-regulating hormones GLP-1 and ghrelin appear not to be influenced by antipsychotic treatment. Our findings provide new clinical insight into the pathophysiologic association with metabolic side effects of antipsychotic treatment and put emphasis on the importance of implementing metabolic screening into psychiatric practice.

Trial Registration: ClinicalTrials.gov identifier NCT00627757

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Nondiabetic antipsychotic-treated patients display an insulin resistant—like pattern, with beta cell hypersecretion, postprandial hyperglucagonemia, and elevated glucose-dependent insulinotropic polypeptide levels, indicating emerging signs of dysmetabolism and a compromised cardiovascular risk profile.

The metabolic perturbations are only partially explained by familial risk of diabetes, obesity, smoking, and physical activity, suggesting that antipsychotic exposure is an independent contributor to dysmetabolism.

Metabolic screening should be implemented into general psychiatric practice.

Participants

Fifty-one antipsychotic-treated male, nondiabetic (fasting plasma glucose ≤ 7.0 mmol/L) patients and 93 healthy male controls matched on age (± 5 years) and waist circumference (± 5 cm), were initially included. All patients were outpatients recruited from the Mental Health Services of the Capital Region of Denmark. We consecutively included patients to the study who were on continuous treatment with a minimum of 1 antipsychotic drug and with a clinical diagnosis in a coarsely defined schizophrenia spectrum (ICD-10 diagnosis: F20, F21, F22, F25, F28, or F60.1). Other inclusion criteria were male gender, white race, and age between 18–45 years. Exclusion criteria were inability to read, write, or speak Danish; a diagnosis of diabetes and/or other severe somatic comorbidity; treatment with cholesterol-lowering, antidiabetic, or antihypertensive medications; ongoing substance abuse; and duration of psychiatric illness > 15 years. For ethical reasons, forensic patients and patients under coercion were not included. Healthy controls were all white subjects recruited from the database at the Research Centre for Prevention and Health, Copenhagen University Hospital, Glostrup, Denmark, and by advertising in newspapers. Healthy controls were excluded in the presence of severe ongoing medical condition or inability to read, write, or speak Danish. Information on familial risk factors, tobacco smoking, daily physical activity, and duration of illness was obtained from interviews and clinical records when available. Characteristics of participants are shown in Table 1.

Experimental Procedures

At the day of investigation, participants arrived in the morning in a fasting state. Also, they were alcohol- and tobacco-free for at least 8 hours. After we collected blood samples for fasting measures, each subject ingested a 360-mL liquid meal (carbohydrates, 66.2 g; proteins, 21.6 g; and fat, 20.9 g [2,268 kJ]; Nutridrink, Nutricia A/S, Allerød, Denmark) over 10 minutes. After 90 minutes, blood was sampled again for postprandial measures. All blood samples (except for glycated hemoglobin A₁c (HbA₁c), which was frozen as heparinized whole blood) were centrifuged for 10 minutes at 3,000g at room temperature or at 4°C for GLP-1, GIP, and glucagon, after which serum and plasma were recovered and stored in aliquots at −80°C until analysis.

Analyses

C-peptide, insulin, ghrelin, leptin, adiponectin, TNF-α, PAI-1, and IL-6 were analyzed by using fluorescently labeled microsphere beads in Milliplex kits according to instructions provided by the producer (Millipore, Billerica, Massachusetts). Proinsulin was analyzed with an enzyme-linked immunosorbent assay according to the producer (Millipore), with minor in-house modifications. Analyses of total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglyceride, CRP, plasma glucose, and HbA₁c were performed by using the Vitros 5.1 (Johnson & Johnson; Rochester, New York). Plasma concentrations of glucagon, GIP, and GLP-1 were measured after extraction of plasma with 70% ethanol (vol/vol, final concentration). The glucagon radioimmunoassay was directed against the C-terminus of the glucagon molecule (antibody code no. 4305).18 For the measurement of total GIP, a C-terminally directed radioimmunoassay was used.19 Plasma concentrations of total GLP-1 were measured by using antiserum code no. 89390, which is specific to the amidated C-terminus of GLP-1.20

Calculations and Statistical Analyses

The homeostasis model assessment (HOMA) was used to obtain an assessment of—mainly hepatic—inulin resistance (HOMA-IR).21 Proinsulin-to-insulin ratio was used to evaluate beta cell function.22

Statistical analyses were performed by using Statistical Package for Social Science software (SPSS, Statistics 20, IBM Corporation; Armonk, New York). Differences between patients and controls were determined by 2-tailed unpaired t tests. Within-group comparisons were performed by 2-tailed paired t tests. Potential confounding effects of familial risk of diabetes, obesity, smoking, and physical activity were controlled for in post hoc analysis of variance (ANOVA) tests. P value threshold for significance was .05. One-way ANOVA with Bonferroni post hoc test was used to explore potential differential metabolic effects of specific antipsychotic compounds where n ≥ 10. Results of these subgroup analyses are reported only where significant differences between the subgroups emerged.
Table 1. Demographic, Anthropometric, and Clinical Characteristics for Antipsychotic-Treated Patients and Healthy Controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 50)</th>
<th>Controls (n = 93)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33.0 ± 6.7</td>
<td>19.0–45.0</td>
<td>.96</td>
</tr>
<tr>
<td>Height, cm</td>
<td>182.2 ± 8.5</td>
<td>166.0–200.0</td>
<td>.54</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>86.8 ± 17.8</td>
<td>55.0–130.0</td>
<td>.86</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.0 ± 4.7</td>
<td>18.0–38.0</td>
<td>.95</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>95.9 ± 13.3</td>
<td>61.0–130.0</td>
<td>.56</td>
</tr>
<tr>
<td>Familial risk of diabetes (yes/no), n</td>
<td>5/45</td>
<td>15/78</td>
<td>.23</td>
</tr>
<tr>
<td>Familial risk of obesity (yes/no/missing), n</td>
<td>5/41/4</td>
<td>2/81/10</td>
<td>.06</td>
</tr>
<tr>
<td>Tobacco smoking (yes/no), n</td>
<td>26/24</td>
<td>20/73</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Daily physical activity (&lt;30 min/≥30 min), n</td>
<td>18/32</td>
<td>5/88</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Duration of illness, y</td>
<td>6.1 ± 3.8</td>
<td>0.5–15.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128 ± 17</td>
<td>75–169</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80 ± 10</td>
<td>47–99</td>
<td>.79</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.7 ± 0.3</td>
<td>5.0–6.4</td>
<td>.60</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.3 ± 0.6</td>
<td>4.4–7.0</td>
<td>.08</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6.0 ± 6.9</td>
<td>0.8–33.6</td>
<td>.11</td>
</tr>
<tr>
<td>Proinsulin-to-insulin ratio</td>
<td>0.3 ± 0.3</td>
<td>0.02–2.2</td>
<td>.09</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.1 ± 1.1</td>
<td>2.9–8.3</td>
<td>.01d</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.1 ± 0.3</td>
<td>0.7–1.8</td>
<td>.06</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.2 ± 0.9</td>
<td>1.6–5.6</td>
<td>.04d</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.8 ± 1.2</td>
<td>0.5–5.4</td>
<td>&lt;.01d</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>4.6 ± 6.5</td>
<td>0.1–33.0</td>
<td>&lt;.01d</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>21.1 ± 89.3</td>
<td>1.2–636.5</td>
<td>.58</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>12.3 ± 5.9</td>
<td>4.0–32.5</td>
<td>.93</td>
</tr>
<tr>
<td>PAI-1, ng/mL</td>
<td>46.1 ± 28.8</td>
<td>15.5–119.8</td>
<td>.15</td>
</tr>
</tbody>
</table>

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controls, exhibited significantly decreased leptin levels after meal ingestion. Adiponectin levels did not differ between the 2 groups in the fasting state nor in the postprandial state (Table 2).

After we controlled for familial risk of diabetes, familial risk of obesity, smoking, and physical activity, the differences between groups in fasting and postprandial GIP disappeared. All other results were unaltered.

Effects of Specific Antipsychotics

Types and mean doses of antipsychotic drugs are displayed in Table 3. To explore effects of specific antipsychotic compounds, we compared healthy controls and patients treated with aripiprazole (n = 10), olanzapine (n = 11), and quetiapine (n = 16). All parameters (fasting as well as postprandial) were evaluated. The mean fasting levels of triglycerides (ANOVA, P = .006) and fasting (P = .04) as well as postprandial (P = .002) levels of TNF-α differed significantly between the 4 groups. The post hoc Bonferroni tests showed that mean ± SD fasting triglyceride levels in olanzapine-treated patients compared with controls tended to be elevated (1.9 ± 1.1 mmol/L vs 1.3 ± 0.7 mmol/L; P = .06). Both fasting and postprandial TNF-α levels were significantly higher in aripiprazole-treated patients as compared with controls (17.9 ± 8.9 pg/mL vs 12.0 ± 5.7 pg/mL, P = .04; 20.3 ± 12.0 pg/mL vs 12.6 ± 5.6 pg/mL, P = .006). No other significant differences in mean levels of other parameters emerged from the analyses of these 3 subgroups of patients and the healthy controls.

DISCUSSION

We provide a detailed investigation of fasting and postprandial levels of incretin hormones, ghrelin, insulin, glucagon, and cardiovascular risk markers in a group of nondiabetic antipsychotic-treated patients and matched healthy controls. We found that the patients exhibited emerging signs of insulin resistance (with beta cell hypersecretion) and postprandial hyperglucagonemia, both of which are known precursors involved in the development of overt metabolic disturbances and weight gain.23,24

Our findings of altered lipid levels (elevated fasting cholesterol, LDL cholesterol, and triglycerides and lower fasting HDL cholesterol) are in agreement with observations of dyslipidemia, even in the absence of weight gain.25,26

Preclinical data have indicated that, by modulating the gene expression, antipsychotics affect the synthesis of cellular fatty acid and cholesterol.27 Thus, it is conceivable that, despite differences between human and rodent metabolism,28 modulation of genetic expression may partly explain our findings.

The elevated fasting plasma levels of the inflammatory marker CRP observed in our patients may further compromise their cardiovascular risk profile.29 However, our data do not confirm previous observations of alterations in other inflammatory markers such as TNF-α,30 PAI-1,31 and IL-632 in antipsychotic-treated patients.

In accordance with previous reports, our patients displayed higher fasting C-peptide levels.33 Although reaching only borderline significance, our patients’ mean HOMA-IR index value was 35% higher as compared with that of the healthy controls (P = .11), and, as such, resembles a pattern of emerging insulin resistance.26,34–38 To this end, our patients exhibited significantly higher fasting and postprandial proinsulin as well as postprandial C-peptide and insulin levels compared with controls. In particular, an increased level of proinsulin is considered an indication of elevated physiological stress and a compromised pancreatic
beta cell function. However, the proinsulin-to-insulin ratio did not differ significantly between patients and controls.

In the present study, fasting glucagon levels did not differ between patients and controls. This finding is in agreement with data from olanzapine-treated (8 days) healthy subjects, but in contrast to a preclinical study in which fasting hyperglucagonemia was observed in antipsychotic-treated rats. Nevertheless, the postprandial glucagon levels increased significantly in our patients, whereas it, as expected, remained stable in the controls. This result is in contrast to the aforementioned short-term study of olanzapine-treated healthy subjects but in line with a recent report showing postprandial hyperglucagonemia after 9 days of olanzapine treatment in healthy subjects. Postprandial hyperglucagonemia may represent an early step in the development of type 2 diabetes. Also, postprandial hyperglucagonemia may be closely linked to the elevated postprandial GIP levels observed in our patients, which is in agreement with preclinical data. In addition to its glucose-dependent insulinotropic effect (incretin effect), GIP also possesses glucose-dependent glucagonotropic properties (stimulating glucagon secretion during normal- to low plasma glucose levels). Our data could therefore suggest that elevated postprandial GIP levels may drive a postprandial hyperglucagonemic response in patients treated with antipsychotics. Interestingly, GIP also has adipogenic properties, and positive correlations between postprandial GIP levels in plasma and BMI have been reported in patients with type 2 diabetes. Thus, it may be speculated that elevated GIP levels may contribute to antipsychotic-induced weight gain.

The gut incretin hormone GLP-1 is pivotal for glucose homeostasis, and GLP-1 receptor agonists are now widely used in treatment of type 2 diabetes. Interestingly, GLP-1 receptor agonists also induce weight loss in both diabetic and nondiabetic patients, and they may therefore be used to treat antipsychotic-induced obesity. Endogenous GLP-1 levels have been reported in 2 studies evaluating the effect of short-term olanzapine treatment in healthy subjects: Vidarsdottir et al showed no effect of olanzapine, whereas Teff et al recently reported increases in postprandial GLP-1 levels. To our knowledge, the present study is the first to report plasma levels of endogenous GLP-1 in patients treated with antipsychotic drugs. Our data suggest that compromised GLP-1 secretion does not play a role in antipsychotic-induced dysmetabolism. This observation parallels a recent meta-analysis on GLP-1 levels in patients with type 2 diabetes. Previous reports on the effect of antipsychotics on the stimulation of the hunger-stimulating hormone ghrelin have provided inconsistent results, possibly explained by differential effects of specific antipsychotic compounds. In our study, the fasting ghrelin levels in patients were similar to those of controls, and patients were able to suppress circulating ghrelin in response to meal ingestion normally, a finding that suggests changes in ghrelin secretion should not be considered a pivotal metabolic “class effect” of antipsychotic drugs.

Studies on adipose-derived hormones have indicated a reduced secretion of adiponectin and increased levels of leptin in antipsychotic-treated patients. Yet, in a recent study, fasting leptin levels were unaffected by short-term treatment with antipsychotics in healthy volunteers. In the present study, we did not find significant differences in levels of adiponectin and leptin between patients and controls. Thus, the role of these adipose-derived hormones in antipsychotic-induced dysmetabolism remains to be clarified.

We acknowledge that some of the above-mentioned negative findings may represent type 2 errors that perhaps could have been avoided by including more antipsychotic-treated patients.

In our exploratory analyses of potential effects of specific antipsychotics, we observed trend-level elevated triglyceride levels in olanzapine-treated patients as compared with controls. Also, we observed that TNF-α levels were significantly higher in patients treated with aripiprazole. As such, the metabolic profiles of our patients treated with specific antipsychotic drugs do not support that the dysmetabolic effect of olanzapine is substantially more pronounced than that of aripiprazole and quetiapine. This finding, which is in contrast to previous reports, may be explained by the cross-sectional, naturalistic design and the limited sizes of our patient subgroups.

Although patients and controls were well matched on our a priori inclusion criteria, the metabolic perturbations appeared only partially explained by familial risk of diabetes, obesity, smoking, and physical activity. This could suggest that antipsychotic exposure is an independent contributor to dysmetabolism in schizophrenia spectrum patients. Duration of illness and BMI were not correlated, yet we cannot exclude that the duration of antipsychotic treatment or other factors, such as dietary habits, may also have influenced the findings. Hence, it should be emphasized that our findings reveal associations between dysmetabolism and antipsychotic exposure, rather than provide proof of a causal relationship.

Another limitation of the present study is that our broadly defined “schizophrenia spectrum” hampers inferences regarding potential interactions between specific psychiatric diagnoses and the liability to acquire metabolic disturbances. Moreover, we included only chronic male patients in this study. Since previous studies have indicated gender differences in antipsychotic-induced dysmetabolism, our findings may not be readily applied on a female population. Except for the absence of gender effects, our naturalistic study design and consecutive enrollment of subjects increase the external validity of the present study.

Finally, some of the observed discrepancies between the present and previous studies may partly be explained by methodological differences. First, we have only 1 measurement in the postprandial phase. Clearly, several measurements would have been optimal, but, in order to increase the recruitment of patients, that design was judged unviable. Second, since not all cytokines are stable, we addressed potential proteolysis by protecting our blood samples from endogenous proteases by immediately adding protease inhibitors to all samples. This potential error factor...
is otherwise almost impossible to account for, as individual analytes will be degraded at different rates, and therefore our preventive procedure may explain some of the conflicting findings. In conclusion, the present study shows that nondiabetic antipsychotic-treated patients display an insulin resistant–like pattern, with beta cell hypersecretion, postprandial hyperglucagonemia, and elevated GIP levels, indicating emerging signs of dysmetabolism and a compromised cardiovascular risk profile. The appetite-regulating hormones GLP-1 and ghrelin appear not to be influenced by antipsychotic treatment. Thus, our findings provide new clinical insight into the pathophysiology associated with metabolic side effects of antipsychotic treatment and put emphasis on the importance of implementing metabolic screening into psychiatric practice.60

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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Author contributions: Drs Ebdrup and Knop contributed equally to this article. Dr Lublin conceived and initiated the study. Dr Lublin was responsible for evaluation of any potential discomfort and/or risk associated with participation in the study, thus ensuring the health and safety of the participating subjects. Furthermore, Dr Lublin was responsible for study conduct according to local, national, and international guidelines and laws.

Potential conflicts of interest: Dr Ebdrup has received lecture fees from Bristol-Myers Squibb, Otsuka Pharma Scandinavia AB, Eli Lilly, and Takeda and is part of the advisory board of Eli Lilly Denmark A/S and Takeda. Dr Knoop has received research funding from Sanofi-Aventis Deutschland GmbH and lecture fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Gilead Sciences, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Zealand Pharma; is part of the advisory boards of Eli Lilly Denmark, A/S and Takeda. Dr Knop has received lecture fees from AstraZeneca, Gilead Sciences, Ono Pharmaceuticals, and Zealand Pharma; and has consulted for AstraZeneca, Gilead Sciences, Ono Pharmaceuticals, and Zealand Pharma. Dr Lublin has received research funding and honoraria for consulting and/or lecture fees from Novo Nordisk A/S. Dr Lublin has received honoraria from and is part of the speakers and/or advisory board of Destin Pharma A/S Denmark and Janssen-Cilag A/S Denmark. Ms Sogaard is an employee of Lundbeck A/S. Drs Mortensen and Szeesi and Ms Madsen have no conflicts of interest to report.

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Role of the sponsor: Lundbeck A/S, as represented by Ms Sogaard, was partly involved in the design of the study (regarding the selection of relevant blood samples).

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REFERENCES


