Well-being and co-morbidity in recent onset schizophrenia
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Chapter 3.1

Hepatic insulin resistance in antipsychotic naive schizophrenic, schizo-affective patients, a detailed study of glucose metabolism with stable isotopes


Hepatic insulin resistance in antipsychotic naïve schizophrenic patients

Abstract

Objective To measure insulin sensitivity and body composition in antipsychotic naïve patients with DSM IV schizophrenia and/or schizoaffective disorder compared with matched controls.

Design Seven antipsychotic medication naïve patients fulfilling the DSM IV A criteria for schizophrenia/schizoaffective disorder were matched for body mass index (BMI), age and sex with seven control subjects. We measured endogenous glucose production and peripheral glucose disposal using a hyperinsulinemic euglycaemic clamp (plasma insulin concentration ~ 200 pmol/l) in combination with stable isotopes. Fat content and fat distribution were determined with a standardized single-slice CT- scan and whole body DEXA scan.

Results Endogenous glucose production during the clamp was 6.7 μmol/kg.min (SD 2.7) in patients versus 4.1 μmol/kg.min (SD 1.6) in controls, \( P = 0.02 \) (95% CI \(-5.2 - 0.006\)). Insulin-mediated peripheral glucose uptake was not different between patients and controls. The amount of subcutaneous abdominal fat in patients was 104.6 ± 28.6 cm³ and 63.7 ± 28.0 cm³ in controls, \( P = 0.04 \) (95% CI 4.4 – 77.2). Intra abdominal fat and total fat mass were not significantly different.

Conclusions Antipsychotic medication naïve patients with schizophrenia or schizoaffective disorder display hepatic insulin resistance compared to matched controls. This finding cannot be attributed to differences in intra abdominal fat mass or other known factors associated with hepatic insulin resistance and suggests a direct link between schizophrenia and hepatic insulin resistance.
Introduction

Before the introduction of antipsychotic medication in 1952, historical publications suggested a possible relationship between diabetes mellitus and mental illnesses, including dementia praecox (Kohen 2004). Recent studies estimate the prevalence of diabetes among schizophrenic patients around 10-15%, which is two to three-times higher than in the reference population (Holt et al 2005). The incidence is estimated between 1.5% and 4.4% (Citrome et al 2004, Leslie et al 2004).

Recently it was shown that first-episode, relatively old, antipsychotic- naïve patients with schizophrenia had higher levels of plasma glucose, insulin, and cortisol than age- and sex- matched controls (Ryan et al 2003). This finding can be attributed to differences in body composition between patients with schizophrenia and healthy controls, since a higher waist-to-hip ratio and higher visceral fat content, as assessed by computed tomography (CT) scan, were reported in two controlled studies (Ryan et al 2004, Thakore et al 2002). By contrast, no differences in glucose and insulin concentrations and visceral fat mass were reported in younger antipsychotic naïve schizophrenic patients compared to healthy controls (Arranz et al 2004, Zhang et al 2004). A recent study, using minimal model analysis of an intravenous glucose tolerance test, showed insulin resistance in a rather small number of drug free patients compared to healthy controls (Cohn et al 2006). These conflicting results may be due to differences in study design or to differences in the definition of insulin sensitivity.

Here we report a matched case-control study comparing glucose metabolism in antipsychotic medication naïve schizophrenic or schizoaffective patients with matched controls, using the hyperinsulinemic euglycemic clamp technique in combination with stable isotopes, which is considered to be the gold standard for measuring insulin sensitivity in vivo (De Fronzo et al 1979). We hypothesized that patients have hepatic and peripheral insulin resistance caused by higher plasma free fatty acids (FFA) (Koutsari et al 2006, Nielsen et al 2004) and an altered secretion of adipokines (Cho et al 2006, Combs et al 2001, Fruebis et al 2001, Yamauchi et al 2001).

The main reason for the recent study, conducted in drug naïve patients with schizophrenia, is to investigate whether an impaired glucose metabolism is a part of the pathophysiology of the primary disorder and is not secondary to the use of medication.
Subjects and Methods

Subjects

Seven antipsychotic medication naïve patients, who were experiencing their first psychotic episode (hallucinations and/or delusions), were included in a cross-sectional study, comparing cases with matched controls. These patients were recruited from the Psychiatric in- and outpatient Clinic of the Academic Medical Center (AMC) of the University of Amsterdam, from February 2004 until March 2006. The patients were eligible for the study if they fulfilled the DSM IV A criteria for schizophrenia or schizo-affective disorder. Characteristic symptoms are two (or more) of the following, each present for a significant portion of time during a 1-month period: delusions; hallucinations; disorganized speech (e.g., frequent derailment or incoherence); grossly disorganized or catatonic behavior and negative symptoms, i.e. affective flattening, alogia, or avolition. Patients were eligible if they had no other axis I or II DSM IV diagnosis that needed treatment, were older than 18 years old, understood the objective of the study and were competent to give informed consent. This competency was evaluated by the nursing team and independent resident involved in the treatment of the patient. Exclusion criteria were: 1) diabetes mellitus (DM) or a medical history or family history for type 2 diabetes mellitus; 2) a recent history (six months or less) of substantial alcohol abuse, or DSM IV criteria for alcohol dependence disorder, psychoactive substance abuse or dependence disorder; 3) alcohol use in the last three days before the start of the study; 4) cannabis use in the last month before the start of the study; 5) the use of antipsychotic medication or any other medication except paracetamol (acetaminophen); 6) somatic illness, including neoplasm, metabolic or endocrine disorders, active infection, or gross structural abnormalities on MRI of the brain; and (7) no informed consent. The diagnosis of schizophrenia according to DSM IV was made by an experienced psychiatrist at baseline and re-evaluated after 6 months during a clinical consensus meeting with 3 psychiatrists. Substance (ab) use and physical health was self reported and confirmed by caregivers, no urine tests were performed. The control group consisted of 7 healthy subjects (medical students) matched for BMI, age and sex.

Because we expected to find differences in fat distribution, and no differences in total fat percentages, patients and controls were matched for BMI, not according to the DEXA or CT fat measures. Patients and controls were not matched for lifestyle parameters or dietary intake. None of the subjects was taking any form of prescribed or over-the-counter medication.
The study was approved by the Medical Ethical Committee of the Academic Medical Center. After a complete description of the study was given, written informed consent was obtained.

Hyperinsulinemic euglycemic clamp

Subjects were admitted to the Metabolic Clinical Research Unit of the Academic Medical Center and studied in the supine position. After a 13 h fast since 7 pm the day before, a catheter was inserted in the dorsal vein of the hand or distal vein of the arm of each arm. One catheter was used for sampling of arterialised blood using a heated hand box (60°C). The other catheter was used for infusion of $[6,6-\text{D}_2]$-glucose, glucose 20% and insulin. At 8.00 am ($t=-2.5h$), after drawing a blood sample for background enrichment of plasma glucose, a continuous infusion of $[6,6-\text{D}_2]$-glucose (>99% enriched, Cambridge Isotopes, Massachusetts, USA) was started at a rate of 0.11 $\mu$mol/kg per min after a priming dose equivalent to 80 min of infusion. After 120, 130, 140 and 150 min blood samples were drawn for determination of glucose enrichments. Subsequently at $t=0h$, a primed continuous infusion of insulin (Actrapid 100U/ml, Novo Nordisk Farma, Alphen a/d Rijn, The Netherlands) was started for 2.5h at a rate of 20mU/m² body surface area per min aiming for a plasma insulin concentration of ~200 pmol/l. Plasma glucose was measured every 5 min (Beckman glucose analyzer 2; Beckman, Palo Alto, California USA) and glucose 20% was infused at a variable rate to maintain plasma glucose at 5.0 mmol/l. $[6,6-\text{D}_2]$-glucose was added to the 20% glucose solution to achieve glucose enrichments of 1% to minimise changes in isotopic enrichment due to changes in the infusion rate of exogenous glucose, and thus to allow for accurate quantification of glucose kinetics. During the last hour of the clamp, blood samples were drawn at 5 min intervals for determination of glucose enrichments. At $t=0h$ and $t=2.5h$ samples for measurement of insulin, glucagon, cortisol, catecholamines, FFA, RBP4 and adiponectin were drawn. During the study, the participants were only allowed to drink water.

Laboratory assays

Stable isotope analysis ($6,6-\text{D}_2$-glucose enrichment) was measured as described earlier (Ackermans et al 2001). Cortisol in plasma was determined with a chemiluminescent immunoassay (Immulate 2000, Diagnostic Products Corporation, Los Angeles, USA). Insulin was determined with a chemiluminescent immunoassay (Immulate 2000, Diagnostic Products Corporation, Los Angeles, USA). Glucagon was determined with the Linco $^{125}$I radioimmunoassay (St. Charles, USA).
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Norepinephrine and epinephrine were determined with an in-house HPLC method. Adiponectin was determined by a radioimmunoassay (Linco, St. Charles, USA). Retinol-binding protein 4 was determined with an ELISA kit (Immundiagnostik, Bensheim, Germany). The free fatty acid concentration was determined with an enzymatic colorimetric method (NEFA-C test kit, Wako Chemicals GmbH, Neuss, Germany).

Two consecutive 24-h urine samples were collected separately at home. During this collection, the urine was kept refrigerated. Of the two 24h urine samples, total volume, as well as concentration of free cortisol (in-house HPLC method) and creatinine (Jaffé method, Hitachi 917, Roche Indianapolis, IN) were measured. To minimize the effects of unreliable collections, we calculated cortisol/creatinine ratio’s in all 24h samples (de Bos et al 1998).

Indirect calorimetry

Oxygen consumption (VO$_2$) and CO$_2$ production (VCO$_2$) were measured with the ventilated hood technique (model 2900; Sensormedics, Anaheim, CA). VO$_2$ and VCO$_2$ were measured continuously during the final 30 min in the basal state and during the hyperinsulinemic euglycemic clamp. The mean rates of VO$_2$ and VCO$_2$ during the final 20 min were used for calculation of glucose and fat oxidation as described by Frayn (1983). Non-oxidative glucose disposal was calculated as the difference between total glucose disposal and glucose oxidation.

Abdominal fat measurements

Total, as well as regional, fat mass was quantified in all patients by DEXA (Hologic QDR-4500W; Hologic, Inc., Bedford, MA; software version whole-body v8.26A: 5), providing a quantitative assessment of peripheral and truncal fat mass in kilograms. A standardized single-slice abdominal CT scan (Mx8000 Quad, Philips Medical Systems, Best, the Netherlands) using 120 kV, 100 mAs and a slice thickness of 1 cm was performed. On the survey image, the level of the fourth lumbar vertebra was chosen, which is the level of the umbilicus in most patients (Dizon 1983). It was shown that the fat volume in a slice at this level is a valid predictor of total abdominal fat in men (Miller et al 1998, Weits et al 1988). The volume of total adipose tissue (TAT), intra-abdominal adipose tissue, and subcutaneous adipose tissue (SAT) was determined by summing the volumes of the voxels with CT-values within the range of -170 to -30 Hounsfield units, and expressed in cubic centimetres. Care was taken to exclude intracolonic contents with Hounsfield units within the same range (Potretzke et al 2004). Radiologists were blind to the subject groups.
Calculations

Endogenous glucose production (EGP) and peripheral glucose uptake (Rd) were calculated using the modified form of the Steele equations as described previously (Finegood et al 1987).

Data Analysis

Mann Whitney U tests (two-tailed) were used to compare results between patients and controls. All results are expressed as means and standard deviations. The data were analyzed using SPSS, version 11 (SPSS, Inc., Chicago, IL). The overall significance level was set at $P = 0.05$ (two-tailed).

Results

There were 13 patients who were asked for informed consent, five refused to participate, and one did not meet the inclusion criteria. Seven patients (two inpatients and five outpatients) and seven controls were included in the study. Five patients fulfilled the diagnostic criteria for (paranoid) schizophrenia and two for schizoaffective disorder. Patients that refused participation were psychiatrically not different from patients that were included in the study. Mean duration of (psychotic) illness in patients was 2.7 years (SD 2.7). Two of the seven patients did not work or go to school due to their illness; four patients worked and one went to school.

All controls went to college. Five of the patients vs. none of the controls smoked nicotine. Cigarette use was not quantified. The characteristics of the seven patients (all male) and the seven controls (all male) with respect to age, weight, height and BMI were nearly identical; 23.8±2.2 years vs 23.0±1.7 years (95% CI −1.5 - 3.1); 74.9±12.6 kg vs 72.3±5.9 kg (95% CI −8.9 − 14.0), 184.3±9.3 cm vs 185.6±3.0 cm (95% CI −10.0 - 7.4), and 21.9±1.5 kg/m² vs 21.3±1.5 kg/m² (95% CI −1.2 − 2.4) respectively.

Glucose metabolism (Table 3.1.1)

Basal plasma glucose concentration did not differ between patients. Fasting insulin concentrations in patients tended to be higher as compared with controls: 49 ± 18 pmol/l (8.2±3 μU/ml), vs. 29 ± 12 pmol/l (4.8±2 μU/ml), $P = 0.07$ (95% CI 2.4 − 35.9). Basal endogenous glucose production was not different between patients and controls. During the hyperinsulinemic euglycaemic clamp, plasma glucose and
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**Table 3.1.1.** Endogenous Glucose Production (EGP), Peripheral Glucose Uptake (Rd), Glucose Oxidation and Non-oxidative Disposal in the Basal State and during Hyperinsulinemic Euglycaemic Clamp.

<table>
<thead>
<tr>
<th></th>
<th>Basal (n=7)</th>
<th>Controls (n=7)</th>
<th>95% CI</th>
<th>Clamp (n=7)</th>
<th>Controls (n=7)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGP</td>
<td>13.4 (1.0)</td>
<td>12.4 (1.0)</td>
<td>-0.26-2.11</td>
<td>6.7 (2.7) *</td>
<td>4.1 (1.6)</td>
<td>-5.2-0.006</td>
</tr>
<tr>
<td>Rd</td>
<td>31.1 (10.3)</td>
<td>27.9 (5.3)</td>
<td>-6.7-13.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose oxidation</td>
<td>8.8 (5.9)</td>
<td>7.4 (5.7)</td>
<td>-5.4-8.1</td>
<td>13.0 (6.6)</td>
<td>11.7 (7.2)</td>
<td>-6.8-9.3</td>
</tr>
<tr>
<td>Non-oxidative glucose disposal</td>
<td>4.6 (5.9)</td>
<td>5.0 (6.1)</td>
<td>-7.3-6.5</td>
<td>18.1 (8.9)</td>
<td>16.2 (9.7)</td>
<td>-8.9-12.8</td>
</tr>
</tbody>
</table>

All values are in μmol/kg.min and expressed as mean (SD). To convert to mg/kg.min, multiply by 0.18.

* P = 0.02

insulin concentrations were not different between patients and controls. EGP during the clamp was significantly higher in patients [6.7 μmol/kg.min (SD 2.7) vs. 4.1 μmol/kg.min (SD 1.6) in controls, P = 0.02, 95% CI -5.2 to 0.006]. Peripheral glucose uptake (Rd), glucose oxidation and non-oxidative disposal were not different between patients and controls.

**Plasma fatty acids and fat oxidation (Table 3.1.2)**

Basal plasma free fatty acids tended to be lower in patients [0.31 mmol/l (SD 0.12) vs. 0.54 mmol/l (SD 0.27), P=0.07, 95% CI -0.48 – 0.02]. During the clamp they were not significantly different. Basal lipid oxidation and lipid oxidation during the clamp were not different.

**Glucoregulatory hormones (Table 3.1.2)**

Glucoregulatory hormones were not significantly different between groups. The mean cortisol/creatinine ratio in 24h urine collections in patients was 8.8 ± 7.0 nmol/mmol and in controls 5.0 ± 1.6 nmol/mmol (P=0.57, 95% CI -2.8 – 10.2).

**Adipokines (Table 3.1.2)**

Basal plasma RBP4 concentrations were not different between patients and controls. Basal adiponectin concentrations and adiponectin concentrations during the clamp were not different between patients and controls.
Abdominal fat measurements

Results from CT-scan and DEXA measurements were obtained in 6 patients and 6 controls; one patient did not show up for the imaging study, and one control subject withdrew consent because of fear of radiation exposure in the DEXA measurement, despite the text in the informed consent form. The amount of subcutaneous abdominal fat was significantly different in patients (104.6 ± 28.6 cm³) compared to controls (63.7 ± 28.0 cm³) (P=0.04, 95% CI 4.4 – 77.2), as well as total abdominal fat tissue (141.1 ± 36.3 cm³ in patients vs. 93.3 ± 39.6 cm³ in controls, P= 0.04, 95% CI –0.0 – 96.7). Intraabdominal fat was not significantly different between groups; 36.6 ± 17.1 cm³ in patients vs. 29.6 ± 12.4 cm³ in controls (P=0.42,95% CI –12.2 – 26.3). Total fat mass as measured with DEXA was not significantly different: 11.1 (15%) ± 3.3 kg in patients vs. 8.3 (12%) ± 2.4 kg 95% CI –0.8 – 6.4), in controls. Total truncal fat was 4.6 ± 1.5 kg in patients vs. 3.5 ± 1.0 kg in controls (P=0.12, 95% CI –0.5 – 2.7). Total arm fat was 1.3 ± 4.5 in patients vs. 0.8 ± 0.2 kg in controls (P=0.05, 95% CI 0.05 – 1.0). Total leg fat was 4.1 ± 1.6 kg in patients vs. 3.0 ± 1.2 kg in controls (P=0.25, 95% CI -0.6 – 3.0).
Discussion

The present study shows that antipsychotic naïve, first episode psychotic patients with schizophrenia or schizo-affective disorder, examined with the gold standard for measurement of glucose metabolism, displayed significant hepatic insulin resistance during the hyperinsulinemic clamp. Peripheral insulin sensitivity did not differ from matched controls. This finding could not be explained by differences in intraabdominal fat, plasma FFA, glucoregulatory hormones, plasma adiponectin or plasma RBP4 concentrations.

Previous studies investigating insulin resistance in antipsychotic naive first episode psychotic patients showed conflicting results (Arranz et al 2004, Cohn et al 2006, Ryan et al 2003). Those studies were conducted with the homeostasis model assessment, which is less precise and less reproducible than the hyperinsulinemic euglycemic clamp technique, especially in small sample sized studies (DeFronzo et al 1979). Our finding of a trend for higher fasting insulin levels was reported earlier (Ryan et al 2003). Other studies could not confirm this finding, but these studies did not match the controls for BMI (Arranz et al 2004, Zhang et al 2004), although after correction with BMI as a covariate, antipsychotic free patients showed significantly higher fasting insulin levels compared to antipsychotic naïve patients and healthy controls (Arranz et al 2004). The reduced hepatic insulin sensitivity in the patients cannot be attributed to cortisol as neither plasma cortisol levels nor cortisol to creatinine ratios were significantly different between the two groups.

Adiponectin levels have been described to positively correlate with (whole body) insulin sensitivity in human subjects (Cohn et al 2006, Stefan et al 2003). However, there was no difference in adiponectin levels between our patients and healthy controls. We did not measure high and low molecular weight adiponectin and, therefore, cannot exclude a significant difference in especially HMW adiponectin between patients and controls, explaining the difference in EGP. Plasma RBP4 (Graham et al 2006) and FFA concentrations (Boden et al 2002, Bajaj et al 2005) are additional important modulators of insulin sensitivity, but are unlikely to play a role in the induction of hepatic insulin resistance in schizophrenia, since we found no differences between patients and controls.

Epidemiological studies have reported an association between abdominal obesity and insulin resistance (Misra et al 2003). Ever since, much research has focused on visceral fat and hepatic insulin sensitivity. A remarkable finding in the present study was the difference in abdominal fat distribution between our patients and controls. Patients showed a higher subcutaneous abdominal fat mass without increase in visceral fat mass, which contradicts reported data in literature (Ryan et al 2004, Thakore et al 2002). An increase in visceral fat in antipsychotic free
and antipsychotic naive patients was reported earlier (Ryan et al 2004, Thakore et al 2002). In one of these studies (Ryan et al 2004) significant differences in life styles between patients and controls (higher saturated fat intake, lower fibre intake and less exercise in the patients) could explain this finding. Patients and controls in our study were not matched for dietary intake, or for smoking or exercise patterns. This may be a confounding variable since smoking per se may affect insulin sensitivity (Kapoor et al 2005). However, insulin sensitivity as noticed in smokers could be related to an increase in counter-regulatory hormones, but to the best of our knowledge nicotine use has not been found to be associated with selective hepatic insulin resistance. Subcutaneous fat is described to be associated with insulin resistance, especially in patients with upper body obesity (Koutsari et al 2006), though a lack of significant effect on hepatic glucose production by subcutaneous fat was also reported (Klein et al 2004). Increased FFA release from visceral adipocytes draining directly into the portal vein is thought to explain the correlation between visceral fat and hepatic insulin resistance (Nielsen et al 2004). The source of increased systemic plasma FFA in upper body obesity seems to be the upper body subcutaneous fat compartment (Koutsari et al 2006). This suggests that hepatic insulin resistance is induced by increased FFA-delivery from enhanced lipolysis from visceral adipocytes and peripheral insulin resistance by increased systemic FFA availability derived from enhanced lipolysis from upper body subcutaneous adipocytes. However, these mechanisms are not relevant for our study, since our subjects showed no differences in truncal fat, and the patients in our study did not have increased plasma FFA levels. Despite similar levels of visceral fat, patients displayed hepatic insulin resistance, suggesting that other mechanisms are responsible for our finding. Obviously, we did not measure portal FFA delivery and therefore cannot rule out any differences in lipolytic activity in visceral adipocytes between patients and controls. Another explanation for the increased subcutaneous abdominal fat mass could be leptin (Cnop et al 2002), as elevated plasma leptin levels correlates with subcutaneous fat deposition.

Finally, neuronal input to the liver may be responsible for our findings (Demuro et al 2006). Recent experiments in rats have shown a very important role for multisynaptic autonomic pathways originating in the hypothalamus, and reaching the liver via the brainstem, in the regulation of hepatic glucose production. The infusion of either insulin or small-molecule insulin mimetics in the third ventricle suppresses glucose production independent of circulating levels of insulin and of other glucoregulatory hormones (Obici et al 2002), though this finding might be species specific since no significant role of brain insulin on hepatic glucose production was found in dogs (Connolly et al 1996). A distal lesion of the parasympathetic input to liver prevents this, resulting in striking insulin resistance with increased hepatic
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Glucose production (Pocai et al 2005). Other experiments in rats have shown a pivotal role for vagal input to white adipose tissue, with an anabolic role in the local regulation of insulin sensitivity (Kreier et al 2002). Together, these studies have demonstrated a crosstalk between the central nervous system on one hand and adipose tissue and liver on the other, coupling central nutrient sensing to peripheral nutrient production. If indeed this crosstalk might be disturbed in schizophrenia this might represent a whole new perspective in metabolic research in schizophrenia (Kreier et al 2006). In addition, alterations in the central nervous system lipid regulation of patients with schizophrenia, such as myelin and fatty acid biosynthesis dysfunction (Tkachev et al 2007), could be accompanied by alterations in liver- and fat tissue lipid regulation and thus explain both the hepatic insulin resistance and altered fat distribution.

In conclusion, antipsychotic naïve, first-episode psychotic patients with a diagnosis of schizophrenia or schizoaffective disorder show hepatic insulin resistance compared with matched controls which cannot be attributed to an increase in visceral fat mass or differences in plasma FFAs, plasma adiponectin or plasma RBP4 concentrations. Our findings suggest a direct link between schizophrenia and hepatic insulin resistance.
References


Connolly CC, Myers Sr, Neal DW, et al. In the absence of counterregulatory hormones, the increase in hepatic glucose production during insulin-induced hypoglycemia in the dog is initiated in the liver rather than the brain. Diabetes 1996;45(12):1805-1813.


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