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Parameters of glucose and lipid metabolism at the fasted state in drug-naïve first-episode patients with psychosis: Evidence for insulin resistance

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ABSTRACT

Diabetes and dyslipidemia are common in patients with psychosis; this association may be partly related to adverse metabolic effects of antipsychotic medications. We assessed glucose and lipid metabolism during the fasted state in drug-naïve patients with psychosis. Fasting serum concentrations of total cholesterol, triglycerides, high density lipoprotein (HDL), glucose, insulin, connecting peptide (C-peptide), homeostatic model assessment index (HOMA-IR), glycated hemoglobin (HbA1C) and serum cortisol were compared between a group of 40 newly diagnosed drug-naïve, first-episode patients with psychosis and a group of 40 healthy controls, matched for age, sex and BMI. Total cholesterol, triglycerides and fasting glucose levels were similar, whereas insulin and C-peptide levels were higher and HDL marginally lower in the patients' group compared to those in healthy controls. Drug-naïve patients with psychosis were more insulin resistant (as assessed by the HOMA-R index) compared to healthy controls. Serum cortisol did not differ between the two groups. There is evidence that drug-naïve, first-episode patients with psychosis are more insulin resistant compared to healthy controls.

1. Introduction

The mortality rate in patients with schizophrenia is two to three times higher and their life expectancy is 13–20 years shorter compared to the general population (Mitchell et al., 2013). The fact that the prevalence of type 2 diabetes is up to three times more common in those patients, may contribute amongst other factors (such as increased suicide rate, poor nutrition and conditions of living, increased prevalence of smoking, neglect of physical health) to the observed reduction in their life expectancy (Ryan et al., 2003; Manzanares et al., 2014). It is worth noting that the first reports of an elevated prevalence of type 2 diabetes in patients with schizophrenia were published in the beginning of the 20th century, well before the discovery and use of antipsychotic medications (Kohen, 2004). Taking aside the methodological limitations and the differences in the criteria used for the diagnosis of schizophrenia and diabetes mellitus, these findings imply a possible pathophysiological connection between schizophrenia and diabetes mellitus (Kohen, 2004). However, most recent studies have been conducted in patients already receiving antipsychotic medication (Papanastasiou, 2013). The presence of dyslipidemia is another potential contributor to the increased cardiovascular morbidity. It has been suggested that this association may be independent of any antipsychotic medication use (Saari et al., 2004; Verma et al., 2009; Wu et al., 2013). On the other hand, other studies found similar serum lipid levels between patients with psychosis and healthy controls (Sengupta et al., 2008; Kirkpatrick et al., 2010).

Lifestyle factors such as poor dietary habits and lack of exercise (both of which are common in patients with psychosis) may contribute to the development of metabolic syndrome in this population. Male adolescent inpatients suffering from first episode schizophrenia-spectrum disorders, were more likely to be overweight compared with a group of unselected controls from the general population (Brown et al., 1999; Joutinen et al., 2008). Many of the commonly used antipsychotics (such as olanzapine and quetiapine among others) have been implicated in weight gain, insulin resistance, metabolic syndrome and type 2 diabetes (Balf et al., 2008; Oud and Meyboom-de Jong, 2009; Perez-Iglesias et al., 2009).

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The aim of the present study was to assess glucose and lipid metabolism during the fasted state in drug-naïve patients with a first episode of psychosis compared to a group of healthy controls matched for age, sex and body mass index (BMI).

2. Methods

2.1. Patients

Patients were recruited from the "Early Intervention in Psychosis Unit" of the Psychiatric Clinic of the "University Hospital of Ioannina" between September 2012 and October 2014. Inclusion criteria were: a) a DSM-IV diagnosis of schizophrenia, schizophreniform disorder or brief psychotic episode; b) patients should have experienced their first psychotic episode; and c) they should be antipsychotic-naïve. We considered the following exclusion criteria a) past major mental illness (psychotic, mood, anxiety disorder); b) DSM-IV diagnostic criteria for alcohol or substance abuse; c) known diabetes mellitus of any type or other serious physical disorder associated with insulin resistance; d) patients were also excluded if they were unable to give informed consent due to their mental state. We contacted overall 48 patients and eight of them were excluded from the study: four because they refused to give informed consent, three due to substance abuse and one because he had a previous history of diabetes mellitus. Twenty four patients were diagnosed with brief psychotic episode, 11 with schizophreniform disorder and five with schizophrenia.

All patients had a complete physical examination by an internist. A urine test was performed in all subjects in order to exclude current substance use. Psychiatric diagnosis was established independently by two experienced psychiatrists using the Structured Clinical Interview for DSM-IV (SCID). The patients' psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS) (Table 1), on the day of blood sample collection. The weight (kg) and height (m) of each study participant were measured using the same scales, and their body mass index (BMI, kg/m^2) was calculated. All participants had a blood sample taken at 08:00 in the morning after a 10 h fast, for determination of serum total cholesterol, HDL, triglycerides, glucose, insulin, C-peptide levels, HbA1c and cortisol. Insulin resistance was estimated by the homeostasis model assessment formula as follows: fasting insulin (μIU/ml) × fasting glucose (mg/dl)/405 (Haffner et al., 1997).

2.2. Control subjects

Forty healthy controls (matched to the patient group subjects for age, sex and BMI), were selected through advertising amongst Ioannina University students and employees as well as from local enterprise employees. Mental health history was evaluated using the SCID NP (non-patient) edition and only those without past or present history of mental disorder (psychotic, mood and anxiety disorder) were included in the study. All control subjects were examined by an internist, were physically healthy and were not taking any medications. Subjects with a history of diabetes mellitus, hypertension, cardiac or thyroid disease were excluded from the study, as well as those who met the DSM-IV criteria for alcohol or substance abuse. All control subjects were tested for use of psychotropic substances with a urine test and those who tested positive were excluded from the study. All subjects in the control group had normal fasting glucose, HbA1c and BMI (fasting glucose < 100 mg/dl, HbA1c < 5.6% and BMI < 25).

All participants received detailed information about the aim of the study and gave informed consent.

2.3. Biochemical analyses

Serum fasting glucose, total cholesterol, HDL and triglycerides were measured by spectrophotometry with Olympus AU5400 analyzer (Beckman-Brea-California-USA) and reagents supplied by Beckman. Serum insulin was determined by chemiluminescence using the DXI 800 (Beckman) analyzer. Hba1c was determined by High Performance Liquid Chromatography BIORAD VARIANT II

Table 1
Baseline characteristics, serum lipids and glucose metabolic parameters in drug-naïve psychotic patients and healthy controls. Values are expressed as means (SD) or median with the range in parentheses and the patients' psychopathology evaluated using the Positive and Negative Syndrome Scale (PANSS).

	Healthy controls ($N=40$)	Drug-naïve patients with psychosis ($N=40$)	Comparisons
Demographic and clinical characteristics			
Age (years)	31.90 (8.29)	32.45 (9.81)	$t=0.271$, $df=78$, $p=0.787$
Gender (male/female)	25/15	27/13	$\chi2=0.220$, $p=0.815$
Smokers/non smokers	12/28	13/27	$\chi2=0.058$, $p=0.809$
BMI[a] (kg/m^2)	22.79 (1.67)	22.88 (3.73)	$t=-0.139$, $df=54.01$, $p=0.890$
Duration of Untreated Psychosis (DUP)	–	10.72 (8.24) weeks	
Psychopathology (PANSS)[b]			
PANSS – p	–	37.02 (3.72)	
PANSS – n	–	12.80 (5.98)	
PANSS – g	–	27.27 (3.15)	
PANSS – t	–	77.1 (8.72)	
Parameters of lipid metabolism			
Total cholesterol (mg/dl)	196.96 (43.57)	188.21 (46.92)	$t=0.723$, $df=78$, $p=0.473$
Triglycerides (mg/dl)	85.54 (40.88))	93.29 (51.87)	$t=-0.621$, $df=78$, $p=0.537$
HDL[c] (mg/dl)	61.68 (16.53)	51.30 (10.75)	$t=0.197$, $df=78$, $p=0.050$
Parameters of glucose metabolism			
Fasting glucose (mg/dl)	86.67(6.35)	87.55 (11.24)	$t=0.428$, $df=61.56$, $p=0.670$
Fasting insulin (μIU/ml)	4.75 (2.00–12.90)	8.25 (1.20–79.30)	$U=366$, $p<0.001$
Fasting C-peptide (ngr/ml)	1.25 (0.80–4.10)	2.30 (0.50–14.00)	$U=403.5$, $p<0.001$
HbA1c[d] (%)	5.25 (0.42)	5.14 (0.43)	$t=-1.125$, $df=78$, $p=0.264$
HOMA-IR[e]	0.92 (0.43–2.67)	1.84 (0.27–16.64)	$U=359$, $p<0.001$
Cortisol (μg/dl)	10.46 (4.64)	10.26 (4.84)	$t=0.180$, $df=78$, $p=0.858$

[a] Body mass index.
[b] Positive and Negative Syndrome Scale (*PANSS – p*: positive, *PANSS – n*: negative, *PANSS – g*: general psychopathology, *PANSS – t*: total score).
[c] High Density Lipoprotein.
[d] *HbA1c*: Glycated hemoglobin.
[e] *HOMA-IR*: Homeostatic model assessment index.