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Research article

Effects of antipsychotic medications in glucose and lipid metabolism at the fasted state in drug-naïve first-episode patients with psychosis after six months and three years of treatment

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ABSTRACT

Diabetes and dyslipidemia are common in patients with psychosis and may be related to adverse effects of antipsychotic medications. Metabolic disturbances in first-episode patients with psychosis are common, even before any antipsychotic treatment, and antipsychotic medications are implicated in the development of metabolic syndrome, at least in the long run. We therefore aimed to follow a group of drug-naïve, first-episode patients with psychosis at different time points (baseline, six months, and 36 months after the initiation of antipsychotic treatment) to evaluate the progression of metabolic abnormalities after antipsychotic therapy and the time course of their onset. We assessed glucose and lipid metabolism during the fasted state in 54 drug-naïve patients with first-episode psychosis (FEP) before the initiation of any antipsychotic treatment and compared them with matched controls. The same parameters were assessed in the patient group (n=54) after six months of antipsychotic treatment and in a subgroup of patients (n=39) after three years of continuous and stable treatment in comparison to baseline. Measurements were obtained for 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 (HbA_{1c}) and body mass index (BMI). Insulin, C-peptide, triglyceride levels, and HOMA-IR index were significantly higher compared to controls. Total cholesterol, triglyceride levels, and BMI, increased significantly in the patient group after six months of antipsychotic treatment. After three years of continuous antipsychotic treatment, we found statistically significant increases in fasting glucose, insulin, total cholesterol, triglyceride levels, HbA1c, HOMA-IR index, and BMI compared to baseline. In conclusion, FEP patients developed significant increases in BMI and serum lipid levels as soon as six months after antipsychotic treatment. These metabolic abnormalities persisted following 36 months of treatment and in addition, increases in fasting glucose, insulin, HbA1c and HOMA-IR were observed compared to baseline.

KEYWORDS: First-episode, schizophrenia, metabolism, insulin resistance, cholesterol, triglycerides.

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Introduction

Patients with schizophrenia have a 20% higher mortality rate than the general population.[1] Epidemiological evidence suggests that type 2 diabetes mellitus, cardiovascular disease, hypertension, and dyslipidemia account for up to 60% of the increased mortality risk.[2] The prevalence of the metabolic syndrome is 40% in patients with chronic schizophrenia,[3] while the hazard ratio of type 2 diabetes (T2D) is 3–4 times higher in patients treated with antipsychotic medication, compared to the general population.[4] In recent years, a significant increase in the incidence and prevalence of metabolic syndrome in the general population has emerged, so some authors suggest that metabolic syndrome in patients with schizophrenia constitutes "an epidemic within an epidemic".[5]

Weight gain, hyperglycemia, and hyperlipidemia are frequent findings in patients with schizophrenia and can be partly attributed to unhealthy behaviors often observed in these patients, such as excessive food intake, smoking, lack of physical activity, or alcohol abuse.[6] Alternatively, these metabolic abnormalities may be linked to the pathophysiology of schizophrenia.[6]

Metabolic and glycemic disturbances have attracted research interest since the introduction and extended use of second-generation antipsychotics (SGA) which have been associated with weight gain, obesity, glucose intolerance, T2D, dyslipidemia, and cardiovascular disease.[6,7] These side effects are more pronounced in antipsychotic naïve patients at the onset of illness.[8] Although in the general population, T2D and morbid obesity take 5–10 years to develop, in patients treated with SGA the process is much shorter, ranging from 6–12 weeks to 12 months.[9]

It is not clear whether the metabolic disturbances caused by SGAs are a result of increased weight or a direct effect of the drugs on tissue function. Two mechanisms have been proposed: (a) an indirect mechanism, where excessive eating, caused by the effects of SGAs in central and peripheral receptors and peptides, leads to obesity and, in the long term, to dyslipidemia and type-2 diabetes; (b) a direct mechanism, where SGAs action on tissues can affect insulin signalling and secretion, glucose transport, b-cell function, and lipid metabolism.[10] Antipsychotics have been shown in vitro to inhibit glucose transporters by direct binding, leading to increased insulin secretion and insulin resistance.[11] Additionally, evidence suggests that genetic predisposition could be responsible for the metabolic side effects. A recent study identified five genomic regions colocalizing schizophrenia and T2D signals and three of them contain loci implicated in both disorders while IGF2B2P polymorphisms have been associated with both schizophrenia and pancreatic βcell dysfunction.[12]

We previously compared drug-naïve patients with psychosis to healthy controls (before initiating antipsychotic treatment) for several glucose and lipid parameters and reported increased insulin and C-peptide levels.[13] In the present study, we followed up a group of newly diagnosed drug-naïve patients with psychosis to compare the same parameters (fasting glucose, insulin, insulin resistance (HOMA-IR), HbA_{1c}, total cholesterol, high-density lipoprotein (HDL), triglyceride, C-peptide levels, and BMI) at two-time points after the initiation of antipsychotic treatment: at 6 months (short-term) and at 3 years (long-term). We aimed to evaluate the progression of metabolic abnormalities after antipsychotic therapy and the time course of their onset.

Material and Method

Patients' selection before the initiation of antipsychotic medication

Patients were recruited from the "Early Intervention in Psychosis Unit" of the Department of Psychiatry of the University Hospital of Ioannina from October 2013 to November 2017. Inclusion criteria were: (a) a diagnosis of schizophrenia, schizophreniform disorder, or a brief psychotic episode according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5); (b) patients should have experienced their first psychotic episode; (c) they should be antipsychotic-naïve. Patients and controls were excluded from the study according to the following criteria: (a) history of major mental illness (psychotic, mood, or anxiety disorder); (b) DSM-5 diagnostic criteria for alcohol or substance abuse; (c) diabetes mellitus and other serious physical disorders associated with insulin resistance; (d) refusal to give informed consent; (e) BMI>25.

We assessed 60 patients for eligibility, and we excluded six for the following reasons: Two patients were excluded because they refused to give informed consent; three were excluded due to substance abuse; and one was excluded because of a previous history of diabetes mellitus. Seventeen patients were also included in our previous study.[13]

Sixteen patients were diagnosed with brief psychotic episodes, twenty-eight with schizophreniform disorder, and ten with schizophrenia. All patients underwent a complete physical examination by an internist. A toxicological urine analysis was performed on all study participants to exclude current substance use. The patients'

psychopathology was assessed on the day of blood sample collection using the Positive and Negative Syndrome Scale (PANSS). The weight (kg) and height (m) of each study participant were measured and their body mass index (BMI, kg/m^2) was calculated.

Patient evaluation six months and three years after the initiation of antipsychotic medication

We evaluated all 54 patients at six months and a subgroup (n=39) three years after the initiation of antipsychotic medication. The subgroup of 39 patients consisted of those from the initial study group who remained at follow-up in the three years without relapses or changes in the antipsychotic medication used. Psychopathology was assessed using the same scale, and their weight and BMI were calculated again. The antipsychotic drugs used in the study were: olanzapine (29 patients) and risperidone (25 patients) for the sample of 54 patients evaluated six months after the initiation of treatment, and olanzapine (25 patients) and risperidone (14 patients) for the sample of 39 patients evaluated three years after antipsychotic treatment. Antipsychotic dose ranges were 10–20 mg for olanzapine and 3–6 mg for risperidone. Doses were adjusted according to clinical indications within the prescribed range, to remain at the lowest effective dose. We found significant increases in total cholesterol, triglyceride, fasting glucose, fasting insulin, HbA_{1c}, HOMA-IR, and BMI in a subgroup of 39 patients after three years of stable antipsychotic treatment. All participants had a blood sample taken at 08:00 in the morning after a 10-hour fast, for the determination of serum total cholesterol, HDL, triglycerides, glucose, insulin, C-peptide levels, and HbA_{1c} in both phases of the study. Insulin resistance was calculated by the homeostasis model assessment formula as follows: fasting insulin (μIU/mL) x fasting glucose (mg/dL)/405.[14]

The complete study protocol was approved before study initiation by the ethics committee of the University Hospital of Ioannina. The participants received detailed information about the aims of the study and gave informed consent in both phases of the study.

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. HbA_{1c} was determined by High-Performance Liquid Chromatography BIORAD VARIANT II (Hercules-California-USA). Measurement of C-peptide was performed on a Gamma Coulter II Wizard (Waltham-Massachussets-USA) by radioimmunoassay (RIA).

Statistical analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to examine the normality of the distribution of the data. Continuous variables (BMI, HDL, fasting glucose, total cholesterol, triglycerides, fasting insulin, fasting C-peptide, HbA_{1c}, and HOMA-IR) were compared among the group of patients at baseline versus healthy controls, and after three years of treatment versus the group of healthy controls, by using the independent-samples t-test (and the Mann-Whitney U test in the case of non-normally distributed data). The comparisons among the group of patients six months after the initiation of antipsychotic medication and baseline, and among the group of patients three years after the initiation of antipsychotic medication and baseline, were performed using the paired samples t-test and repeated measures Analysis of Variance (ANOVA) and the tests of Wilcoxon signed rank and Friedman in the case of non-normally distributed data. Multiple comparison post-hoc tests were performed in case of statistically significant results. Finally, we compared the glucose and lipid parameters among patients who received risperidone and patients who received olanzapine for the time points of 6 and 36 months after the initiation of medication separately, by using the independent-samples t-test (and the Mann-Whitney U test in the case of non-normally distributed data). All analyses were performed with IBM-SPSS Statistics for Windows (version 26) or Graphpad Prism 6 (Graphpad Software Inc., San Diego, CA, USA). A p-value of less than 0.05 (2-tailed) was used for statistical significance.

Results

Description of the sample

The median age of the initial group of 54 patients was 27 years, with a range of 18-48 years. Thirty-three patients (61%) were male. The mean duration of untreated psychosis (DUP) in our study population at the beginning of the study was 11.46 weeks (SD=7.56), as these patients were investigated during the acute phase of their illness. Results of the positive and negative syndrome scale (PANSS), used to assess patients' psychopathology before, six months, and three years after antipsychotic treatment, are shown in table 1. Demographic characteristics of the subset of 39 pa-

Table 1. Socio-demographic and clinical characteristics of drug-naïve, first-episode patients with psychosis, in a tertiary center in Greece (Six months follow-up: N=54; 3 years follow-up: N=39).

Variable	N=54 patients (6 months follow-up)		N=39 patients (3 years follow-up)	
Gender				
Male	33 (61%)		25 (64.1%)	
Female	21 (39%)		14 (35.9%)	
Age[median(range)]	25.5 years (18–49)		26 years (18–47)	
DUP [mean (SD)]	11.46 weeks (7.56)		11.30 weeks (7.94)	
Smoking [N (%)]	28 (51.85%)		23 (58.97%)	
Diagnosis				
Schizophrenia	10 (18.52%)		10 (25.64%)	
Schizophreniform disorder	28 (51.85%)		28 (71.79%)	
Brief psychotic episode	16 (29.63%)		16 (41.02%)	
Severity of Symptoms [median (range)]		6 months after		3 years after
PANSS-p	33 (28–39)	7 (7–10)	33 (28–39)	7 (7–9)
PANSS-n	22 (17–38)	17 (7–28)	22 (17–38)	16 (10–24)
PANSS-g	42 (30–51)	19 (16–27)	42 (30–51)	20 (15–28)
PANSS-t	98 (78–119)	43.5 (30–63)	101 (78–119)	43 (34–60)

SD: Standard deviation; PANSS: Positive and Negative Syndrome Scale (PANSS-p: positive, PANSS-n: negative, PANSS-g: general psychopathology, PANSS-t: total score)

tients that were followed up for three years are also shown in table 1.

Glucose and lipid parameters in the group of 54 drug-naïve FEP patients compared to healthy controls

Table A1 provides the results of the comparison between the patients and healthy controls at baseline (Supplementary material). The mean age of FEP patients was similar to that of the healthy control subjects (25.50 years range=18-49 years versus 27 years range=18-48 years respectively, p=0.7). The patient group did not differ from healthy controls concerning BMI (U=1322, p=0.403). HbA_{1c} percentage was similar in patients compared to healthy controls (U=1417.5, p=0.803). FEP patients were more insulin resistant, as reflected by their higher HOMA-IR score (U=728, p<0.001). Finally, FEP patients had statistically significantly lower levels of HDL and higher levels of fasting insulin, fasting C-peptide, and triglycerides compared to healthy controls (Table A1).

Table A2 provides the results of the comparison of the patients after three years of treatment and the group of healthy controls (Supplementary material). For the 39 FEP patients that were followed for 3 years after treatment, the comparison showed statistically significant increases in total cholesterol, triglycerides, fasting glucose, fasting insulin, fasting C-peptide, HbA_{1c}, and HOMA-IR and a statistically significant decrease in HDL compared to the group of healthy controls (table 2).

Glucose and lipid parameters in the group of 54 patients after six months of treatment compared to baseline

We observed a statistically significant increase in total cholesterol, triglycerides, and BMI after 6 months of treatment compared to baseline (167 mg/dL vs. 194 mg/dL, p<0.001 for total cholesterol; 79.5 mg/dL vs. 109 mg/dL, p<0.001for triglycerides; 22.79 kg/m2 vs. 24.61 kg/m2, p<0.001 for BMI). HDL levels did not significantly differ after 6 months of treatment compared to baseline (47.4 mg/dL vs. 46.7 mg/dL, p=0.535). Fasting glucose levels remained similar (88.96 ± 10.29 mg/dL vs. 88.63 ±9.84 mg/dL respectively, p=0.867). The same was observed for fasting insulin levels (7.7 μIU/mL vs. 7.9 μUI/mL, p=0.74), fasting C-peptide levels (2.8 ng/mL vs. 2.8 ng/mL, p=0.886), HOMA-IR index (1.69 vs. 1.88, p=0.702) and HbA_{1c} (5% vs. 5%, p=0.913) (table 2; figure 1). Concerning the comparisons of glucose and lipid parameters among the patients who received risperidone and those who received olanzapine, non-statistically significant results were observed at the time point of six

Table 2. Parameters of glucose and lipid of drug-naïve, first-episode patients with psychosis, before and after six months of antipsychotic treatment in a tertiary center in Greece (N=54).

Parameters of lipid metabolism	Baseline (before treatment)	After 6 months of treatment	Statistic	Effect size
Total cholestero [Median (range)]	167 mg/dL (104–289)	194 mg/dL(126–371)	Z=–4.875, p<0.001	r=–0.664
Triglycerides [Median (range)]	79.5 mg/dL (41–369)	109 mg/dL (45 –399)	Z=–3.656, p<0.001	r=–0.498
BMI [mean (SD)]	22.79 kg/m^2 (2.63)	24.61 kg/m^2 (3.07)	t=–5.9, p<0.001	Cohen's d=0.802
HDL [Mean (SD)]	47.4 mg/dL (10)	46.7 (9.05)	t=0.624, p=0.535	Cohen's d=0.082
Parameters of glucose metabolism				
Fasting glucose [Mean (SD)]	88.96 mg/dL (10.29)	88.63 mg/dL (9.84)	t=0.168, p=0.867	Cohen's d=0.023
Fasting insulin [Median (range)]	7.7μ IU/mL (1.9–79.3)	7.9 μ UI/mL (2.3–75)	Z=–0.332, p=0.74	r=–0.045
Fasting C-peptide [Median (range)]	2.8 ng/mL (0.9–14)	2.8 ng/mL(1–14.3)	Z=–0.19, p=0.886	r=–0.025
HbA_{1c} [Median (range)]	5% (4.3–6.1%)	5% (4.5–5.8%)	Z=–0.109, p=0.913	r=–0.014
HOMA–IR [Median (range)]	1.69 (0.33–19.19)	1.88 (0.49–16.11)	Z=–0.383, p=0.702	r=–0.052

Z from Wilcoxon signed–rank test; t from Paired t–test; BMI: Body Mass Index; SD: Standard deviation

months after the initiation of antipsychotic medication (table A3).

Comparison of glucose and lipid parameters in a subgroup of 39 patients after three years of treatment, six months of treatment, and at baseline

Regarding the comparison of the subgroup of the 39 stable patients over the three-time points (baseline, 6 months of treatment, and 3 years of treatment), we observed significant differences for the three-time points on total cholesterol, triglycerides, BMI, fasting glucose, fasting insulin, HbA_{1c}, and HOMA-IR. More specifically, total cholesterol had a statistically significant increase over the three time points (p<0.001). More specifically, total cholesterol differed statistically significantly between baseline and 6 months (165 mg/dL vs. 198 mg/dL, p<0.001), among baseline and three years of treatment (165 mg/dL vs. 205 mg/dL, p<0.001), and among 6 months and three years of treatment (198 mg/dL vs. 205 mg/dL, p=0.022). Furthermore, triglycerides and BMI differed significantly between baseline and 6 months (81mg/dL vs. 116 mg/dL, p<0.001 for triglycerides; 22.81 kg/m^2 vs. 24.92 kg/m^2, p<0.001 for BMI), and among baseline and 3 years of treatment (81mg/dL vs. 134 mg/dL, p<0.001 for triglycerides; 22.81 kg/m^2 vs. 25.79 kg/m^2, p<0.001 for BMI). Moreover, fasting glucose levels, HbA_{1c}, and HOMA-IR differed significantly among baseline and 3 years of treatment (87.97 mg/dL vs. 97.82 mg/dL, p<0.001 for fasting glucose levels; 5% vs. 5.3%, p<0.001 for HbA_{1c}; 1.64 vs. 3.16, p=0.003 for HOMA-IR) and among 6 months and 3 years of treatment (89.15 mg/dL vs. 97.82 mg/dL, p<0.001 for fasting glucose levels; 5% vs. 5.3%, p<0.001 for HbA_{1c}; 1.61 vs. 3.16, p=0.038 for HOMA-IR). Finally, fasting insulin differed significantly between baseline and three years of treatment (7.3μ IU/mL vs. 13.2μ IU/mL, p=0.040) (table 3; figure 2). Concerning the comparisons of glucose and lipid parameters among the patients who received risperidone and those that received olanzapine, non-statistically significant results were observed at the time point of three years after the initiation of antipsychotic medication (table A4).

Discussion

We assessed several parameters of glucose and lipid metabolism in a group of 54 drug-naïve FEP with psychosis and compared them with matched controls. We assessed the same parameters in the same group of patients after six months and in a subgroup of 39 patients after three years of antipsychotic treatment and com-

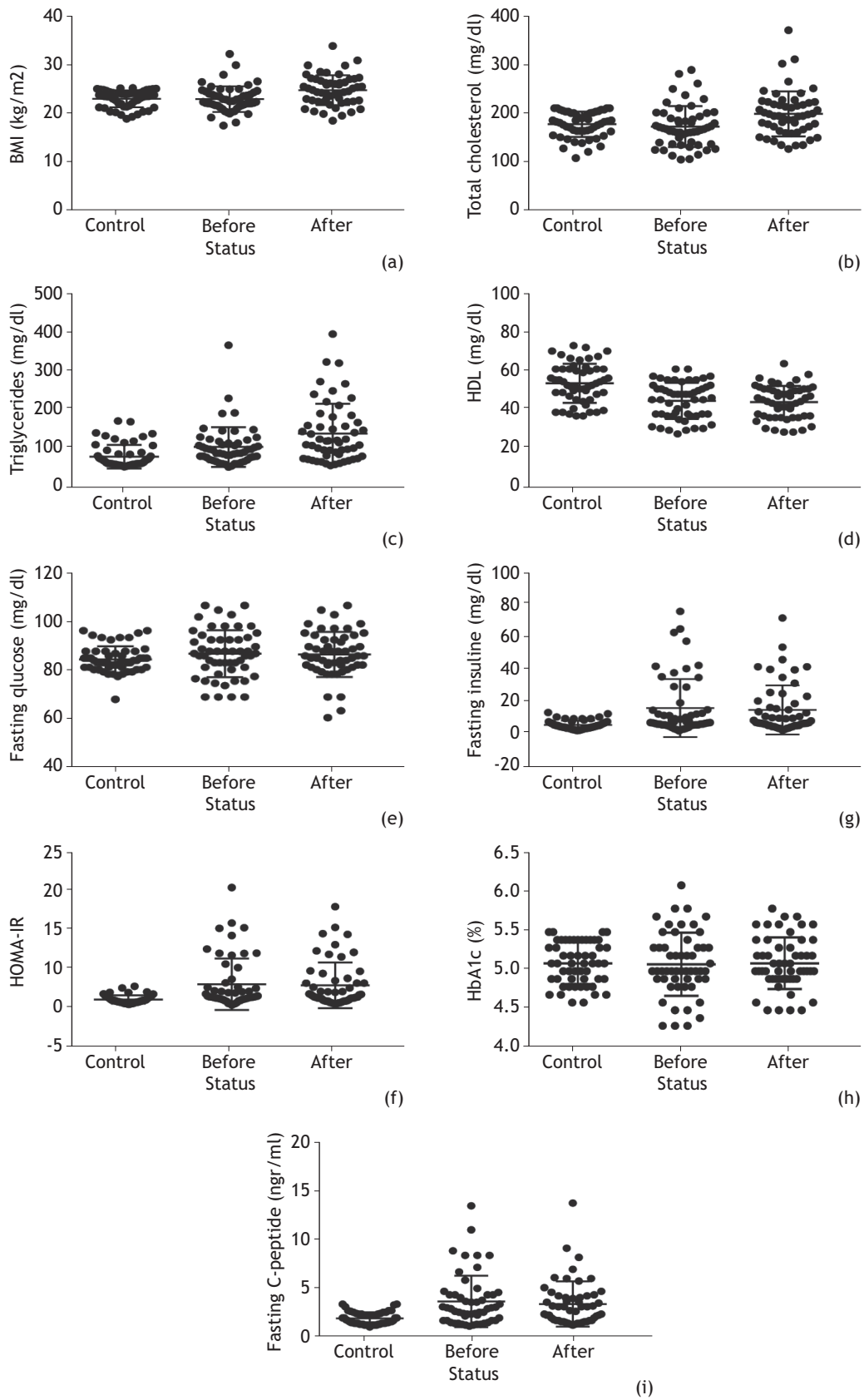

Figure 1. Scatter dot plot showing baseline characteristics, serum lipids, and glucose metabolic parameters in first-episode patients with psychosis before and after 6 months of treatment and healthy controls. Values are expressed as means with SD.

Table 3. Parameters of glucose and lipid of drug-naïve, first-episode patients with psychosis, at baseline, after six months of treatment, after 3 years of antipsychotic treatment in a tertiary center in Greece (N=39).

Parameters of lipid metabolism	Baseline (before treatment)	After 6 months of treatment	After 3 years of treatment	Statistic	Effect size
Total cholesterol [Median (range)]	165 mg/dL (104–289)	198 mg/dL(126–371)	205 mg/dL (131–366)	chi–sq=30.44, p<0.001	Kendall's W=0.39
Triglycerides [Median (range)]	81 mg/dL (44–187)	116 mg/dL (51 –399)	134 mg/dL (41 –578)	chi–sq= 26.39, p<0.001	Kendall's W=0.34
BMI[mean (SD)]	22.81kg/m^2 (2.68)	24.92 kg/m^2 (3.26)	25.79 kg/m^2 (2.76)	F=31.28, p<0.001	Partial eta–sq=0.452
HDL [Mean (SD)]	47.5 mg/dL (9.8)	46.23 (8.74)	45.9 (9.9)	F=0.694, p=0.503	Partial eta–sq=0.018
Parameters of glucose metabolism					
Fasting glucose [Mean (SD)]	87.97 mg/dL (9.63)	89.15 mg/dL (11.18)	97.82 mg/dL (9.95)	F=10.22, p<0.001	Partial eta–sq= 0.112
Fasting insulin [Median (range)]	7.3μ IU/mL (1.9–79.3)	6.9 μ UI/mL (2.8–56.2)	13.2 μ UI/mL (3.7, 105.4)	chi–sq=7.05, p=0.029	Kendall's W= 0.09
Fasting C–peptide [Median (range)]	2.8 ng/mL (1–14)	2.5 ng/mL(1.1–14.3)	3.5 ng/mL(1.1–14.4)	chi–sq=4.44, p=0.111	Kendall's W= 0.05
HbA_{1c} [Median (range)]	5% (4.3–6.1)	5% (4.5%–5.7%)	5.3% (4.5–7)	chi–sq=18.18, p<0.001	Kendall's W= 0.23
HOMA–IR [Median (range)]	1.64 (0.33–19.19)	1.61 (0.54–12.80)	3.16 (0.8–29.1)	chi–sq=10.30, p=0.006	Kendall's W= 0.13

chi-sq from Friedman test; F from Repeated measures ANOVA; BMI: Body Mass Index; SD: Standard deviation

pared them to baseline values. We also compared the effect of the two prescribed antipsychotics (risperidone and olanzapine) on the aforementioned parameters.

Significant increases in total cholesterol, BMI, and triglyceride levels were observed in the patient group (n=54) after six months of antipsychotic treatment, while significant increases in total cholesterol, triglyceride, fasting glucose, fasting insulin, HbA_{1c}, HOMA-IR, and BMI were observed in a subgroup (n=39) of patients after three years of stable antipsychotic treatment. In addition, at baseline, drug-naïve patients had significantly higher levels of fasting insulin, fasting C-peptide, and triglycerides, lower levels of HDL, and were more insulin resistant compared to matched for age, sex, BMI, and smoking status healthy controls. These are by the results of a previous study from our group,[13] in which we compared glucose and lipid metabolism parameters between a group of forty drug-naive first-episode patients and forty healthy controls matched for age, sex, BMI, and smoking status and reported higher levels of fasting insulin and C-peptide and a higher HOMA-IR score compared to controls.

A meta-analysis conducted by Pillinger et al (2017)[15] reported decreased total and LDL cholesterol levels but increased triglyceride levels in FEP patients and no difference in HDL and leptin levels between patients and controls. According to the authors, these findings suggest impaired glucose homeostasis in FEP, because hypertriglyceridemia is considered a precursor to the development of T2D. In contrast, in chronic schizophrenia patients, evidence suggests elevated levels of total cholesterol and LDL. Perry et al (2016)[16] in their meta-analysis, found FEP to be related to impaired glucose tolerance and insulin resistance, suggesting a link between these pre-diabetic markers and psychosis. Greenhalgh et al (2017)[17] found higher levels of fasting glucose, insulin, and insulin resistance in antipsychotic-naïve FEP patients with non-affective psychosis.

In the present study, fasting insulin, C-peptide, and HOMA-IR were already elevated compared to matched controls even before the initiation of antipsychotic treatment but did not change after six months of antipsychotic treatment. Perez-Inglesias et al (2009)[18] found a statistically significant increase in insulin, total cholesterol, LDL cholesterol, triglyceride levels, and insulin resistance index in a group of 145 FEP patients after one year of antipsychotic treatment with haloperidol, olanzapine, or risperidone. Weight gain was positively correlated with insulin and triglyceride levels and insulin resistance index. The authors did not find significant differences between the three antipsychotics administered as far as metabolic side effects were concerned.

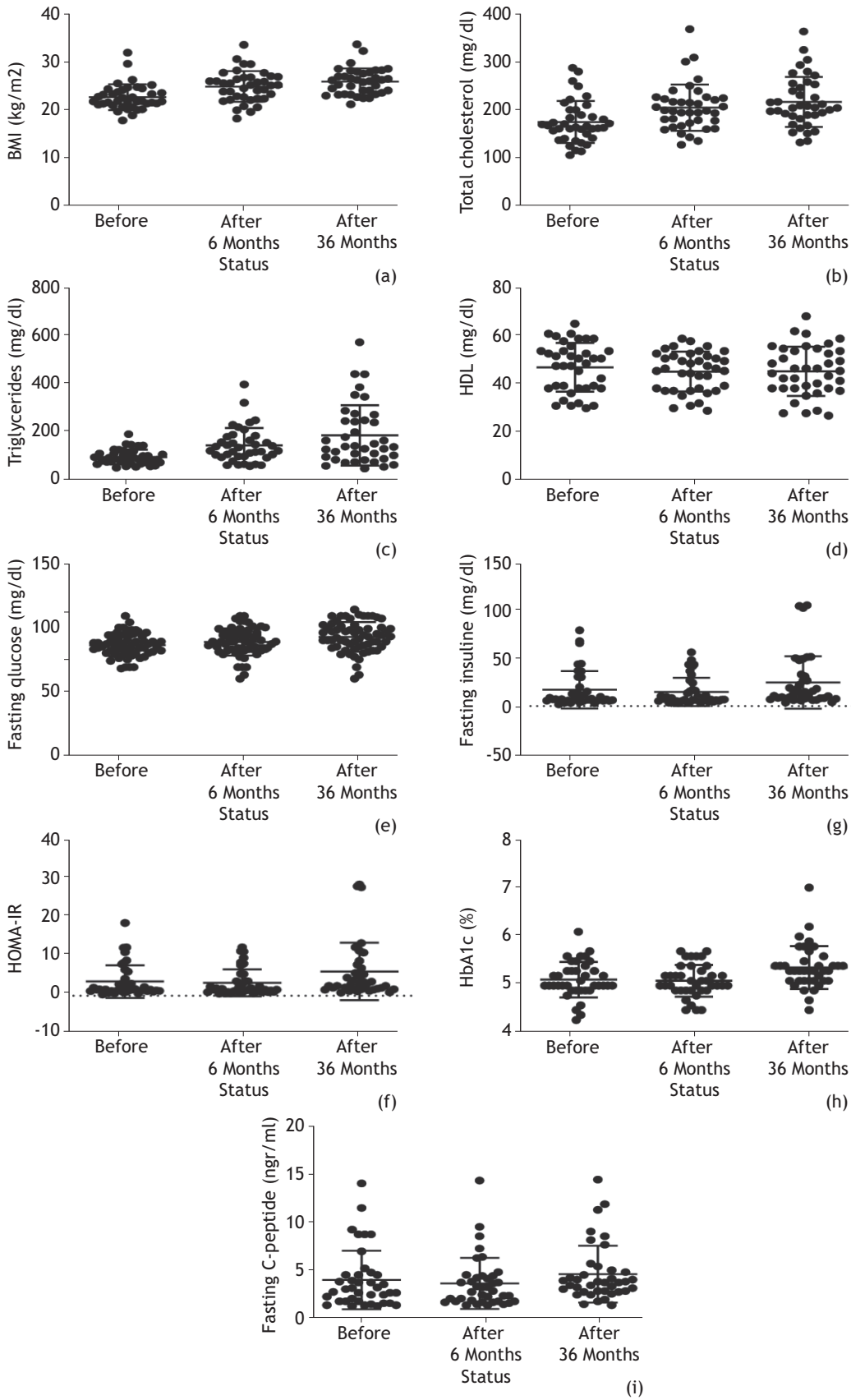

Figure 2. Scatter dot plot showing baseline characteristics, serum lipids, and glucose metabolic parameters in first-episode patients with psychosis before, after 6 months, and 3 years (36 months) of treatment. Values are expressed as means with SD.

We also did not find any significant differences between the two antipsychotics used in our study regarding metabolic disturbances. Perez-Inglesias et al (2014)[19] reported a significant increase in total cholesterol and LDL cholesterol compared to baseline in a group of 202 FEP patients after 12 weeks of treatment with quetiapine, aripiprazole, and ziprasidone. Quetiapine-treated patients had a higher increase in LDL cholesterol compared to the patients treated with aripiprazole or ziprasidone. Fasting glucose, insulin, HOMA index, and triglycerides did not differ significantly compared to baseline.

Keinanen et al (2015)[20] found after one-year follow-up no changes in glucose and lipid parameters in a group of FEP patients, but a high HOMA index at baseline was found to be an independent predictor of weight gain and an increase in waist circumference. At the end of the study, 60% of the participants were overweight or obese, especially those treated with olanzapine. Otano et al (2013)[5] report elevated levels of fasting glucose and triglyceride levels and a 26.3% incidence of metabolic syndrome after six months of antipsychotic treatment. Strassnig et al (2007)[21] found an association between weight gain and higher negative symptom scores in a group of 98 FEP patients, while Correll et al (2011)[8] suggest that women are more prone to antipsychotic-induced weight gain than men.

After three years of antipsychotic treatment, we found significant increases in total cholesterol, triglycerides, fasting glucose, fasting insulin, HbA_{1c}, HOMA-IR, and BMI in a subgroup of 39 patients compared to their baseline values and, except fasting insulin, compared also to their values after six months of treatment. In the same period, we observed a statistically significant increase in almost all glycemic parameters studied. Nine out of 39 patients developed metabolic syndrome (23%) and one developed diabetes mellitus. No statistically significant differences were observed between the olanzapine and risperidone subgroups.

In a Belgian study,[3] among 430 patients with chronic schizophrenia, 36% fulfilled the criteria of metabolic syndrome, a rate two-fold higher compared to an age-adjusted control sample, while in a sample of 650 Taiwanese patients with schizophrenia or schizoaffective disorder, the prevalence of metabolic syndrome was 35%.[22]

Cohen et al (2006)[23] reported a 14.5% prevalence of T2D in a group of 200 patients with schizophrenia, but the development of diabetes was unrelated to the duration of antipsychotic treatment or a specific antipsychotic medication, suggesting that schizophrenia and not the antipsychotic treatment determined the higher risk for diabetes. Although weight gain induced by antipsychotics is considered to be the main explanatory mechanism for metabolic disturbances in such patients, some cases of glucose dysregulation cannot be explained by weight gain only.[24] Inflammation has also been reported as a common mechanism in schizophrenia and T2D. Increased pro-inflammatory cytokines, such as IL-1β, IL-6, and Tumor Necrosis Factor-α (TNF-α), have been implicated in the pathophysiology of schizophrenia and probably increase insulin resistance and reduce pancreatic-β cell activity, leading to the development of T2M. The Akt/GSK3pathway is supposed to play a role in schizophrenia (GSK3 down-regulates D2 receptors and is a target for antipsychotic medications), while Akt and GSK3 are both regulated by the Disrupted in Schizophrenia 1 (DISC1) gene, which is implicated in both disorders.[25]

Atypical antipsychotics increase lipogenesis, leading to the accumulation of triglycerides.[7] Insulin resistance leads to an increase in the synthesis of fatty acids and triglycerides in hepatocytes.[7] In addition, up-regulation of the sterol regulatory element binding protein-2 (SREPB-2) may be implicated in antipsychotic-induced dyslipidemias.[7] Russell et al (2015)[1] reported that increases in highly sensitive CRP in a sample of 53 FEP patients were associated with increases in triglyceride levels, independently of changes in weight gain, at a three-month follow-up. Pro-inflammatory cytokines can cause hypertriglycemia by inhibiting the clearance of triglycerides through the reduction of lipoprotein-lipase or by inducing the release of Very Low-Density Lipoprotein (VLDL).

Although we tend to consider metabolic and glycemic disorders in patients with psychosis as a single entity, we should probably consider them separately. Glycemic disorders seem to pre-exist in at least some of those patients and to worsen more slowly over time (within three years of treatment), while lipid disturbances worsen significantly in the first months of treatment. Changes in lipid parameters (total cholesterol, triglycerides) and BMI occur early after the initiation of antipsychotic treatment in antipsychotic naïve FEP patients treated with olanzapine and risperidone. Glycemic disturbances were present before any antipsychotic treatment, did not change after six months, but worsened after three years of antipsychotic treatment. Monitoring of lipid and glycemic parameters at regular intervals is of utmost importance to detect and treat metabolic disorders that seem to appear early in the course of antipsychotic treatment.

The following may be considered strengths of the present study: (a) The baseline assessment without previous treatment with antipsychotics in all patients

included in the study. (b) Because of the small DUP in our study, any lifestyle changes due to psychosis could be considered minimal and did not considerably impact our results. (c) the length of the follow-up period (up to three years). (d) The relatively low drop-out rate (15/54 patients).

Limitations of our study are the small sample size and the use of only two antipsychotics. Although the patients remained in monotherapy (risperidone or olanzapine), during the study, daily doses were adjusted according to clinical indications.

Conclusion

Drug-naive, FEP patients had significantly higher insulin, C-peptide, triglyceride levels, and HOMA-IR compared to controls. They developed significant increases in total cholesterol, triglyceride levels, and BMI as soon as six months after the initiation of antipsychotic treatment compared to baseline. These metabolic abnormalities persisted following 36 months of treatment, and in addition, increases in fasting glucose, insulin, $HbA_{1c,}$ and HOMA-IR were observed compared to baseline.

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Ερευνητική εργασία

Οι επιπτώσεις των αντιψυχωτικών φαρμάκων στον μεταβολισμό της γλυκόζης και των λιπιδίων σε ασθενείς πρώτου ψυχωτικού επεισοδίου έξι μήνες και τρία χρόνια μετά την έναρξη της φαρμακευτικής αγωγής

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ΠΕΡΙΛΗΨΗ

Ο διαβήτης και η δυσλιπιδαιμία παρατηρούνται συχνά στους ασθενείς με ψύχωση και συνήθως αποδίδονται στις ανεπιθύμητες ενέργειες των αντιψυχωτικών φαρμάκων. Δεδομένου ότι ασθενείς πρώτου ψυχωτικού επεισοδίου φαίνεται να εμφανίζουν μεταβολικές διαταραχές ήδη πριν την έναρξη αντιψυχωτικής θεραπείας και του γεγονότος ότι τα αντιψυχωτικά εμπλέκονται στην εμφάνιση μεταβολικού συνδρόμου, τουλάχιστον μακροπρόθεσμα, σκοπός της μελέτης μας ήταν να παρακολουθήσουμε ασθενείς πρώτου ψυχωτικού επεισοδίου σε διαφορετικές χρονικές στιγμές (πριν την έναρξη αντιψυχωτικής θεραπείας, έξι μήνες και 36 μήνες μετά την έναρξή της) για να διερευνήσουμε πόσο νωρίς κατά τη διάρκεια της αντιψυχωτικής αγωγής εμφανίζονται ή επιδεινώνονται μεταβολικές διαταραχές και ποιες). Εκτιμήσαμε τον μεταβολισμό γλυκόζης και λιπιδίων σε κατάσταση νηστείας σε 54 ασθενείς με πρώτο ψυχωτικό επεισόδιο (ΠΨΕ) πριν την έναρξη αντιψυχωτικής αγωγής και τους συγκρίναμε με αντίστοιχη ομάδα ελέγχου. Εκτιμήσαμε τις ίδιες παραμέτρους στην ομάδα των 54 ασθενών έξι μήνες μετά την έναρξη της αγωγής και ύστερα από 36 μήνες συνεχούς και σταθερής αντιψυχωτικής αγωγής σε υποομάδα 39 ασθενών και συγκρίναμε με τις τιμές των ίδιων ασθενών προ της ενάρξεως της θεραπείας και στις δύο περιπτώσεις. Οι μετρήσεις έγιναν ενώ οι ασθενείς ήταν νηστικοί για τη συγκέντρωση ολικής χοληστερόλης, τριγλυκεριδίων, λιποπρωτεΐνης υψηλής πυκνότητας (HDL), γλυκόζης, ινσουλίνης, συνδετικού πεπτιδίου (C-πεπτιδίου), εκτίμησης της αντίστασης στην ινσουλίνη με τον δείκτη HOMA-IR, γλυκοζυλιωμένης αιμοσφαιρίνης και δείκτη μάζας-σώματος. Στους 54 ασθενείς πρώτου επεισοδίου άνευ θεραπείας βρήκαμε υψηλότερες τιμές ινσουλίνης νηστείας, C-πεπτιδίου, τριγλυκεριδίων και του δείκτη αντίστασης στην ινσουλίνη-HOMA-IR σε σχέση με ισάριθμη ομάδα ελέγχου. Η ολική χοληστερόλη, οι συγκεντρώσεις των τριγλυκεριδίων και το BMI, βρέθηκαν στατιστικά σημαντικά αυξημένες στην υπό μελέτη ομάδα ασθενών μετά από έξι μήνες αντιψυχωτικής θεραπείας σε σύγκριση με τις προ θεραπείας τιμές. Παράλληλα, μετά από 36 μήνες αντιψυχωτικής θεραπείας, σε 39 από τους ανωτέρω ασθενείς βρήκαμε στατιστικά σημαντική αύξηση των τιμών της γλυκόζης νηστείας, της ινσουλίνης νηστείας, της γλυκοζυλιωμένης αιμοσφαιρίνης-HbA1c, του δείκτη αντίστασης στην ινσουλίνη-HOMA-IR index, της ολικής χοληστερόλης, των τιμών των τριγλυκεριδίων και του δείκτη μάζας σώματος (BMI) σε σύγκριση με τις αντίστοιχες τιμές των 39 ασθενών αυτών πριν την έναρξη της αντιψυχωτικής θεραπείας.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Πρώτο ψυχωτικό επεισόδιο, σχιζοφρένεια, μεταβολισμός, αντίσταση στην ινσουλίνη, χοληστερόλη, τριγλυκερίδια.

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