Received: 25 October 2016 | Revised: 28 February 2017 | Accepted: 25 April 2017

DOI: 10.1111/eip.12457

WILEY

ORIGINAL ARTICLE

Antipsychotic treatment is associated with inflammatory and metabolic biomarkers alterations among first-episode psychosis patients: A 7-month follow-up study

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Funding information
European Union through the European Regional Development Fund, Grant/Award number: 2014-2020.4.01.15-0012; Estonian Research Foundation, Grant/Award numbers: IUT 20-41, IUT 20-42, IUT 20-45.

Aim: Second-generation antipsychotics are commonly used to treat schizophrenia, but may cause metabolic syndrome (MetS) in a subset of patients. The mechanisms of antipsychotic-related metabolic changes remain to be established, especially in first-episode psychosis (FEP) patients.

Methods: In the present study, we used a chip technology to measure metabolic (C-peptide, insulin, leptin, adiponectin and resistin) and inflammatory biomarkers (ferritin, interleukin-6, interleukin-1α, tumour necrosis factor-α and plasminogen activator inhibitor-1) in the serum samples of a population of FEP patients before and after 7 months of antipsychotic drug treatment, compared to control subjects (CS).

Results: The comparison of these markers in antipsychotic-naïve FEP patients (N = 38) and CS (N = 37) revealed significantly higher levels of ferritin (P = .004), and resistin (P = .03) and lower level of leptin (P = .03) among FEP patients group. Seven months of antipsychotic drug treatment in patients (N = 36) ameliorated clinical symptoms, but increased significantly body mass index (BMI; P = .002) and these changes were accompanied by increased levels of C-peptide (P = .03) and leptin (P = .02), as well as decreased level of adiponectin (P = .01).

Conclusions: Seven months of antipsychotic drug treatment suppressed the clinical symptoms of psychosis whereas caused imbalance in metabolic biomarkers and increased BMI. These findings provide insight into antipsychotic-induced MetS and refer to problems in insulin processing already present in the early stage of the chronic psychotic disorder.

KEYWORDS

antipsychotic drug treatment, body mass index, first-episode psychosis, inflammatory biomarkers, metabolic biomarkers

1 | INTRODUCTION

Metabolic syndrome (MetS) and other cardiovascular risk factors are highly prevalent in people with schizophrenia (SCZ). MetS (comprising obesity, hyperlipidemia, hyperglycemia and hypertension) is present in one-third of these patients (McEvoy et al., 2005; Mitchell, Vancampfort, De Herdt, Yu, & De Hert, 2013). The report of Parks, Svendsen, Singer, and Foti (2006) has demonstrated that people with SCZ die on average 25 years earlier than those in general population, and although suicide and other un-natural causes account for about 40% of excess mortality, roughly 60% of premature deaths are from natural causes, such as cardiovascular and pulmonary diseases.

Analysis of literature shows an association between MetS and SCZ (Vancampfort et al., 2013), suggesting that metabolic phenotype is intrinsic to SCZ. Before the antipsychotic drug era, cohort studies revealed increased incidence of abnormal glucose metabolism in people with SCZ (Henneman, Altschule, & Goncz, 1954). These observations are in line with cross-sectional results demonstrating that the prevalence of diabetes is greater in patients of SCZ compared to the general population (Kohen, 2004). A recent meta-analysis has

confirmed these findings, and has revealed impaired glucose tolerance (IGT) in antipsychotic-naïve first-episode psychosis (FEP) patients, as compared to control subjects (CS) (Greenhalgh et al., 2017). IGT has also been demonstrated in non-psychotic, first-degree relatives of patients of SCZ, further indicating a heritable phenotype that tracks with the risk of psychosis, but is independent of the actual development of a psychotic disorder (Spelman, Walsh, Sharifi, Collins, & Thakore, 2007). The risk of metabolic abnormalities further increases significantly with the duration of disease with those who have chronic disease showing increased rates of metabolic dysfunction compared to FEP patients and antipsychotic-naïve FEP patients (Mitchell et al., 2013). In part, these cardiometabolic risk factors are attributable to unhealthy lifestyle, including poor diet and sedentary behaviour (De Hert, Schreurs, Vancampfort, & VAN Winkel, 2009).

In addition, the treatment of choice in SCZ is antipsychotic medications, and over recent years it has become apparent that antipsychotic agents can have a negative impact on some of the modifiable risk factors (De Hert et al., 2009). Concerns regarding the metabolic side-effects of antipsychotic drugs greatly increased following the introduction of the "second generation" or "atypical" drugs, which have come to dominate the antipsychotic drug market.

Interestingly, antipsychotic drugs have long been known to cause immunomodulatory effects, targeting cytokine networks and raising the possibility of an alternative explanation for the actions of these agents (Kato et al., 2011). Studies on the effect of antipsychotic treatment on inflammation, and more specifically on cytokine levels, have demonstrated inconsistent findings, showing an increase, a decrease or unchanged levels of cytokines after antipsychotic treatment (Zajkowska & Mondelli, 2014). One possible explanation for the varying findings is that antipsychotic agents might exert different effects on the immune system, having both a direct anti-inflammatory activity and an indirect pro-inflammatory activity, mediated by their effect on weight gain and increased adiposity (Mondelli & Howes, 2014).

The observation that metabolic disorder has been associated with low-grade systemic inflammatory conditions has led to studies linking these two pathways. The immune response and metabolic regulation are highly integrated, and their proper functioning is interdependent. Indeed, obesity, insulin resistance and type II diabetes have been shown to be closely associated with chronic inflammation, characterized by the activation of inflammatory signalling pathways and by abnormal cytokine production (Hotamisligil, 2006). It is possible that such mechanisms are also operating in psychosis. Moreover, it could be that existence of the low-grade inflammation and antipsychotic treatment contributes to the metabolic abnormalities seen in SCZ. Therefore, studies in antipsychotic-naïve FEP patients with normal weight are preferable to better understand the role of inflammation in SCZ and the antipsychotic drug treatment impact on the metabolic parameters. Despite the above reported evidence, little is known regarding the relationship between inflammation and metabolic outcomes in FEP patients. Previous studies have reported altered inflammatory markers in patients with chronic psychotic disease (Nunes et al., 2006; Potvin et al., 2008), and in patients with FEP (de Witte et al., 2014; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Upthegrove, Manzanares-Teson, & Barnes, 2014). In support of this, using high-sensitive inflammatory biomarkers assay, we have demonstrated that antipsychotic-naïve FEP patients had significantly elevated levels of epidermal growth factor (EGF), interleukin-4 (IL-4) and IL-6 and reduced level of IL-1β compared to CS. Furthermore, 7 months of antipsychotic drug treatment reduced significantly levels of EGF, vascular endothelial growth factor (VEGF), interferon-γ (INF-γ), IL-2, IL-4, IL-6, IL-8 and IL-1α in these patients compared to the premedication levels of these markers, and elevated body mass index (BMI) (Haring et al., 2015). To elaborate our previous results and to establish the concurrent impact of antipsychotic treatment on inflammatory and metabolic biomarkers as well as BMI, we implemented alternative biochip array technology, which allowed to perform simultaneous assessment of metabolic and inflammatory biomarkers on the same cohort.

The goal of the present study was to examine pre-treatment inflammatory and metabolic status of FEP patients compared to CS and analyse the development of signs of MetS in FEP patients in response to 7-month antipsychotic treatment. In the first set of our study, differences in BMI, and also in inflammatory [ferritin, IL-6, IL-1α, tumour necrosis factor-α (TNF-α), plasminogen activator inhibitor-1 (PAI-1)], and metabolic (C-peptide, insulin, leptin, adiponectin and resistin) biomarkers were compared between FEP patients and CS. Second, these indices were compared before and after 7-month antipsychotic treatment in FEP patients group and also between treated patients and CS groups to demonstrate the 7-month antipsychotic treatment effect on BMI and the measured biomarkers levels.

2 | MATERIALS AND METHODS

2.1 | Participants

Thirty-eight FEP patients (21 males and 17 females; mean age 25.4 ± 0.89 years) were recruited from the Psychiatric Clinic of Tartu University Hospital, Estonia. The patients fulfilled the following inclusion criteria: were aged between 18 and 45; had experienced a FEP; duration of their untreated psychosis had been less than 3 years; no antipsychotic treatment received before the first contact with medical services for psychosis. Patients were excluded from the study if they had psychotic disorders owing to a general medical condition or had substance-induced psychosis. FEP diagnoses were based on clinical interviews according to the International Classification of Diseases, Tenth Edition (ICD-10) criteria (World Health Organization, 1992).

Thirty-six FEP patients underwent treatment using antipsychotic medication (2 refused) and were included in the follow-up analysis. History of antipsychotic medication was collected according to reviews of patients' medical charts. Patients were treated with various antipsychotic medications according to what was clinically indicated, and treatments changed over the course of the 7-month interval. During the follow-up period, patients received either atypical (N = 24), typical (N = 1) or mixed (N = 11) antipsychotic medication; the mean theoretical chlorpromazine daily dose equivalent (Gardner, Murphy, O'Donnell, Centorrino, & Baldessarini, 2010) was 396 ± 154 mg (range 80–640). Twenty-eight patients were treated

only with antipsychotics, but 5 patients additionally needed mood stabilizers and 6 patients also received antidepressants or hypnotics.

Thirty-seven mentally healthy subjects participated in the study as CS (16 males and 21 females, mean age 24.8 ± 0.86 years). The CS sample was recruited by advertising in the same geographical area the FEP patients came from. Both patients and CS were interviewed by experienced psychiatric doctors in order to avoid the inclusion of subjects as controls with mental disorders. Exclusion criteria for the control group also included psychotic disorders among close relatives. The study was approved by the Ethics Committee of the University of Tartu, Estonia. Written informed consent was also obtained from all participants.

The sample of this study contains same participants as our previous study by Haring et al. (2015)

2.2 | Procedure

For the FEP patients, fasting blood samples, clinical, demographic and BMI [weight (kg)/height $(m)^2$] data were collected at 2 time points: on admission and after the follow-up period (mean duration 7.18 ± 0.73 months). The time duration between 2 occasion consisted of initial stabilization of acute psychotic symptoms (took approximately a month) and further 6 months continuous treatment with antipsychotics. Symptom severity was measured using the Positive and Negative Syndrome Scale (PANSS) (Kay, Flszbein, & Opfer, 1987), a rating instrument that evaluates the presence and severity of positive, negative and general psychopathology using 30 items, each scored from 1 (absent) to 7 (severe), and total scores were calculated and used in further analyses. Blood samples, BMI and demographic data from CS were collected cross-sectionally.

2.3 | Blood collection and clinical laboratory measurements

Blood samples of the participants were collected between 9:00–11:00 AM. Blood (5 mL) was sampled using anticoagulant-free tubes and kept for 1 hour at 4°C (for platelet activation) before serum was isolated (centrifugation at 2000 rpm for 15 minutes at 4°C). Serum was kept at −20°C before testing.

2.4 | Metabolic and inflammatory biomarkers assays

Biochip array technology (Randox Biochip, RANDOX Laboratories Ltd, Crumlin, UK, Metabolic Syndrome Array I for Evidence Investigator™) was used to perform simultaneous quantitative detection of multiple analytes from a single serum sample of CS or FEP patient as we have described previously (Kaur, Zilmer, Leping, & Zilmer, 2012).

The following inflammatory and metabolic biomarkers: C-peptide, insulin, leptin, resistin, ferritin, IL-6, IL-1α, TNF-α and PAI-1 were measured according to the manufacturer's protocol. Results are expressed as picograms and nanograms per millilitre. The reproducibility of the assay for individual cytokines was determined using the quality control method provided with the kit. Intra-assay and inter-assay precision are given in Table S1, Supporting information, units and sensitivity in Table S2. The plasma concentrations of adiponectin (ng/mL) were analysed by a quantitative sandwich enzyme immunoassay technique, using a commercially available kit (R&D Systems, Minneapolis, MN, USA); intra-assay and inter-assay precision are given in Table S3.

2.5 | Statistical analyses

Group differences with regard to demographic measurements were analysed using the *t*-test, or Chi-square test. The application of Shapiro–Wilk tests indicated that the inflammatory and metabolic values were not normally distributed ($P < .05$). A Mann–Whitney *U*-test was applied to compare the raw data of two independent samples (FEP patients before treatment and CS) and a Wilcoxon Matched Pairs Test to compare the two dependent samples (FEP patients' pre- and post-treatment condition). For within-subjects analyses, patients were paired one by one. The Bonferroni correction was applied for the number of biomarkers within the particular analysis. Differences between FEP patients and CS (based on the Mann–Whitney *U*-test), and differences between the pre- and post-treatment values within the patients group (based on the Wilcoxon Matched Pairs Test) were considered significant at $P < .05/10$, and trends at $P < .10/10$. Effect sizes were interpreted as small, medium and large, with corresponding eta-squared ranging from 0.01–0.05, 0.06–0.13 and ≥0.14, respectively (Cohen, 1988).

The Spearman's rank correlation analysis was applied to establish the correlations between metabolic and low-grade inflammation markers, in FEP patients' group (before and after 7-month antipsychotic treatment).

General linear models (GLMs) were used to demonstrate biomarkers levels differences between antipsychotic-naïve FEP patient and CS. Because GLM analyses required normally distributed data, biomarkers values were $\log_{10}$-transformed to approximate normality. To establish the treatment main effect (ie, difference between pre- and post-treatment measurement occasion) on BMI and serum biomarkers levels (dependent variables) within-subjects' analysis (GLM: repeated measures, adjusted for gender and smoking status) were utilized. Categorical (disease, gender and smoking status) and continuous (age) covariates were used in the GLM to compare biomarkers levels (dependent variables) between groups, and *P* values less than .05 were considered to be statistically significant.

The statistical analyses were performed using Statistical software (StataCorp LP, 2013) for Windows.

3 | RESULTS

3.1 | General description of the study groups

There were no statistically significant differences between antipsychotic-naïve FEP patients and CS in terms of age ($t = .49$, df = 73, $P = .62$), gender ($\chi^2 = 1.08$, df = 1, $P = .30$), or mean (± SD) scores of BMI (22.55 ± 2.94 and 23.02 ± 3.05, respectively; $t = -.69$, df = 73, $P = .49$). 7-month treatment caused significant change in BMI ($t = -8.07$, df = 35, $P < .000001$). Mean BMI gain at 7-month follow-up was 2.97 kg/m^2 (±2.21). In addition, the

differences in tobacco use (8 patients [21.1%] vs 7 controls [18.9%]) was not statistically significant (χ^2 = .05, df = 1, P = .82).

3.2 | Correlations between biomarkers

Spearman correlation matrices were generated to explore preliminary relationships among the metabolic and inflammatory markers for pre- and post-treatment occasions within the FEP patients group. These matrices are shown in Table S4 and Table S5. As expected, the most prominent positive correlation emerged between insulin and C-peptide.

3.3 | Differences in levels of biomarkers between antipsychotic-naïve FEP patients and CS

The comparison of inflammatory and metabolic biomarkers (Mann–Whitney *U*-test, raw data) revealed a significant elevation of ferritin and resistin in antipsychotic-naïve FEP patients compared to CS (Table 1). Assessment of measured biomarker values difference trends indicated that patients had higher PAI-1, IL-6 and lower leptin levels compared to CS (Table 1). According to our sample, differences in the abovementioned biomarker levels demonstrated medium-size effects of the disease.

Table 2 presents the results of a multivariate GLM analysis, $\log_{10}$-transformed biomarker levels were treated as dependent variables. Age, gender and smoking status were taking under control. We found a significant main effect of disease (FEP patients vs CS) on the levels of leptin, resistin and ferritin. FEP patients demonstrated higher levels of resistin and ferritin and lower levels of leptin (Table 2). The proposed model appeared to fit well in estimating the difference between antipsychotic-naïve FEP patients and CS as measured by biomarkers levels, $F(10, 32) = 3.12$, df = 10,32, P = .007, partial η^2 = .49. In addition, gender main effect with regard to ferritin emerged (t = 4.70, P = .00003), indicating that males demonstrated higher values of that biomarker. Age and smoking status were not significant predictors for measured biomarkers.

TABLE 2 Regression coefficients (ß) and significance values of $\log_{10}$-transformed biomarkers levels with disease, adjusted for gender, age and smoking status

Biomarkers	ß	ß (95% CI)	*t*-value	*P* value
C-peptide	−0.16	−0.46, 0.15	−1.05	0.30
Insulin	−0.10	−0.40, 0.21	−0.64	0.53
Leptin	−0.33	−0.63, −0.04	−2.31	0.03*
Adiponectin	0.07	−0.24, 0.38	0.44	0.66
Resistin	0.34	0.03, 0.64	2.23	0.03*
Ferritin	0.37	0.13, 0.61	3.10	0.004*
IL-6	0.23	−0.07, 0.53	1.57	0.13
IL-1α	−0.03	−0.34, 0.28	−0.19	0.85
TNF-α	−0.004	−0.32, 0.31	−0.03	0.98
PAI-1	0.27	−0.02, 0.55	1.89	0.07

CI, confidence intervals; IL-1 α, IL-6, interleukins; TNF-α, tumour necrosis factor-α; PAI-1, plasminogen activator inhibitor-1.

*P < .05.

3.4 | Effects of antipsychotic drugs on psychotic symptoms, BMI and inflammatory and metabolic biomarkers

As expected, there was a statistically significant 7-month antipsychotic treatment effect on the psychopathology (PANSS) total score (t = 10.95, df = 1,70, P < .000001) (GLM-repeated measures).

TABLE 1 Comparisons of inflammatory and metabolic biomarkers levels (pg/mL) between first-episode psychosis (FEP) patients at baseline and control subjects (CS)

Biomarkers	Number of participants n/n	CS Median (min–max)	FEP Median (min–max)	Z-value	*P* value	Effect size η^2
C-peptide	37/36	1.20 (0.37–2.28)	0.80 (0.12–4.48)	−1.29	0.20	0.02
Insulin	37/36	8.47 (1.80–126.9)	7.30 (3.10–60.6)	−0.55	0.58	0.00
Leptin	35/36	1.41 (0.38–6.69)	0.85 (0–2.22)	−2.73	0.006	0.11
Adiponectin	26/26	7076.00 (2382.00–4273.00)	7335.50 (2093.00–2334.00)	0.52	0.60	0.01
Resistin	37/36	2.66 (1.59–4.10)	2.96 (1.69–8.58)	2.79	0.005*	0.11
Ferritin	37/36	22.1 (1.22–184.7)	56.0 (4.26–238.7)	2.86	0.004*	0.11
IL-6	37/36	0.53 (0.23–1.54)	0.84 (0.12–8.64)	2.53	0.01	0.09
IL-1α	36/36	0.32 (0.20–1.67)	0.30 (0–1.78)	−1.29	0.20	0.03
TNF-α	37/36	5.17 (3.42–8.73)	5.43 (2.92–10.73)	0.13	0.90	0.03
PAI-1	37/36	21.4 (7.57–49.9)	25.7 (8.92–48.6)	2.75	0.006	0.10

Notes: Z-adjusted values according to Mann–Whitney *U*-test (FEP patients compared to CSs).

IL-1 α, IL-6, interleukins; TNF-α, tumour necrosis factor-α; PAI-1, plasminogen activator inhibitor-1.

*P values, adjusted with the Bonferroni correction of alpha (.05/10 = .005).

TABLE 3 Comparisons of inflammatory and metabolic biomarkers levels (pg/mL) between first-episode psychosis (FEP) patients at baseline and FEP patients after 7-month treatment with antipsychotics

Biomarkers	Number of participants n/n	FEP (baseline) Median (min–max)	FEP (after treatment) Median (min–max)	Z-value	*P* value	Effect size η^2
C-peptide	34/34	0.80 (0.12–4.48)	1.90 (0.28–7.71)	3.10	0.002*	0.14
Insulin	35/35	7.30 (3.10–60.6)	10.10 (3.03–66.8)	1.26	0.21	0.02
Leptin	32/32	0.85 (0–2.22)	1.21 (0–9.29)	3.38	0.0007*	0.16
Adiponectin	24/24	7335.50 (2093.00–2334.00)	5591.00 (1084.00 –10223.00)	2.43	0.02	0.12
Resistin	35/35	2.96 (1.69–8.58)	2.80 (1.42–4.76)	2.61	0.009	0.10
Ferritin	35/35	56.0 (4.26–238.7)	30.9 (4.75–150.0)	4.19	0.00003*	0.25
IL-6	35/35	0.84 (0.12–8.64)	0.75 (0.23–1.64)	2.16	0.03	0.07
IL-1α	29/29	0.30 (0–1.78)	0.24 (0–1.77)	2.47	0.01	0.11
TNF-α	35/35	5.43 (2.92–10.73)	5.10 (2.84–9.30)	0.01	0.99	0.00
PAI-1	35/35	25.7 (8.92–48.6)	22.0 (7.06–57.1)	2.24	0.03	0.07

Notes: Z-values according to Wilcoxon Matched Pairs Test (FEP patients, pre- and post-treatment occasions).

IL-1 α, IL-6, interleukins; TNF-α, tumour necrosis factor-α; PAI-1, plasminogen activator inhibitor-1.

**P* values, adjusted with the Bonferroni correction of alpha (.05/10 = .005).

Several biomarkers were significantly changed after 7-month antipsychotic treatment in FEP patients (Table 3). The strongest decline was established for ferritin, followed by resistin, IL-1α, adiponectin, PAI-1 and IL-6 (Table 3). Change in ferritin level survives the Bonferroni correction for multiple testing and significant changing trends emerged in the levels of resistin and IL-1α. By contrast, the levels of C-peptide and leptin were significantly elevated after treatment (Table 3). The effect size of 7-month antipsychotic treatment on C-peptide, leptin and ferritin levels changes ranged between 0.14 and 0.25, suggesting that the clinical magnitude of the intervention on these markers was strong. Moreover, treatment effect tended to produce a medium effect size in terms of adiponectin, resistin, IL-6, IL-1α, as well as PAI-1 levels changes, and with the large sample size, these biomarkers would have been survived the Bonferroni correction for multiple comparisons.

The number of patients displaying the level of C-peptide higher than 2 pg/mL before treatment was 5 out of 35, whereas after the treatment the respective number of such patients increased to 17. Moreover, the calculation of ratio between insulin and C-peptide revealed a significant shift in favour of the precursor molecule ($Z = 3.29$, $P < .001$; Wilcoxon Matched Pairs Test) after 7-month antipsychotic treatment. Also treatment caused a significant shift ($Z = 3.91$, $P = .00009$, Wilcoxon Matched Pairs Test) in favour of leptin compared to adiponectin.

With respect to the differences along the biomarkers levels before and after 7-month antipsychotic treatment, the repeated-measures GLM showed a significant main effect of time accompanied by continuous treatment with antipsychotics on the levels of C-peptide, leptin which were increased and adiponectin which was decreased during the treatment (see Table 4). Furthermore, the same model revealed the significant main effect of the treatment condition on BMI, which was elevated significantly during 7 months (Table 4). Gender and smoking status were not significant predictors in this model. Thereafter, inflammatory and metabolic status of treated FEP patients was compared with CS. Significant difference emerged only in C-peptide level (Table 5), whereas previously (Table 2) demonstrated elevated levels of resistin and ferritin as well as diminished level of leptin were turned into the levels of CS. Age, gender and smoking status were not significant

TABLE 4 Regression coefficients (ß) and significance values of 7-month treatment effect on BMI and $\log_{10}$-transformed biomarkers levels, adjusted for gender and smoking status

Variables	ß	ß (95% CI)	*t*-value	*P* value
C-peptide	0.39	0.04, 0.74	2.25	0.03*
Insulin	0.31	−0.06, 0.67	1.67	0.10
Leptin	0.38	0.07, 0.70	2.46	0.02*
Adiponectin	−0.48	−0.84, −0.12	−2.73	0.01*
Resistin	−0.27	−0.66, 0.12	−1.39	0.17
Ferritin	−0.25	−0.54, 0.04	−1.75	0.09
IL-6	−0.13	−0.51, 0.26	−0.65	0.52
IL-1α	0.14	−0.25, 0.54	0.74	0.47
TNF-α	−0.09	−0.42, 0.23	−0.57	0.57
PAI-1	−0.20	−0.53, 0.14	−1.19	0.24
BMI	0.57	0.23, 0.91	3.40	0.002*

CI, confidence intervals; IL-1 α, IL-6, interleukins; TNF-α, tumour necrosis factor-α; PAI-1, plasminogen activator inhibitor-1; BMI, body mass index.

* $P < .05$.

TABLE 5 Regression coefficients (ß) and significance values of log_{10}-transformed biomarkers levels in first-episode psychosis (FEP) patients group after 7-month treatment with antipsychotics compared to control subjects, adjusted for gender, age and smoking status

Biomarkers	ß	ß (95% CI)	*t*-value	*P* value
C-peptide	0.36	0.07, 0.65	2.46	0.02*
Insulin	0.20	−0.11, 0.51	1.32	0.19
Leptin	0.23	−0.05, 0.51	1.68	0.10
Adiponectin	0.25	−0.56, 0.06	1.65	0.10
Resistin	0.10	−0.22, 0.43	0.65	0.52
Ferritin	0.18	−0.06, 0.43	1.50	0.14
IL-6	0.15	−0.15, 0.45	0.99	0.33
IL-1α	0.06	−0.26, 0.38	0.36	0.72
TNF-α	−0.17	−0.46, 0.13	−1.12	0.27
PAI-1	0.04	−0.26, 0.34	0.26	0.79

CI, confidence intervals; IL-1 α, IL-6, interleukins; TNF-α, tumour necrosis factor-α; PAI-1, plasminogen activator inhibitor-1.

*$P < .05$.

predictors with regard to measured biomarkers levels differences between treated FEP group and CS.

4 | DISCUSSION

Initial comparison of antipsychotic-naïve FEP patients with CS group revealed several apparent differences between these two groups. The levels of ferritin (ie, an acute phase protein), PAI-1 (which has an important role in the regulation of fibrinolysis), IL-6 (ie, a monocyte-/macrophage-related pro-inflammatory cytokine involved predominantly in inflammation and also in the regulation of metabolic processes) and resistin (ie, originally described as an adipocyte-specific hormone, provides a link between obesity, insulin resistance and diabetes) were significantly augmented in antipsychotic-naïve FEP patients. By contrast, the level of leptin (ie, a hormone made by adipose cells, to help regulate energy balance) was reduced in patients before treatment.

The elevation of above-described factors can be taken as a possible sign of inflammatory response during the FEP. This is characterized by an elevation of IL-6, and acute phase proteins (ie, ferritin and PAI-1). Several previous studies have also noted elevated IL-6 (Di Nicola et al., 2013; Stojanovic et al., 2014; Upthegrove et al., 2014), as well as increased levels of ferritin and PAI-1 (Hoirisch-Clapauch, Amaral, Mezzasalma, Panizzutti, & Nardi, 2016; Schwarz et al., 2010) in FEP or chronic patients. Reduced leptin level may be taken as reduced nutritional status of patients, reflecting somewhat reduced amount of fat tissue in antipsychotic-naïve FEP patients.

In this study, we found that antipsychotic-naïve FEP patients did not significantly differ from CS in their baseline measurements of fasting plasma levels of insulin, C-peptide and adiponectin. These findings are in contrast to previous studies reporting higher levels of insulin and C-peptide levels in the FEP patients' group compared to those in CS (Pillinger et al., 2017; Wu et al., 2013). However, other studies found no significant difference in insulin resistance between drug-naïve patients with psychosis and CS (Arranz et al., 2004; Sengupta et al., 2008). The discrepancy between our study and previous studies may be partly explained by the sample size.

GLM analysis established a strong positive relationship of disease with ferritin and resistin and inverse relationship with leptin, and confirmed involvement of inflammation and metabolic-related factors during the early stage of the FEP. Adipokines have multidirectional actions or interplay with other molecules in a variety of functions. In rodents, resistin expression is limited to adipose tissue (Steppan et al., 2001), and is a potential mediator of the obesity and insulin resistance link (Kusminski, Mcternan, & Kumar, 2005). However, the translation of these findings to humans has been less conclusive (Lazar, 2007). In humans, resistin appears to be an inflammatory molecule primarily expressed in monocytic cells, from which it is secreted (Patel et al., 2003). The correlation between resistin with inflammatory markers (eg, IL-6, TNF-α) is particularly noteworthy given the observation that resistin is produced by macrophages in response to inflammatory cytokines (Stejskal, Adamovská, Bartek, Juráková, & Prosková, 2003), and on the other hand, resistin itself is able to contribute to the inflammatory conditions by mediating enhanced activation of cytokines (IL-6, TNF-α) and nuclear factor kappa B (NF-κB) (Stofkova, 2010). Thus, the interplay between adipocytes and macrophages may lead to hyper-resistinemia even if human resistin is mainly expressed in macrophages.

Serum ferritin is also a well-known inflammatory marker, and abnormally elevated serum ferritin levels represent a consequence of cell stress and damage (Kell & Pretorius, 2014). In accordance with our results, a report published by Schwarz et al. (2010) described an assortment of 51 analytes which included ferritin among others, as a potential marker which could distinguish first- and recent-onset SCZ patients ($N = 250$) from CSs ($N = 230$). Furthermore, consistent with the report of Ramsey et al. (2013), we found significant ferritin levels sex differences in our sample. They demonstrated that serum from male first-episode antipsychotic-naïve SCZ patients ($N = 79$) contained significantly higher levels of ferritin compared to female ($N = 54$).

With regard to leptin, preclinical studies have demonstrated the potential interplay between resistin and leptin. These studies suggest leptin may exert insulin resistance-ameliorating effects via counter-regulatory interactions and potentially suppressive mechanisms towards resistin (ie, suppressing resistin gene expression and protein levels) (Asensio, Cettour-Rose, Theander-Carrillo, Rohner-Jeanrenaud, & Muzzin, 2004; Rajala et al., 2004). However, in humans mixed findings have been emerged (Lazar, 2007). According to our results, pre-treatment condition was associated with elevated resistin and reduced leptin levels, and on the contrary, 7-month antipsychotic treatment was characterized by elevated leptin and insignificant change in resistin levels. Previously, Pérez-Iglesias et al. (2008) also demonstrated that the resistin level in patients with the first episode of psychosis, treated a year with antipsychotics, was not significantly changed. Furthermore, the same research group demonstrated that medication-naïve FEP patients 12 weeks treatment with aripiprazole ($N = 40$) caused significant increase in leptin levels compared to ziprazidone ($N = 35$) among women, and no significant changes in insulin parameters were observed (Pérez-Iglesias et al., 2014). Our study had a naturalistic design and FEP patients were treated with

various antipsychotic drugs and while necessary, dosage adjustments and active substance changes were made during the follow-up period. Therefore, it is difficult to draw any major conclusions about the effects of particular antipsychotic drugs. Nevertheless, treatment with antipsychotic drugs caused a significant reduction in the psychopathology total (PANSS) score. However, this positive change was accompanied by the marked increase in BMI, the frequently seen side-effect of antipsychotic medication (Bak, Fransen, Janssen, van Os, & Drukker, 2014; De Hert et al., 2009; McEvoy et al., 2005). It is important to note that difference in BMI values between antipsychotic-naïve FEP patients and CS was not statistically significant. An increase in BMI can be induced by certain antipsychotic drugs (such as olanzapine and clozapine) (Bak et al., 2014; De Hert et al., 2009), but also by changes in circumstances surrounding the patients, including everyday care. Moreover, the limited physical activity of patients seems to play a role as well. Besides, atypical antipsychotic agents may cause a dysregulation of hormones that control appetite and food intake, such as insulin, leptin and adiponectin (Sentissi, Epelbaum, Olie, & Poirier, 2008).

The simultaneous measurement of inflammatory and metabolic factors after the 7-month antipsychotic treatment demonstrated that the markers displaying initial increase (ie, resistin, ferritin) or decrease (ie, leptin) returned to the level of CS. Furthermore, treatment increased significantly serum concentration of C-peptide (ie, a precursor of insulin) and pointed to a predominance of insulin resistance among treated FEP patients compared to pre-treatment FEP patients and CS metabolic state.

Altogether, it is apparent that the antipsychotic treatment reduced the indices of inflammation and caused unwanted metabolic alterations already at the early stage of the disease.

We found significant relationships between 7-month antipsychotic treatment and increase in BMI. More importantly, evaluating relationships between antipsychotic usage during the 7-month disease period and BMI as well as selected inflammatory and metabolic biomarkers revealed a significant main effects of the treatment on BMI as well as the levels of C-peptide, leptin and adiponectin (ie, an anti-atherogenic and anti-inflammatory protein that enhances insulin sensitivity and is inversely correlated with BMI). Our results are in agreement with previous studies (Bak et al., 2014; Potvin et al., 2008) suggesting that chronic psychotic disorder is associated with metabolic disturbance, evidenced by elevated levels of C-peptide and leptin. According to our results, the number of patients with C-peptide level higher than 2 pg/mL was raised from 5 to 17 after medication with atypical antipsychotic drugs. There was a significant shift in favour of C-peptide when the ratio of C-peptide was calculated to insulin after antipsychotic treatment. The elevation of C-peptide apparently reflects problems in insulin processing after treatment with antipsychotic drugs. With respect to leptin, we replicated previous results (Panariello, Polsinelli, Borlido, Monda, & De Luca, 2012; Pérez-Iglesias et al., 2008; Potvin et al., 2008) demonstrating that long-term antipsychotic treatment is associated with elevated leptin level. There is agreement by researchers that leptin increase during antipsychotic treatment is a result of weight gain rather than a direct impact of atypical antipsychotics on leptin physiology (Jin, Meyer, Mudaliar, & Jeste, 2008; Panariello et al., 2012; Potvin, Zhornitsky, & Stip, 2015).

With regard to adiponectin, this biomarker level was significantly decreased among FEP patients after the 7-month treatment. Previously, Bartoli, Lax, Crocamo, Clerici, and Carrà (2015) demonstrated in the extended meta-analysis that the levels of adiponectin were not affected in patients of SCZ when compared to CS. However, treatment with second-generation antipsychotics (clozapine, olanzapine) caused a significant reduction of adiponectin. These findings are in accordance with our results. Besides, the ratio between adiponectin and leptin was shifted in favour of leptin after 7-month antipsychotic treatment. Again, the established change could be taken as an unfavourable shift in the regulation of metabolism that could promote MetS and cardiovascular disease.

Previously, Pérez-Iglesias et al. (2008) analysed the effect of three antipsychotic drugs (haloperidol, olanzapine and risperidone) on peptides involved in energy balance (insulin, leptin, adiponectin and resistin) in a population of antipsychotic-naïve FEP patients after 1-year treatment. They described a significant elevation of body weight, BMI and the fasting levels of insulin and leptin. The elevation in insulin and leptin concentrations was highly correlated with the increase in body weight and BMI. They suggested that these changes seemed to be a consequence of bigger fat stores. Furthermore, our results are in agreement with meta-analysis by Tarricone, Ferrari Gozzi, Serretti, Grieco, and Berardi (2010) which comprised antipsychotic-naïve patients and reported that BMI increases substantially after first exposure to antipsychotics, particularly during the first 2 months and continues increasing up to a year of treatment or beyond. In addition, Bak et al. (2014) have emphasized that increased weight gain over time is associated with prolonged exposure to antipsychotic treatment, and longitudinal studies which comprises antipsychotic-naïve patients are more informative than switch studies among patients with SCZ, as weight change is not influenced by the level of overweight due to a previous antipsychotic treatment.

Some limitations of this study need consideration: first, the limited sample size may create important generalizability problems. Small cohort size in our study arised from the rarity of first-episode, antipsychotic-naïve patients. We suggest that further studies including more patients with a longer follow-up period are necessary to draw a firm conclusion regarding the association between treatment with antipsychotic drugs and the levels of adipose-derived hormones, adipokines and pro-inflammatory markers. Second, we collected data from CS at one point in time and did not control their health condition or metabolic and inflammatory biomarker levels after the same follow-up period as was done for the FEP patients group. Furthermore, we did not evaluate either the participants dietary or their physical activity habits. This is worth to mention, since disease chronicity and continuous antipsychotic treatment may adversely affect lifestyle factors in the group of patients with psychotic disease.

Nevertheless, our findings may shed light on the molecular underpinnings of second-generation antipsychotic-induced MetS and may help to design novel therapeutic approaches to reduce the side-effects associated with these drugs.

In conclusion, our findings indicate that antipsychotic-naïve FEP patients are characterized by low-grade inflammation evidenced predominantly by increased ferritin level and metabolic disturbance evidenced by elevated level of resistin and declined level of leptin.

Treatment with antipsychotic drugs induced a significant amelioration of psychotic symptoms and caused the elevation in BMI. Simultaneously, 7-month antipsychotic treatment condition was related to elevated levels of C-peptide and leptin, and reduced level of adiponectin. One can conclude that treatment reduces the inflammatory biomarkers, but induces alterations in metabolism evidenced by affected leptin and adiponectin levels and insulin processing. Therefore, it is apparent that one has to find a way how to avoid unwanted changes in the metabolic status of FEP patients.

ACKNOWLEDGEMENTS

This research was supported by the European Union through the European Regional Development Fund (Project No. 2014-2020.4.01.15-0012), and grants from the Estonian Research Foundation (IUT 20-41, IUT 20–42, IUT 20-45). The authors are grateful to patients and healthy controls for their participation in the study and the colleagues who facilitated our work.

Conflict of interest

The authors declare no potential conflict of interest.

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How to cite this article: Balõtšev R, Haring L, Koido K, et al. Antipsychotic treatment is associated with inflammatory and metabolic biomarkers alterations among first-episode psychosis patients: A 7-month follow-up study. *Early Intervention in Psychiatry*. 2019;13:101–109. https://doi.org/10.1111/eip.12457