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# Leptin resistance in patients with chronic schizophrenia

## Leptynooporność u pacjentów z przewlekłą schizofrenią

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## Abstract

**Aim:** Leptin is produced by the adipose tissue and reduces body weight by decreasing appetite and increasing metabolism. Patients treated with antipsychotics often have treatment-induced weight-gain, leading to other metabolic complications. Obese subjects often have leptin resistance, which is defined as the presence of hyperleptinemia in obesity. We evaluated leptin resistance in subjects with schizophrenia in comparison with healthy controls of similar body composition. **Methods:** We determined fasting serum leptin levels and body composition parameters in 30 subjects with schizophrenia and 30 healthy, age- and sex-matched controls. Both groups were of comparable amount of body fat and lean body mass. Leptin resistance was measured as the ratio between resting energy expenditure (REE, calculated using the results of body composition analysis) and the leptin level. **Results:** There was no difference in the level of fasting serum leptin between the patients and the control group; there were also no differences between men in the schizophrenia and in the control groups and between women in the schizophrenia and in the control groups. Women had a significantly higher level of leptin in the schizophrenia group, in the control group and in the whole study sample ($p < 0.001$ for all comparisons). REE was comparable between both study groups. REE was higher in men in the whole study sample and in both study groups ($p < 0.001$ for all comparisons). The REE:leptin ratio did not differ between both groups. As above, the REE:leptin ratio was significantly higher in men in the schizophrenia group, in the control group and in the whole study sample ($p < 0.001$ for all comparisons). **Conclusion:** We found no differences in REE, fasting serum leptin levels and leptin resistance. However, certain differences in leptin resistance between schizophrenia patients and healthy controls may play a role in weight gain induced by antipsychotics.

**Keywords:** schizophrenia, leptin resistance, body composition, metabolic syndrome

## Streszczenie

**Cel:** Leptyna jest wytwarzana przez tkankę tłuszczową i zmniejsza wagę ciała poprzez zmniejszenie apetytu i zwiększenie metabolizmu. Pacjenci leczeni lekami przeciwpsychotycznymi często borykają się z wywołanym leczeniem przyrostem masy ciała, co prowadzi do innych komplikacji metabolicznych. Osoby otyłe nierzadko mają stan leptynooporności, który określa się jako obecność podwyższonego stężenia leptyny pomimo otyłości. W niniejszej pracy oceniona została leptynooporność u osób ze schizofrenią w porównaniu z osobami zdrowymi o podobnym składzie ciała. **Metody:** Oznaczono stężenia leptyny w surowicy na czczo i parametry składu ciała u 30 osób z rozpoznaniem schizofrenii i 30 zdrowych, dopasowanych pod względem wieku i płci. Obie grupy miały porównywalną ilość tłuszczu i beztłuszczowej masy ciała. Oporność na leptynę mierzono jako stosunek wydatku energii spoczynkowej (*resting energy expenditure*, REE; obliczony na podstawie wyników składu ciała) i stężenia leptyny. **Wyniki:** Nie stwierdzono różnicy w stężeniu leptyny w surowicy między pacjentami a grupą kontrolną; nie było również różnic między mężczyznami w grupie schizofrenii i w grupie kontrolnej oraz między kobietami w grupie schizofrenii i w grupie kontrolnej. Kobiety miały istotnie wyższe stężenie leptyny w grupie schizofrenii, w grupie kontrolnej i całej badanej próbie ($p < 0{,}001$ dla wszystkich porównań). REE był porównywalny między obiema grupami. Uzyskano wyższy wskaźnik REE u mężczyzn w całej próbie badawczej i w obu grupach badawczych ($p < 0{,}001$ dla wszystkich porównań). Stosunek REE:stężenie leptyny nie różnił się między obiema grupami. Ponadto stosunek REE:stężenie leptyny był istotnie statystycznie wyższy u mężczyzn w grupie schizofrenii, w grupie kontrolnej i całej badanej próbie ($p < 0{,}001$ dla wszystkich porównań). **Wnioski:** Nie stwierdzono różnic w zakresie wartości REE, stężenia leptyny w surowicy na czczo i nasilenia leptynooporności. Pewne różnice w zakresie leptynooporności pomiędzy pacjentami ze schizofrenią a zdrowymi osobami mogą jednak odgrywać rolę w przyroście masy ciała indukowanym lekami przeciwpsychotycznymi.

**Słowa kluczowe:** schizofrenia, leptynooporność, skład ciała, zespół metaboliczny

## INTRODUCTION

Atypical antipsychotics have significantly reduced the frequency of acute extrapyramidal symptoms and improved the quality of life in patients with schizophrenia. However, pharmacotherapy results in increased body weight commonly accompanied by increased appetite, and eventually leads to obesity and an increased risk of development of various chronic diseases and the metabolic syndrome. Among atypical antipsychotics, clozapine and olanzapine appear to have the greatest potential to induce weight gain, diabetes and dyslipidaemia (Baptista et al., 2008; Wetterling, 2001). Weight gain is associated with impaired physical functioning and negative body appraisal (Bachmann et al., 2012), both of which may significantly affect the quality of life. Also, there are several important consequences of obesity (e.g. pressure overload on the lungs, joints and bones), including life-threatening diseases (cardiovascular disease, type 2 diabetes and certain cancers).

The mechanisms responsible for antipsychotic-induced weight gain are complex and include antagonism at histamine $H_1$ receptors (Kroeze et al., 2003) and serotonin 5-$HT_{1B}$ and 5-$HT_{2C}$ receptors, activation of hypothalamic adenosine monophosphate-activated protein kinase, modulation of hormonal signalling of ghrelin and leptin, changes in the production of cytokines such as tumour necrosis factor-alpha and adipokines such as adiponectin, and the impact of genes: melanocortin 4 receptor, serotonin 2C receptor, leptin, neuropeptide Y (NPY) and cannabinoid receptor 1 genes (Himmerich et al., 2015). Various receptors, including 5-$HT_{1B}$ and 5-$HT_{1C}$, regulate the activity of the hypothalamic nuclei (particularly the arcuate nucleus, which plays the key role in appetite regulation). The activity of the arcuate nucleus is also regulated by anorexigenic hormones: leptin, pancreatic polypeptide, cholecystokinin, glucagon-like peptide-1, oxyntomodulin, peptide YY (PYY) and orexigenic ghrelin (Druce et al., 2004).

Of all appetite-regulating hormones, leptin is one of the most potent anorexigenic agents known (Morton and Schwartz, 2001). Leptin is produced by the white adipose tissue. It was initially identified as an anti-obesity hormone and operates in a negative feedback pathway to control energy homeostasis (Kershaw and Flier, 2004; Tilg and Moschen, 2006). The level of circulating leptin is directly proportional to the size of body fat (Benoit et al., 2004). Leptin is synthesised primarily by adipocytes, to a greater extent in the subcutaneous fat tissue than visceral fat tissue (Baumgartner et al., 1999). Leptin suppresses energy consumption and reduces food intake. Within the arcuate nucleus, leptin activates anorexigenic pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons and inhibits orexigenic NPY/agouti-related protein (AgRP) neurons, resulting in the inhibition of energy consumption by reducing food intake (Weigle et al., 1995) and increased energy expenditure. Other mechanisms of leptin action include: inhibition of expression of orexins (Beck and Richy, 1999), increased sensitivity of glucoresponsive neurons of the hypothalamus (Muroya et al., 2004), regulation of mRNA expression of CART in the arcuate nucleus (Kristensen et al., 1998), inhibition of noradrenergic neurotransmission in the periventricular nucleus (Kutlu et al., 2010), reduction of secretion of endogenous cannabinoids in the hypothalamus (Di Marzo et al., 2001) and reduced reward associated with food intake (Fulton et al., 2000).

In obese people the sensitivity of neurons to leptin is reduced. This is accompanied by an increased blood level of leptin and impaired leptin transport across the blood–brain barrier (due to the saturation of the leptin transporter with high concentrations of leptin peripheral). We can therefore speak of a leptin resistance associated with obesity. However, it is still questioned how it should be defined (Myers et al., 2012). One definition is that leptin resistance is the presence of hyperleptinemia in obesity. The second definition of leptin resistance is the failure of exogenous leptin administration to provide therapeutic benefit. Lustig et al. (2004) suggested another definition of leptin resistance as the ratio between resting energy expenditure (REE) and the leptin level. According to these authors lean, leptin-sensitive individuals are able to maintain a high REE at a low leptin level, whereas high leptin levels are required to maintain a normal REE in obese, leptin-resistant subjects (Lustig et al., 2004). Leptin resistance defined as hyperleptinemia in obesity is generally found in all obese subjects (and animal models). It may contribute to antipsychotic-induced weight gain (since the amount of leptin is related to the amount of body fat), while treatment-induced weight gain should result in increased leptin levels and leptin resistance could be the reason why increased amount of body fat does not translate into the inhibition of appetite and weight gain by leptin. It is unknown whether weight-gaining patients taking antipsychotics have higher leptin resistance. Therefore, the aim of the study was to evaluate leptin resistance in schizophrenic patients during antipsychotic treatment.

## METHODS

Data for 30 European Caucasian adult patients with paranoid schizophrenia (295.30 according to the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, F20.0 according to the International Statistical Classification of Diseases and Related Health Problems, ICD-10) were included into the study. Most patients were in a stable phase of the disease (i.e. no acute psychosis). During the study all subjects were taking clozapine for at least 2 months prior to the assessments with a minimum dose of 100 mg/day and were taking various antipsychotics in the past. The control group included 30 healthy subjects and was gender- and age-matched with patients in the clozapine group. No data were missing for any of the study subjects. The healthy volunteers reported neither personal or familial psychiatric history nor medication history on semi-structured



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interview and had normal laboratory findings. The health status of the control subjects was determined on the basis of a simple physical examination, including vital signs and an interview. All subjects had a normal blood profile; alanine transaminase (ALT), aspartate transaminase (AST), urea, creatinine, bilirubin and electrolytes were within normal ranges. Subjects with acute and chronic inflammatory conditions (e.g. pneumonia, rheumatoid arthritis), immunological disorders (e.g. AIDS, allergy) and cancer were excluded from the study. All patients and volunteers included in the study expressed their written informed consent for participation in this study. The study protocol was approved by the local Bioethics Committee.

The blood samples for the chemistry panel were collected between 7 a.m. and 8 a.m., after ensuring at least 8 hours of overnight fasting. The samples were immediately transferred to the central laboratory, where they were analysed. Glucose and lipid levels were measured using a Dirui CS-400 analyser (Dirui, China). Insulin immunochemistry assessments were performed using a Cobas E411 analyser (Roche Diagnostics, Switzerland). The levels of clozapine and leptin were measured in blood serum using ELISA (enzyme-linked immunosorbent assay) method. Prior to assays, serum samples were stored at −80°C for up to 6 months. ELISA assays were performed using commercial kits (intra-assay: coefficient of variation, CV <10%, inter-assay: CV <15%) manufactured by RayBiotech (USA), according to protocol provided by its manufacturer**.**

The subjects' height was measured with a wall-mounted height measure to the nearest 0.5 cm. Weight was measured with a spring balance that was kept on a firm horizontal surface. The subjects wore light clothing, stood upright without shoes and their weight was recorded to the nearest 0.5 kg. Body mass index (BMI) was calculated as body weight in kilograms divided by the height in meter squared (kg/m$^2$). Waist and hip circumferences were measured using a non-stretchable fibre measuring tape. The waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. WHR cut-off points were defined according to World Health Organization recommendations (0.85 for women and 0.9 for men). Fat mass index (FMI) was calculated as total body fat in kilograms divided by the height in meter squared (kg/m$^2$). Excessive body fat according to FMI classification ranges was defined as FMI >6 for men and FMI >9 for women (Kelly et al., 2009).

Metabolic syndrome and abdominal obesity were defined according to the International Diabetes Federation (IDF) criteria (Alberti et al., 2006). Impaired fasting glucose was defined as fasting plasma glucose ≥100 mg/dL. BMI <25 kg/m$^2$, 25–30 kg/m$^2$ and ≥30 kg/m$^2$ were defined as normal weight, overweight and obesity, respectively. Insulin resistance was estimated from fasting glucose and insulin levels by homeostasis model assessment, using the formula: HOMA-IR = [fasting plasma glucose (mg/dL) × insulin (mU/L)]/405. Insulin resistance was defined as HOMA-IR >2.0.

Biochemical and anthropometric measurements were combined with body composition determined using bioelectric impedance analysis (BIA), which provides accurate measurements of body fat, lean body mass and body water (Bosy-Westphal et al., 2008). Briefly, BIA determines the electrical impedance, or opposition to the flow of an electric current through body tissues which can then be used to calculate an estimate of total body water, which can be used to estimate fat-free body mass and, by difference with body weight, body fat. Body composition was measured using the Maltron BF-906 Body Fat Analyser (Maltron, UK), a single frequency bioelectrical impedance analyser, at 50 Hz. Standard operating conditions were observed by a trained operator, including preparation of the participant, electrode placement and operation. The measurement using BIA was taken immediately prior to anthropometry measurements with participants lying supine, in a rested state. Proprietary equations developed by Maltron were used to calculate fat mass (FM) and fat-free mass (FFM), expressed both in kilograms and as the percentage of body weight. REE was calculated using BIA-measured FM and FFM and the formulas provided by Nielsen et al. (2000): for women REE (kcal/day) = 16.2 × FFM (kg) + 8.0 × FM (kg) − 4.7 × age (years) + 714 and for men REE (kcal/day) = 15.6 × FFM (kg) + 7.8 × FM (kg) − 5.2 × age (years) + 888. Leptin resistance index was calculated according to Lustig et al. (2004) as REE:leptin concentration ratio.

Statistical procedures were performed with STATA 14.1 (StataCorp, USA). Simple descriptive statistics (means, standard deviations) were generated for continuous variables. For discrete variables the number of patients and percentages are given. Normality of distribution was tested with Shapiro–Wilk test. Variables with normal distribution were analysed using two-tailed *t*-test or one-way analysis of variance (ANOVA), otherwise Mann–Whitney *U* and Kruskal–Wallis tests were used. The difference between proportions was analysed by Fisher's exact test. Associations were tested by Pearson's (for variables with normal distribution) or Spearman's (for other variables) correlation coefficients. The significant level was set at $p < 0.05$.

## RESULTS

For the schizophrenia group the mean age was 38.8 ± 12.6 years and it was 36.8 ± 12.3 years for the control group ($p = 0.53$). In both groups there were 17 (56.7%) men and 13 (43.3%) women. In the clozapine group 17 (56.7%) subjects smoked cigarettes and 10 (33.3%) did in the control group ($p = 0.12$). The mean duration of monotherapy with clozapine was 54.0 ± 74.5 months and the mean clozapine dose was 359.6 ± 147.7 mg/day, with a corresponding mean serum level 385.6 ± 412.3 ng/mL. There was no correlation between clozapine dose and its concentration ($p = 0.27$) due to non-linear relationship between both variables.

| | Schizophrenia $n = 30$ | Control $n = 30$ | $p$ |
|---|---|---|---|
| Weight [kg] | 78.8 ± 12.9 | 74.4 ± 15.4 | NS |
| BMI [kg/m$^2$] | 26.9 ± 3.5 | 25.1 ± 3.9 | NS |
| FMI [kg/m$^2$] | 8.6 ± 3.2 | 7.6 ± 3.2 | NS |
| Waist circumference [cm] | 96.3 ± 9.0 | 86.7 ± 11.6 | <0.001 |
| Hip circumference [cm] | 99.2 ± 7.9 | 96.1 ± 7.8 | NS |
| WHR | 0.97 ± 0.05 | 0.90 ± 0.08 | 0.009 |
| SBP [mm Hg] | 122.8 ± 13.1 | 136.4 ± 16.5 | 0.001 |
| DBP [mm Hg] | 82.3 ± 8.7 | 84.5 ± 14.7 | NS |
| TC [mg/dL] | 187.7 ± 49.9 | 210.2 ± 63.1 | NS |
| HDL [mg/dL] | 42.6 ± 12.4 | 55.2 ± 14.5 | <0.001 |
| LDL [mg/dL] | 116.3 ± 40.5 | 125.8 ± 39.2 | NS |
| TGA [mg/dL] | 146.2 ± 115.7 | 96.3 ± 75.1 | 0.02 |
| FPG [mg/dL] | 102.0 ± 28.6 | 87.9 ± 10.9 | 0.03 |
| Insulin [μU/mL] | 11.64 ± 7.68 | 7.42 ± 3.52 | 0.007 |
| HOMA-IR | 3.16 ± 3.09 | 1.63 ± 0.86 | 0.002 |

Data given as: mean ± standard deviation.
**BMI** – body mass index; **FMI** – fat mass index; **WHR** – waist-to-hip ratio; **SBP** – systolic blood pressure; **DBP** – diastolic blood pressure; **TC** – total cholesterol; **HDL** – high-density lipoproteins; **LDL** – low-density lipoproteins; **TGA** – triglycerides; **FPG** – fasting plasma glucose; **HOMA-IR** – homoeostasis model assessment of insulin resistance.

*Tab. 1. Results of anthropometric measurements and laboratory tests*

Detailed results for anthropometric measurements and laboratory tests are shown in Tab. 1. Detailed results for BIA body composition analysis are shown in Tab. 2. As can be seen, there were no inter-group differences for body composition analysis. As expected, FFM was higher in men in the whole study sample and in both study groups ($p < 0.001$ for all comparisons). Also, FM (expressed as the percentage of body weight) was significantly lower in men in the whole study sample and in both study groups ($p < 0.05$ for all comparisons). REE calculated using FM and FFM was comparable between both groups: schizophrenia 1627.2 ± 266.9 kcal/day vs. control 1678.6 ± 232.6 kcal/day ($p = 0.43$). Similarly to FFM, REE was higher in men in the whole study sample and in both study groups ($p < 0.001$ for all comparisons).

There was no significant difference for fasting serum levels of leptin between the schizophrenia group and the control group (3.14 ± 2.63 vs. 2.20 ± 1.91 ng/mL, $p = 0.22$); also, there were no differences between men in the schizophrenia and in the control groups ($p = 0.50$) and between women in the schizophrenia and in the control groups ($p = 0.11$). Compared with men, women had a significantly higher level of leptin in the schizophrenia group (5.07 ± 2.54 vs. 1.67 ± 1.55 ng/mL, $p < 0.001$), in the control group (3.69 ± 1.98 vs. 1.06 ± 0.74 ng/mL, $p < 0.001$) and in the whole study sample (4.38 ± 2.34 vs. 1.36 ± 1.24 ng/mL, $p < 0.001$).

The REE:leptin ratio was comparable ($p = 0.37$) between both groups: schizophrenia 2517.9 ± 4640.1 (median: 600.7) vs. control 2298.7 ± 4622.3 (median: 1164.3). As above, the REE:leptin ratio was significantly higher in men in the schizophrenia group ($p < 0.001$), in the control group ($p < 0.001$) and in the whole study sample ($p < 0.001$). REE:leptin was not correlated with age ($p = 0.54$). In the whole study sample REE:leptin was increased in subjects with central obesity ($p = 0.008$) or with insulin resistance ($p = 0.036$), but not in subjects with excessive total body fat ($p = 0.18$) or with impaired fasting glucose ($p = 0.38$). REE:leptin was increased in subjects with central obesity both in the schizophrenia ($p < 0.001$) and control ($p = 0.003$) groups, while for insulin resistance the difference was significant in the control group ($p = 0.04$) and not in the schizophrenia group. Moreover, in the whole study sample the REE:leptin ratio was the highest ($p = 0.04$) in subjects with BMI <25 kg/m$^2$ (3934.5 ± 6814.3) and the lowest in subjects with BMI >30 kg/m$^2$ (526.6 ± 388.6). Similar differences were observed in the schizophrenia group ($p = 0.02$), but not in the control group ($p = 0.96$) (Fig. 1). The REE:leptin ratio was positively correlated with the dose of clozapine ($r = 0.51$, $p = 0.004$). No correlations between REE:leptin and duration of schizophrenia ($p = 0.61$), duration of treatment with clozapine ($p = 0.13$) or clozapine serum concentration ($p = 0.19$) were found.

| | Schizophrenia $n = 30$ | Control $n = 30$ | $p$ |
|---|---|---|---|
| FM [kg] | 24.9 ± 8.6 | 21.3 ± 7.9 | NS |
| FM [% of body mass] | 31.5 ± 8.9 | 28.3 ± 7.7 | NS |
| FFM [kg] | 53.9 ± 10.0 | 53.2 ± 11.0 | NS |
| FFM [% of body mass] | 68.6 ± 8.7 | 71.7 ± 7.7 | NS |

Data given as: mean ± standard deviation.
**FM** – fat mass; **FFM** – fat-free mass.

*Tab. 2. Results of body composition analysis*

## DISCUSSION

The objective of the present study was to compare estimated leptin resistance in patients with chronic schizophrenia and healthy age- and sex-matched controls. To the best of our knowledge, this is the first attempt to evaluate leptin resistance in patients with schizophrenia, as all previous studies only measured leptin levels.

We have found that the differences between two groups of subjects with comparable body composition in fasting serum leptin levels, REE and the REE:leptin ratio were not significant. Our observation that there are gender-related differences (higher REE:leptin ratio in men) is not



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surprising and probably can be explained by the fact that men had more fat-free (muscle) mass and less fat mass, while both the concentration of leptin and the calculated REE depend upon fat-free mass and fat mass. However, we have also found that there are certain differences between schizophrenic patients and healthy controls regarding the REE:leptin ratio. The observed inter-group differences could indicate that certain differences in leptin resistance between schizophrenia patients and healthy controls may play a role in weight gain induced by antipsychotics.

Previous results on the effect of leptin concentrations during treatment with clozapine or olanzapine are inconclusive. A recent meta-analysis shows that olanzapine, clozapine and quetiapine (which are known to increase appetite, body weight and metabolic abnormalities) produce moderate leptin elevations, whereas haloperidol and risperidone (which have a smaller metabolic risk) are associated with non-significant leptin changes (Potvin et al., 2015). In first-episode male patients with psychosis Basoglu et al. (2010) found increased leptin levels after 6-week treatment with olanzapine. Kim et al. (2008) observed an increased level of leptin after 24-week treatment with olanzapine, which was probably secondary to weight gain. Murashita et al. (2005) also noted increased leptin levels after 6-month treatment with olanzapine, probably secondary to increased total body fat. Kraus et al. (1999) compared clozapine and olanzapine with haloperidol and found significant increases in weight, body mass index

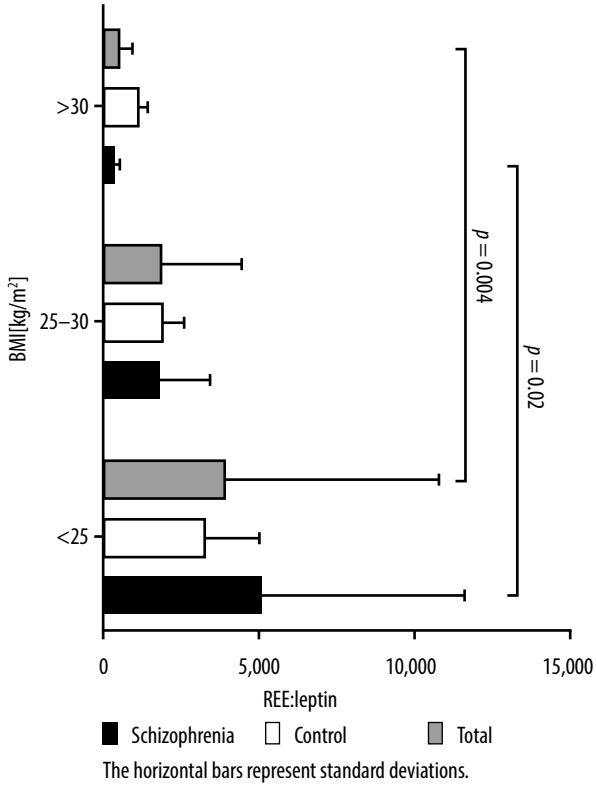


*Fig. 1. Leptin resistance in the study groups stratified by BMI category*

and leptin level in patients receiving clozapine or olanzapine, but not in patients receiving haloperidol. Also, some authors found that genetic variability in the leptin gene and leptin receptor may predispose some individuals to excessive weight gain from increased exposure to olanzapine (Ellingrod et al., 2007; Templeman et al., 2005). Several authors reported no difference in leptin levels between patients taking antipsychotics and healthy controls, for example Herrán et al. (2001). They suggest that the elevation of leptin levels induced by chronic antipsychotic treatment can be attributed to weight gain and not to the treatment itself. Also, Graham et al. (2005) found no changes in leptin levels after 12-week treatment with olanzapine. All these data seem to indicate that the changes in the leptin level are secondary to increased body fat and weight gain and do not result directly from treatment with antipsychotics. Moreover, treatment-induced weight gain may result from leptin resistance since increased leptin levels do not inhibit energy consumption. Monteleone et al. (2002) have found that pronounced early increase in circulating leptin predicts a lower weight gain during clozapine treatment. No previous studies evaluating leptin resistance are available for schizophrenia.

To sum it up, the results of our study indicate that certain differences in leptin resistance between schizophrenia patients and healthy controls may play a role in weight gain induced by antipsychotics. However, the low number of study subjects may limit the probability of finding inter-group differences due to the lack of statistical power. Another limitation is the lack of behavioural data (i.e. appetite ratings or food intake logs). Due to the cross-sectional study design causal relationships cannot be established and the effect of previous antipsychotic treatment cannot be excluded. Dual-energy X-ray absorptiometry (DXA) should be used additionally to measure body composition and adipose tissue mass more accurately. Leptin levels in this study are low in comparison with other studies reporting the same units in the general population [where obese subjects had mean leptin levels 31.3 ± 24.1 ng/mL, while normal subjects had 7.5 ± 9.3 ng/mL leptin levels (Considine et al., 1996)] and a patient population [where schizophrenia patients had 18.1 ± 22.1 ng/mL leptin levels (Cortés et al., 2014)]. The reported levels rather correspond to the normal, non-obese population. Our method of calculating REE and the REE:leptin ratio is derivative. However, the accuracy of REE equations used in our study was verified using indirect calorimetry (Nielsen et al., 2000). As for leptin resistance, currently there are no other better clinical measures of leptin sensitivity short of leptin administration, which is not feasible or practical. Due to the complex structure of interactions between anabolic and catabolic adipokines and neuropeptides, a longitudinal study with detailed assessment of body composition and resting metabolic rate is crucial for understanding the mechanisms of antipsychotic-induced weight gain.



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**Conflict of interest**

*All authors have no conflict of interest.*

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