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The effect of aripiprazole on leptin levels of patients with chronic schizophrenia and a comparison of leptin, acute phase protein, and cytokine levels with regard to body mass and body composition indexes

Jarosław Sobiś[1], *Łukasz Kunert*[1], *Monika Rykaczewska-Czerwińska*[2], *Elżbieta Świętochowska*[3], *Piotr Gorczyca*[1]

[1]*Department of Psychiatry, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland*
[2]*Chair and Department of Pharmacology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland*
[3]*Department of Medical and Molecular Biology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland*

Abstract

Introduction: The aim of this study was to test the effect of aripiprazole on leptin, insulin, acute phase proteins, and selected cytokines levels in patients with chronic schizophrenia. Additionally, levels of leptin, insulin, acute phase proteins, and cytokines were compared with body mass and body composition indexes.

Material and methods: Levels of leptin, insulin, serum amyloid A (SAA), tumour necrosis factor alpha (TNF-α), and interleukins 17A (IL-17A) and 18 (IL-18) in blood serum were measured for 17 patients before and after 28 days of administering aripiprazole by means of enzyme-linked immunosorbent assay (ELISA). Before and after the study, body mass and waist circumference (WC) were also measured, and body mass index (BMI) and body fat percentage (BF%) were estimated. The sex of each patient was taken into account.

Results: After administration of aripiprazole the reduction of levels of leptin, insulin, SAA, and TNF-α were statistically significant, similarly to body mass reduction and decrease in WC, BMI, and BF%, which were also statistically significant. A positive correlation between leptin and BF% and negative correlation between insulin and body mass and body composition indexes were observed before and after the study. High sensitivity C-reactive protein (hsCRP) and HsCRP/albumin positively correlated with BMI before the treatment. In the group of women a statistically significant positive correlation between TNF-α and IL-17A and body mass and body composition indexes was observed, and in the group of men a negative correlation between IL-18 and BMI, WC, and BF% was noted.

Conclusions: The effect of aripiprazole is connected to its anti-inflammatory activity. A 28-day treatment resulted in reduction of adipose tissue, and in the group of women it returned their leptin sensitivity to normal levels. A change of psychotropic treatment and administration of aripiprazole reduces cardiometabolic risks. **(Endokrynol Pol 2022; 73 (1): 35–42)**

Key words: *aripiprazole; chronic schizophrenia; leptin*

Introduction

Despite the cardiometabolic risks connected with the use of atypical neuroleptics, there are few publications on inflammatory condition marker levels during neuroleptics administration [1]. Presumably, the levels of cytokines and acute phase proteins in blood are specific for a given antipsychotic drug or group of drugs [2]. Due to that a possibility, it appears that some metabolic effects of these drugs result from fluctuations in the levels of acute phase proteins and cytokines [1]. During the research on clozapine, it was discovered that 6–8 weeks of treatment with that drug resulted in a marked increase in pro-inflammatory cytokines [interleukins (IL): IL-1β, IL-6, IL-8, IL-17, IL-23, tumour necrosis factor alpha (TNF-α), soluble tumour necrosis factor receptor 1/2 (sTNF-R1/2)], leptin, and high sensitivity C-reactive protein (hsCRP) and an accompanying increase of body mass index (BMI) [3–5]. A similar effect of cytokine increase was observed after 6 weeks of treatment with olanzapine [4]. It should be noted that almost all neuroleptics cause a body mass increase, which becomes larger over time if the treatment with a given drug is continued [6]. There are factors that explain the body mass increase after treatment with neuroleptics and the influence of the length of treatment with these drugs on body mass. Antipsychotics, especially second-generation antipsychotics (i.e. atypical), cause greater appetite due to central antagonism towards many receptors. Studies on animal models show that atypical neuroleptics increase

Łukasz Kunert, Katedra Psychiatrii, ul. Pyskowicka 49 42-612 Tarnowskie Góry, tel. 605092031; e-mail: lkunert@sum.edu.pl

lipogenesis and inhibit lipolysis [7, 8]. The disorder itself (schizophrenia) has additional influence due to a large degree of observed metabolic dysregulation [6, 9]. Especially large body mass increase results from clozapine and olanzapine [6], whereas amisulpride, aripiprazole, and ziprasidone act more neutrally with respect to body mass, and even cause slight weight loss for some patients [10].

During positive caloric balance adipocytes initially undergo hypertrophy. If adipogenesis is to some extent disturbed, a further increase in the size of adipocytes may lead to their metabolic-immune dysfunction [11]. Hypertrophied adipocytes cause chronic systemic inflammation as they are more prone to inflammation than small adipocytes. Constant slow expansion of adipose tissue results in further development of chronic systemic low-grade inflammation in the body [12].

One of the peripheral signal factors that disrupt the signalling pathway responsible for feeling hungry and stimulating pathways connected to feeling satiety at the level of hypothalamus is an adipose tissue hormone — leptin [13]. It is synthesized mainly in the adipocytes of subcutaneous adipose tissue and the synthesis is affected by the size of adipocytes — the larger the cells, the greater amount of produced hormone [14]. The higher concentration observed in women is linked to greater amounts of subcutaneous adipose tissue in comparison to men [15]. Overweight and obese people have increased concentrations of leptin in blood and its appetite suppression effect is abolished (leptin resistance) [13]. Leptin shows pro-inflammatory effects in such cases. It activates dendritic cells, monocytes, macrophages, and Th1 lymphocytes, which results in the increased production and secretion of pro-inflammatory cytokines [IL-1β, IL-6, TNF-α, IL-12, IL-8, IL-2, interferon gamma (IFN-γ)]. It also suppresses Th2 lymphocytes thus diminishing secretion of anti-inflammatory cytokines IL-10 and IL-4 [16]. In in vitro studies this adipocytokine raises hsCRP expression; therefore, this is an another (potential) pro-inflammatory effect of leptin [17]. In the research among overweight students leptin and hsCRP showed statistically significant positive correlation with body fat percentage (BF%) [18]. Leptin levels positively correlate also with insulin levels [19].

There are data confirming that atypical antipsychotics significantly increase leptin levels. The increase in its levels is especially visible in the first weeks of treatment with these drugs, and the highest levels of leptin are observed in the case of olanzapine and clozapine [20, 21].

The aim of this work was to explore the effect of aripiprazole on leptin, insulin, serum amyloid A (SAA), TNF-α levels and anthropometric parameters (body mass, waist circumference), BMI, and body fat percentage (BF%) in patients with chronic schizophrenia.

Material and methods

The study covers 17 patients with chronic schizophrenia treated in the Psychiatry Clinic (Tarnowskie Góry) of the Medical University of Silesia from November 2011 to October 2012. The research project was approved by the Bioethics Committee of the Medical University of Silesia (KNW/0022/KB1/117/11 of 21.06.2011). All the patients gave their written consent to participate in the study. The participants were previously treated with neuroleptics (mainly olanzapine or quetiapine). For ethical reasons previous psychotropic drugs were tapered off over the first three days of the research and aripiprazole was administered in the dose of 10 mg up to a maximum dose of 30 mg in the 2nd, 3rd, or 4th week of the study in order to minimize the risks of significant deterioration of the patients' psychological condition. The final dose of aripiprazole was decided individually depending on the severity of the disease symptoms. In case of anxiety or insomnia lorazepam was administered (1–4 mg/day). Diagnosis was given based on ICD-10 and DSM-IV diagnostic criteria. The psychological condition of the patients was assessed using the PANSS (Positive and Negative Syndrome Scale) [22]. All the patients were subjected to somatic condition test, former psychological and somatic treatment was analysed, and basic laboratory tests were carried out. Inclusion criteria were as follows: age 25–80 years and duration of disease over 10 years. Exclusion criteria were as follows: addiction to and/or abuse of psychoactive substances other than nicotine, acute infection, mental retardation, allergies and autoimmune diseases, neurological diseases, other psychical disorders, and treatment with non-steroidal anti-inflammatory drugs and statins. In order to measurement concentration of leptin in serum, blood was taken twice from each patient — before the treatment and after 28 days of treatment with aripiprazole. Fasted patients had their native blood taken at 7 a.m. from a basilic vein. Serum obtained by means of centrifugal separation was stored in appropriate sample tubes in a freezer at –70°C. Serum marker level tests were conducted by means of the enzyme-linked immunosorbent assay (ELISA) for leptin (BioVendor).

Anthropometric measurements were taken in compliance with common practice in the morning from fasted patients without outer garments and shoes. Body height and mass were measured with a medical balance with an accuracy of 0.10 cm (body height) and 0.10 kg (body mass), whereas waist circumference (WC) was measured in centimetres midway between the bottom of the costal arch and the top of ilium. Norms for WC were adopted following the criteria by metabolic syndrome of the International Diabetes Federation (IDF) from 2005, i.e. for men WC ≥ 94 cm, for women WC ≥ 80 cm. Based on data concerning body mass and height body the body mass index (BMI) was estimated in kg/m^2.The body fat percentage was estimated according to the following formula:

$$BF\% = -44.988 + (0.503 \times age) + (10.689 \times sex) + (3.172 \times BMI) - (0.026 \times BMI^2) + (0.181 \times BMI \times sex) - (0.02 \times BMI \times age) - (0.005 \times BMI^2 \times sex) + (0.00021 \times BMI^2 \times age),$$

where man = 0, and woman = 1 [23].

According to the vast literature on the subject, the following BMI values were adopted: less than or equal to 18.4 — underweight, 18.5–24.9 — normal weight, 25.0–29.9 — overweight, equal to or over 30 — obesity. BF% for men: 12–20% — normal result, 20.1–24.9% — overweight, equal to or over 25% — obesity. BF% for women: 20–30% — normal result, 30.1–34.9% — overweight, equal to or over 35% — obesity [23, 24].

According to the literature, the following values were adopted as criteria for chronic low-grade inflammation: hsCRP > 1.0 ≤ 10.0 mg/L, TNF-α ≥ 3.5 pg/mL [25], SAA ≥ 8 μg/mL [26], leptin ≥ 15 ng/mL [27, 28].

Additionally, we compared acute phase proteins (hsCRP, albumin, hsCRP/albumin), leptin, insulin, and pro-inflammatory cytokine (TNF-α, IL-17A, IL-18) levels with body mass, BMI, waist circumference (WC), and BF% before and after the treatment with respect to gender.

Table 1. *Demographic and clinical data*

Study group characteristics	
Group size	17
Male	10
Female	7
Age in years, mean (SD)	51.1 (11.8)
Duration of illness in years, mean (SD)	28.1 (9.9)
Current smoking	14
Medical comorbidity (medication status)	Type 2 diabetes, hypertension (glimepiride, metformin, enalapril) (n = 1) Arrhythmia (bisoprolol) (n = 1)
BMI (female + male):	
Underweight	1
Normal weight	7
Overweight	6
Obese	3

SD — standard deviation; BMI — body mass index

As part of the statistical analysis of the research, expected values and standard variations were estimated. As regards measurable features, a hypothesis on normality of decomposition was verified (Shapiro-Wilk test). Comparisons were made before and after the treatment, and the paired sample test was used (when the hypothesis on normality of decomposition was not rejected) as well as the Wilcoxon test (when the hypothesis on normality of decomposition was rejected). For selected resulting features an attempt was made to assess the correlation variability. Correlations were assessed by means of the Pearson correlation coefficient. A hypothesis on the significance of the Pearson correlation coefficient was verified. The statistical analysis takes into account the following significance levels: $p > 0.05$ (no statistical significance), $p < 0.05$ (statistical significance), $p < 0.01$ (high statistical significance), and $p < 0.001$ (very high statistical significance).

Results

Table 1 shows the demographic and clinical characteristics of the participants. Table 2 compares BMI and BF% for each patient using norms for these indexes for women and men, respectively. Table 3 contains a comparison of body mass and body composition indexes before and after treatment with respect to gender.

Levels of TNF-α, SAA, and leptin in the serum are shown in Table 4; additionally, the table includes insulin levels before and after the treatment

Tables 5–9 and 10 include comparisons of levels of leptin, insulin, hsCRP, albumin, cytokines (TNF-α, IL-17A, IL-18), and hsCRP/albumin to body mass, BMI, WC, and BF%, respectively, before and after the treatment with aripiprazole in women, men, and all. The tables include only the tested parameters that correlated to body mass and body composition indexes in a statistically significant way.

Table 2. *Comparison of body mass index (BMI) and body fat percentage (BF%) before and after arpiprazole treatment (women and men)*

	BMI		BF%	
	Before treatment	**After treatment**	**Before treatment**	**After treatment**
Women				
1	Normal weight	Normal weight	Obese	Obese
2	Overweight	Overweight	Obese	Obese
3	Normal weight	Normal weight	Overweight	Overweight
4	Normal weight	Normal weight	Overweight	Overweight
5	Overweight	Overweight	Obese	Obese
6	Overweight	Overweight	Obese	Obese
7	Normal weight	Normal weight	Overweight	Normal weight
Men				
1	Obese	Overweight	Obese	Obese
2	Normal weight	Normal weight	Normal weight	Normal weight
3	Normal weight	Normal weight	Normal weight	Normal weight
4	Normal weight	Normal weight	Normal weight	Normal weight
5	Overweight	Overweight	Obese	Obese
6	Obese	Obese	Obese	Obese
7	Obese	Obese	Obese	Obese
8	Overweight	Normal weight	Obese	Obese
9	Overweight	Overweight	Obese	Obese
10	Underweight	Underweight	Normal weight	Normal weight

Table 3. *Body mass and body composition indexes before and after aripiprazole treatment*

Body mass and body composition indexes	Before treatment mean (SD)	After treatment mean (SD)	p
Women			
Body mass [kg]	62.3 (9.9)	61.0 (11.0)	p = 0.0244**
BMI [kg/m²]	24.95 (3.28)	24.41 (3.65)	p = 0.0252**
WC [cm]	83.9 (9.7)	82.1 (10.8)	p = 0.0115**
BF%	36.93 (5.25)	35.89 (6.22)	p = 0.0373**
Men			
body mass [kg]	83.2 (18.7)	80.7 (18)	p = 0.0011**
BMI [kg/m²]	25.69 (5.17)	24.95 (5.08)	p = 0.0008**
WC [cm]	90.9 (17.0)	88.7 (17.2)	p = 0.0004**
BF%	25.48 (6.64)	24.44 (6.63)	p = 0.0007**
All			
body mass [kg]	74.6 (18.6)	72.6 (18.1)	p < 0.0001*
BMI [kg/m²]	25.38 (4.38)	24.73 (4.43)	p = 0.0001**
WC [cm]	88.0 (14.5)	86.0 (14.9)	p < 0.0001**
BF%	30.19 (8.30)	29.15 (8.54)	p < 0.0001*

*Wilcoxon test; **paired sample test; BF% — body fat percentage; WC — waist circumference; BMI — body mass index; SD — standard deviation

Table 4. *Comparison of leptin, insulin, serum amyloid A (SAA), and tumour necrosis factor alpha (TNF-α) levels before and after treatment*

Analysed parameter	Before treatment mean (SD)	After treatment mean (SD)	p
Women			
TNF-α [pg/mL]	8.43 (1.88)	7.40 (1.50)	p = 0.0022**
SAA [μg/mL]	24.45 (4.39)	22.27 (3.86)	p = 0.0263**
Leptin [ng/mL]	22.39 (2.92)	19.39 (2.74)	p = 0.0036**
Insulin [μIU/mL]	13.81 (4.70)	12.76 (4.32)	p = 0.0298**
Men			
TNF-α [pg/mL]	8.00 (2.35)	7.24 (2.02)	p = 0.0021**
SAA [μg/mL]	19.11 (2.21)	17.59 (2.57)	p = 0.0010*
Leptin [ng/mL]	14.48 (2.03)	11.85 (2.27)	p < 0.0001**
Insulin [μIU/mL]	13.04 (4.07)	11.94 (4.17)	p = 0.0057**
All			
TNF-α [pg/mL]	8.18 (2.12)	7.31 (1.78)	p < 0.0001**
SAA [μg/mL]	21.31 (4.16)	19.51 (3.87)	p = 0.0001*
Leptin [ng/mL]	17.74 (4.65)	14.95 (4.51)	p < 0.0001**
Insulin [μIU/mL]	13.36 (4.22)	12.28 (4.12)	p = 0.0005**

*Wilcoxon test; **paired sample test; SD — standard deviation

Table 5. *Comparison of leptin, albumin, interleukin 17A (IL-17A), tumour necrosis factor alpha (TNF-α) levels, and high sensitivity C-reactive protein (hsCRP)/albumin (alb) with body mass and body mass index (BMI) (women) (Pearson's correlation coefficient)*

Analysed parameter	Body mass before treatment *vs.* analysed parameter before treatment	Body mass after treatment *vs.* analysed parameter after treatment	BMI before treatment *vs.* analysed parameter before treatment	BMI after treatment *vs.* analysed parameter after treatment
Leptin		– p = 0.0325		
Albumin				
CRP/alb				
IL-17A			+ p = 0.0323	+ p = 0.0394
TNF-α	+ p = 0.0289		+ p = 0.0075	+ p = 0.0391

The table includes only the tested parameters that correlated (+; –) to body mass and body composition indexes in a statistically significant way

Table 6. *Comparison of leptin, albumin, interleukin 17A (IL-17A), tumour necrosis factor alpha (TNF-α) levels, and high sensitivity C-reactive protein (hsCRP)/albumin (alb) with waist circumference (WC) and body fat percentage (BF%) (women) (Pearson's correlation coefficient)*

Analysed parameter	WC before treatment *vs.* analysed parameter before treatment	WC after treatment *vs.* analysed parameter after treatment	BF% before treatment *vs.* analysed parameter before treatment	BF% after treatment *vs.* analysed parameter after treatment
Leptin		– p = 0.0434		
Albumin				– p = 0.0372
hsCRP/alb			+ p = 0.0493	
IL-17A			+ p = 0.0456	+ p = 0.0472
TNF-α			+ p = 0.0142	

The table includes only the tested parameters that correlated (+; –) to body mass and body composition indexes in a statistically significant way

Table 7. *Comparison of insulin and interleukin 18 (IL-18) with body mass and body mass index (BMI) (men) (Pearson's correlation coefficient)*

Analysed parameter	Body mass before treatment *vs.* analysed parameter before treatment	Body mass after treatment *vs.* analysed parameter after treatment	BMI before treatment *vs.* analysed parameter before treatment	BMI after treatment *vs.* analysed parameter after treatment
Insulin	– p = 0.0032	– p = 0.0059	– p = 0.0051	– p = 0.0089
IL-18				– p = 0.0479

The table includes only the tested parameters that correlated (+; –) to body mass and body composition indexes in a statistically significant way

Table 8. *Comparison of insulin and interleukin 18 (IL-18) with waist circumference (WC) and body fat percentage (BF%) (men) (Pearson's correlation coefficient)*

Analysed parameter	WC before treatment *vs.* analysed parameter before treatment	WC after treatment *vs.* analysed parameter after treatment	BF% before treatment *vs.* analysed parameter before treatment	BF% after treatment *vs.* analysed parameter after treatment
Insulin	– p = 0.0179	– p = 0.0436	– p = 0.0104	– p = 0.0147
IL-18	– p = 0.0105	– p = 0.0112	– p = 0.0262	– p = 0.0228

The table includes the tested parameters that correlated (+; –) to body mass and body composition indexes in a statistically significant way

Table 9. *Comparison of leptin, insulin, high sensitivity C-reactive protein (hsCRP), interleukin 18 (IL-18) levels, and hsCRP/albumin with body mass and body mass index (BMI) (all) (Pearson's correlation coefficient)*

Analysed parameter	Body mass before treatment vs. analysed parameter before treatment	Body mass after treatment *vs.* analysed parameter after treatment	BMI before treatment *vs.* analysed parameter before treatment	BMI after treatment *vs.* analysed parameter after treatment
Leptin	– p = 0.0147	– p = 0.0229		
hsCRP/alb			+ p = 0.0224	
hsCRP			+ p = 0.0202	
Insulin	– p = 0.0171	– p = 0.0112	– p = 0.0424	– p = 0.0221
IL-18			– p = 0.0298	– p = 0.0292

The table includes only the tested parameters that correlated (+; –) to body mass and body composition indexes in a statistically significant way

Discussion

In the previous study on the same group of patients we discovered that the reduction of points in all the subscales of the PANSS scale was statistically significant after the 28-day treatment with aripiprazole [29]. Additionally, we noticed a statistically significant decrease of levels of the following cytokines in serum: IL-1β, IL-6, TNF-α, sTNF-R1, IL-12, IL-23, IFN-γ, IL-Ra, TGF-β1, and IL-4 as well as hsCRP and insulin. We observed a statistically significant increase in IL-10 [29]. We also observed a (statistically significant) decrease of IL-18, IL-17A, and

Table 10. *Comparison of leptin, insulin, high sensitivity C-reactive protein (hsCRP), interleukin 18 (IL-18) levels, and hsCRP/albumin with body composition indexes (all) (Pearson's correlation coefficient)*

Analysed parameter	WC before treatment *vs.* analysed parameter before treatment	WC after treatment *vs.* analysed parameter after treatment	BF% before treatment *vs.* analysed parameter before treatment	BF% after treatment *vs.* analysed parameter after treatment
Leptin			+ p = 0.0049	+ p = 0.0091
hsCRP/alb				
hsCRP				
Insulin	– p = 0.0204	– p = 0.0280		
IL-18	– p = 0.0385	– p = 0.0476		

The table includes only the tested parameters that correlated (+; –) to body mass and body composition indexes in a statistically significant way

SAA levels in the serum and a (statistically significant) increase in albumin level (unpublished data). All the subjects had normal levels of glycaemia before, during, and after the 28-day treatment with aripiprazole. In the previous study the level of hsCRP was measured, which was 4.07 (1.70) mg/L and 1.59 (1.07) mg/L before and after the study, respectively.

As according to the latest data BF% better than BMI reflects the risk of developing a cardiovascular disease, diabetes or metabolic syndrome [30]. Also, it should be mentioned that the BF% index seems especially useful in the case of patients treated with atypical neuroleptics because it is a more sensitive indicator of cardiometabolic risks [31]. Moreover, data exist indicating that men suffering from schizophrenia have an increased body fat percentage and at the same time decreased muscle mass, which results in fast development of sarcopaenia at a relatively young age [32, 33]

In the previous study (the same group of patients) we proved that an improvement of psychical condition (point reduction in PANSS scale) correlated positively with an increase in IL-10 anti-inflammatory cytokine after treatment, whereas IL-12 pro-inflammatory cytokine correlated negatively with the PANSS scale points before the study [29]. This may indicate that the effect of aripiprazole is linked to an anti-inflammatory activity. Previous treatment (mainly with olanzapine or quetiapine) was related with pro-inflammatory activity because the IL-12 pro-inflammatory cytokine correlated positively to better psychical condition of the patients. Because cytokine and acute phase protein expression increase in the case of overweight or obese patients, a vast panel of these biomarkers was marked. In the initial phase of adipose tissue inflammation cytokines and acute phase proteins act locally. In the case of overweight/obese patients, the levels of the above-mentioned in serum increase (endocrine effect), causing among others lower insulin sensitivity of tissues [34].

According to the adopted chronic low-grade inflammation criterion, the inflammation affected all the tested patients. Twenty-eight days of treatment with aripiprazole resulted in a significant decrease of chronic low-grade inflammation markers. This was probably influenced by discontinuation of previous treatment with a neuroleptic, but, as was presented in the previous study [29], the level of hsCRP in the serum decreased during the first week of treatment from 4.07 (1.70) to 2.17 (0.95), which may indicate a strong anti-inflammatory effect of aripiprazole itself. It must be remembered that previous antipsychotics were taken alongside aripiprazole for the first three days of the study. Aripiprazole also decreased the insulin level, which is a desired effect because hyperinsulinaemia is the first indicator of growing insulin resistance of tissues, and it may result from treatment with atypical antipsychotics.

Having compared BMI with BF%, it was confirmed that the latter is a more sensitive parameter for determining cardiometabolic risk (Tab. 2). Before the study seven patients had normal results (proper body mass), but according to BF% only four patients fell within the norm. After 28 days of treatment with aripiprazole statistically significant decreases in body mass, BMI, WC, and BF% were noticed (Tab. 3). According to the literature, it is likely that further improvement of these parameters is also possible after long-term (several months) treatment with this neuroleptic [35–37].

Tables 5–7 present only statistically significant results. Negative correlation between leptin and body mass and WC (Tab. 5 and 7) may indicate at least partly maintained function of this adipocytokine, i.e. restricting the orexigenic centre and stimulating satiety centre (no leptin resistance). This phenomenon especially affected women (body mass and WC) after treatment with aripiprazole. The high significantly positive correlation between leptin and BF% (women and men) confirms the leptin production by adipose tissue.

Insulin correlated negatively with body mass, BMI, WC, and in the case of men also BF%. The result seems surprising because in obesity insulin resistance usually grows; insulin should correlate positively with body mass index, WC, and BF%. In the case of overweight and obese patients the compensation mechanism of the body includes increased secretion of insulin by the patient's pancreas; it usually takes many years until the mechanism fails and frank diabetes develops. However, there is another possible explanation for this apparently paradoxical result. After many years of treatment with clozapine or olanzapine an increase in adipose tissue in the body is observed (mainly subcutaneous adipose tissue). This phenomenon is described as compensatory because the subcutaneous adipose tissue has an ability to gradually absorb glucose excess, which balances developing (or already developed) insulin resistance at the level of skeletal muscles [38]. Findings shows that by greater expression of SREBP-1 (sterol regulatory element-binding protein) in the subcutaneous adipose tissue, olanzapine increases the expression of GLUT4 (glucose transporter type 4) in this tissue [39, 40]. This means that the insulin sensitivity of the subcutaneous adipose tissue increases while it decreases in skeletal muscles [8]. What is stated above is partly confirmed by the common occurrence of sarcopaenia among men with schizophrenia. Because before, during, and after the study the patients had normal glucose levels, the above data may explain the paradoxically negative correlation between insulin and body mass and body composition indexes.

The level of albumin (negative acute phase protein) increased in a statistically significant way during the study (unpublished data). In the group of women, after 28 days of treatment with aripiprazole albumin correlated negatively with BF%, which confirms aripiprazole's anti-inflammatory effect.

The estimated hsCRP/albumin relation correlated positively with BF% before the treatment in the group of women, whereas both hsCRP and hsCRP/albumin correlated positively with BMI before the treatment for the whole group. Reduction of the patients' body mass by an average of 2 kg was observed after 28 days of the study; also, aripiprazole caused a decrease in pro-inflammatory cytokines such as IL-1, IL-6, TNF, and IL-17 [29], which stimulate the liver to produce hsCRP.

In the group of women a statistically significant positive correlation between TNF-α and IL-17A cytokines and body mass and body composition indexes was observed. The variation concerned only women because they have a larger body fat percentage. It is generally known that TNF is produced mainly by adipose tissue, which supposedly also produces and secretes IL-17A [41].

Pro-inflammatory IL-18 cytokine correlated negatively with BMI, WC, and in the group of men also with BF%. This negative correlation results from the fact that this cytokine correlates positively with fat-free body mass [42, 43]. Additionally, sarcopaenia among men with schizophrenia is worth bearing in mind. In our research the average level of IL-18 for men was 78.6 (13.4) pg/mL (unpublished data), whereas the norm for healthy people is 80-120 pg/mL [44], which may indicate obvious sarcopaenia and increased BF% in the group of men.

A limitation of our study was the short duration of the study. However, recent database studies and a large naturalistic trial suggest that the favourable metabolic profile of aripiprazole may persist for up to one year [35–37]. Another limitation was the lack of a control group.

Conclusions

The effect of aripiprazole is linked to its anti-inflammatory activity.

In the course of treatment aripiprazole markedly limits the development of chronic low-grade inflammation and contributes to adipose tissue reduction.

In the group of women, it returned their leptin sensitivity to normal levels.

As well as measurement of body mass, waist circumference, and BMI estimation, an additional measurement of body fat percentage seems justified to determine the effect of a given antipsychotic drug on body mass and body composition parameters.

A change of psychotropic treatment and administration of aripiprazole may reduce cardiometabolic risk for patients with chronic schizophrenia.

Conflicts of interest

The authors declare no conflict of interest.

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