


# Systemic concentration of apelin, but not resistin or chemerin, is altered in patients with schizophrenia

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## ABSTRACT

It has been suggested that immune-inflammatory processes might be involved in the etiopathogenesis of schizophrenia. Since growing evidence indicates that adipokines strongly modulate the course of immune response and inflammatory processes, it is currently suggested the contribution of those factors in the etiology of schizophrenia as well. The aim of this study was to determine the serum levels of 4 adipokines—apelin, resistin, chemerin, and omentin—in patients with schizophrenia as compared with healthy subjects. Fifty-seven adult patients with schizophrenia and 31 healthy volunteers were included in this prospective study. ELISA was used to measure the serum concentration of resistin, apelin, omentin-1, and chemerin. No difference in the mean concentration of resistin ( $p=0.20$ ) and chemerin ( $p=0.30$ ) between patients with schizophrenia and the healthy group was observed. Apelin concentration was significantly ( $p=0.004$ ) lower in patients with schizophrenia as compared with controls. A significant difference in apelin level between men with schizophrenia and control group ( $p=0.04$ ) was reported. Apelin concentration was significantly correlated with waist-to-hip ratio, whereas chemerin concentration was significantly correlated with the Positive and Negative Syndrome Scale G score. There exists evidence that apelin might be involved in the pathogenesis of schizophrenia.

## INTRODUCTION

Schizophrenia (SCHZ), a severe, common mental illness, which affects approximately 1% of the total population, is characterized by hallucinations, delusions, cognitive deficits, and formal thought disorders.<sup>1</sup> Although there are many theories about the etiology of SCHZ, its exact pathomechanism is still not fully understood. A growing body of evidence indicates that an imbalance in the production of neurotransmitters, such as serotonin, dopamine, glutamate, and  $\gamma$ -aminobutyric acid, might play a role in the pathogenesis of SCHZ. In patients with

## Significance of this study

### What is already known about this subject?

- ▶ There is information that immune-inflammatory processes might be involved in the etiopathogenesis of schizophrenia.
- ▶ Growing evidence indicates that adipokines strongly modulate the immune response and inflammatory processes as they possess proinflammatory, anti-inflammatory, and/or immunoregulatory properties.
- ▶ It is currently suggested that adipokines may contribute to the pathogenesis of schizophrenia.

### What are the new findings?

- ▶ We have documented that subjects with schizophrenia have significantly lower level of apelin as compared with controls.
- ▶ We observed no difference in the mean concentration of resistin and chemerin between patients with schizophrenia and the healthy group.
- ▶ We have found correlations between levels of chemerin and clinical symptoms of schizophrenia.
- ▶ We have found correlations between levels of apelin and waist-to-hip ratio.

### How might these results change the focus of research or clinical practice?

- ▶ The present results provide support for the hypothesis that apelin might be involved in the pathogenesis of schizophrenia and could potentially be used in the future as a diagnostic, therapeutic or side effects marker of schizophrenia.

SCHZ, changes in the expression level of some neurotransmitter receptors, including dopamine receptors (D1R; D2R), serotonin receptors (5HT2A), or the alpha-7 nicotinic receptor, were reported as well.<sup>2–7</sup> Moreover, alterations in neurotrophin synthesis are now considered as the potential mechanism responsible for the development of SCHZ.<sup>8</sup>

It is well recognized that patients with SCHZ are more likely to develop



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**Table 1** Clinical, laboratory and anthropometric characteristics of subjects

	SCHZ n=57	HC n=31	
<b>Clinical data</b>			
Smoking	34 (59.7%)	5 (16.1%)	P<0.001*
Smoking pack-year	9.2 (12.2) (6.0 to 12.5)	2.5 (6.6) (0.1 to 5.0)	
Median	4	0	z=-3.99 P<0.001
Treatment duration (y)	15.4 (10.8) (12.5 to 18.2)	–	–
Median	13	–	–
Antipsychotic dose (DDD)	2.42 (1.13) (2.12 to 2.73)	–	–
Antipsychotic dose (CPZ eq)	728.6 (341.3) (638.0 to 819.1)	–	–
<b>Antipsychotics (n)</b>			
1	14 (24.5%)	–	–
2	36 (63.2%)	–	–
3	6 (10.5%)	–	–
4	1 (1.7%)	–	–
<b>Medications</b>			
SGA	54 (94.7%)	–	–
FGA	20 (35.1%)	–	–
Antidepressants	7 (12.3)	–	–
Mood stabilizers	22 (38.6%)	–	–
<b>PANSS score</b>			
Total	68.1 (15.3) (64.1 to 72.2)	–	–
Positive subscore	15.9 (5.1) (14.6 to 17.3)	–	–
Negative subscore	19.3 (5.0) (18.0 to 20.7)	–	–
General subscore	32.9 (7.4) (30.9 to 34.9)	–	–
CDSS score	3.0 (3.5) (2.1 to 3.9)	–	–
<b>Laboratory parameters</b>			
CRP (mg/dL)	2.81 (3.29) (1.94 to 3.69)	3.87 (8.33) (0.82 to 6.93)	
Median	1.3	0.9	z=-1.24 P=0.21
Glucose (mg/dL)	94.3 (25.0) (87.7 to 101.0)	87.8 (14.8) (82.4 to 93.2)	
Median	91.4	86.1	z=-1.72 P=0.09
Total cholesterol (mg/dL)	192.7 (36.7) (183.0 to 202.5)	207.5 (40.5) (192.7 to 222.4)	t(86)=1.69 P=0.10
HDL (mg/dL)	48.3 (14.2) (44.6 to 52.1)	53.5 (13.2) (48.6 to 58.3)	t(86)=1.69 P=0.10
LDL (mg/dL)	115.9 (32.7) (107.3 to 124.6)	119.9 (35.5) (106.8 to 132.9)	t(86)=0.51 P=0.61
Triglycerides (mg/dL)	133.1 (50.5) (119.8 to 146.5)	0	
Median	133.6	133.6	z=0.76 P=0.45
<b>Anthropometric parameters</b>			
BMI (kg/m <sup>2</sup> )	28.2 (5.9) (26.7 to 29.8)	25.9 (5.5) (23.9 to 27.9)	
Median	26.9	25	z=-1.85 P=0.06
WHR	0.96 (0.08) (0.94 to 0.98)	0.87 (0.09) (0.83 to 0.91)	t(86)=-4.34 P<0.001

Continued

Table 1 Continued

	SCHZ n=57	HC n=31	
Blood pressure: systolic (mm Hg)	125.2 (15.2) (121.2 to 129.2)	131.0 (17.7) (124.5 to 137.5)	t(86)=1.53 P=0.13
Blood pressure: diastolic (mm Hg)	79.8 (10.7) (76.9 to 82.6)	82.9 (11.0) (78.9 to 87.0)	t(86)=1.30 P=0.20
Total body fat (%)	34.9 (8.3) (32.6 to 37.1)	30.2 (8.9) (26.8 to 33.6)	t(83)=-2.34 P=0.02
Fat-free mass (%)	62.8 (8.9) (60.4 to 65.2)	66.0 (8.5) (62.8 to 69.2)	t(83)=1.60 P=0.11
Visceral adipose tissue (%)	1.62 (0.93) (1.37 to 1.88)	1.04 (0.93) (0.69 to 1.39)	
Median	1.61	0.83	z=-2.83 P=0.005
FMI (kg/m <sup>2</sup> )	10.1 (4.2) (9.0 to 11.4)	8.0 (4.1) (6.5 to 9.6)	t(83)=-2.23 P=0.03

Data presented as mean (SD) (95% CI) or n (%).

\*Fisher's exact test.

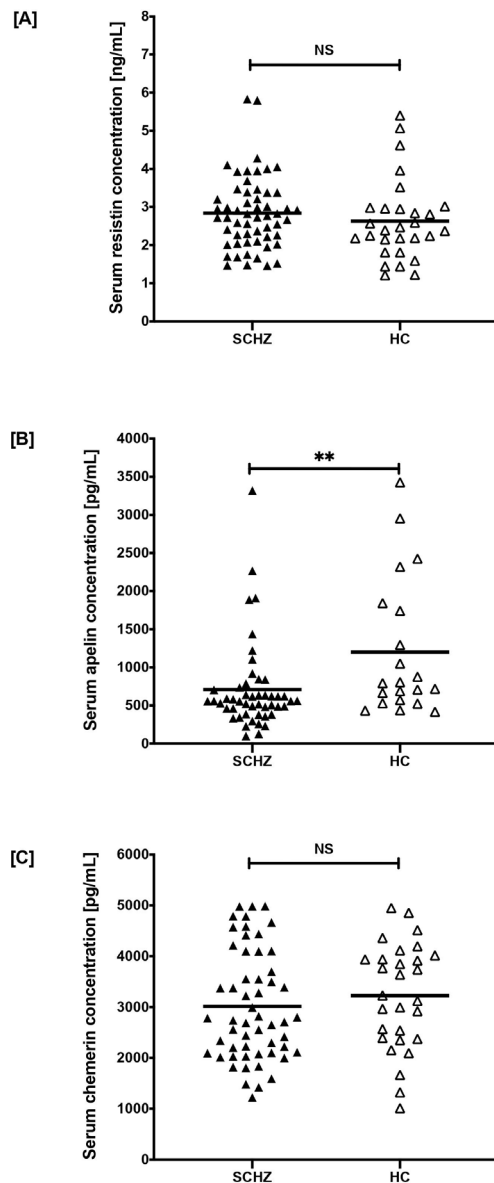
BMI, body mass index; CDSS, Calgary Depression Scale for Schizophrenia; CPZ eq, chlorpromazine equivalent; CRP, C-reactive protein; DDD, defined daily dose; FGA, first-generation antipsychotic; FMI, fat mass index; HC, healthy controls; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PANSS, Positive and Negative Syndrome Scale; SCHZ, schizophrenia; SGA, second-generation antipsychotic; WHR, waist-to-hip ratio.

cardiometabolic comorbidities, such as dyslipidemia, obesity, metabolic syndrome, type 2 diabetes, and cardiovascular diseases including hypertension, myocardial infarction, or stroke. It is currently also established that antipsychotics (especially second generation, such as clozapine or olanzapine) play a significant role in the development of cardiometabolic complications. Antipsychotics may dysregulate the level of adipokines by influencing the hormonal pathways of energy homeostasis and, as a consequence of this phenomenon, they influence the impairment of lipid and glucose metabolism and the development of obesity. Additionally, unhealthy lifestyle, that is, low-quality and high-sucrose and fat diet, smoking, early-life stress, and low level of physical activity, may strongly affect the development of metabolic abnormalities in patients with SCHZ. There is also growing evidence indicating a significant link between immune-inflammatory imbalance and metabolic syndrome in patients with SCHZ.<sup>9 10</sup>

To date, some changes in the functioning of the immune system have been observed in patients with SCHZ.<sup>11</sup> There exists increasing evidence demonstrating changes in the number of circulating immune cells, including B and T lymphocytes, natural killer cells, monocytes, and granulocytes occurring in the course of SCHZ, as compared with healthy subjects.<sup>11-13</sup> Furthermore, multiple reports indicate that in patients with SCHZ, the activity of cells engaged in immune-inflammatory processes is altered. The expression level of Toll-like receptors, molecules that in particular regulate the immune cell sensitivity to alarmins, was found to be changed in peripheral blood mononuclear cells (PBMCs) obtained from patients with SCHZ.<sup>14-16</sup> Also, differences in the ability to synthesize immunoregulatory cytokines/chemokines in response to various stimuli were observed in PBMCs derived from patients with SCHZ as compared with healthy subjects. Rapaport and Bresee reported significantly elevated interleukin 2 (IL-2) production and reduced IL-6 synthesis by PBMCs from patients with SCHZ in response to

mitogen stimulation.<sup>17</sup> Similarly, Cazzullo *et al* documented the increased generation of IL-2 and interferon gamma (IFN- $\gamma$ ) by phytohemagglutinin-stimulated PBMCs in patients with SCHZ.<sup>18</sup> Additionally, increased PBMC sensitivity to lipopolysaccharide (LPS) stimulation was observed in patients with SCHZ.<sup>19</sup> In response to LPS, enhanced synthesis of chemokines (ie, CCL2, CCL3, and CXCL8) as well as cytokines (ie, IL-4, IL-18, and IFN- $\gamma$ ) by PBMCs, in contrast to reduced production of another chemokine (ie, CCL5), was reported.<sup>19</sup> It has been also observed that in the course of SCHZ the serum levels of some humoral factors influencing immune-inflammatory processes are altered. In particular, the concentrations of proinflammatory mediators, including C-reactive protein (CRP), cytokines (ie, IL-1 $\beta$ , IL-6, tumor necrosis factor, IFN- $\gamma$ ) and chemokines (ie, CCL2, CCL4, CXCL8, and CXCL10), were elevated.<sup>20-25</sup> Conversely, IL-17 and IL-10 levels were found to be significantly reduced.<sup>26 27</sup> Interestingly, our previous study demonstrated a significantly lower serum concentration of cathelicidin LL-37, a molecule with proinflammatory activity, in patients with SCHZ in comparison with healthy controls (HC).<sup>28</sup>

Adipokines comprise a wide spectrum of biologically active molecules, predominantly produced by adipocytes. Some of them are also synthesized by multiple other cells, such as hepatocytes, cardiomyocytes, muscle cells, epithelial and endothelial cells as well as cells of the immune system, that is, PBMCs, macrophages, neutrophils, basophils, and mast cells. Adipokines may act systemically as circulating hormones or may locally influence various cell types. Therefore, they are involved in the control of food intake, energy homeostasis, lipid or glucose metabolism, and insulin sensitivity.<sup>29</sup> Interestingly, many adipokines are currently known to play a crucial role also in other physiological processes, since they may exert regulatory effects on heart function, blood pressure, angiogenesis, and adipogenesis.<sup>29</sup> Growing evidence indicates that adipokines strongly modulate the immune response



**Figure 1** Comparison of serum (A) resistin, (B) apelin, and (C) chemerin levels between patients with schizophrenia (SCHZ) and healthy controls (HC) in the whole study group. Black lines represent means; \*\* $p < 0.01$ . NS, non-significant.

and inflammatory processes as they possess proinflammatory, anti-inflammatory, and/or immunoregulatory properties.<sup>30</sup> Since in the mechanism of various mental disorders, the immune-inflammatory processes may play an important role, it is currently suggested that adipokines may as well contribute to the pathogenesis of SCHZ. Keeping in mind that many metabolic disorders develop in the course of SCHZ and that there is now a growing interest about the role of adipokines in the development of these conditions in SCHZ, the aim of our study was to determine possible differences in serum levels of 4 adipokines—apelin, with proinflammatory properties; resistin, chemerin, and omentin—all 3 with regulatory properties in patients with SCHZ as compared with HC.

## MATERIALS AND METHODS

### Study subjects

Fifty-seven adult European Caucasian patients (aged 18–60 years) with paranoid SCHZ were recruited from psychiatric outpatient clinics. All subjects underwent a structured interview according to the International Classification of Diseases 10th Revision (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria of SCHZ. Patients with SCHZ with the following results, that is, 295.30 according to DSM-IV and F20.0 according to ICD-10, were included in this prospective study (SCHZ group). HC group consisted of 31 randomly selected volunteers. They were interviewed according to ICD-10-based standard, a semistructured medical form routinely used in our hospital. Any subject with a self-reported personal or familial psychiatric history, or any previous psychiatric treatment, was excluded from the study. All control subjects were physically, neurologically, and endocrinologically healthy and their results for the following laboratory tests were in the reference range: complete blood count, CRP, alanine aminotransferase, aspartate aminotransferase, thyroid-stimulating hormone, bilirubin, urea, creatinine, and electrolyte level. The exclusion criteria comprised the presence of immunological disorders (eg, allergy, asthma, or AIDS), acute or chronic inflammatory conditions (eg, pneumonia or rheumatoid arthritis), systemic diseases, or cancer. All subjects enrolled in the study were informed about the objectives and methods employed in this study and provided written informed consent for participation.

### Clinical assessments

The clinical symptoms of SCHZ were assessed in accordance with the Positive and Negative Syndrome Scale (PANSS) and its positive (P), negative (N), and general (G) subscales. The severity of depressive symptoms was measured on the basis of the Calgary Depression Scale for Schizophrenia (CDSS).

### Laboratory tests

Venous blood samples were collected between 8:00 AM and 9:00 AM, after at least an 8-hour overnight fast into vacuum tubes with clot activator and gel separator (serum separating tubes). Immediately after collection, blood samples were allowed to clot at room temperature for approximately 30 minutes. Subsequently, the serum was obtained by centrifugation at  $2500 \times g$  for 10 minutes. Serum glucose and lipid levels were measured using a Dirui CS-400 analyzer (Dirui, China). CRP serum level was assessed using latex-enhanced immunoturbidimetry. For the measurement of adipokines, the rest of the sera were immediately distributed in aliquots and frozen at  $-80^{\circ}\text{C}$  until the time of analysis. Sandwich ELISA for quantitative detection of human adipokines was used to measure the serum concentration of resistin (R&D Systems, Minneapolis, MN, USA), apelin (Wuhan Fine Biological Technology, Wuhan, China), omentin-1 (EIAab), and chemerin (R&D Systems). All samples were assayed in duplicate. Protocols were performed according to the manufacturer's instructions. The sensitivity of the assay was 0.026 ng/mL for resistin,  $<37.7$  pg/mL for apelin, 0.051 ng/mL for omentin-1, and 4.13 pg/mL for chemerin. The absorbance was measured on a Multiskan FC Microplate

Photometer (Thermo Fisher Scientific, Waltham, MA, USA) at 450 nm. All the samples were compared with the standard curve.

### Anthropometry

Body height was measured with a wall-mounted height measure with an accuracy of 0.5 cm. Body mass 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 with an accuracy of 0.5 kg. Body mass index (BMI) was calculated as body weight (kg)/height (m)<sup>2</sup>. Waist and hip circumferences were measured using a non-stretchable fiber measuring tape. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

### Body composition

Body composition was measured using dual-energy X-ray absorptiometry (DXA) with a Lunar iDXA scanner (GE Healthcare, UK) and CoreScan V.15 software. Standard operating conditions (including preparation of the subjects, electrode placement, and measurement procedures) were monitored by a trained operator. The DXA measurements were performed immediately prior to anthropometry measurements with subjects resting in a supine position.

Briefly, bioelectrical impedance analysis is based on determining the electrical impedance of body tissues. This method can be used to assess total body water content and to estimate fat-free body mass and thus, the overall body fat content, by calculating the difference with the body weight. In DXA, 2 X-ray beams with different energy levels are pointed at the patient. On the basis of differences in the absorption, the presence of different tissue types, including bone, muscle, and fat, can be identified.

DXA was used to measure total body fat (TBF), lean body mass (LBM), visceral adipose tissue (VAT) mass, and VAT volume. TBF and LBM were converted to the percentage of total body mass. Fat mass index (FMI) was calculated as TBF in kilograms divided by the square of the height in meters (kg/m<sup>2</sup>).

### Statistical analysis

We report all data exclusions (if any), all manipulations, and all measures carried out in the study. Statistical analysis was performed with STATA V.15.1 software (StataCorp, USA). Continuous variables are presented as mean (SD) (95% CI). For discrete variables, the number of patients and percentages are given. The normality of distribution was tested visually (histogram, normal probability plot) and with the Shapiro-Wilk test. Variables with no normal distribution are presented as medians and were compared using the non-parametric Mann-Whitney test. We used Pearson's correlation for variables with normal distribution and Spearman's correlation for variables without normal distribution. All 3 adipokines did not follow the normal distribution, with apelin being strongly skewed to the left. Therefore, prior to further analysis, concentrations of apelin, resistin, and chemerin were log transformed. Log-transformed data had kurtosis and skewness close to normal distribution. Therefore, we presented both parametric t-test for log-transformed variables and non-parametric tests

for non-transformed data. For all t-tests, we used unequal variances, Welch's t-test if necessary. All correlations were pairwise and were confirmed using the bootstrap validation technique (1000 replications). The level of significance was set at  $p < 0.05$  (two sided). Additional details for statistical analysis are given in the manuscript.

### RESULTS

Fifty-seven patients with SCHZ and 31 healthy subjects were enrolled in this study. The mean age was  $39.6 \pm 10.8$  years for patients with SCHZ and  $37.2 \pm 10.4$  years for HC. All clinical, laboratory and anthropometric parameters of the study groups are presented in detail in [table 1](#).

In study and control groups, comparable values of parameters measured in the clinical, laboratory, and anthropometric tests were observed. Results of SCHZ group treatment with first-generation and second-generation antipsychotics were highly heterogeneous. Unfortunately, in all investigated samples (in patients with SCHZ and in HC), levels of omentin-1 were undetectable in the concentrations range (0.85–50 ng/mL) of the ELISA test, which we used in this study. For this reason, we excluded this adipokine from further analysis. Other adipokines below detection threshold included: resistin in 3 subjects (SCHZ: 1; HC: 2), chemerin in 4 subjects (SCHZ: 2; HC: 2) and apelin in 18 subjects (SCHZ: 8; HC: 10). In the analysis, we included subjects with at least 1 measured adipokine level.

Serum levels of adipokines in patients with SCHZ and healthy group are shown in [figure 1](#). The mean serum level of resistin in patients with SCHZ and HC was  $2.84 \pm 0.95$  and  $2.63 \pm 1.06$  ng/mL, respectively. No statistically significant difference was observed in mean resistin concentration between these groups ( $p = 0.20$ ) ([figure 1A](#)). The mean serum apelin level in patients with SCHZ and HC was  $708.8 \pm 577.7$  and  $1201.7 \pm 896.3$  ng/mL, respectively. Also, mean apelin concentration was significantly ( $p = 0.004$ ) lower in patients with SCHZ as compared with HC ([table 2](#) and [figure 1B](#)). In SCHZ group, the Cohen's d effect size for apelin was 0.72 (95% CI 0.19 to 1.24). Additionally, a significant difference in mean serum apelin level between men with SCHZ and control group ( $p = 0.04$ ) was observed ([table 3](#)). The mean serum concentration of chemerin was  $3014.8 \pm 1076.2$  pg/mL in subjects with SCHZ, and  $3226.0 \pm 1039.3$  pg/mL in HC ([figure 1C](#)). However, the difference was not statistically significant ( $p = 0.30$ ).

There was a significant difference in the percentage of smokers and the severity of smoking between the study and control groups. Therefore, we performed an analysis involving a robust linear multiple regression model with serum apelin level as the outcome and SCHZ and smoking (pack-years) as predictors. Overall, the model was significant:  $F(3, 66) = 12.87$ ,  $p < 0.001$ ,  $R^2 = 0.33$ , root mean square error = 601.66. No significant effect of SCHZ:  $\beta_{SCHZ} = -0.07$  ( $t = -0.60$ ,  $p = 0.55$ ) and significant effects of smoking:  $\beta_{smoking} = 1.13$  ( $t = 4.28$ ,  $p < 0.001$ ) and their interaction:  $\beta_{SCHZ \# smoking} = -1.33$  ( $t = -4.75$ ,  $p < 0.001$ ) were observed. Further analysis of Bonferroni-adjusted predictive margins showed that at fixed mean value (ie, 6.69 for smoking (pack-years)), there was a significant difference in apelin level between both groups: SCHZ: 738.1 (95% CI 564.2 to 912.0) pg/mL and HC: 1528.6 (95% CI 1225.2 to



**Table 2** Differences in serum levels of apelin, resistin and chemerin in the whole study groups

	SCHZ n=57	HC n=31	
Resistin (ng/mL)	2.84 (0.95) (2.59 to 3.09)	2.63 (1.06) (2.23 to 3.03)	$t(83)=-1.16$ P=0.24*
Median	2.75	2.39	$z=-1.30$ P=0.20
Apelin (pg/mL)	708.8 (577.7) (542.9 to 874.7)	1201.7 (896.3) (793.7 to 1609.7)	$t(68)=3.03$ P=0.003*
Median	559.3	792.5	$z=2.88$ P=0.004
Chemerin (pg/mL)	3014.8 (1076.2) (2723.9 to 3305.7)	3226.0 (1039.3) (2830.6 to 3621.3)	$t(82)=0.79$ P=0.43*
Median	2742	3231	$z=1.04$ P=0.30

Data presented as mean (SD) (95% CI).

\*t-test for log-transformed data.

HC, healthy controls; SCHZ, schizophrenia.

1831.9) pg/mL (figure 2). Also, to confirm that the difference in apelin levels is not only due to the intergroup difference in smoking, we ran random sampling in the SCHZ group to create random samples with the percentage of smokers (16%) equal to the HC group. Comparison between these groups confirmed significantly ( $t(45)=2.15$ ,  $p=0.018$ ; one-sided t-test for log-transformed data) lower apelin level in the SCHZ group (818.6 (740.0) (95% CI 519.7 to 1117.4)) as compared with the HC group (1201.7 (896.3) (95% CI 793.7 to 1609.7)).

In our study, no statistically significant correlations between serum levels of adipokines in the entire schizophrenic and control groups were found (figure 3). Likewise, there was no significant correlation between the level of adipokines when the study group was divided with respect to gender. Additionally, we observed that apelin concentration was significantly correlated with WHR ( $r=-0.27$ ,  $p=0.03$ ), but bootstrapping did not confirm significance of this correlation ( $r=-0.22$ ,  $p=0.045$  (95% CI  $-0.45$  to  $-0.005$ )). Similarly, we have found 1 significant correlation between chemerin and PANSS G score ( $r=-0.30$ ,  $p=0.04$ ), but again—it was not significant after bootstrapping ( $r=-0.21$ ,  $p=0.13$  (95% CI  $-0.48$  to  $0.06$ )). There were no other correlations or differences between individual adipokine levels ( $p>0.05$ ) and between resistin, apelin or chemerin and age ( $p>0.05$ ), smoking pack-years ( $p>0.05$ ), antipsychotic treatment duration ( $p>0.05$ ), number of SCHZ episodes ( $p>0.05$ ), antipsychotic dose ( $p>0.05$ ),

PANSS and CDSS scores ( $p>0.05$ ), fasting glucose, triglycerides and cholesterol ( $p>0.05$ ), BMI ( $p>0.05$ ), FMI ( $p>0.05$ ), WHR ( $p>0.05$ ), blood pressure ( $p>0.05$ ) or any of the body composition parameters ( $p>0.05$ ).

## DISCUSSION

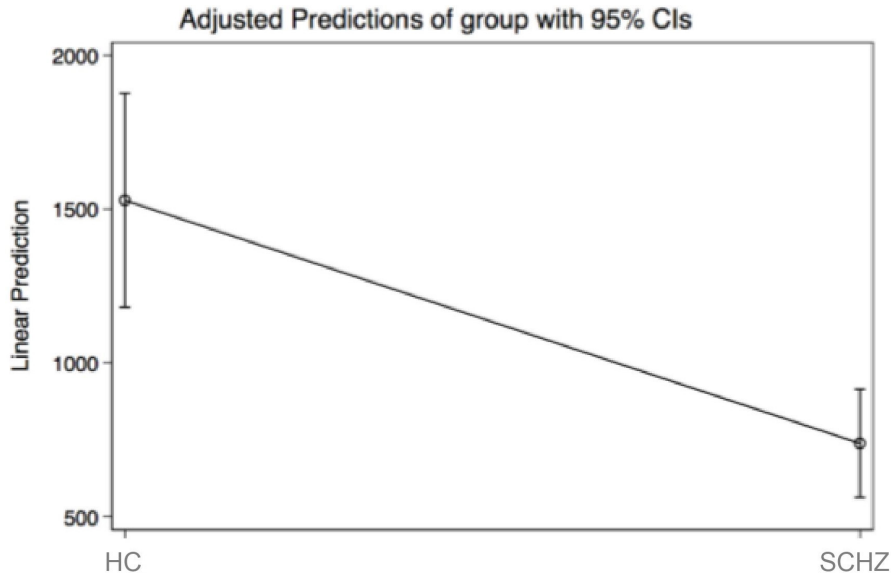
Currently, increasing evidence indicates that adipokines are not only engaged in the control of energy homeostasis and body metabolism. It has been suggested that some adipokines may regulate various physiological and pathophysiological processes, including cardiac function, blood pressure, or angiogenesis and adipogenesis. Interestingly, certain adipokines might serve as valuable predictive markers for some pathological conditions. For example, lower adiponectin level but increased leptin, chemerin, and apelin levels might be indicators of developing insulin resistance or type 2 diabetes mellitus.<sup>31</sup> Additionally, the increased systemic concentration of resistin and visfatin but low level of omentin might serve as biological markers suggesting the establishment of cardiovascular diseases.<sup>32</sup> There exist data indicating that leptin and adiponectin may serve as a potential prognostic or predictive marker for certain types of tumors.<sup>33</sup> Moreover, the leptin/adiponectin ratio may be a diagnostic biomarker of metabolic syndrome in patients with SCHZ.<sup>34</sup> Importantly, both these mediators strongly modulate the immune response and inflammatory processes as well. Nowadays, extensive

**Table 3** Concentration of adipocytokines in patients with schizophrenia and control group by sex

	SCHZ	HC	t	P value
<b>Women</b>	<b>n=21</b>	<b>n=11</b>		
Resistin (ng/mL)	2.75±1.01 (2.4)	2.85±1.14 (2.6)	0.203	0.84
Apelin (pg/mL)	848.73±826.75 (575.3)	1385.33±915.22 (1294)	1.513	0.18
Chemerin (pg/mL)	2896.10±1109.74 (2577.0)	3270.90±1222.41 (3123)	1.875	0.09
<b>Men</b>	<b>n=36</b>	<b>n=20</b>		
Resistin (ng/mL)	2.89±0.92 (2.9)	2.49±1.01 (2.3)	0.681	0.50
Apelin (pg/mL)	627.56±357.79 (557.2)	1062±895.54 (765.2)	2.211	0.04*
Chemerin (pg/mL)	3082.65±1066.86 (2822.0)	3198.50±947.54 (3436.0)	0.813	0.42

Data presented as mean±SD (median); \* $p<0.05$ .

HC, healthy controls; SCHZ, schizophrenia.



**Figure 2** Linear prediction of apelin level adjusted for smoking. HC, healthy control; SCHZ, patients with schizophrenia.

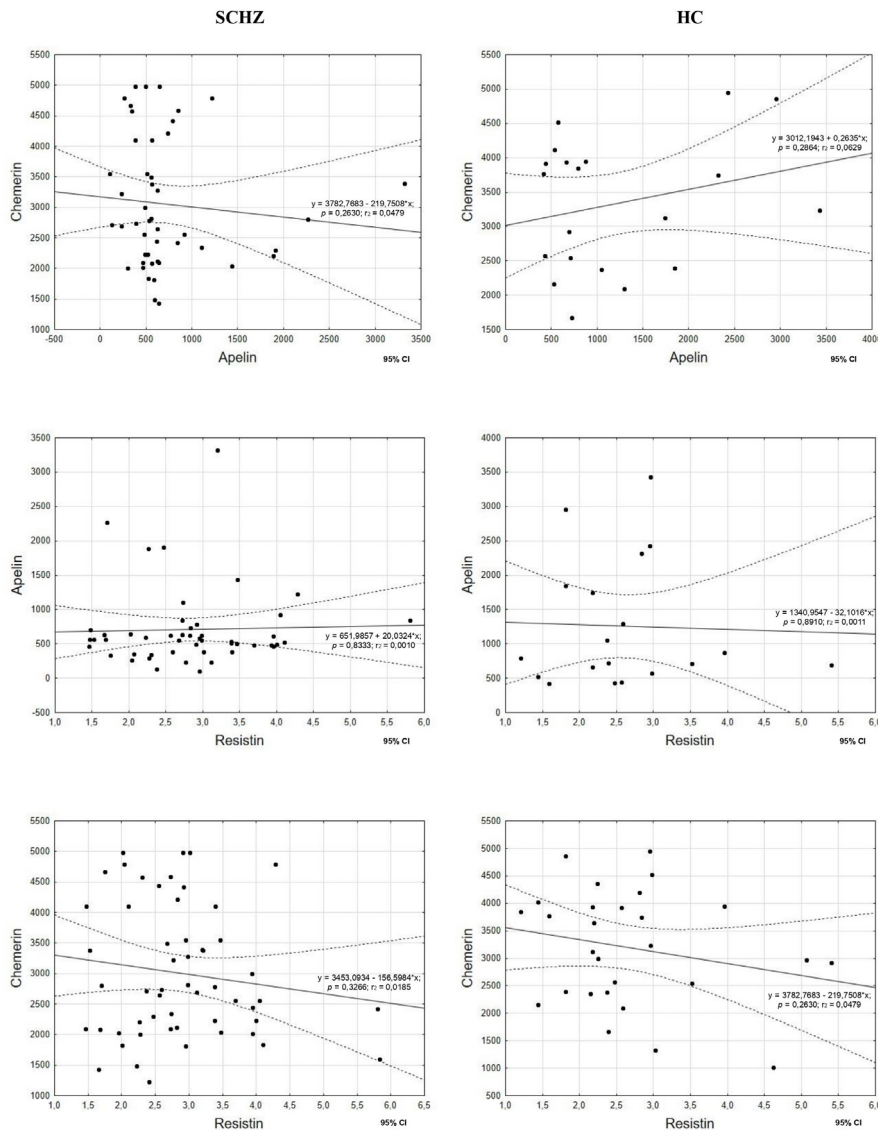
evidence demonstrates an important role of adipokines in the etiology, clinical presentation, and outcome of different mental disorders. However, little data are still available regarding these issues, whereas the existing reports describe ambiguous results. It seems that we are at the beginning of the understanding of adipokine importance in the mental disorder pathogenesis.

Several scientific reports demonstrated that the level of adiponectin, an adipokine with anti-inflammatory properties, was lower in depressed patients as compared with healthy subjects.<sup>35–36</sup> Also, the serum concentration of leptin, a proinflammatory adipokine, was reduced in currently depressed subjects in comparison with controls.<sup>37</sup> On the contrary, Çakici *et al* indicated that patients with major depressive disorder had an elevated level of leptin in comparison to HC group.<sup>38</sup> Lehto *et al* reported no difference in the serum level of proinflammatory adipokine (ie, resistin) in patients with the major depressive disorder as compared with the healthy group.<sup>35</sup> Additionally, the serum concentration of immunoregulatory adipokine (ie, apelin) was significantly elevated in subjects with depression in contrast to the control group.<sup>39</sup> Likewise, in patients with bipolar disorder, alterations in the level of some adipokines were observed; however, the available data provide highly inconsistent results. It has been reported that concentrations of leptin, adiponectin, and resistin in patients with bipolar disorder were increased or unchanged in comparison with the control group.<sup>40–43</sup> Moreover, no difference in the serum level of ghrelin, an adipokine with immunoregulatory properties, between patients with bipolar disorder and healthy subjects was observed.<sup>41</sup> To the best of our knowledge, so far a limited number of studies have investigated the relationship between adipokine levels and other mental disorders. In patients with autism spectrum disorder, the plasma level of leptin was elevated, resistin level was increased, adiponectin level was unaltered and apelin level was reduced as compared with the control group.<sup>44–45</sup> Lower plasma concentration of adiponectin in

patients with panic disorder as compared with the HC was documented as well.<sup>46</sup>

So far, only a few studies investigating the relationship between psychotic disorders and levels of adipokines have been performed. Balōtšev *et al* documented a decreased serum leptin concentration in antipsychotic-naïve patients with first-episode psychosis, whereas Wang *et al* demonstrated higher serum leptin level as compared with HC.<sup>47–48</sup> Likewise, the data regarding leptin concentrations in patients with SCHZ are highly inconsistent, since both increased<sup>38–49–51</sup> and reduced<sup>52</sup> serum levels of this adipokine were documented in comparison with healthy subjects. Additionally, Martorell *et al* reported that leptin levels were higher in patients with the first-episode psychoses than in the healthy subjects.<sup>53</sup> Wysokiński and Dietrich-Muszalska reported no difference in the level of fasting serum leptin between patients with SCHZ and the control group.<sup>54</sup> Interestingly, Hosojima *et al* demonstrated that serum leptin concentration in patients with SCHZ increased after 4 weeks of olanzapine treatment.<sup>55</sup> Also, a significantly higher adiponectin level in the serum of schizophrenic subjects as compared with HC was observed.<sup>21–56</sup> On the contrary, some authors documented that the concentration of adiponectin in patients with SCHZ was significantly lower<sup>49–57</sup> or unchanged<sup>50–55–58</sup> as compared with healthy subjects. Additionally, Tsai *et al* reported no significant difference in ghrelin serum level in schizophrenic subjects in comparison with HC, whereas Hosojima *et al* demonstrated a decrease in serum ghrelin concentration in patients with SCHZ after 4 weeks of olanzapine treatment.<sup>50–55</sup> Moreover, Sahpolat and Ari noted that the plasma nesfatin-1 level was lower in the patients with the first attack psychosis than in the HC group; however, this result did not reach a statistical significance.<sup>59</sup>

In our study, we assessed the serum level of 4 adipokines—apelin, resistin, chemerin, and omentin—in patients with SCHZ in comparison with HC. We found no difference in the levels of resistin and chemerin between subjects with



**Figure 3** Correlation between serum adipocytokine levels in patients with schizophrenia (SCHZ) and healthy controls (HC).

SCHZ and HC, whereas the presence of omentin was not detected. On the contrary, Sahpolat *et al* indicated that plasma concentration of resistin in patients with first-episode psychosis and chronic SCHZ was significantly higher than in the controls.<sup>60</sup> Additionally, Balotšev *et al* indicated that drug-naïve patients with first-episode psychosis had significantly higher resistin levels than the patients with chronic SCHZ.<sup>47</sup> The most critical finding in our study is that we found apelin concentration was significantly lower in schizophrenic subjects than in the control group. Sahpolat *et al* recently documented that individuals with SCHZ in first-episode psychosis had higher plasma levels of apelin than individuals with chronic SCHZ and control group.<sup>60</sup> It is also worth noting that Catak *et al* reported a higher level of serum apelin in patients with SCHZ treated with stable doses of oral antipsychotic medication than in the control group.<sup>61</sup> It is worth mentioning that patients with SCHZ in the study conducted by Catak *et al* had a very similar level of apelin as in our study, which was however different with respect to healthy subjects (in the control group of Catak

*et al*, apelin level was substantially lower as compared with ours; exact apelin concentrations were not given in the paper by Catak *et al*).<sup>61</sup>

The observations that the apelin level in the course of SCHZ may fluctuate seem to be very intriguing. It has been reported that apelin and its receptor APJ are widely expressed in neurons and oligodendrocytes of the central nervous system. Therefore, this adipokine might be potentially involved in the neuronal signaling pathways. Extensive data indicate that apelin may exert neuroregenerative and neuroprotective effects, as it inhibits neuronal apoptosis and reduces excitotoxicity. It has been documented that apelin plays a role in inflammation-mediated neuronal damage as well. Finally, it is worth noting that it also participates in hypothalamic-pituitary-adrenal axis regulation.<sup>62–66</sup>

Nonetheless, our study has some limitations in the context of which our findings need to be interpreted carefully. First, in this study there was a relatively low number of subjects. Second, all subjects with SCHZ were on heterogeneous treatment. It cannot be ruled out that antipsychotic drugs



may have varied effects on in vivo synthesis of adipokines. Therefore, studies with more homogeneous antipsychotic therapy groups concerning individuals with SCHZ are needed. Third, its cross-sectional design limits our abilities to establish a causal relationship.

In conclusion, there exists evidence supporting the concept that apelin might be involved in the pathogenesis of SCHZ. However, it is necessary to conduct further studies in order to elucidate the relationship between SCHZ and apelin, and to determine whether apelin level could be used as a diagnostic, therapeutic or side effects marker of SCHZ.

**Contributors** EK, AW, EBB and PŻ conceived and designed the experiments. AW and EK collected the sample information. EK and PŻ performed the experiments. EK, AW, and PŻ analyzed the data. EK, PŻ, AW, and EBB wrote the manuscript.

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