Plasma Apelin, Visfatin and Resistin Levels in Patients with First Episode Psychosis and Chronic Schizophrenia

Musa Sahpolat1, Mustafa Ari2, Mehmet Hanifi Kokacya2

1Department of Psychiatry, Kilis State Hospital, Kilis, 2Department of Psychiatry, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey

Objective: This study aims to investigate the possible relationship between plasma concentrations of apelin, visfatin and resistin levels of first episode psychosis patients and chronic schizophrenia patients.

Methods: A total number of 29 untreated patients with first episode psychosis, 30 chronic schizophrenia and 29 randomly selected weight- and body mass index-matched healthy volunteers were included. The Diagnostic and Statistical Manual of Mental Disorders 4th edition, Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression Scale were applied to the patient groups. The enzyme-linked immunosorbent assay method was used to measure plasma apelin, visfatin and resistin levels.

Results: There was no difference in age, marital status, occupation, and BMI between the groups. Plasma apelin levels were significantly higher in first episode psychosis group than chronic schizophrenia and control group. There was no statistically significant difference in plasma visfatin levels between the groups: first episode psychosis group, chronic schizophrenia and control group. Plasma resistin levels were higher in both first episode psychosis group and chronic schizophrenia group than the control group. There was no statistically significant correlation between plasma apelin and resistin levels and total PANSS scores in the group of patients.

Conclusion: To our knowledge, this study is the first which investigates the plasma apelin, visfatin and resistin levels in patients with first episode psychosis and chronic schizophrenia. Based on the results of this study, apelin and resistin may be related with some central nervous system pathologies, including the severity of a psychiatric disorder.

KEY WORDS: First episode psychosis; Schizophrenia; Apelin; Nicotinamide phosphoribosyltransferase; Resistin.

INTRODUCTION

Schizophrenia is a complex disease and a devastating neuropsychiatric illness affecting approximately 1% of the total population worldwide over the average lifetime [1,2]. Its etiology is unclear yet. One of the important hypotheses to explain its pathogenesis is about immune dysfunction [1,2]. One of the most interesting and challenging areas of research is the role of adipocytes in the etiology of mental disorders [2,3]. There are numerous descriptions of an association between chronic inflammation and adipokines of the central nervous system (CNS), and schizophrenia [2-4]. Several types of adipocyte receptor have been found in several central nervous system areas, and have been shown to affect brain function through neuroplastic processes [4-6]. These findings clearly showed the immune theory of psychiatric diseases such as schizophrenia [1,3,6,7].

Adipose tissue, it secretes a protein called adipokine, which is known to play roles in several physiological processes in the body such as eating, appetite, energy balance, insulin and glucose metabolism, lipid metabolism, regulation of blood pressure, vascular remodeling, coagulation, inflammation [8]. Some secretions of this tissue are interleukin (IL)-6, tumor necrosis factor (TNF)-α, insulin-like growth factor-1, C-reactive protein, sex hormones, adiponectin, resistin, apelin and visfatin [9].

Apelin is a relatively newly discovered neuropeptide that is the endogenous ligand for the G-protein-coupled (APJ) receptor, and it impacts by binding to APJ [10].
Apelin is expressed in both brain and peripheral tissues in human. In the brain, apelin is expressed in thalamus, frontal cortex and hippocampus, while it is also expressed in placenta, heart, lung and other peripheral tissues. The apelin receptors and apelin are widely distributed in the CNS [10,11] suggesting that apelin may be of importance in the regulation of certain CNS functions. Some studies have shown that apelin plays role in cardiovascular function, anterior pituitary function, regulation of certain CNS functions and the regulation of fluid homeostasis; also takes part in the suppression of apoptosis and acts as a co-receptor in human immunodeficiency virus (HIV) infection [10,11].

Visfatin has been recently identified as a peptide predominantly expressed in and secreted from visceral fat in both humans and mice. It is stated that plasma visfatin levels are associated with visceral fat mass, Type 2 diabetes mellitus and metabolic syndrome in humans [12]. Visfatin was originally identified as a pre-B cell colony enhancing factor and is thought to play roles in immune response and inflammation. Moreover, human recombinant visfatin treatment increases the secretion of inflammatory cytokines IL-1, IL-6, TNF-α [13]. Thus, there is some evidence to suggest that visfatin activates proinflammatory cytokines in human monocytes [14]. However, little is known about its function in the brain.

Resistin is a recently identified proinflammatory adipocytokine. Human resistin has also been detected in tissues like placenta, skeletal muscle, small intestine, spleen, stomach, thymus, thyroid gland, and uterus. However, resistin is predominantly expressed in macrophages in humans [15,16]. Recently, resistin has been found to be involved in inflammation and regulation of other cytokines as well. On the other hand, some proinflammatory cytokines can induce the expression of resistin [15,16]. One study reported that resistin effects closely mirror leptin-induced inhibition of dopamine and norepinephrine release in the hypothalamus, supporting a role for both catecholamines as central mediators of adipocyte-repleted signaling in the CNS [16].

It is known that inflammatory process plays a role in the etiology of schizophrenia. In this study, we aimed to investigate the possible relationship between first episode psychosis, chronic schizophrenia and plasma concentrations of apelin, visfatin and resistin in the inflammatory process.

METHODS

Participants
This study included a total of 29 untreated patients with first episode psychosis, 30 chronic schizophrenia and 29 randomly selected weight- and body mass index-matched healthy volunteers admitted to Mustafa Kemal University, Faculty of Medicine, Training and Research Hospital, Psychiatry outpatient clinic were included. Three groups were formed for the study. The first group consisted of patients with non-effective drug-naïve first episode psychosis. Second group consisted of patients with chronic schizophrenia. And the third group was healthy control group. Diagnoses of the patients were made in accordance with the Diagnostic and Statistical Manual of Mental Disorders 4th edition schizophrenia diagnosis criteria. The patients with the first attack who take antipsychotics and patients with affective psychosis were excluded from the study. Individuals with any other chronic disease such as diabetes mellitus, hypertension, hyperlipidemia, or neurological disorders, who were under 18 years of age and those over 65 years of age and pregnant women in the menstrual cycle were excluded from the study. People with any additional psychiatric condition were excluded; also those with mental retardation and those with organic brain damage were not included in the study. For the control group, people with any psychiatric or medical condition were excluded from the study. Before enrollment, the relationship between plasma apelin, visfatin and resistin levels and socio-demographic characteristics was examined. A written informed consent was obtained from each participant. The study protocol was research ethics approval was obtained from the Ethics Committee of the Medical School of Mustafa Kemal University (no. 201335). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Socio-demographic data, such as age, sex, educational level, marital status, occupational status, mental status, smoking, height, weight, and body mass index (BMI), was collected. The severity of psychosis symptoms in the patients was evaluated using the Positive and Negative Syndrome Scale (PANSS) [17]. Physical and neurological examinations were performed in all participants.
Table 1. Sociodemographic characteristics of the groups

| Variable             | First episode psychosis group (n = 29) | Chronic schizophrenia group (n = 30) | Healthy control group (n = 29) | Significance |
|----------------------|----------------------------------------|-------------------------------------|------------------------------|-------------|
| Age (yr)             | 31.14 ± 12.12                          | 33.87 ± 10.49                       | 30.21 ± 8.13                 | $p = 0.374^a$, F = 0.995 |
| Sex (female/male)    | 12/17                                  | 13/17                               | 16/13                        | $p = 0.521^b$, $\chi^2 = 1.303$ |
| BMI (kg/m²)          | 24.89 ± 5.14                           | 26.59 ± 4.71                        | 23.94 ± 3.94                 | $p = 0.089^a$, F = 2.491 |
| Total PANSS          | 101.90 ± 16.35                         | 92.07 ± 21.56                       | -                            | $p = 0.046^{**}$, U = 303.50 |

Values are presented as mean ± standard deviation or number only.
BMI, body mass index; PANSS, Positive and Negative Syndrome Scale.

RESULTS

All groups had similar demographic characteristics. The demographic and biochemical characteristics were shown in Table 1.

Statistically significant differences were found between the groups for apelin levels ($p = 0.026$; $\chi^2 = 7.338$). According to pairwise comparisons; apelin levels of the first episode psychosis patients were significantly higher than the chronic schizophrenia and control group patients ($p = 0.034$; $p = 0.012$, respectively). There was no significant difference in apelin levels between the chronic schizophrenia and control group patients ($p = 0.644$). There was no statistically significant difference in visfatin levels between the groups ($p = 0.109$; $F = 2.272$). In the comparison of resistin levels between the groups, a high level of statistically significant differences was found ($p = 0.007$; $\chi^2 = 10.000$). According to pairwise comparison; resistin levels of the first episode psychosis and chronic schizophrenia groups were significantly higher than the controls ($p = 0.003$; $p = 0.016$, respectively). There was no statistically significant difference in resistin levels between the first episode psychosis and chronic schizophrenia patients ($p = 0.490$). It was shown in Table 2.

There was no statistically significant difference in sociodemographic variables in terms of the mean plasma apelin, visfatin and resistin levels between three groups. Plasma apelin, visfatin and resistin levels of three groups were not statistically significantly associated with BMI and smoking ($p > 0.05$). There was no statistically significant relationship between the Total PANSS score and plasma apelin, visfatin, resistin levels in patients with first episode psychosis and chronic schizophrenia ($p > 0.05$).
Table 2. Plasma apelin, visfatin and resistin evaluations for groups

| Variable | First episode psychosis group (n = 29) | Chronic schizophrenia group (n = 30) | Healthy control group (n = 29) | Significance | Pairwise comparisons<sup>c,d</sup> (p value) |
|----------|----------------------------------------|------------------------------------|-------------------------------|--------------|-----------------------------------------|
| Apelin   |                                        |                                    |                               |              |                                         |
| Min−Max (median) | 26.1−311.3 (147.9) | 10.0−236.9 (107.9) | 32.0−260.8 (93.3) | *p = 0.026<sup>b,**</sup>, *χ² = 7.338 | 0.034* |
| Mean ± standard deviation | 156.88 ± 86.09 | 108.04 ± 59.47 | 104.01 ± 56.60 | *χ² = 0.361 | 0.644 |
| Visfatin |                                        |                                    |                               |              |                                         |
| Min−Max (median) | 3.2−7.6 (5.9) | 4.4−11.3 (6.0) | 4.8−8.2 (6.4) | *p = 0.109<sup>a</sup>, *F = 2.272 | 0.361 |
| Mean ± standard deviation | 5.78 ± 1.10 | 6.24 ± 1.35 | 6.38 ± 0.86 | *F = 1.000 | 1.000 |
| Resistin |                                        |                                    |                               |              |                                         |
| Min−Max (median) | 10.7−16 (14.9) | 9.7−16 (14.1) | 9.1−15.9 (13.2) | *p = 0.007<sup>b,**</sup>, *χ² = 10.000 | 0.490 |
| Mean ± standard deviation | 14.19 ± 1.44 | 13.89 ± 1.62 | 12.79 ± 1.80 | *χ² = 0.003<sup>**</sup> | 0.016* |

<sup>a</sup>One-way ANOVA test, <sup>b</sup>Kruskal–Wallis test, <sup>c</sup>Mann–Whitney U test, <sup>d</sup>Adjustment for Multiple Comparisons: Bonferroni post-hoc test; *p < 0.05, **p < 0.01.

**DISCUSSION**

There is limited information about the role of apelin, visfatin, and resistin in psychiatric disorders such as schizophrenia in the inflammatory process. This study was designed to determine whether plasma levels of apelin, visfatin, and resistin were altered in schizophrenia without additional comorbid diseases. To eradicate the possible effect of obesity on the apelin, visfatin and resistin levels, plasma concentrations of apelin, visfatin and resistin were corrected with the BMI.

Dysregulation of immune system has a significant place in the proofs related to etiopathogenesis of schizophrenia. It is thought to be there is a close relation between schizophrenia and autoimmune processes. There are strong data particularly on proinflammatory processes in schizophrenia [1,3]. Findings of our study are also supportive of this hypothesis.

One of the most substantial finding in our study is that we found plasma apelin levels of first episode psychosis patients were significantly higher than the chronic schizophrenic group and control groups. There are studies about the emotional consequences of apelin administration to the CNS and studies investigating the relationship between plasma apelin levels and some psychiatric disorders; but no human study focusing on the apelin levels in patients with chronic schizophrenia and the first episode psychosis was available. Apelin was reported to be in many areas of the brain, such as cortex, hypothalamus, hippocampus, pituitary, spinal cord, cerebellum, corpus callosum, substantia nigra, the dorsal raphe nucleus, the central gray matter, amygdala, subthalamic nucleus, caudate nucleus, and especially in supraoptic and paraventricular nuclei [19-21]. These areas are known to be related to emotions and being released from these areas suggests a possible role of apelin in emotional behavior. Suppression of eating behavior with apelin-13 [22,23] and the close relationship between eating behavior and emotional behavior [24,25] support this opinion. For example, the anorexigenic CRF and α-MSH showed an anxiety and depression-like effect [26,27]. The orexigenic Neuropeptide Y and ghrelin reduces the anxiety-depression dependent behavior [28,29]. Apelin has been demonstrated to exert neuroprotective action under a number of experimental conditions [21,30]; in culture, it markedly prevents apoptosis in mouse cortical neurons [31] and it protects hippocampal neurons against N-Methyl-D-aspartate excitotoxicity [32]. No data are as yet available regarding its action on psychosis.

One of the most substantial finding in our study is that plasma visfatin levels were not statistically difference between the three groups. In contrast to other studies in literature, our finding suggests that visfatin has no effect on both acute and chronic phases of psychosis. Visfatin, also known as pre-B-cell colony-enhancing factor, plasma levels correlated with inflammation cytokines or mediator. Visfatin has been found to be also expressed in animal and human brain [33,34]. Moreover, higher plasma visfatin levels are associated with ischemic stroke [35], and visfatin has a neuroprotective effect in ischemia through its enzymatic activity for nicotinamide adenine dinucleotide production that can ameliorate mitochondrial dys-
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function [36]. One study demonstrated that increasing levels of TNF-α in the serum of children with autism spectrum disorders and also observed a significant positive correlation between TNF-α and resistin and visfatin [37]. Some studies suggest that there was no significant association between the concentration of circulating visfatin and presence of eating disorders [38,39]. At present, there are no sufficient studies to explain the relationship between visfatin and psychosis.

The most substantial finding in our study is that we found high plasma resistin levels in both first episode psychosis and chronic schizophrenia patients. This, in line with the literature, suggests a role of resistin in inflammatory process in both acute and chronic phase of psychosis. According to our findings, resistin may be a component of inflammatory process both acute and chronic stress. In humans, resistin appears to be an inflammatory molecule primarily expressed in monocytic cells, from which it is secreted. The correlation between resistin with inflammatory markers (e.g., IL-6, TNF-α) is especially considerable given the observation that resistin is produced by macrophages in response to inflammatory cytokines [7,40].

Resistin has been implicated in the pathogenesis of several inflammatory central nervous system disorders [40]. Recently studies suggested that there is an association between inflammatory agents produced by adipose tissue and risk of depression [7]. Some studies have reported a positive correlation between resistin levels in the blood and atypical, melancholic subtypes of major depressive disorders [41,42]. This association may be related to the reduction in intrasynaptic concentration of monoamines by resistin via inhibition of release of norepinephrine and dopamine in the hypothalamus [43]. It has been suggested that resistin is involved in the pathogenesis of bipolar disorder. A recent study reported increased levels of resistin in patients with bipolar disorder, the specific role of resistin in the pathogenesis of the illness is still unknown [44]. Some studies reported reduced concentration of resistin have been observed in patients with anorexia nervosa [45], autism spectrum disorders [46] and obsessive compulsive disorder [47]. In a study by Balotsev et al. [48] was found ferritin and resistin levels of drug naive first episode psychosis patients were significantly higher than the chronic schizophrenic patients. It was shown that after seven months of antipsychotic drug treatment in first episode psychosis patients the strongest decline was established for ferritin, followed by resistin. This study supports our findings on relation between resistin and psychosis.

Nonetheless, there are some limitations to this study. This is a cross-sectional study with a small sample size. There is not sufficient data about the first episode psychosis and chronic schizophrenia as a study which compares these molecules (apelin, visfatin, and resistin) have not been done. Levels of other inflammatory markers (e.g., ferritin, IL-6, TNF-α) could be examined, together with apelin, visfatin and resistin.

In conclusion, to our knowledge, this study is the first which investigates the plasma apelin, visfatin and resistin levels in patients with first episode psychosis. Based on the results of this study, apelin and resistin may be related with some central nervous system pathologies, including the severity of a psychiatric disorder. However, further large-scale studies are required to establish a conclusion.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Musa Sahpolat, Mustafa Ari, Mehmet Hanifi Kokacya. Data acquisition: Musa Sahpolat. Formal analysis: Musa Sahpolat, Mustafa Ari, Mehmet Hanifi Kokacya. Funding: Musa Sahpolat, Mustafa Ari, Mehmet Hanifi Kokacya. Supervision: Musa Sahpolat, Mustafa Ari, Mehmet Hanifi Kokacya. Writing—original draft: Musa Sahpolat. Writing—review & editing: Musa Sahpolat, Mustafa Ari, Mehmet Hanifi Kokacya.

ORCID

Musa Sahpolat https://orcid.org/0000-0002-0022-2389
Mustafa Ari https://orcid.org/0000-0002-8003-1661
Mehmet Hanifi Kokacya https://orcid.org/0000-0002-2961-7229

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