Full Length Research Article

Relationship between Interleukin 6 (Il-6) and Leptin Levels with BMI (Body Mass Index) in Schizophrenia Patients Receiving Antipsychotic Therapy

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ABSTRACT

Background: Schizophrenia is a severe mental disorder . Although antipsychotic medication is essential for symptom control, it may contribute to weight gain and other metabolic abnormalities. Changes in pro-inflammatory cytokines have also been reported in patients with schizophrenia... IL-6 and leptin are involved in inflammatory and metabolic processes in schizophrenia and may be associated with changes in Body Mass Index (BMI).

Methods: This cross-sectional study analyzed stored serum samples from 34 patients with schizophrenia who were receiving antipsychotic treatment at Prof. HB Saanin Mental Hospital, Padang. Stored serum samples were selected using convenience sampling. Eligible samples were obtained from patients aged 18– 65 years who had a confirmed diagnosis of schizophrenia and complete demographic data.

Results: Serum IL-6 was not correlated with BMI (r = −0.008, p = 0.962). Leptin showed a weak positive correlation with BMI, but the association was not statistically significant (r = 0.224, p = 0.202).

Conclusion : Serum IL-6 and leptin levels were not significantly associated with BMI in schizophrenia patients receiving antipsychotic therapy. Future research using larger, multi- center cohorts is necessary to clarify how systemic inflammation and body composition interact in this patient group.

EDITORIAL NOTE

Editorial Note on Version of Record

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INTRODUCTION

Schizophrenia is a disorder that affects stakeholders, such as patients, families, and health-care systems. The World Health Organization estimates that around 24 million people around the world live with schizophrenia, which accounts for 0.32% of the global population. Among adults, the rate is higher, with estimation at 0.45% or 1 in 222 people [1]. The situation in Indonesia possesses particular concerns, shown by the 2018 Riskesdas data with a national schizophrenia prevalence of 7.0%. Several regions show different concentrations of cases, with Bali reporting the highest prevalence at 11.1%, followed by Yogyakarta and West Nusa Tenggara (NTB) both at 10.0%. Moreover, West Sumatra is on the fourth position with a prevalence of 9.1% [2,3]. The prevalence of its capital, Padang, stands at 7.05% [3]. In 2021, the Padang City Health Office recorded 25.598 visits for mental disorders to the Prof. HB Saanin Mental Hospital in Padang.[4].

Schizophrenia is a disorder that affects multiple areas of psychological functions. Schizophrenia influences thought, perception, mood, language, cognition, self- care, and behavior. Its symptoms are commonly grouped into positive symptoms, such as delusions and hallucinations, and negative symptoms, such as reduced motivation, emotional expression, speech, and social engagement [5]. Positive symptoms represent additions to normal mental function and include disconnected speech patterns, delusions, hallucinations, various cognitive disturbances, and abnormal motor behaviors ranging from catatonic confusion to excitement. In contrast, negative symptoms showcase losses of normal function, consisting of reduced interest and motivation, spontaneous speech, emotional expression, capacity to experience pleasure, and increased social withdrawal [6]. Because schizophrenia involve persistent psychotic symptoms and substantial disability, it has been widely studied [5,7].

Physical health comorbidities are an important clinical concern in patients with schizophrenia. Multiple studies show that patients with schizophrenia tend to have higher BMI levels than healthy controls, a difference that is often more prevalent among women. Demographic variables, such as age and education level, generally fail to be tracked with this increase. Additionally, antipsychotics show similar impacts on overall BMI.

The medical treatment of schizophrenia mainly relies on antipsychotic medications, which are broadly classified into typical and atypical categories based on their receptor affinity profiles and historical development. Typical antipsychotics mainly act by blocking dopamine D2 receptors in several dopaminergic pathways in the central nervous system. in the central nervous system. In contrast, atypical antipsychotics have a broader receptor profile and block both 5-HT2A serotonin and dopamine D2 receptors.”. Blockade of 5-HT2C receptor has been implicated in appetite dysregulation, prolonged meal duration, heightened caloric intake, and visible alterations in lipid and glucose homeostasis.[7]. This mechanism causes antipsychotic-induced weight gain (AIWG), a common side-effect in patients receiving antipsychotic therapy [8].

Beyond the metabolic complications associated with pharmacotherapy, schizophrenia manifests significant immunological abnormalities. Patients frequently show evidence of low-grade peripheral inflammation, with elevated levels of several pro-inflammatory mediators.[9]. Immune-inflammatory signaling molecules possess key roles in neuronal signaling and have been increasingly implicated in the underlying pathophysiology of schizophrenia [1,2,8]. Substantial evidence from multiple investigations has confirmed elevated concentrations of the pro-inflammatory cytokine IL-6 in individuals with schizophrenia. IL-6 is a pleiotropic cytokine involved in the acute- phase response and in the regulation of immune and inflammatory processes. However, when expressed excessively, IL-6 may function as both a diagnostic indicator and severity marker in schizophrenia [9,10]. The relationship between inflammation and body weight is further complicated by the observation that overweight individuals typically exist in a state of chronic, low-grade inflammation, with concomitant elevations in plasma IL-6 concentrations, suggesting that this adipocyte-derived cytokine may influence BMI trajectories

to a larger extent [11].

Other inflammatory mediators may also be involved in schizophrenia, including leptin. This adipose- derived hormone participates in various cerebral functions including neurodevelopmental processes, neuronal survival mechanisms, behavioral modulation, and cognitive operations. Leptin modulates mesolimbic dopaminergic neuronal activity in hypothalamic circuits that may be involved in schizophrenia. High leptin levels without a corresponding reduction in food intake may indicate leptin resistance, which could contribute to continued weight gain [10]. Previous studies have reported a positive correlation between circulating leptin concentrations and BMI [12]. Increased levels of IL-6 and leptin may contribute to a persistent pro-inflammatory state that characterizes many individuals with schizophrenia [10].

The relationship between metabolic disruption, inflammation, and schizophrenia is not yet fully understood. Examining these relationships may improve understanding of metabolic and inflammatory changes in patients receiving antipsychotic treatment. The high prevalence of metabolic syndrome and cardiovascular disease in patients with schizophrenia makes it important to better understand these mechanisms. In addition, regional differences in schizophrenia prevalence in Indonesia may be related to genetic, environmental, and socio-cultural factors and need further study. The high number of hospital visits shows the need for mental health services in the area. Further research could examine whether inflammatory markers change with disease progression possible markers for early detection, and clinical trials targeting specific inflammatory pathways in schizophrenia treatment.

METHODS

Study Design: This analytical cross-sectional study was conducted at the Biomedical Laboratory of Baiturrahmah University's Faculty of Medicine between March 2021 and February 2024. The study protocol was approved by the university ethics committee.

Population and Sampling: The study population consisted of patients with schizophrenia confirmed through DSM-5 diagnostic criteria. Their serum samples were stored in the university biobank. By using convenience sampling, we selected 34 biobank serum samples from patients aged 18– 65 with a confirmed schizophrenia diagnosis and complete demographic records. Furthermore, acute inflammatory conditions, severe metabolic disorders, and current use of anti-inflammatory medications are covered in the exlucion criteria.

Laboratory Methods: Serum IL-6 and leptin levels were measured using high- sensitivity sandwich ELISA kits. The experiment involved sample preparation, generating standard dilution series (IL-6: 0.4-6.4 ng/ml; leptin: 20-320 ng/ml), 60-minute incubation at 37°C, washing with PBS buffer containing 0.05% Tween-20, TMB substrate addition, and reaction termination with sulfuric acid. We measured optical density at 450 nm using a microplate reader. All measurements were conducted twice, with standard curves generated for each assay.

Statistical Analysis: Data were analyzed using SPSS version 26. The normality was evaluated using the Shapiro–Wilk test. Because the variables were not normally distributed, associations were assessed using Spearman's rank correlation. The significance threshold was set at $p < 0.05$. Afterward, multiple linear regression was planned to determine each independent variable's contribution to predicting BMI. This was applied only if significant correlations were established during the initial bivariate analysis. The significance level was set at $p < 0.05$.

Ethical Aspects: The study adhered to norms and obtained formal ethics approval from the university committee. The retrospective nature of the research using anonymized biobank samples waived the requirement for individual informed consent.

Limitations: Main limitations included the absence of a healthy control group, a small sample size, convenience sampling, and a cross-sectional design that prevents causality interpretation. Additionally, inability to measure other inflammatory and metabolic markers adds more limitation to the study.

RESULTS

Table 1 presents the clinical characteristics of schizophrenia patients receiving antipsychotic

therapy. Most patients were aged 36– 45 years (58.8%) and predominantly male (88.2%). Obesity, comprising Grade I and Grade II categories, was present in 14 participants (41.2%). Twelve participants (35.3%) had normal BMI, and eight (23.5%) were overweight. Because this study had no untreated or healthy comparison group, these findings cannot be attributed specifically to antipsychotic treatment. Atypical antipsychotics are the most commonly prescribed medications (64.7%), meaning a preference because of their effectiveness and lower side- effect profile. These findings suggest that weight and metabolic health should be monitored regularly. Overall, these findings describe the characteristics of the patients included in this study.

Table 2 shows the correlations between IL-6 and BMI, as well as between leptin and BMI in patients diagnosed with schizophrenia. The correlation coefficient for IL-6 and BMI is r = -0.008, with a corresponding p- value of 0.962, indicating no significant correlation. Similarly, the correlation between leptin levels and BMI is moderate (r = 0.224, p = 0.202) and statistically insignificant. The correlation analysis ias based on 34 patients. Bivariate analyses showed no significant correlation between BMI and either IL-6 (p = 0.962) or leptin (p = 0.202). Because these initial associations were non-significant, planned multiple linear regression analyses were omitted.in schizophrenia patients receiving antipsychotic treatment.

Schizophrenia patients experienced elevated IL-6 levels compared to healthy controls, showing a chronic inflammatory state. IL-6 is associated with worse mental and physical well-being, with the possible influence of antipsychotic medication and illness duration in this relationship. Despite the elevated IL-6 levels, no significant correlation with BMI was observed.

Figure 2 presents a scatterplot of leptin levels versus BMI among patients with schizophrenia. The distribution shows considerable variability in leptin concentrations, with many individuals clustering at lower BMI values and a smaller subset exhibiting elevated leptin at higher BMI.

Figures

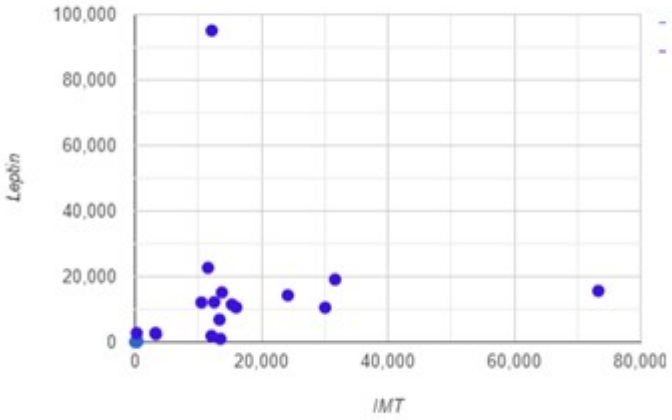


Figure 1: Schizophrenia patients experienced elevated IL-6 levels compared to healthy controls, showing a chronic inflammatory state. IL-6 is associated with worse mental and physical well-being, with the possible influence of antipsychotic medication and illness duration in this relationship. Despite the elevated IL-6 levels, no significant correlation with BMI was observed.

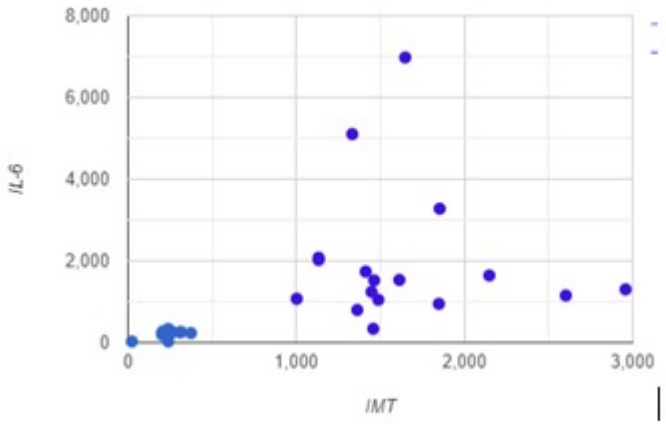


Figure 2: Scatterplot of Leptin Levels and BMI. This scatter plot shows the relationship between leptin levels and BMI in patients with schizophrenia. Each point represents an individual patient, with leptin levels on the y-axis and BMI on the x-axis. The plot shows wide variation in leptin levels, with most data points concentrated at lower BMI values and a few patients with higher leptin levels at higher BMI values.

Tables

Demographic Characteristics	Value	%
Age:		
2. 17-25 years-old	3	8.8
3. 26-35 years-old	4	11.8
4. 36-45 years-old	20	58.8
5. 46-55 years-old	7	20.6
Gender:		
Man	30	88.2
Woman	4	11.8
BMI:		
Normal grade	12	35.3
Overweight grade	8	23.5
Obesity grade I	10	29.4
Obesity grade II	4	11.8
Antipsychotics:		
Typical	1	2.9
Atypical	22	64.7
Combination	11	32.4

Table 1: Clinical Data on Schizophrenia Patients Receiving Antipsychotic Therapy, namely Age, Gender, BMI, and Antipsychotics

Variable	BMI
IL-6	r = - 0.008 p = 0.962 n = 34
Leptin	r = 0.224 p = 0.202 n = 34

Table 2: Correlation between IL-6 and BMI, and the correlation between leptin levels and BMI.

DISCUSSION

Differences between studies may be related to sample size, sample handling, cytokine assay methods, and confounding factors such as age, sex, BMI, smoking habits, chronic disease status, and antipsychotic treatment duration [1]. Regardless, the positive association between leptin, gender, and BMI observed in several studies stays consistent with previous literature [2]. The results suggest that metabolic and inflammatory factors may be related in schizophrenia.

Figure 1 illustrates that schizophrenia patients exhibit elevated IL-6 levels compared to healthy controls, showing a chronic inflammatory state commonly described in the disorder [3]. A previous study has suggested that higher IL-6 concentrations are associated with worse mental and physical well- being, although antipsychotic medication, illness duration, and symptom severity can influence IL-6 fluctuations [4]. Despite the increased IL-6 levels, no significant correlation between IL-6 and BMI was found in this study.

In the current research, IL-6 levels in schizophrenia patients did not show any significant correlation with BMI. Leptin levels also lacked significant association with BMI, further that inflammatory changes in schizophrenia may not be explained by BMI alone. The absence of correlation between IL-6 and BMI is consistent with several previous studies. For example, Arabska et al. [13] reported no relationship between IL-6 concentrations and BMI in antipsychotic-controlled schizophrenia patients ($p = 0.35$) , while Fang et al. [14] similarly found no association between IL-6 and demographic or clinical variables, including BMI ($p > 0.05$). Lee et al. [15] also noted that IL-6 levels were only slightly reduced after adjustment for BMI, suggesting that systemic inflammation in schizophrenia is not driven solely by changes in body mass [7].

IL-6 is a pro- inflammatory cytokine that plays an important role in immune regulation. [8]. Interestingly, IL-6 expression in the central nervous system has been reported to negatively correlate with adipose tissue enlargement during obesity, suggesting that CNS- specific IL-6 dynamics differ from peripheral inflammatory signaling [9]. Changes in fat mass and body weight happen regarless of food intake and it indicates a role for IL-6 in energy metabolism [10]. Higher IL-6 circulation may partly reflect its role as an adipokine and its involvement in lipid metabolism, insulin sensitivity, and vascular regulation [11]. Uncontrollable weight gain triggers systemic oxidative stress, and eventually disrupts adipokine production. That includes IL-6 and causes metabolic syndrome [12]. These mechanisms could be relevant to schizophrenia, in which metabolic abnormalities are related to the illness, lifestyle, and antipsychotic treatment.

Antipsychotic therapy is known to influence inflammatory and metabolic pathways. Numerous studies reveal that antipsychotic exposure leads to obesity and weight gain, which may elevate IL-6 levels [13]. Changes in cytokine levels after starting antipsychotic treatment reflect both drug-related metabolic effects and inflammation associated with schizophrenia [14]. Higher IL-6 has also been associated with cognitive deficits in schizophrenia. Studies of CSF IL-6 suggest that it tends to be involved in neuroinflammatory processes related to disease progression, including acute psychotic episodes, chronic deterioration, and potential autoimmune mechanisms [15].

Evidence suggests that starting antipsychotic therapy reduces inflammation, supporting the idea that untreated schizophrenia contributes to neuroinflammation and neurodegeneration [16]. In certain studies, initial IL-6 measurements declined after three months of therapy regardless of antipsychotic class, although the reduction was not significantly different between typical and atypical agents [17]. Meanwhile, other studies found no significant differences in serum IL-6 between antipsychotic-treated patients and healthy controls [18]. Indeed, a reduction in IL-6 was observed after treatment among first- episode psychosis patients and those with recurrent episodes. Hence, it suggests that improvements in IL-6 may be related to later weight gain and metabolic disorders[19].

Antipsychotics modulate immune function in complex and agent-specific ways. Clozapine has been shown to temporarily raise IL-6 levels during the initial two weeks of treatment, but this effect tends to diminish over time [20]. Other studies report no significant IL-6 changes with risperidone or haloperidol intake [21]. Stopping haloperidol medication in patients experiencing schizophrenia exacerbation has been associated with decreased plasma IL-6 levels. It possibly reflects acute inflammatory resolution [22].

Animal studies additionally showed that olanzapine induces low- grade inflammation characterized by IL-6 elevation in the hypothalamus and both white and brown adipose tissues [23]. This inflammatory response is accompanied by increases in adipocyte size and enhanced macrophage infiltration. Although schizophrenia is frequently linked to elevated IL-6 levels, our findings are consistent with previous research since these increases do not depend on BMI. Factors, such as illness duration, medication history, smoking status, and underlying clinical comorbidities, likely play a larger role in driving IL-6 variation.

Although previous studies have reported a positive association between leptin and BMI, the present study did not identify a statistically significant association. Differences in sample size, sex distribution, antipsychotic exposure, disease duration, and metabolic status may account for the inconsistent findings. Differences in leptin's physiological roles may explain the findings. Centrally, leptin functions as a metabolic hormone that suppresses appetite and increases energy expenditure [25]. In peripheral tissues, leptin also affects keratinocyte and fibroblast proliferation, showing that leptin also has functions outside energy regulation [26]. Within the brain, leptin directly modulates NMDA receptor activity, allowing learning, memory, and synaptic signaling in cortical and cerebellar circuitry [27]. Additionally, Leptin may affect dopaminergic mesolimbic pathways in the ventral tegmental area (VTA), which have been linked to schizophrenia [28].

Leptin crosses the blood– brain barrier and signals central neural circuits about peripheral energy stores [29]. Through its interaction with serotonin (5-HT) signaling and neuropeptide Y (NPY), leptin plays a key role in appetite regulation [30]. Serotonin modulates NPY activity: 5HT2C receptor agonism suppresses appetite, while antagonism promotes increased food intake [31]. NPY stimulates orexin release, which enhances appetite. Meanwhile, leptin generally suppresses this pathway. The interaction between leptin and 5HT2C receptors may link metabolic regulation with neurotransmitter changes in schizophrenia [32].

According to previous research, leptin levels remain elevated in schizophrenia compared to healthy controls, even after adjustment for gender, age, and BMI [33]. Elevated leptin concentrations appear not only in patients receiving atypical antipsychotics but also in drug-free or drug-naïve individuals, suggesting disease-related dysregulation. Higher leptin levels have also been associated with less severe positive symptoms, showing potential compensatory neurobiological roles [34].

In the present study, leptin did not correlate significantly with BMI. This may mean that BMI alone does not explain the metabolic changes observed in schizophrenia.. However, the small sample size and cross-sectional design make this finding difficult to interpret.. Differences in disease chronicity, inflammation, insulin resistance, neurohormonal activation, antipsychotic type, treatment duration, and illness course may explain differences across studies. Potvin et al. informed that leptin concentrations were higher among schizophrenic patients not receiving antipsychotics. Furthermore, leptin dysregulation appeared in early illness stages or after long-term treatment [27].

During prolonged antipsychotic therapy, leptin levels usually correlate with weight gain. It reflects feedback signaling from adipose tissue. High leptin levels may cause its resistance. As a consequence, it reduces leptin's regulatory efficacy and worsens obesity risk [35]. Specific antipsychotics—including olanzapine, clozapine, and quetiapine—produce strong effects due to high affinity for muscarinic M3 and histamine H1 receptors. They caused enhanced appetite and weight gain [36].

Sentissi and colleagues [31] observed that leptin levels often increase within hours after starting atypical antipsychotics, continue to do between weeks 6 and 10, and then stagnate over months. Fasting or malnutrition reduces leptin levels, although caloric intake can rapidly restore them. Neelamekam [10] found no significant correlation between IL-6 and leptin in schizophrenia ($\beta = 0.012$; $p = 0.949$). Previous studies show that IL-6 and leptin levels are lower in healthy individuals than in schizophrenia patients. It suggests that, when inflammatory stimuli are absent, baseline leptin and IL-6 stay relatively low and are only weakly associated [10].

In this sample of patients with schizophrenia receiving antipsychotic treatment, neither serum IL-6 nor leptin was significantly associated with BMI. The findings are limited by the small sample size, convenience sampling, lack of a control group, and cross-sectional design.Mental Hospital HB Saanin Padang. These results suggest that metabolic and inflammatory changes may not be explained by BMI alone.

Future studies should use a more rigorous methodology. First, future studies should include more participants to obtain more reliable and generalizable results. Further studies should examine the relationship between IL-6 and leptin. Future studies could collect fasting blood samples under standardized conditions and record the sampling time, as leptin levels vary with

circadian rhythm, nutritional status, and sleep. Because leptin secretion varies throughout the day and is influenced by sleep and nutritional status, nighttime sampling may provide a more consistent measure of leptin levels. Finally, future studies could also examine appetite dysfunction in major depressive disorder. Further research on appetite changes in depression may help clarify how metabolic processes are related to neuropsychiatric symptoms including psychotic features, across a range of severe mental illnesses, which help explain the relationship between metabolic processes and neuropsychiatric symptoms.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Dita Hasni: Designed the study, conducted data analysis, and wrote the initial draft of the manuscript. Audina Maharani and Eko Perdana Putra: Contributed to the study design and data collection and provided critical revision of the intellectual content. Ade Yuli Amellia: Assisted in data collection and performed statistical analyses. Eko Perdana Putra: Participated during data interpretation and reviewed the manuscript for intellectual content. Gangga Mahatma: Supervised and managed all stages of the research, contributed to data analysis, and approved the final version of the manuscript. All authors have read and approved the final manuscript.

Statement on Use of AI

During the preparation of this manuscript, generative artificial intelligence (AI) tools were used to assist with language refinement and improvement of English grammar, clarity, and readability. As reflected in the Turnitin AI detection report, the detected AI use is predominantly concentrated in the sections preceding the data analysis. We hope this may be understood in the context of language refinement rather than the fabrication or generation of authentic research data. The authors have reviewed and revised the AI- assisted text and take full responsibility for the content, accuracy, integrity, and authenticity of the manuscript, including all data presented and the conclusions drawn. No AI tool was used to fabricate or manipulate the research data.

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