Research Article

Profile of Leptin Levels in Schizophrenic patients Receiving Antipsychotic Therapy in Prof. Dr. HB Saanin Hospital Padang

Profil Kadar Leptin pada Pasien Skizofrenia yang Mendapat Terapi Antipsikotik di RSJ Prof. Dr. HB Saanin Padang

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ABSTRACT

Weight-gain is one of the antipsychotic side effects, and it can increase the risk factor of metabolic syndrome. Several studies relate it to increase leptin levels. This research was conducted to determine the profile of leptin levels in schizophrenic patients who were receiving antipsychotic therapy at Prof. DR. HB Saanin Mental Hospital. The research was conducted from November 2019 to January 2020 on schizophrenic patients who were taking antipsychotic drugs. This research was conducted on 50 samples by using consecutive sampling techniques. Data analysis using univariate are presented in geometric mean and CI 95%. Moreover, a Comparison of leptin levels between groups was performed by T-test and one-way ANOVA. The average leptin level from 50 samples of schizophrenic patients was 5.12µg/ml (CI 95%=3.32-7.90). The highest average leptin level is from the 46-55 year age group which is 11.32µg/ml (CI 95% =5.24 - 24.42), female is 13.29µg/ml (CI 95%=5.84-30.26), BMI ≥30kg/m^2 is 12.84µg/ml (CI 95%=4.31-38.23), subjects with above-average waist circumference is 5.54µg/ml (CI 95%=3.45-8.90), and the atypical group of drugs is 6.08µg/ml (IK 95%=3.41-10.84). Increasing levels of leptin occur in schizophrenic patients who were 46-55 y.o, female BMI ≥30kg/m^2, above-average waist circumference, and receiving atypical antipsychotics.

Keywords: Antipsychotic drugs, leptin, schizophrenia, weight-gain

ABSTRAK

Peningkatan Berat Badan merupakan salah satu keluhan yang sering muncul pada pemberian antipsikotik, dan dapat meningkatkan risiko terjadi nya Sindroma Metabolik. Beberapa literartur mengaitkan hal ini dengan peningkatan kadar leptin. Penelitian dilakukan untuk mengetahui profil kadar leptin pada pasien skizofrenia yang mendapat terapi antipsikotik di RSJ Prof. DR. HB Saanin. Penelitian ini dimulai dari November 2019 sampai Januari 2020 dan dilakukan pada pasien skizofrenia, yang mengkonsumsi obat antipsikotik. Penelitian ini dilakukan terhadap 50 sampel dengan teknik *consecutive sampling.* analisa data dengan univariat disajikan dalam bentuk rerata geometrik dan IK 95%. dan data perbandingan kadar leptin antar kelompok dilakukan uji T dan ANOVA. Rerata kadar leptin dari 50 sampel pasien skizofrenia yaitu 5.12µg/ml (IK 95%=3.32-7.90). Rerata kadar leptin tertinggi ditemukan pada kelompok usia 46-55 tahun yaitu 11.32µg/ml (IK 95% =5.24-24.42), subjek perempuan yaitu 13.29µg/ml (5.84-30.26), kelompok pasien dengan Indeks Massa Tubuh ≥30kg/m^2 yaitu 12.84µg/ml (IK 95%=4.31-38.23), pasien dengan lingkar pinggang diatas normal yaitu 5.54µg/ml (IK 95%=3.45-8.90), dan pada kelompok obat atipikal yaitu 6.08µg/ml (IK 95%=3.41-10.84). Dapat disimpulkan Terjadi peningkatan kadar leptin pada pasien skizofrenia yang berusia 46-55 tahun, perempuan, IMT ≥30kg/m^2, dengan lingkar pinggang diatas normal dan mendapat terapi antipsikotik atipikal.

Kata Kunci: Leptin, obat antipsikotik, peningkatan berat badan, skizofrenia

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INTRODUCTION

Schizophrenia is a mental disorder with various symptoms, including impaired context thinking, thought form, affect, perception, sense of self, motivation, behavior, and interpersonal functions. Schizophrenia has a prevalence of 1% of the world's population (of average 0.85%). The incidence rate of Schizophrenia is 1 per 10,000 people per year (1). The prevalence of Schizophrenia, according to data from the Health Department of the Republic of Indonesian in 2013, was 1.7 per mile or 400,000 people, and the figure increased to 7 per mile in 2018 (2).

Antipsychotic drugs are pharmacological therapies indicated for Schizophrenia and another mental disorder. In general, antipsychotic drugs are categorized into two, namely the first-generation antipsychotic drugs (APG I) or typical antipsychotics and the second-generation of antipsychotic drugs (APG II) or atypical antipsychotics (3). Typical antipsychotic drugs such as haloperidol inhibitory the dopamine receptors, especially D2 and D3. Atypical antipsychotics exhibit an action on other receptors in addition to dopamine D2, including dopamine receptors D1, D4, serotonin receptors (5HT1a, 5-HT1d, 5-HT2c, 5-HT6, 5HT7), M3 muscarinic receptors, histamine H1 receptors and adrenergic receptors (alpha 1 and Alpha 2). Additionally, atypical antipsychotics such as clozapine is known to work as an antagonistic effect of NMDA receptor hypofunctions at the center of conduct (4,5).

Typical antipsychotics are effective in addressing the positive symptoms of Schizophrenia but are less effective in addressing negative symptoms as well as causing extrapyramidal symptoms (EPS) side effects. Atypical antipsychotics have lower EPS side effects than typical antipsychotics and can improve cognitive function, but have side effects of a metabolic disorder condition called metabolic syndrome. Metabolic disorders include obesity, hyperlipidemia, diabetes, and weight gain (6,7).

Extrapyramidal symptoms (EPS) side effects, such as dyskinesia, and neuroleptic malignant syndrome occur due to inhibitory dopamine D2 receptors in the dorsal striatum. Metabolic side effects are also related to the antagonism of D2 receptors in the tuberoinfundibular and increase serum prolactin. Prolactin has the effect of stimulating the proliferation of beta cells and glucose-stimulated insulin secretion (GSIS) (4,8).

Weight gain is another side effect that is often complained of after antipsychotic treatment. In the study conducted by Althof Sona reports that 56.7% of his research subjects complained of weight gain after consuming antipsychotics more than three months in HB. Saanin Mental Hospital. His other research conducted by Saraswati at Mental Hospital, Province Bali, reported 70.4% of his research subjects suffered from post-psychotic obesity treatment in more than three months (8,9). Antipsychotic-induced weight gain or also called antipsychotic-induced weight gain (AIWG). It can affect the risk of adult-onset diabetes mellitus and cardiovascular disease, poor compliance level, quality of life, and psychiatric readmission (8,9).

Several studies reported the causes of AIWG is increased calorie intake due to inhibition of histamine H1 receptors by antipsychotic drugs. This H1 receptor blockade effect will activate AMP-activated Protein Kinase (AMPK), which serves as a food regulator. The research conducted by Lian in 2015 reported the administration of risperidone in rats could increase food intake and reduce locomotor activity (5). In addition to the effect of sedation due to antipsychotic administration will also reduce the physical activity of schizophrenia patients and increase the risk of weight gain.

The amount of body fat has a positive correlation with leptin circulating levels. Leptin is a cytokine hormone produced and secreted from adipose tissue. It is responsible for the regulation of body weight that functions in managing hunger and satiety. The increased leptin level and its relationship with the body mass index (BMI) showed that leptin acts as a negative feedback signal in case of increased fat. Leptin level that is too high will cause leptin resistance in which leptin cannot function well and result in a chaotic signal system, which means the signals for hunger and satiety settings do not work. The chaos of this system leads to impaired food intake control, which can subsequently result in weight gain and obesity (10,11).

The meta-analysis performed by Ragguett reports that leptin plays an important role in antipsychotic-induced weight gain through hyperlipidemia in schizrenia patients (8). A similar report from Monteleone, *et al.* prospectively measured the leptin levels in 22 chronic resistant schizophrenic patients given monotherapy of clozapine. The researchers found that the leptin levels doubled after two weeks of clozapine administration. Significant differences were observed between men and women in the initial average value in leptin plasma (5.0±3.4 vs. 14.7±7.7µg/ml). Hosojima et al. conducted a study on 13 schizophrenic patients receiving monotherapy of Olanzapine for four weeks (3.2±2.7 vs. 4.6±4.1µg/ml). However, the research results conducted by Kivircik et al. reported that 19 patients with Schizophrenia who received clozapine therapy for ten weeks did not reveal significant changes in leptin (11.87±9.70 vs. 13.11±10.08µg/ml), but expressed significant changes in weight change that was 5% increase (12). The research of Monteleone, *et al.* and Kivircik, *et al.* showed inconsistent results on the change of leptin levels in schizophrenic patients with antipsychotic therapy; therefore, Researchers interested in confirming previous research results in our population. To know the profile of leptin levels in schizophrenia patients in HB. Saanin Mental Hospital and used as a marker to be more vigilant with the risk of metabolic syndrome due to the use of antipsychotics.

METHODS

Ethical Approval

The study was obtained Description of Ethical Approval from the Health Research Ethics Committee, Prof. HB. Saanin Mental Hospital, Padang. The principal investigator achieved informed consent from all of the participants.

Participants and Study Procedures

The study was conducted at Prof. Dr. HB Saanin Mental Hospital Padang from 28 November 2019 until 22 January 2020. This cross-sectional study was involved in participants voluntarily. Inclusion criteria were age >18 years, a diagnosis of Schizophrenia (F20), and current treatment with antipsychotics for at least three months. History of diabetes, hypertension, and cardiovascular disease before receiving the therapy were exclusion criteria. Patients (n=50) were recruited by a consecutive sampling method and signed the informed consent.

Instruments and Leptin Analysis

investigators filled in the characteristic of participant's data form detailing age, sex, diagnosis, drugs, height, weight, BMI, waist circumference. Calculation of BMI was using the formula : BMI = weight(kg)/(height)^2 (m^2). The BMI value classified into three groups were the first group for less than 25.0kg/m^2, the second group for between 25.0 and 29.9 kg/m^2 and the third group for similar and more than ≥30kg/m^2.

Measurement of waist circumference was carried out at the level of midway the distance between the lower border of the 12th rib and spine ischiatic major. The measurement value classified into two groups was the first for <90cm for men and <80cm for women and the second group for >90cm for men and >80cm for women.

The blood sampling was taken from the peripheral vein as much as 3ml and inserted into Vacutainer gel separator tubes. The blood samples obtained were centrifuged for 10 minutes at 3000 rpm. After the serum and the plasma were separated, samples were inserted in labeled tubes and stored at -20°C. Analysis of leptin levels was performed after the total number of samples were accumulated. Leptin analysis was performed in the Biomedical Sciences Laboratory of Faculty of Medicine UNBRAH using ELISA.

Statistical Analyses

The Shapiro-Wilk test was used to asses the normality of data distribution of leptin levels. Abnormal data were to be transformed into logarithmic data. Then test normality was returned and normally distributed. The data was presented in geometric mean and CI 95%. Age, gender, BMI, waist, and drug data were presented in categoric data, i.e., frequency and percentage. The One-Way ANOVA was conducted to comparing between groups, and Post Hoc Benferoni was applied to identify the group that poses a difference in leptin levels of age data, BMI, and medications. The T-Test test was applied to assess the ratio of leptin based on gender and waist circumference.

RESULTS

Characteristics of the Schizophrenic Patients Receiving Antipsychotic Therapy

Fifty schizophrenic patients fulfilled the inclusion and exclusion criteria and involved the study. The final sample comprise of 34 male and 16 female. The most commonly found patients were in the early adulthood of 26-35 years as many as 14 people (28%).

Table 1 shows that from 50 samples of schizophrenic patients receiving antipsychotic therapy, as many as 38 people (76%) were obese covering 27 people (54%) in 25.0 -29.9 kg/m^2 and 11 people (22%) in ≥30 kg/m^2, more than half of the participants had waist circumference above the normal average as many as 43 people (86%). The most widely used type of drug is atypical that was given to 32 people (64%).

Table 1. Characteristics of 50 schizophrenic patients who received antipsychotic therapy

Characteristics	n (%)
Usia	
18 – 25 yo	7 (14.0)
26 -35 yo	14 (28.0)
36 – 45 yo	11 (22.0)

Table 1. Characteristics of 50 schizophrenic patients who received antipsychotic therapy (Cont.)

Characteristics	n (%)
Usia	
46 – 55 yo	13 (26.0)
> 56 yo	5 (10.0)
Gender	
Male	34 (68.0)
Female	16 (32.0)
Indeks Massa Tubuh	
< 25.0 kg/m^2	12 (24.0)
25.0 -29.9 kg/m^2	27 (54.0)
≥30 kg/m^2	11 (22.0)
Waist Circumference	
Male <90cm or female <80cm	7 (14.0)
Male ≥ 90cm or female ≥ 80cm	43 (86.0)
Antipsychotics	
Typical	4 (8.0)
Atypical	32 (64.0)
Combination	14 (28.0)

Data of the Leptin Levels of Schizophrenic Patients Receiving Antipsychotic Therapy

Result show that 50 therapy showed a leptin level of 5.12μg/ml (CI 95% =3.32 -7.90). The data can be interpreted that the average leptin level on the entire participants is 5.12μg/ml and suggest to have an average rate of leptin in the population of all schizophrenic patients who get antipsychotics in RS HB. Padang Saanin between the range of grades 3.32 and 7.90μg/ml.

In table 3, there is a comparison of leptin levels in age, gender, BMI, waist circumference, and medications used. the highest mean of leptin level is found in the age group of 46-55 years that is 11.32μg/ml (CI 95%=5.24-24.42); women group that is 13.29μg/ml (CI 95%=5.84-30.26), a group that has ≥30kg/m2, which is 12.84μg/ml (CI 95%=4.31-38.23). A group with waist circumference for Male ≥90cm or female ≥80cm is 5.54μg/ml (CI 95%=3.45-8.90) and in group given Atypical drug is 6.08μg/ml (CI 95%=3.41-10.84). After the Comparison of leptin levels between groups, the only gender has a statistically significant difference.

Table 2. Comparison of Leptin levels o based on characteristics of schizophrenic patients received antipsychotic therapy

Characteristics	Mean^a (CI 95%)	Nilai p
Age		
18 – 25 yo	2.35 (0.72-7.64)	0.141^b
26 -35 yo	4.58 (1.60-13.13)	
36 – 45 yo	5.46 (2.08-14.36)	
46 – 55 yo	11.32 (5.24-24.42)	
> 56 yo	2.28 (0.55-9.37)	
Gender		
Male	3.27 (2.07-5.17)	0.002^c
Female	13.29 (5.84-30.26)	
Body Mass Index		
<25.0kg/m^2	3.73 (1.88-7.40)	0.074^b
25.0 -29.9 kg/m^2	4.05 (2.19-7.49)	
≥30kg/m^2	12.84 (4.31-38.23)	

Table 2. Comparison of Leptin levels o based on characteristics of schizophrenic patients received antipsychotic therapy (Cont.)

Characteristics	Mean[a] (CI 95%)	Nilai p
Waist Circumference		
Male <90cm or female <80cm	3.14 (0.82 -11.96)	0.365[c]
Male ≥90cm or female ≥80cm	5.54 (3.45-8.90)	
Antipsychotics		
Typical	4.12 (1.65-10.27)	0.575[b]
Atypical	6.08 (3.41-10.84)	
Combination	3.68 (1.52-8.92)	

Note:
[a] Geometric Mean
[b] Tested by One-way ANOVA
[c] Tested by Unpaired T-test

DISCUSSION

Characteristics of Schizophrenic Patients Receiving Antipsychotic Therapy in the Form of BMI, Waist Circumference

From 50 samples of schizophrenic patients receiving antipsychotic therapy, as much as 38 people (76%) were overweight and obesity, covering 27 people (54%) in BMI 25.0-29.9kg/m2 and 11 people (22%) in BMI ≥30kg/m2 category. The results of this research are in line with the previous research conducted by Ayu in 2019 that identified the prevalence of obesity in Schizophrenia as much as 87.7%. Arya also found Schizophrenia in obesity category as much as 87.3% (13,14).

Obesity that occurred can be caused by the side effects of the atypical antipsychotic drugs. Increased weight in atypical antipsychotics is found to be higher than in typical antipsychotics. The effect of increases in weight varies among atypical antipsychotics. Clozapine and Olanzapine have the most significant weight gain effect in long-term or short-term use. Risperidone has a moderate effect on weight loss. Quetiapine gives a minimum to moderate effect depending on the length of therapy, and Ziprasidone has the lowest weight gain effect (15).

Atypical antipsychotics such as Risperidone and Clozapine, able to bind serotonin and histamine is known to be associated with atypical antipsychotic mechanisms in causing an increase in body weight. Serotonin has been known as the primary neurotransmitter involved in dietary intake regulation, 5HT2C, 5HT3, and 5HT1A, which are the receptors that have the most significant possibility in its involvement in inducing weight enhancement based on their physiological characteristics. 5HT1A and 5HT2C receptor agonists have the opposite effect of food intake. 5HT1A receptor agonists increase food intake, but 5HT2C receptor agonists decrease it (3,16).

The previous study found that serotonin has a role in controlling Y neuropeptide (NPY), which is a neuropeptide that stimulates appetite by stimulating the release of Orexins. Antagonistic drugs 5HT2C can increase NPY levels and increase food intake because 5HT2C receptor agonist causes a decrease in food intake through the reduction of NPY levels in paraventricular nuclei in the hypothalamus where the area has a high number of serotonin receptors. NPY stimulates the release of Orexins (appetite) in the lateral hypothalamus region, and Orexins are potent stimulators of food intake. Besides, there is evidence that there is an interaction between 5HT2C and leptin, which is a hormone circulating and released by Adipocyte as a response to increasing fat deposits (17,18).

On the schizophrenic patient samples receiving antipsychotic therapy, most male patients had a waist circumference of ≤40 inches (102 cm) as many as 28 people (56%), and most women had >35 inches (89 cm) as many as 14 (28%). The results of this research were in line with the study conducted by Maisyarah in 2014 that identified male patients with Schizophrenia mostly had a normal waist size (78%), while the male patients mostly had above average size waist circumference (52%) (19).

The cause of the increased waist circumference can be various, including lifestyle, improper diet, sedentary lifestyle, and excessive consumption of food higher from the energy needed. Excess fatty tissues will generally be stored in adipose tissue under the skin in the abdominal cavity. Any amount of fat and carbohydrate food that is not directly used will be stored in adipose tissue in the form of triglycerides. The accumulation of body fat happens especially in the waist or abdominal area so that the fat distribution is central (13,20).

Comparison of Leptin Levels in Schizophrenic Patients Receiving Antipsychotic Therapy

From the schizophrenic patient receiving antipsychotic therapy, the average leptin level was 5.12μg/ml (CI 95%=3.32-7.90) with the highest mean level in the age group of 46-55 years of (11.32μg/ml) and females (13.29μg/ml). The highest leptin level is found in the ≥30kg/m2 group (12,84μg/ml), in Male with waist circumference ≥90cm or female ≥80cm (5.54μg/ml). The highest level of leptin was found in the group using atypical drugs (6.08μg/ml). But in statistical tests, only gender groups have significantly different levels of leptin. It can be interpreted that there are not statistically different levels of leptin in various age groups, BMI, waist circumference, and antipsychotic drug Administration, either typical or atypical.

Previous research conducted by Wang, *et al.* in 2017 found a mean leptin level of 73,32±5.28μg/ml. Elderly people have a risk of obesity and the incidence of metabolic syndrome that is related to food consumption patterns and physical activity. The elderly have a low level of physical activity resulting in an imbalance between food intake and calorie burning, which can subsequently cause obesity. Leptin is an important factor in explaining the incidence of obesity and metabolic syndrome (21).

Suruchi, *et al.* in 2015 who examined leptin levels in 355 males and 375 women found the mean leptin level in men is 7.92±1.13μg/ml and mean leptin level in women is 22.7±2.9μg/ml (22). Leptin levels can be influenced by sex hormones, namely the hormone estrogen and progesterone in women and the hormone testosterone in men. Female sex hormones, namely estrogen, and progesterone, have a positive correlation with leptin levels, and it is known that sex hormones in women have a role in the induction of the leptin hormone. While the male sex hormone testosterone has a negative correlation with the leptin hormone (23).

The results of this research are in line with previous research conducted by Komang, *et al.* in 2016 on 52 obese samples that found an average leptin level of

50.53±23.57ng/mL in female groups and 22.65±8.33ng/mL in male groups (20). Leptin is a 16-kDa protein, which is encoded by the obese gene and binds to the status of nutrients with neuroendocrine function and immune function. Leptin serves as a satiety factor and causes obesity and insulin resistance. Decreasing leptin levels are found during hunger and malnutrition, but it is reversible by supplementing calorie. Leptin also plays a vital role in the central nervous system and peripheral nervous system. Leptin receptors are identified in the non-hypothalamic neurons in the hippocampal and cortical. Leptin is postulated to be involved in the development and maintenance of the brain and contributes to cognitive function and behavior. In the brains of adults, leptin synapses directly into the N-methyl-D-aspartate (NMDA) receptors and is responsible for learning, and the memory also regulates various signaling pathways and synaptic activity in the cortex and cerebellum. Furthermore, leptin also modulates the activities of the dopaminergic mesolimbic neurons in the ventral tegmental area (VTA) that implicates in Schizophrenia (23,24).

Leptin has a vital role in energy homeostasis, both central and peripheral. Leptin works centrally as a metabolic hormone through negative feedback mechanisms to suppress appetite and improve calorie burning through increased body activity. Leptin peripheral work can trigger the proliferation and differentiation of keratinocytes and fibroblast cells. Leptin is excreted into the circulation system by adipose tissue. Leptin can pass the blood-brain barrier and cerebrospinal fluid. Once secreted by adipose tissue, leptin will signal to the brain and provide information related to the energy supply status in the body. This information can lead to decreased appetite and increased energy expenditure from free fats (11,25).

The results of this research are in line with previous research conducted by Wang, *et al.* in 2017 that 30 women with metabolic syndrome with an average waist circumference of 98,07±9,98 had an average leptin level of 18.57μg/ml (21). The high ratio of waist circumference is a sign of central obesity, as it has been known that the body fat accumulation and obesity influence leptin levels. Adipose tissue on body fat will give a signal to the hypothalamus to secrete leptin hormone as a feedback signal of the occurrence of fat accumulation. The more the body fat deposits, the more the hormones leptin produced, so the leptin level in people with central obesity also increases (26).

Findings of this study are in line with previous research conducted by Monteleone et al. measure the leptin level after monotherapy clozapine, which is 14.7±7.7μg/ml(12). The overall leptin level during long-term antipsychotic treatment is strongly correlated with the incidence of obesity, which is characterized by changes in body weight and body mass index (BMI). Increased weight induced by antipsychotics is responsible for the elevated serum leptin level. Cross-sectional studies on patients on various medications generally find that people exposed to Olanzapine and clozapine have higher body weight and higher leptin serum levels (11,23). Increased levels of leptin on the administration of antipsychotics such as Olanzapine, clozapine, and Quatipine due to the high affinity of the drug against Muscarinic M3 and Histamin H1 receptors that contribute to increased food intake and weight gain. In typical antipsychotics such as haloperidol and chlorpromazine can increase levels of leptin through inhibition of D2 receptors in the tuberoinfundibular, thereby causing metabolic and weight-gain effects (4). According to research conducted Sentissi, increased levels of leptin compared with baseline occurred several hours after administration of the first treatment of atypical antipsychotic drugs, and increased between week 6 and 10, and remained stable up to several months (27).

Leptin is considered to play various functions in humans, such as lowering appetite by stimulating and maintaining energy expenditure and acts as a metabolic hormone in various processes by binding to receptors in the brain. Leptin serves mainly as an anti-obesity hormone. The concentration of leptin in healthy individuals is positively correlated with body fat levels but is negatively correlated when energy intake is reduced and energy deposits in fat decrease (12).

Limitations of the current work include small sample sizes for the study and absence of controls that do not consume antipsychotics as compared to antipsychotic agents associated with elevated leptin levels. However, This research concludes that there are increased levels of leptin in schizophrenic patients who were 46-55 y.o, female BMI ≥30kg/m^2, above-average waist circumference, and receiving atypical antipsychotics

ACKNOWLEDGMENT

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