Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 Aug 03; 9(B):600-607.
https://doi.org/10.3889/oamjms.2021.6378
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Psychiatry*

Levels of Interleukin 6 as a Predictor of Metabolic Syndrome in Schizophrenic Patients Receiving Combination Therapy of Typical and Atypical Antipsychotics

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Edited by: Mirko Spiroski
Citation: Saidah S, Sonny LT, Lilik H, Burhanuddin B, Haerani R, Wempy T. Levels of Interleukin 6 as a Predictor of Metabolic Syndrome in Schizophrenic Patients Receiving Combination Therapy of Typical and Atypical Antipsychotics. Open Access Maced J Med Sci. 2021 Aug 03; 9(B):600-607. https://doi.org/10.3889/oamjms.2021.6378
Keywords: Schizophrenia; Metabolic syndrome; Typical and atypical antipsychotics; IL-6
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Received: 29-Jan-2021
Revised: 14-Jun-2021
Accepted: 23-Jul-2021

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Schizophrenia is a severe psychiatric disorder that causes disability and is often accompanied by physical illness. Based on the American Heart Association criteria, metabolic syndrome is common in schizophrenic patients, with a prevalence of 43% in Clinical Antipsychotic Trials of Intervention Effectiveness. The metabolic syndrome in patients with schizophrenia results from the side effects of antipsychotics. The metabolic syndrome will also show high levels of IL-6. This situation can have biological implications, which can then affect the health of schizophrenic patients.

AIM: This study aims to determine serum IL-6 levels as a predictor of metabolic syndrome in patients with metabolic syndrome due to side effects of using antipsychotic therapy.

METHODS: This prospective cohort study was not randomized, with the number of subjects was 28 schizophrenic patients who were evenly divided into two groups, namely, the group receiving atypical and typical combination therapy. Therapy was given to both groups for 3 months, and measurements and checks of bodyweight, abdominal circumference, blood pressure, BMI, TG, GDP, and Il-6 levels were carried out at baseline and 3rd month. Comparative and correlation tests were carried out between groups.

RESULTS: Some schizophrenic patients were categorized as metabolic syndrome and not a metabolic syndrome in both therapy groups ($p < 0.020$). However, atypical antipsychotic drug combinations are more likely to experience the metabolic syndrome. There was a change in the mean Il-6 levels at baseline and the 3rd month in both groups ($p < 0.0001$). There was a more excellent mean value of IL-6 levels at 3rd month with metabolic syndrome than those without metabolic syndrome. There was a greater mean value of IL-6 levels at third month with metabolic syndrome compared with those without metabolic syndrome in the haloperidol and chlorpromazine groups ($p <0.005$), the risperidone and clozapine groups ($p <0.002$).

CONCLUSION: Metabolic syndrome is more common in schizophrenic patients receiving atypical than typical combination therapy. The body's response to the metabolic syndrome results in an increase in IL-6 levels due to an inflammatory process in visceral fat which accumulates due to weight gain due to the administration of antipsychotics. In schizophrenic patients with metabolic syndrome, IL-6 levels are higher than those without metabolic syndrome, so that IL-6 levels can be used as a predictor of metabolic syndrome in schizophrenic patients receiving antipsychotic therapy.

Introduction

Schizophrenia is the most common psychotic disorder, where symptoms usually appear in late adolescence or young adulthood. Onset in males is usually between 15 and 25 years and in females between 23 and 35 years. The lifetime prevalence of schizophrenia is between 0.3% and 0.7%, although there are variations between races, countries, and geographic conditions. Schizophrenia is a chronic disease, where a small part of the patient's life is in an acute condition, and most of the sufferers are longer (years) in the residual phase. During the residual phase, the patient is more withdrawn or isolated. The course of schizophrenia can be classified as continuous, episodic, with or without residual symptoms between episodes, or single episodes with partial or complete remission [1], [2].

Immune system involvement, namely, infection and/or autoimmune theory, neuroinflammation, neurotoxicity, neuronal degeneration, or decreased neurogenesis. It is schizophrenic neuropathology closely related to microglial activation, indicated by the inhibitory effect of typical and atypical antipsychotics against the release of inflammatory cytokines and free radicals. The immunological basis strong indicators of schizophrenia etiopathology can be seen from signs of inflammation and activation of microglia in postmortem brain tissue, blood-brain barrier dysfunction, increased retroviral activity, etc. [3].

Schizophrenia also causes long-term disability in more than 50% of sufferers. Mortality in schizophrenic patients is 2–3 times greater than in the general population [4]. Based on the American Heart Association criteria, metabolic syndrome is common in schizophrenic patients, with a prevalence of 43% in Clinical Antipsychotic Trials of Intervention

Effectiveness [5]. Thus, many schizophrenic patients have an increased risk of mortality associated with metabolic syndrome.

The study showed an increase in total cholesterol, triglyceride, LDL, and VLDL levels and a significant decrease in HDL levels in the group using antipsychotics compared to the control [6]. Studies with MRI examinations prove an increase in subcutaneous fat and intra-abdominal fat in patients using antipsychotics (Risperidone and chlorpromazine) accompanied by increased levels of triglycerides and LDL cholesterol [7].

Typical antipsychotics are classified as high potency or low potency agents based on their relative ability to block dopamine receptors. The first generation of antipsychotics (FGA) acted through dopamine D2 neuroreceptor blockade. A new line of antipsychotics was then developed with a more potent dopamine blockade. Antipsychotics can be classified by chemical structure (phenothiazines and non-phenothiazines) and have significant side effects such as EPS, sedation, anticholinergic, and cardiovascular effects [1]. Chlorpromazine is known to block glucose uptake into human erythrocytes. Besides, mitochondrial dysfunction also occurs due to antipsychotics changing mitochondrial function toward metabolic enzymes and carbon metabolism and electron transport during oxidative phosphorylation. It causes a decrease in glucose metabolism, insulin resistance, and an increased risk of T2DM [8]. Typical antipsychotics can also increase body weight by inhibiting Dopamine D2 receptors [9]. Inhibition of these receptors can cause hyperprolactinemia, resulting in decreased insulin sensitivity and fat [10].

Atypical antipsychotics effectively treat acute and chronic psychoses (schizophrenia and schizoaffective) in adults and adolescents. From a clinical perspective, the term atypical refers to clinical properties that differentiate it from conventional or typical antipsychotics. Pharmacologically, the properties of atypical antipsychotics are divided into four types, namely: dopamine serotonin antagonists, D2 antagonists with rapid dissociation, D2 partial agonists, and Serotonin partial agonists. Atypical antipsychotics have additional binding to various subtypes of neurotransmitter receptors, namely, serotonin (5 HT1A, 5HT2d, 5HT6, and 5HT7), dopamine (D1, D3, and D4) on H1 histamine receptors, muscarinic receptors (M1, M2, M3, M4, and M5), and adrenergic receptors (α1 and α2) [11]. Antipsychotic-induced weight gain (AIWG) is a common side effect, according to some measurements of schizophrenic patients receiving acute or maintenance treatment. AIWG has been documented since the advent of chlorpromazine with reports of continued weight gain with treatment that rapidly decreased after drug discontinuation. AIWG appears to occur more frequently with second-generation antipsychotics (SGA) than with FGA and with a greater probability for some SGA than for others.

AIWG is a significant risk factor for obesity and other metabolic disorders (e.g. dyslipidemia, hyperglycemia, and diabetes mellitus) and vascular (e.g., cardiovascular and cerebrovascular disease, arterial hypertension, and ventricular arrhythmias), and premature death. Furthermore, antipsychotics can exacerbate the preexisting metabolic irregularities observed at a lower frequency and/or severity in untreated schizophrenia [12]. Metabolic syndrome is also defined as the presence of insulin resistance (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes mellitus) in addition to the following two risk factors: Obesity (waist-to-hip ratio or body mass index), hyperlipidemia (hypertriglyceridemia and cholesterol lipoprotein [HDL]), low density, hypertension, or microalbuminuria [13].

Continuously elevated levels of systemic IL-6 can lead to insulin resistance, whereas transient elevations of IL-6 may aid normal glucose homeostasis. IL6 appears to have multiple functions depending on the tissue and metabolic state. During exercise, IL-6 increases glucose uptake in skeletal muscle, leading to muscle hypertrophy and myogenesis and AMPK-mediated fatty acid oxidation and anti-inflammatory effects. However, in adipose and liver tissue, IL-6 exerts pro-inflammatory activity and increases insulin resistance by increasing SOCS3 (cytokine signaling suppressor 3), destroying insulin-induced insulin receptors phosphorylation of IRS1. IL-6 can increase the dysregulation of fatty acid metabolism in WAT (white adipose tissue) because it increases the proliferation of mesenchymal stem cells, keeps cells undifferentiated, and inhibits adipogenesis [14].

IL-6 can also affect other adipokines. In particular, IL-6 can reduce adiponectin expression and secretion in human adipocytes and other markers of adipocyte differentiation. Overall, IL6 can play an essential role in metabolic diseases, including obesity [14].

Material and Methods

Subjects

In this controlled trial, 28 subjects met the inclusion criteria, namely, 18–50 years of age, male, and female, met the diagnostic criteria for schizophrenia according to the DSM V, schizophrenic patients dropped out of drugs for at least 6 months, using the antipsychotic haloperidol combination chlorpromazine or risperidone combination clozapine. Furthermore, patients were excluded if they met the criteria, namely, not willing to participate in the study, had a history of chronic diseases (tuberculosis, HIV, diabetes mellitus,

malignancy, hypertension, and autoimmune disease). Schizophrenic patients with epilepsy, mental retardation, severe systemic disease, stroke, endocrine, immune, metabolic diseases, patients taking oral antibiotics, non-steroidal anti inflammatory drugs (NSAIDs), corticosteroids, and/or other immunomodulating agents, substance and alcohol abuse, and patients with poor nutrition or patients with overnutrition.

Procedure

The Ethics Commission is ethically approved this study of Medical Research of Hasanuddin University. Subjects were recruited from RSKD, South Sulawesi Province Hospital, Indonesia. The study was conducted from December 2020 until December 2021.

At the initial assessment, the subjects had to meet the inclusion criteria. The two groups of subjects who received antipsychotic therapy also underwent a process of measuring body weight, height to assess BMI, then measuring blood pressure and taking blood as much as three cc to check triglycerides, blood sugar, and IL-6 levels. In the 3rd month of the two groups, the exact measurements and examinations were carried out again. Measurement of blood sugar levels was carried out using blood sugar sticks, then tests of triglycerides and measurement of IL-6 levels in the laboratory and at the Hasanuddin University Hospital Research Laboratory.

Measures

Demographics

Demographic information was collected by looking at the patient's medical record and family all anamnesis, including age, gender, and history of the previous illnesses.

Metabolic syndrome

Metabolic syndrome was measured using the NCEP ATP-III criteria. If it meets at least three of the five agreed criteria, including abdominal circumference for men ≥ 102 cm or women ≥ 88 cm, hypertriglyceridemia (serum triglyceride levels ≥ 1.69 mmol/L), HDL-C levels <40 mg/dL for men, and <50 mg/dL for women, blood pressure ≥ 130/85 mmHg, fasting blood glucose level ≥ 110 mg/dL adapted from the American Heart Association, Lung and Blood Institute report [13].

Interleukin 6

Interleukin 6 samples were taken by phlebotomy in the median cubital vein of each subject, which was taken twice. Subject. The sample was sent to the Hasanuddin University Hospital Research Laboratory, and then centrifuged to take the serum for restoration at a temperature of -30ºC until all samples were collected. On completion, all plasma samples were thawed, and the concentration of interleukin six was measured using the IL-6 ELISA Kit. The concentration of interleukin 6 is converted to ng/L units.

Data analysis

Statistical analysis was performed using SPSS 23.0. The first demographic variable was analyzed using a descriptive form which shows the percentage and average. Comparison of mean values for each metabolic syndrome indicator in the two groups given the typical and atypical antipsychotic combination drug at baseline and after 3 months of treatment. It is to detect statistically significant differences using paired t-test and Wilcoxon test. A Chi-square test was performed to see the metabolic syndrome distribution and not the metabolic syndrome in each group of typical and atypical combination drugs at the 3rd month of therapy. It is to determine after the intervention of atypical and typical combination drugs occurs metabolic syndrome in both groups. Changes in IL-6 levels at baseline and month 3 were analyzed statistically using paired t-test. In contrast, IL-6 levels at the 3rd month were measured in both groups with metabolic syndrome and non-metabolic syndrome analyzed using the independent t-test.

Results

The number of female and male subjects in the group receiving the combination of Risperidone and clozapine was 50%, while male subjects were more significant in the group receiving haloperidol and chlorpromazine, namely, 100%. Most of the two groups were aged 31–40 years, namely, 64.3% in the haloperidol + chlorpromazine group and 50% in the risperidone + clozapine group. Most occupations in the two groups were not working, where in the combination group of haloperidol and chlorpromazine drugs it was 71.4%, while in the combination group of drugs risperidone and clozapine it was 64.3%. Most patients were found with elementary and high school education, in the group that received the most haloperidol and chlorpromazine combination therapy, around 50.0% had primary school education, while the group that received the most combination therapy of Risperidone and clozapine had high school education, namely, 57.1%. Marital status in the two groups is mainly married with a percentage of 50% and 64.3% (Table 1).

In Table 2, it is found that in the initial measurement of the haloperidol and chlorpromazine combination therapy group BMI in the normal category

was 100%, and at the 3rd month, the overweight criteria were 14.3%, and 21.4% were in the obese category I.

Table 1: Demographic characteristic of subjects (n=28)

	Haloperidol + Chlorpromazine (n=14)		Risperidone + Clozapine (n=14)		p-value
	n (%)		n (%)		
Gender					0.006
Man	14	(100)	7	(50)	
Women	0	(0)	7	(50)	
Age (years)					0.038*
18 – 30	0	(0)	5	(35.7)	
31 – 40	9	(64.3)	7	(50)	
41 – 50	5	(35.7)	2	(14.3)	
Profession					1.000
Does not work	10	(71.4)	9	(64.3)	
Work	4	(28.6)	5	(35.7)	
Education					0.007
Unschooled	2	(14.3)	0	(0.0)	
Elementary school	7	(50)	1	(7.1)	
Junior high school	4	(28.6)	5	(35.7)	
Senior high school	1	(7.1)	8	(57.1)	
Marital Status					0.703
Married	7	(50)	9	(64.3)	
Single	7	(50)	5	(35.7)	

Primary data, 2021

About 7.1% of the sample entered the category of central obesity at the 3rd month. There were 100% with normal triglyceride levels at the beginning of the measurement, and there were 7.1% with triglyceride levels at the highest limit, 14.3% with high triglyceride levels at the 3rd month examination. There were 42.9% non-DM and 57.1% with uncertain DM criteria at the initial measurement of GDP levels, while 7.1% were included in the criteria for non-DM, 71.4% were not sure for DM, and 21.4% were criteria for DM at the 3rd month measurement. At the initial measurement of blood pressure in normal conditions, 78.6%, 21.4% were included in the criteria for prehypertension, and at the 3rd month of examination, 35.7% were prehypertension, and 21.4% were in the criteria for hypertension.

Table 2: Characteristics of indicator measurement results at baseline and 3rd month

Indikator	Haloperidol + Chlorpromazine				Risperidone + Clozapine			
	Early		3rd month		Early		3rd month	
	n	%	n	%	n	%	n	%
BMI								
Normal	14	100	9	64.3	10	71.4	0	0.0
Overweight	0	0.0	2	14.3	4	28.6	4	28.6
Obesity I	0	0.0	3	21.4	0	0	11	71.4
TG								
Normal	14	100	11	78.6	13	92.9	11	78.6
Highest limit	0	100	1	7.1	0	100	1	7.1
Height	0	0	2	14.3	1	7.1	2	14.3
FBS								
Not DM	6	42.9	1	7.1	2	14.3	0	0.0
Not sure DM	8	57.1	10	71.4	12	85.7	4	28.6
DM	0	0.0	3	21.4	0	0.0	10	71.4
BP								
Normal	11	78.6	6	42.9	6	42.9	2	14.3
Prehypertension	3	21.4	5	35.7	8	57.1	3	21.4
Hypertension	0	0	3	21.4	0	0.0	9	64.3
AC								
Normal	14	100	12	85.71	13	92.9	7	50.0
Central obesity	0	100	2	14.28	1	7.1	7	50.0

Primary data, 2021

In the risperidone + clozapine combination therapy group, 71.4% BMI was normal at baseline, 28.6% were categorized as overweight, while at the 3rd month, 28.6% were considered overweight, and 78.1% were obese I. At baseline measurement, the abdominal circumference was about 7.1% abnormal in males and females, whereas about 64.3% were categorized as central obesity in the 3rd month. There were 7.1% with high triglyceride levels at the start of the measurement, and at the 3rd month measurement, high triglyceride levels were 14.3%, and the triglycerides were in the highest limit of 7.1%. There are 85.7% with uncertain DM criteria, 14.3% not DM in the initial GDP measurement, 28.6% criteria for non-DM, and 71.4% for DM at the 3rd month measurement. At the initial blood pressure measurement, 57.1% were included in the prehypertension criteria. In comparison, there were 21.4% criteria for prehypertension at the 3rd month measurement, and 64.3% were included in the hypertension criteria.

In Table 3, there were two people or 14.3% who had metabolic syndrome and 12 people or 85.7% who were not a metabolic syndrome in the group of patients who received haloperidol + chlorpromazine antipsychotic therapy. Meanwhile, nine patients or 64.3% of patients who received the antipsychotic combination therapy risperidone + clozapine had metabolic syndrome, and five people who were not. There is a significant difference ($p < 0.05$).

Table 3: Distribution of metabolic and non-metabolic syndrome in the two groups at the 3rd month

	Haloperidol + Chlorpromazine		Risperidone + Clozapine		p-value
	Frequency	Percentage	Frequency	Percentage	
Metabolic syndrome	2	14.3 %	9	64.3%	0.020*
Non metabolic syndrome	12	85.7 %	5	35.7%	

Primary data, 2021

Table 4 compares each indicator between the initial observation and the 3rd month observation in the haloperidol + chlorpromazine treatment group. The analysis found an increase in the indicators of abdominal circumference, triglycerides, systole, and systolic blood pressure, and the statistical test results showed that the value of $p < 0.05$.

While the comparison of each indicator between the initial observation and the 3rd month observation in the risperidone + clozapine treatment group. From the analysis, it was found that there was an increase in the indicators of bodyweight, abdominal circumference, body mass index, triglycerides, fasting blood sugar, and triglycerides. The results of statistical tests show that $p < 0.05$.

In Table 5, the comparison of changes in the mean value of IL-6 levels at baseline and the 3rd month in the haloperidol + chlorpromazine group, namely, 49.60 ng/L ± 19.73 and 39.99 ng/L ± 19.23 where there were significant differences ($p < 0.05$). Whereas in the risperidone + Clozapine group, the mean IL-6 values at the start and the 3rd month were 54.52 ng/L ± 28.31 and 46.47 ± 28.32 ng/L where there were also significant differences ($p < 0.05$).

In Table 5, the comparison of changes in the mean value of IL-6 levels at baseline and the 3rd month in the haloperidol + chlorpromazine group, namely, 49.60 ng/L ± 19.73 and 39.99 ng/L ± 19.23 where there were significant

Table 4: Comparison of the mean and difference in metabolic syndrome indicators in the combination therapy group Haloperidol + chlorpromazine and Risperidone + Clozapine

Indicator	Haloperidol + Chlorpromazine			Risperidone+ Clozapine		
	Mean (s.b)	Difference (s.b)	p-value	Mean (s.b)	Difference (s.b)	p-value
Baseline wt (kg)	58.50±6.28	4.00±7.08	0.054[a]	57.86±8.90	12.14±4.26	0.000[a]*
3rd month wt (kg)	62.50±8.75			70.00±8.94		
Baseline AC (cm)	75.36±6.05	3.93±5.48	0.019[a]*	75.64±7.73	13.21±6.77	0.000[a]*
3rd month AC 3(cm)	80.21±8.82			90.00±8.53		
Baseline BMI (kg/m2)	20.98±1.61	1.43±2.53	0.059[a]	21.94±1.51	5.07±2.40	0.000[a]*
3rd month BMI (kg/m2)	22.40±2.69			27.05±2.04		
Baseline TG (mg/dl)	54.3±34.69	48.43±45.63	0.002[b]*	81.86±47.99	49.00±75.99	0.001[b]*
3rd month TG(mg/dl)	104.86±68.90			131.28±80.56		
Baseline FBS (mg/dl)	95.00±14.15	13.79±25.00	0.060[a]	107.64±9.54	25.71±18.16	0.000[a]*
3rd month FBS(mg/dl)	109.29±21.09			133.36±15.05		
Baseline SBP (mmHg)	111.43±11.67	7.14±12.67	0.047[b]*	125.00±12.86	2.14±5.79	0.180[b]
3rd month SBP (mmHg)	118.57±10.58			127.14±9.94		
Baseline DBP (mmHg)	75.71±11.58	2.14±8.93	0.366[b]*	88.43±9.29	0.71±6.16	0.655[b]
3rd Month DBP (mmHg)	77.88±9.75			87.14±10.69		

Primary data, 2021

differences ($p < 0.05$). Whereas in the risperidone + Clozapine group, the mean IL-6 values at the start and the 3rd month were 54.52 ng/L ± 28.31 and 46.47 ± 28.32 ng/L where there were also significant differences ($p < 0.05$).

Table 5: Mean IL-6 levels at baseline and 3rd month in both drug groups

Subject	Interleukin 6			Delta (SD)
	Baseline	3rd month	p-value	
	Mean (SD)	Mean (SD)		
Haloperidol + Chlorpromazine	49.60 ± 19.73	39.99 ± 19.23	0.0001[a]*	9.61 (4.39)
Risperidone + Clozapine	54.52 ± 28.31	46.47 ± 28.32	0.0001[a]*	8.05 (4.17)

Primary data, 2021

In Table 6, the Haloperidol + Chlorpromazine treatment group with metabolic syndrome, the mean level of interleukin 6 at month 3 was 86.75 ng/L ± 0.00, and those without metabolic syndrome were 36.09 ng/L ± 13.71. In the Risperidone + clozapine treatment group with metabolic syndrome, the mean interleukin 6 at month 3 was 64.66 ng/L ± 23.17. In contrast, the mean IL-6 levels that were not a metabolic syndrome at month 3 were 21.00 ng/L ± 3.27 Table 6. Mean IL-6 at month 3 had metabolic syndrome and not a metabolic syndrome in each treatment group.

Table 6: Mean IL-6 at 3rd month with metabolic syndrome and non-metabolic syndrome in each treatment group

Subject	IL-6 3rd month (ng/L)	p-value
	Mean ± SD	
Haloperidol + Chlorpromazine		
Metabolic syndrome	86.75 ± 0.00	0.005a*
Non-metabolic syndrome	36.09 ± 13.71	
Risperidone + Clozapine		
Metabolic syndrome	64.66 ± 23.17	0.002a*
Non-metabolic syndrome	21.00 ± 3.27	

Primary data, 2021

Discussion

In this study, a sample of 28 people with schizophrenia was male, 14 in the group that received the combination of haloperidol and chlorpromazine antipsychotic therapy, and 7 each were male and female in the group using the combination antipsychotic therapy risperidone and clozapine with an average age of 31-40 years, do not have a job and have the highest education is high school. This is consistent with the onset of schizophrenia at productive age and occurs in low socioeconomic and educational conditions.

Weight gain was seen in patients receiving the combination therapy of the drugs risperidone and clozapine. This increase is in accordance with the results of another study where the results for schizophrenic patients had almost the same subjective weight gain in patients who consumed typical and atypical patients, amounting to 59.6% and 60.0%, respectively, while in combination treatment it was 53.2% [15]. In a systematic review, 40-62% of the schizophrenia sample experienced weight gain or obesity after taking atypical antipsychotics, especially clozapine and olanzapine [16]. Atypical antipsychotic agents can induce body weight changes and are responsible for changes in glucose metabolism through the 5-HT2C receptor mechanism [17]. Typical antipsychotic agents can also increase body weight by inhibiting Dopamine D2 receptors [9]. Inhibition of these receptors can cause hyperprolactinemia, resulting in decreased insulin sensitivity and leads to fat [10]. Several neurotransmitters such as serotonin, dopamine, acetylcholine, and histamine also increase body weight and develop insulin resistance. Furthermore, differences in the level of affinity of antipsychotic drugs with receptors in the serotonergic, dopaminergic, cholinergic, histaminergic, and other neurotransmitter systems also increase body weight.

The increase in abdominal circumference also occurred more in subjects who received atypical antipsychotic therapy compared to seven people who used typical antipsychotics or by 50% at month 3; the results of this study are in line with the previous studies where there was an increase in body weight, BMI, and abdominal circumference. And a significant reduction in HDL cholesterol levels ($p < 0.05$) after 2 months of atypical antipsychotic therapy [18]. Abdominal circumference or waist circumference is an anthropometric index to assess the status of obesity, especially central obesity [19].

The use of both typical and atypical antipsychotic drugs can cause hyperglycemia. In this study, the results showed an increase in the mean difference in fasting

blood sugar levels in patients who used a combination therapy of haloperidol and chlorpromazine and those who received risperidone and clozapine therapy. The statistical test results showed that the group used atypical antipsychotic combination therapy. Metabolic disturbances in the use of atypical antipsychotics can directly result from changes in insulin sensitivity and/or insulin secretion. Atypical antipsychotic binding to histamine and muscarinic acetylcholine receptors is associated with weight gain and metabolic disorders [20]. Impaired parasympathetic regulation of pancreatic beta-cell activity contributes to metabolic risk [21].

Triglyceride levels were increased in the group receiving risperidone and clozapine therapy with statistically significant results where these results are in line with other studies. In another study abroad, there were differences in triglyceride levels in the group receiving risperidone with mean and standard deviation of 187.1 ± 24.73 mg/dl, compared to controls with mean and standard deviation 135.9 ± 25.05 mg/dl ($p < 0.001$) [22]. The abnormality that causes small dense LDL is hypertriglyceridemia. Small dense LDL is closely related to cardiovascular risk. Research shows that small dense LDL will not be found until plasma triglycerides reach 1.5 mmol/l [23]. Antipsychotic drugs that induce weight gain can not only be explained by one functional pathway. However, there is evidence that histaminergic transmission is influenced by homeostatic energy [24].

The use of atypical antipsychotics can also increase blood pressure. Dopamine receptors play a role in regulating blood pressure, and changes in the system can cause hypertension. Receptors D1, D3, and D4 interact with the renin-angiotensin-aldosterone system, whereas D2 and D5 with post-ganglia presynaptic sympathetic nerves. When activated, the receptors inhibit norepinephrine production at sympathetic nerve endings, leading to increased blood pressure [25]. In this study, there was also an increase in blood pressure's mean value in the 3rd month after giving antipsychotic drug therapy. However, an increase in blood pressure in accordance with the criteria for hypertension was found only in a few subjects.

The results of the measurement of several indicators of metabolic syndrome were obtained in patients who received haloperidol + chlorpromazine antipsychotic therapy, experienced changes in levels in several indicators. However, these changes in levels could not be included in the criteria for metabolic syndrome according to NCEP ATP III, so that the distribution chart of patients with metabolic syndrome in this group there were only two people. However, the change in levels could be used as an initial reference that some indicators had increased their levels, so we had to be more careful in administering the drug. In contrast, in subjects receiving risperidone + clozapine antipsychotic therapy, almost all metabolic syndrome indicators increased significantly so that they met the criteria for metabolic syndrome in patients who were given atypical antipsychotics. The increase in this indicator is due to the increase in body weight due to the use of atypical antipsychotics, where risperidone and clozapine are antipsychotics that have a risk of AIWG, a high risk of causing an increase in body weight on clozapine and a moderate risk for risperidone. Whereas the haloperidol drug has a low risk, chlorpromazine has moderate risk. Weight gains due to the side effects of using antipsychotics are reversible and rapidly decreases after discontinuation of the drug. Some patients who use antipsychotic drugs for a long time actually experience stagnation in increasing body weight in clinical experience. Even patients tend to experience weight loss, perhaps due to increased family and patient knowledge by adjusting diet and nutritional balance after receiving education provided by doctors and patient activities increasing or other unknown factors.

The increase in some of these indicators can indicate that schizophrenic patients who receive atypical and typical combination antipsychotic therapy will develop metabolic syndrome, which can be determined through the criteria of the National Cholesterol Education Program Adult Treatment Panel (NCEP III), which must meet at least three of the five existing criteria. There were two people or 14.3% who had metabolic syndrome and 12 people or 85.7% who had no metabolic syndrome in the group of patients who received haloperidol + chlorpromazine antipsychotic therapy. Meanwhile, nine patients or 64.3% of patients who received the antipsychotic combination therapy risperidone + clozapine had metabolic syndrome, and five people who were not. Both of these antipsychotic drugs can cause metabolic syndrome, but it is more common in atypical antipsychotics because these antipsychotics have a better way of working on 5HT1A agonist neurotransmitters, 5HT2C antagonists, H1 antagonists, alpha 1 adrenergic antagonist, and muscarinic antagonists where they are direct. It affects Neuropeptide Y on PVN in the hypothalamus and increases appetite so that food intake also increases; besides, there is also an effect on noradrenaline from PVN and shortens the time of satiety which leads to an increase in food intake. The sedation effect that appears also results in reduced activity of a person, increasing body weight. Some work directly to block the pancreatic M3 receptors, leading to insulin resistance. Due to an increase in body weight, visceral fat will be formed, which will affect the body's metabolism and increase pro-inflammatory factors.

There was a change in IL-6 levels before and after giving therapy at month 3 where the haloperidol + chlorpromazine combination group had changes in IL-6 levels with an initial mean of 49.60 ± 19.73 ng/L and month 3, 39.99 ± 19.23 ng/L with $p < 0.05$, whereas in the combination drug risperidone + clozapine there was a change in the initial mean value of 54.52 ± 28.31 ng/L and at month 3 was 46.47 ± 24.32 ng/L with $p < 0.005$.

Administration of antipsychotics at the beginning of treatment provides anti-inflammatory effects, where the symptoms of schizophrenia are one of the causes of neuronal degeneration and decreased neurogenesis from the neuroinflammatory process. In the initial IL-6 measurement, there was a high level; after the patient received antipsychotic therapy for 3 months, it was seen that the inflammatory process had decreased, but the decrease was not too significant in typical and atypical antipsychotics. Initially, atypical and typical antipsychotics provide benefits by improving clinical symptoms in schizophrenia patients. However, each drug administration has side effects that will arise in the future, one of which is the side effect of increasing body weight which will affect the body's metabolic processes and re-cause the inflammatory process due to fat accumulation visceral, where visceral fat is closely related to an inflammatory process that causes the production of pro-inflammatory cytokines, one of which is IL-6. So that in the results of this study, patients with metabolic syndrome in both groups who received antipsychotic therapy showed that IL-6 levels were still high compared to patients without metabolic syndrome with the lower values at month 3. This study's results are in line with previous studies, with results showing that patients receiving atypical antipsychotic therapy had significantly higher levels of IL-6 compared to healthy controls [26]. Patients with metabolic syndrome have higher plasma IL-6 levels than those without metabolic syndrome. IL-6 is an important pro-inflammatory cytokine and plays an essential role in the immune response [27]. Understanding the mechanisms of antipsychotic treatment that can lead to metabolic disorders and obesity-related diseases is essential to reduce mortality and improve the quality of life for psychosis patients. Although atypical antipsychotics cause more metabolic side effects, this drug is still better and superior to typical drugs in causing other side effects such as extrapyramidal symptoms. This effect of EPS causes patient non-compliance in taking the drug so that effective treatment will not be achieved. Maximum and worsens the prognosis, whereas with atypical antipsychotic drugs, these side effects are minimal and tend to be absent; besides that, the decrease in cognitive function due to the administration of typical antipsychotics is more significant so that in patients of productive age, it is better if atypical antipsychotics are given so that patients can function better if they come back in a community environment and can be more productive.

Limitation

Several limitations in our study should be pointed out. More samples and longer study time are required for better research accuracy and results. This study was limited to examining several indicators that fall under the criteria for metabolic syndrome, then examining levels of interleukin 6 at the start of treatment and at 3 months in patients experiencing metabolic syndrome due to the use of typical and atypical antipsychotics and linking them. This study did not precisely examine when IL-6 levels began to improve due to atypical and typical antipsychotics. This study did not determine the cutoff value of interleukin 6 levels in schizophrenic patients with metabolic syndrome so that it can be used as a reference value for the future.

Conclusion

Metabolic syndrome is more common in schizophrenic patients receiving atypical than typical combination therapy. The body's response to the metabolic syndrome results in an increase in IL-6 levels due to an inflammatory process in visceral fat which accumulates due to weight gain due to the administration of antipsychotics. Then, in schizophrenic patients with metabolic syndrome, IL-6 levels were higher than those without metabolic syndrome, so that IL-6 levels could be used as a predictor of metabolic syndrome in schizophrenic patients receiving antipsychotic therapy.

Acknowledgments

The authors would like to acknowledge and thank the participants who volunteered and participated in this study. We also would like to acknowledge the important support and contribution of the medical faculty, Hasanuddin University, Makassar.

References

1. Kaplan HI, Sadock BJ. Synopsis of Psychiatry: Behavioral Sciences Clinical Psychiatry. Baltimore: Lippincott Williams and Wilkins Co.; 1988.
2. Amir N. Buku Ajar Psikiatri: Skizofrenia. Jakarta: Badan Penerbit Fakultas Kedokteran Universitas Indonesia; 2013.
3. Monji A, Kato TA, Mizoguchi Y, Horikawa H, Seki Y, Kasai M, *et al*. Neuroinflammation in schizophrenia especially focused on the role of microglia. Prog Neuropsychopharmacol Biol Psychiatry. 2013;42:115-21. https://doi.org/10.1016/j.pnpbp.2011.12.002 PMid:22192886
4. Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. Br J Psychiatry. 2010;196(2):116-21. https://doi.org/10.1192/bjp.bp.109.067512 PMid:20118455
5. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, *et al*. Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the clinical antipsychotic trials of intervention effectiveness (CATIE)

schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res. 2005;80(1):19-32. https://doi.org/10.1016/j.schres.2005.07.014
PMid:16137860

6. Gupta A, Jadhav AA, Petkar SB, Dubey V. Study of lipid derangement in pyschiatric disorder. Indian Med Gazette. 2005;147(7):253-6.
7. Zhang ZJ, Yao ZJ, Liu WE, Fang QU, Reynolds GP. Effects of antipsychotics on fat deposition and changes in leptin and insulin levels: Magnetic resonance imaging study of previously untreated people with schizophrenia. Br J Psychiatry. 2004;184(1):58-62. https://doi.org/10.1192/bjp.184.1.58
PMid:14702228
8. Xu H, Zhuang X. Atypical antipsychotics-induced metabolic syndrome and nonalcoholic fatty liver disease: A critical review. Neuropsychiatr Dis Treat. 2019;15:2087. https://doi.org/10.2147/ndt.s208061
PMid:31413575
9. Holt RI. Association between antipsychotic medication use and diabetes. Curr Diab Rep. 2019;19(10):96. https://doi.org/10.1007/s11892-019-1220-8
PMid:31478094
10. Meyer JS, Quenzer LF. Psychopharmacology: Drugs, the Brain, and Behavior. United States: Sinauer Associates; 2005.
11. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. Cambridge: Cambridge University Press; 1996.
12. Fonseka TM, Müller DJ, Kennedy SH. Inflammatory cytokines and antipsychotic-induced weight gain: Review and clinical implications. Mol Neuropsychiatry. 2016;2(1):1-4. https://doi.org/10.1159/000441521
PMid:27606316
13. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis. 2017;11(8):215-25. https://doi.org/10.1177/1753944717711379
PMid:28639538
14. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: Cells, cytokines, and chemokines. ISRN Inflamm. 2013;2013:139239. https://doi.org/10.1155/2013/139239
PMid:24455420
15. Hasni D, Sona A, Anissa M, Heppy F. Identifikasi keluhan peningkatan berat badan pada pasien skizofrenia yang mendapat terapi antipsikotik di RSJ HB. Saanin Padang. J Kedokteran Kesehatan. 2020;16(1):6-11. https://doi.org/10.24853/jkk.16.1.6-11
16. Manu P, Dima L, Shulman M, Vancampfort D, De Hert M, Correll CU. Weight gain and obesity in schizophrenia: Epidemiology, pathobiology, and management. Acta Psychiatr Scand. 2015;132(2):97-108. https://doi.org/10.1111/acps.12445
PMid:26016380
17. Meltzer HY. Update on typical and atypical antipsychotic drugs. Ann Rev Med. 2013;64:393-406. https://doi.org/10.1146/annurev-med-050911-161504
PMid:23020880
18. Saidah S, Agustine M, Hawaidah H, Sonny TL. Changes of body weight and triglyceride level in schizophrenia patients treated with atypical antipsychotics. Int J Clin Psychiatry. 2018;6(2):40-6.
19. Perkumpulan Endokrinologi Indonesia Perkeni. Konsesus Penelolaan Diabetes Mellitus Tipe 2 di Indonesia. Jakarta: PB Perkeni; 1998.
20. Matsui-Sakata A, Ohtani H, Sawada Y. Receptor occupancy-based analysis of the contributions of various receptors to antipsychotics-induced weight gain and diabetes mellitus. Drug Metab Pharmacokinet. 2005;20(5):368-78. https://doi.org/10.2133/dmpk.20.368
PMid:16272755
21. Silvestre JS, Prous J. Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. Methods Find Exp Clin Pharmacol. 2005;27(5):289-304. https://doi.org/10.1358/mf.2005.27.5.908643
PMid:16082416
22. Paunipagar PV, Sharma R, Gumaste A. Effect of risperidone on lipid profile and related risk for coronary heart disease. Indian Med Gazette. 2012;145(7):266-8.
23. Kolovou GD, Anagnostopoulou KK, Cokkinos DV. Pathophysiology of dyslipidaemia in the metabolic syndrome. Postgrad Med J. 2005;81(956):358-66. https://doi.org/10.1136/pgmj.2004.025601
PMid:15937200
24. Moghadamnia M. Metabolic effect of olanzapine medication on weight gain. Life Sci J. 2013;3:10.
25. Alves BB, Oliveira GD, Moreira Neto MG, Fiorilli RB, Cestário ED. Use of atypical antipsychotics and risk of hypertension: A case report and review literature. SAGE Open Med Case Rep. 2019;7:1-6. https://doi.org/10.1177/2050313x19841825
PMid:31007920
26. Fang X, Wang Y, Chen Y, Ren J, Zhang C. Association between IL-6 and metabolic syndrome in schizophrenia patients treated with second-generation antipsychotics. Neuropsychiatr Dis Treat. 2019;15:2161. https://doi.org/10.2147/ndt.s202159
PMid:31534339
27. Zhang C, Wu Z, Zhao G, Wang F, Fang Y. Identification of IL6 as a susceptibility gene for major depressive disorder. Sci Rep. 2016;6(1):1-6. https://doi.org/10.1038/srep31264
PMid:27502736