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EFFECT OF STATIN ADJUVANT THERAPY ON IL-6, LIPID PROFILE EXAMINATION AND CLINICAL SYMPTOMS IN SCHIZOPHRENIC PATIENTS TREATED WITH RISPERIDONE

Ardiansyah, Syamsuddin Saidah[1] *, Liaury Kristian[2], Seweng Arifin[3], Limoa Erlyn[4], Bahrun Uleng[5], Lisal T Sonny[6]

[1*, 2, 3, 6]Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia.
[4]Department of Public Health, Faculty of Public Health, Hasanuddin University, Makassar, Indonesia
[5]Department of Clinical Pathology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi Indonesia

***Corresponding Authors:** - Syamsuddin Saidah
*Department of Psychiatry, Faculty of Medicine, Hasanuddin University, Jalan Perintis KemerdekaanKm.10, Tamalanrea, Makassar, South Sulawesi, Indonesia, 90245
Telp: (+62411) 5040011, Fax: (+62411) 586297

Abstract

Background: Schizophrenia is a mental illness caused by gene-environment interaction. There is a role for dysregulation of inflammation in the pathogenesis of schizophrenia which is characterized by increased levels of interlukin-6. The use of first-generation antipsychotics can cause negative symptoms of schizophrenia. Treatment using anti-inflammatory adjuvants has the potential to have a better effect by reducing negative symptoms. Statins have been introduced as anti-inflammatory agents that can be used as adjuvant therapy for schizophrenia.

Objective: To determine the effect of adjuvant statin therapy on IL-6, lipid profile and clinical symptoms in schizophrenic patients treated with risperidone.

Methods: This study is an experimental study with a randomized clinical trial design with a double-blind approach. The study was conducted on 36 schizophrenic patients who were treated at Dadi Regional Special Hospital, South Sulawesi Province. Patients were randomized into 2 groups: 18 patients were given 4-6 mg/day of risperidone and 40 mg/day of oral simvastatin adjuvant therapy for 8 weeks (treatment) and 18 patients were given 4-6 mg/day of risperidone (control). A total of 18 healthy individuals were used to control IL-6 levels. IL-6 levels and lipid profiles were measured in the form of triglyceride, cholesterol, HDL and LDL levels before therapy and the 8th week. PANSS clinical symptoms were measured before therapy, week 4 and 8 after therapy. Data were analyzed using the Independent sample t test, Mann Whitney, Wilcoxon, Spearman correlation and chi square.

Results: IL-6 levels in schizophrenic patients were significantly higher than healthy individuals and IL-6 levels after both therapy with and without statin adjuvants were not significantly different from IL-6 levels in healthy individuals. There was a significant decrease in serum IL-6 levels in the treatment group, but not in the control group. Nonetheless, changes in serum IL-6 levels after 8 weeks

of therapy were not significantly different between the treatment and control groups. There was a significant change in lipid profile in the treatment group, but not in the control. Lipid profile changes after 8 weeks of therapy differed significantly between the treatment and control groups. In the treatment group there was a decrease in triglyceride, cholesterol and LDL levels and an increase in HDL levels. There was a significant improvement in the clinical symptoms of schizophrenia patients in the treatment and controls at the 4th and 8th week of therapy. There were significant differences in changes in clinical symptoms between the treatment and the controls. In schizophrenic patients receiving statin risperidone adjuvant therapy, decreasing serum IL-6 levels is correlated with a decrease in PANSS score, which means that it causes an improvement in clinical symptoms.

Conclusion: Simvastatin adjuvant therapy orally 40 mg/day for 8 weeks can reduce clinical symptoms, reduce serum IL-6 levels and clinical symptoms better than therapy with risperidone alone.

Keywords: interleukin-6, risperidone, schizophrenia, statins

1. Introduction

Schizophrenia is a severe mental disorder characterized by disturbances in thought, perception and behavior (Shalehuddin et al., 2019). Schizophrenia is a relatively rare mental disorder, approximately 1% of the adult population but has a high overall mortality rate (Challa et al., 2021). An 11-year prospective study stated that out of 3470 schizophrenic patients reported a mortality rate of 14% (Bushe et al., 2010). The incidence of schizophrenia in the world is around 23 million people in 2018. The incidence of schizophrenia in Indonesia is 6.7 per 1000 households in 2018 (Basic Health Research (Riskesdas), 2018; World Health Organization, 2017). The incidence of schizophrenia in South Sulawesi in 2018 reached 8.85% (Riskesdas, 2018).

The pathogenesis of schizophrenia is widely believed to be based on gene-environment interactions. Genetic studies show that genes related to the inflammatory response contribute to the pathophysiology of the disease. Dysregulation of inflammatory cytokines is suggested as a common pathway of genetic and environmental components in the pathogenesis of schizophrenia that occurs either early in life or during an acute state in adults (Neelamekam et al., 2014). The role of dysregulation of inflammation in the pathogenesis of schizophrenia is characterized by increased levels of pro-inflammatory cytokines such as interlukin-6 (IL-6) in schizophrenic patients compared to healthy controls (Kim et al., 2019).

The main treatment for schizophrenic patients is antipsychotic drugs (first and second generation). Although the use of first-generation antipsychotics has been known to cause negative symptoms of schizophrenia, it is therefore recommended to use second-generation antipsychotics (APG-2) or atypical antipsychotics such as Risperidone because they work on dopamine D2 receptors and 5-HT2A receptors while also having affinity for high in alpha 1, alpha 2 adrenergic receptors, good for improving positive and negative symptoms and cognitive function (Labbate et al., 2009; Sinaga, 2007). Anti-inflammatory treatment offers several beneficial effects on schizophrenia (Chaudhry et al., 2013). This is supported by the results of a study in 62 randomized double-blind clinical trials studying 2914 patients with schizophrenia that the use of adjuvant anti-inflammatory therapy had higher efficacy and safety than the use of antipsychotics alone (Cho et al., 2019).

Statins are competitive inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGR). Statins work by competitively blocking the active site of the first and key rate-limiting enzyme in the mevalonate pathway, HMG-CoA reductase. Inhibition of this site prevents substrate access, thereby blocking the conversion of HMG-CoA to mevalonic acid. Statins also have an additional effect as an anti-inflammatory due to inhibition of the synthesis of isoprenoid intermediates from the mevalonate

pathway (Talreja et al., 2022; Ward et al., 2019). The additional effect of statins means that statins have been used as adjuvant therapy in the treatment of patients with schizophrenia to reduce negative symptoms (Andrade, 2018; Kim et al., 2019). Statins such as simvastatin have been introduced as agents that may have beneficial effects on schizophrenia with respect to their anti-inflammatory properties (Tajik-Esmaeeli et al., 2017).

Several studies have reported that the effect of using simvastatin in adjuvant therapy for schizophrenia can reduce clinical symptoms, both negative and positive symptoms (Chaudhry et al., 2013; Shen et al., 2018). However, different results were reported that adding simvastatin to atypical antipsychotic treatment did not have a significant beneficial effect on negative and positive symptoms in patients with schizophrenic disorders (Postma et al., 2017; Tajik-Esmaeeli et al., 2017). Several studies have also reported that the use of simvastatin can reduce IL-6 levels in atherosclerosis, ischemic and cardiovascular strokes (Berthold et al., 2013; Meo et al., 2021; Park et al., 2019), but studies of the effects of simvastatin adjuvant therapy on Serum IL-6 level in schizophrenic patients has never been done before.

The effect of adjuvant statin therapy on clinical symptoms of schizophrenia is still controversial and research on the effect of adjuvant statin therapy on serum IL-6 levels in the treatment of schizophrenia has never been done before. The existence of significant findings in this study can provide information regarding optimizing pharmacological management of schizophrenic patients by adding statin therapy and will ultimately improve the prognosis of the disorder. The presence of a serum IL-6 biomarker that is comparable to clinical symptoms can be a simple and accurate measurement tool in predicting the prognosis of schizophrenia treatment. On this basis, researchers are interested in conducting a study on the effect of adjuvant statin therapy on serum IL-6 levels, lipid profiles and clinical symptoms in schizophrenic patients treated with risperidone. Based on the above background, the formulation of the problem in this study is: What is the effect of statin adjuvant therapy on serum IL-6 levels, lipid profiles and clinical symptoms in schizophrenic patients treated with risperidone?. The general objective of this study was to determine the effect of adjuvant statin therapy on serum IL-6, lipid profile and clinical symptoms in schizophrenic patients treated with risperidone. Meanwhile, the specific objectives were to compare clinical symptoms based on the PANSS score in the treatment group and the control group at 4 weeks and 8 weeks of therapy, to compare serum IL-6 levels in the treatment group and the control group at the baseline of the study and 8 weeks of therapy, to compare the lipid profile in the treatment group and the control group at the baseline of the study and 8 weeks of therapy, and determine the correlation of serum IL-6 levels and clinical symptoms of patients in the treatment and control groups. The hypothesis of this study is that statin adjuvant therapy can reduce serum IL-6 levels, improve lipid profiles and clinical symptoms of schizophrenic patients receiving risperidone.

In this study, the IL-6 level of schizophrenic patients was higher than that of healthy individuals. This relates to the role of IL-6 in the pathophysiology of schizophrenia. This result is in line with previous research that pro-inflammatory cytokines were reported to be higher in schizophrenia (Müller, 2018). IL-6 is a proinflammatory cytokine that can be produced by microglia. IL-6 increases the synthesis of acute phase proteins, including C-reactive protein (CRP), which can affect the permeability of the blood-brain barrier and microglia proliferation (Dawidowski et al., 2021). Microglia activation is involved in the inflammatory process in the schizophrenic central nervous system (Müller, 2018). This is because microglia are the most important components of the local central nervous system's immune system. Microglia play a major role in nerve inflammation and provide the first line of defense in case of injury or disease. Microglia are activated when the body is exposed to a systemic infection, for example, and are involved in the synthesis of central pro-inflammatory cytokines that are released in the event of an infection resulting in various mental conditions including schizophrenia (Müller, 2018). Serum IL-6 levels in schizophrenic patients have a large standard deviation because

increased serum IL-6 levels in schizophrenic patients can be affected by clinical status, duration of illness, and symptoms that affect IL-6 levels in cerebrospinal fluid and serum (Reale et al., 2021).

2. Research Methods

This research is an experimental study with a randomized clinical trial design, measuring pre- and post-tests with random group selection. Variable measurements were made before and after treatment. This study also used a double-blind approach This research was conducted at the Dadi Regional Special Hospital in South Sulawesi Province and sample testing was carried out at the UNHAS RSPTN Research Laboratory in March 2023 - April 2023. This research was conducted at the Dadi Regional Special Hospital in South Sulawesi Province and at the Unhas RSPTN Research Laboratory. The population in this study were all schizophrenic patients who were treated at Dadi Regional Special Hospital, South Sulawesi Province. The sample in this study were all patients with stable phase schizophrenia who were treated at Dadi Special Hospital in South Sulawesi Province who met the inclusion and exclusion criteria. The sample size is determined by the sample formula which performs a paired numerical comparative test of two more groups, namely:

$$\mathrm{n} = 2\left(\frac{(Z\alpha + Z\beta)\mathrm{S}}{x1 - x2}\right)^2 = \left(\frac{(1{,}96 + 0{,}84)\mathrm{x}\ 25{,}25}{22{,}09}\right)^2$$

$$n = 17{,}25 = 18 \text{ (rounded)}$$

Based on the calculation results, the minimum number of samples for each group is 18 people. This research was conducted on two sample groups so that the total sample was 36 people.
Information:
n = Minimum number of subjects per group
α = Type one error, set at 5%, one-way hypothesis
Zα = The standard value of α is 5%, which is 1.96
β = Type two error, set at 20%
Zβ = Standard value of 20% β, which is 0.84
x1-x2 = The difference in IL-6 levels which is considered significant, is set at 22.09 (Saidah et al., 2021)
s = Combined standard deviation = 23.17 (Saidah et al., 2021)

The sampling technique for each group was carried out by means of Consecutive Sampling, namely taking samples from all the subjects observed and meeting the criteria until the required number of samples was met. The inclusion criteria for the treatment group were patients diagnosed with schizophrenia according to PPDGJ III, patients aged 20-45 years, patients with disease onset <3 years, patients who had passed the acute phase (PANSS-EC <15), received risperidone therapy 4-6 mg/day, willing to get simvastatin adjuvant therapy, and non-obese if BMI < 25 kg/m2. The inclusion criteria for the control group included patients diagnosed with schizophrenia according to PPDGJ III, patients aged 20-45 years, patients with disease onset < 3 years, patients who had passed the acute phase (PANSS-EC < 15), received risperidone 4-6 mg/day. days, and non-obese if BMI <25 kg/m2.

The exclusion criteria were having organic co-morbidities, having a history of consuming drugs before being admitted to the hospital, using anti-inflammatory drugs and antibiotics such as urinary tract infections, tuberculosis, HIV and other infections. For Drop Out criteria, including not regularly following the entire statin adjuvant therapy, not regularly taking risperidone drugs, research subjects refusing to continue the study, and research subjects dying.

The instruments in this study were informed consent sheets, PPDGJ III instruments, clinical symptom instruments in the form of a Positive and Negative Symptoms Scale (PANSS), risperidone,

simvastatin, BMI (body mass index) measurements, lipid profiles, blood sampling kits and assays. IL-6, and ELISA kits. Data processing was carried out using the SPSS 23.0 computer program. A comparison test of two unpaired groups with numerical data was carried out by using the Independent T-test if the data distribution was normally distributed and using the Mann Withney test if the data distribution was not normal. The test was used to examine the comparison of clinical symptoms and serum IL-6 levels between the treatment and control groups. Differences in clinical symptoms, lipid profiles and serum IL-6 levels between before and after treatment in each group were carried out in a paired two-group comparison test using the Paired T test if the data distribution was normal and the Wilcoxon test if the data distribution was not normal. To measure the correlation of clinical symptoms and IL-6 levels, Pearson's test was used if the data distribution was normal and Spearman's test if the data distribution was not normal.

3. Results

3.1 Characteristics of research subjects

This study was conducted on 36 schizophrenic patients who were treated at Dadi Regional Special Hospital, South Sulawesi Province. The study subjects were randomly divided into two groups: 18 research subjects were given risperidone therapy and adjuvant statin therapy as the treatment group and 18 research subjects were given risperidone alone as the control group. Therapy carried out for 8 weeks. All subjects in this study were male, had disease onset <3 years, and had normal BMI. Comparison of the characteristics of the research subjects of the two groups can be seen in Table 1.

Table 1. Characteristics of research subjects

Characteristics	Treatment	Control	Total	p
	n (%)	n (%)		
Age (years)	31,44 ± 7,92*	34,22 ± 7,01*	32,83 ± 7,50*	0,273[a]
Education				
Elementary school	11 (61,1)	10 (55,6)	21 (58,3)	0,566[b]
Junior high school	6 (33,3)	5 (27,8)	11 (30,6)	
Senior high school	1 (5,6)	3 (16,7)	4 (11,1)	
Work				
Work	6 (33,3)	5 (27,8)	11 (30,6)	0,717[b]
Doesn't work	12 (66,7)	13 (72,2)	25 (69,4)	
Marital status				
Marry	7 (38,9)	3 (16,7)	10 (27,8)	0,137[b]
Not married yet	11 (61,1)	15 (83,3)	26 (72,2)	

* Data are shown with the mean ± standard deviation,, [a]*Independent sample t test*, [b]chi square test

Based on Table 1, it shows that there were no significant differences in all the characteristics of the research subjects, namely age, education, employment, and marital status between the treatment group and the control group. These results indicate that the characteristics of the research subjects in both groups are declared homogeneous. To measure the PANSS score and baseline serum IL-6 levels in the treatment and control groups, both groups measured the PANSS score at baseline which can be seen in Table 2.

Table 2. Measurement results based on the PANSS score and baseline serum IL-6 levels in the treatment and control groups

Group	Treatment	Control	p-value
	Mean±SD	Mean±SD	
PANSS Baseline	99,50 ± 4,68	91,78 ± 9,42	0,031*
IL-6 Serum Baseline Levels	169,10 ± 218,99	155,39 ± 190,38	0,527

*Significan $p < 0.05$ (The Mann Whitney test)

In the treatment group, the mean baseline PANSS value was 99.50 and in the control group 91.78 after the Mann Whitney test, the results were significant with a p value <0.05. Meanwhile, for the baseline serum IL-6 levels in the two groups, the values varied with a large standard deviation, where the baseline serum IL-6 level in the treatment group was 169.10, which was seen to be higher than the baseline serum IL-6 level in the control group. namely 155.39, but after the Mann Whitney test the results were not significant with a p>0.05.

To compare the PANSS scores in the treatment group and the control group after 4 weeks and 8 weeks of therapy, after measuring clinical symptoms at baseline, both groups were given the antipsychotic risperidone, in the treatment group other than the risperidone antipsychotics they were also given additional simvastatin at a dose of 40 mg/day. To see changes in clinical symptoms in the treatment and control groups, an examination of the PANSS score was carried out after 4 weeks and 8 weeks of therapy and also between 4 weeks to 8 weeks of therapy with the result that there was a significant decrease in both the treatment and control groups which can be seen in Table 3.

Table 3. Comparison of PANSS scores in the treatment group and the control group 4 weeks of therapy and 8 weeks of therapy

PANNS	Treatment			Control		
	Mean ± SD	difference	p-value	Mean ± SD	difference	p-value
Baseline	99,50 ± 4,68	25,22 ± 5,22	<0,001*[a]	91,78 ± 9,42	7,39 ± 3,42	<0,001 *[a]
4 week	74,28 ± 5,59			84,38 ± 7,47		
4 week	74,28 ± 5,59	18,28 ± 5,08	<0,001*[b]	84,38 ± 7,47	14,28 ± 4,56	<0,001 *[b]
8 week	56,00 ± 5,76			70,11 ± 4,68		
Baseline	99,50 ± 4,68	43,50 ± 6,42	<0,001*[b]	91,78 ± 9,42	21,67 ± 6,11	<0,001 *[b]
8 week	56,00 ± 5,76			70,11 ± 4,68		

signifikan p < 0.000; [a]Wilcoxon; [b]Uji paired t test

In Table 4, the results of the PANSS scores measured at baseline, 4 weeks and 8 weeks of therapy showed a significant decrease in both the treatment and control groups from baseline to 4 weeks, 4 weeks to 8 weeks, and from baseline to 8 weeks of therapy. In the treatment group that received adjuvant statins, the PANSS value decreased from the baseline to 8 weeks of therapy by 43.50 with an SD value of 6.42. Whereas in the control group who only received antipsychotic therapy with risperidone, the mean decrease in PANSS values at the 8th week baseline was 21.67 with an SD value of 6.11. The difference in reduction between the treatment and control groups was 21.83 and after being tested with Mann Whitney in both groups the results were significant.

Table 4. Differences in the difference in PANSS scores in the treatment and control groups from baseline, 4 weeks and 8 weeks after therapy

Group	**PANSS score**						**P-value**
	Baseline	**4 week**	**8 week**	**Average difference 0-4 week**	**The average difference is 4-8 weeks**	**The average difference is 0-8 weeks**	
Treatment	99,50 ± 4,68	74,28 ± 5,59	56,00 ± 5,76	-25,22 ± 5,22	-18,28 ± 5,08	-43,50 ± 6,42	<0,001*
Control	91,78 ± 9,42	84,38 ± 7,47	70,11 ± 4,68	-7,39 ± 3,42	-14,28 ± 4,56	-21,67 ± 6,11	

Signifikan p < 0.000 (Mann Whitney)

After measuring changes in the PANSS score from baseline, 4 weeks, and 8 weeks, a calculation of the percentage of improvement in clinical symptoms was carried out with the results of improving

clinical symptoms from the percentage decrease in the PANSS score in the treatment group of 62.0% with the interpretation of clinical symptoms very much improvement, whereas in the control group the control percentage decreased the PANSS score by 35.0% with the interpretation of clinical symptoms only moderate improvement. Changes in these values can be seen in Table 5 and Figure 12.

Table 5. Improvement in clinical symptoms based on the percentage reduction in PANSS scores in the treatment and control groups from baseline, 4 weeks and 8 weeks after therapy

Group	Treatment					p-value	Control					p value
	Mean± SD	% Decrease 0-4 week	% Decrease 4-8 weeks	% Decrease 0-8 weeks	Interpre-tation		Mean± SD	% Drop 0-4 weeks	% Drop 4-8 weeks	% Drop 0-8 weeks	Interpre-tation	
PANSS Total baseline	99,50 ± 4,68	**36,3**		**62,0**	**Improvement Very much clinical symp-toms**	< 0,001*	91,78 ± 9,42	**12,0**		**35,0**	**Moderate Repair Clinical symptoms**	0,001*
PANSS Total 4 weeks	74,28 ± 5,59		**41,28**				84,38 ± 7,47		**26,2**			
PANSS Total 8 weeks	56,00 ± 5,76						70,11 ± 4,68					

*Significant p < 0.000(Uji Wilcoxon)

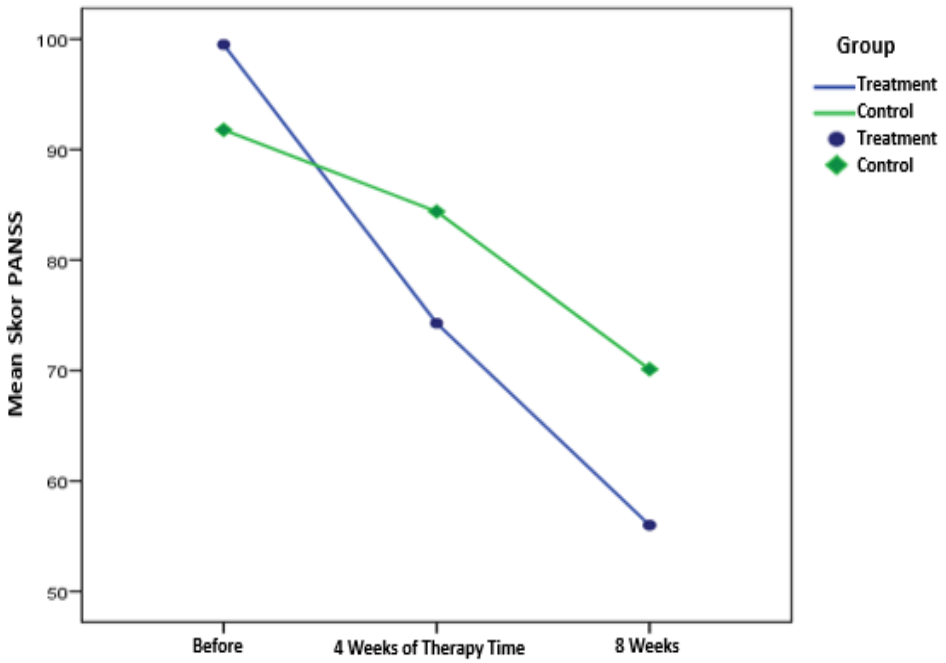

Figure 1. Comparison of clinical symptoms of the two groups before therapy, 4 weeks of therapy and 8 weeks of therapy

Figure 1 shows that the treatment group had a greater decrease in the PANSS score or experienced a better improvement in clinical symptoms at 8 weeks of therapy than the control. To determine the comparison of serum IL-6 levels, after measuring the baseline serum IL-6 levels in Table 4 and administering risperidone to the control group and an additional statin in addition to giving risperidone to the treatment group, after 8 weeks the IL-6 levels were measured again in both groups. group. The results showed that the serum IL-6 level in the treatment group was 82.71 pg/ml with an SD of 141.56 pg/ml while in the control group it was 103.77 pg/ml with an SD value of 165.63 pg/ml. Furthermore, a calculation of the difference in levels between baseline and 8 weeks of therapy was

carried out with the result that in the treatment group there was a significant decrease in IL-6 levels of 86.39 pg/ml or 51.1% from baseline to 8 weeks of therapy. In the control group that only received the antipsychotic risperidone, there was a decrease in the average baseline serum IL-6 level to 8 weeks of therapy of 51.62 pg/ml or 33.2%, but after the Wilcoxon test it could be said that the decrease was not significant or in other words it was not there is a decline. The results of the data analysis can be seen in Table 6.

Table 6. Changes in serum IL-6 levels in the treatment group and control group at baseline and after 8 weeks.

Group	Treatment				Control			
	Mean±SD	Differences in mean IL-6 levels	% Decrease in IL-6 levels	p-value	Mean± SD	Differences in mean IL-6 levels	% Decrease in IL-6 levels	p-value
Baseline IL-6 levels	169,09 ± 218,99	-86,39	51,1	< 0,001*	155,39 ± 190,38	-51,62	33,2	0,064
IL-6 levels 8 weeks	82,71 ± 141,56				103,77 ± 165,63			

*Significant p < 0.000(Wilcoxon test)

This study measured lipid profiles in the form of cholesterol, triglyceride, HDL and LDL levels. Results of comparison of lipid profiles of schizophrenic patients between baseline and after 8 weeks of therapy both in patients who were given risperidone therapy and adjuvant statin therapy (treatment) and in patients who were only given risperidone therapy (control). The results showed that there was a significant decrease in cholesterol, triglycerides and LDL and an increase in HDL between before and after being given risperidone therapy and adjuvant statin therapy with a p value <0.001. In the group that was only given risperidone, there was no significant increase in cholesterol, triglycerides and LDL and a decrease in HDL after 8 weeks of therapy with a p value > 0.05. The results can be seen in Table 7.

Table 7. Comparison of lipid profiles of schizophrenic patients between before and after therapy

Group	**Lipid profile**		**p-value**
	Baseline	**8 weeks**	
Cholesterol			
Treatment	147,94 ± 33,52	100,72 ± 5,35	<0,001
Control	143,94 ± 42,07	147,44 ± 37,32	0,420
Triglycerides			
Treatment	140,33 ± 30,31	85,44 ± 23,03	<0,001
Control	130,00 ± 87,15	136,17 ± 69,63	0,433
LDL			
Treatment	63,68 ± 38,85	7,79 ± 5,36	<0,001
Control	56,01 ± 32,59	60,14 ± 31,97	0,500
HDL			
Treatment	54,17 ± 16,15	76,50 ± 6,71	<0,001
Control	62,72 ± 20,39	59,05 ± 15,41	0,306

*Significant p < 0.000(Wilcoxon test)

Results of comparison of changes in lipid profile between baseline and after 8 weeks of therapy in patients who were given risperidone therapy and statin adjuvant therapy (treatment) with patients who were only given risperidone therapy (control). The results showed that there was a decrease in cholesterol, triglyceride and LDL levels and an increase in HDL levels in the treatment group.

Meanwhile in the control group there was an increase in cholesterol, triglyceride and LDL levels and a decrease in HDL levels. Statistical test results obtained p value <0.001 for all parameters of the lipid profile indicating that there was a significant difference in changes in the lipid profile between the treatment and control groups. The results are presented in Table 8.

Table 8. Comparison of post-therapy changes in lipid profile between the treatment and control groups

Lipid profile	Changes in lipid profile levels from baseline to 8 weeks after therapy		p-value
	Treatment (mg/dl)	Control (mg/dl)	
Cholesterol	-47,22 ± 31,00	3,50 ± 16,28	<0,001
Triglycerides	-54,89 ± 18,88	3,17 ± 22,77	<0,001
HDL	22,33 ± 15,24	-3,67 ± 14,02	<0,001
LDL	-55,89 ± 37,84	4,13 ± 22,23	<0,001

*Significant p < 0.000 (Mann Whitney test

To determine the correlation of IL-6 levels and changes in clinical symptoms in patients receiving risperidone therapy and statin adjuvant therapy, this study conducted a correlation test of serum IL-6 levels and clinical symptoms in schizophrenic patients receiving risperidone and statin adjuvant therapy, the results of which are presented in Table 9.

Table 9. Correlation of serum IL-6 levels and clinical symptoms

		IL-6	
		p-value	p-value
Treatment	PANSS Total	0,396	0,017**
Control	PANSS Total	0,185	0,281

Spearman correlation test
Significant *p<0.05, **p<0.01, ***p<0.001 (Spearman Test), r = strength of correlation; 0.1 - 0.3 weak; 0.4 - 0.6 medium; 0.7 - 0.9 strong.

Table 9. The results of the correlation analysis using the Spearman correlation test showed that the correlation between the total PANSS score and serum IL-6 levels in the treatment group showed a significant relationship (p <0.05) with moderate correlation strength and in a positive direction. The correlation between the PANSS scores and serum IL-6 levels in the control group showed no significant results (p>0.05).

In this study, risperidone therapy in schizophrenic patients can reduce IL-6 levels. This result is in line with the research of Feng et al. (2020) that there was a significant decrease in serum IL-6 levels after risperidone treatment. Changes in IL-6 levels can interfere with neurogenesis and reduce glutamate reuptake. Soluble IL-6 receptors (sIL-6R) can bind IL-6 cytokines, further increasing their biological activity. Treatment with the antipsychotic risperidone resulted in a decrease in peripheral sIL-6R levels (Dawidowski et al., 2021). In addition, risperidone suppresses cytokine-induced microglial activation (MacDowell et al., 2013). Because microglial activity is a pathophysiology of schizophrenia, reduced microglial activity can treat schizophrenia and decrease IL-6 levels.

In this study, risperidone therapy and statin adjuvant therapy and risperidone therapy in schizophrenic patients improved clinical symptoms at 4 weeks and the improvement was greater at 8 weeks. Risperidone therapy and statin adjuvant therapy significantly provided better clinical improvement than risperidone therapy in schizophrenic patients. Risperidone treatment can improve clinical symptoms based on the PANSS score which is a measure of positive and negative symptoms in schizophrenic patients. Improvement in positive symptoms following risperidone treatment is thought to be achieved through blockade of D2 receptors, particularly in the mesolimbic pathway. The ability

of antipsychotics to block D2 receptors in the prefrontal cortex and nucleus accumbens is important in improving schizophrenia symptoms (McNeil et al., 2022). Risperidone also has dominant 5-HT2 antagonist activity which is related to negative symptoms of schizophrenia (Madaan, 2009).

In this study, risperidone therapy and adjuvant statin therapy significantly reduced triglyceride and LDL cholesterol levels and increased HDL levels, but not risperidone therapy. This shows the effect of statins on improving the lipid profile of schizophrenic patients. These results are in line with previous research that the use of statins can significantly reduce triglyceride and LDL cholesterol levels and increase HDL levels (Aslani et al., 2023; Shuhaili et al., 2017).

The results showed that there was a significant relationship between serum IL-6 levels and clinical symptoms (PANSS) in schizophrenic patients who received risperidone therapy and statin adjuvant therapy. This result is in line with Lumbantoruan's study (2019) which reported that there was a significantly positive relationship between the PANSS score and IL-6 levels in schizophrenic patients. In contrast to studies that report that there is no significant relationship between the PANSS score and IL-6 levels.

4. Conclusion

Based on the results of this study, it can be concluded that there was a greater decrease in serum IL-6 levels in schizophrenic patients who received adjuvant statin therapy (51.1%) compared to schizophrenic patients who only received risperidone therapy (33.2%). There was a great deal of improvement in clinical symptoms in schizophrenic patients who received statin adjuvants, but in the absence of adjuvants, the improvement in clinical symptoms was only moderate. All lipid levels, namely cholesterol, triglyceride and LDL levels decreased and HDL levels increased after 8 weeks of therapy. In schizophrenic patients receiving statin risperidone adjuvant therapy, decreasing serum IL-6 levels is correlated with a decrease in PANSS score, which means that it causes an improvement in clinical symptoms.

As a suggestion, giving statin adjuvants to schizophrenic patients can be considered because it is proven to improve clinical symptoms, reduce serum IL-6 levels and improve lipid profile levels. Similar studies could be conducted with a larger number of subjects because there is wide variation in IL-6 levels. The practical benefit of this research is as a reference material for Psychiatrists/Psychiatrists in the management of schizophrenic patients. Theoretical benefit is to increase knowledge and understanding regarding the effect of adjuvant statin therapy on serum IL-6 levels, lipid profile and clinical symptoms measured by PANSS in schizophrenic patients and to make a scientific contribution, especially in psychosocial approaches regarding the effect of adjuvant statin therapy on serum IL-6 levels. Lipid profile and clinical symptoms were measured by PANSS in schizophrenic patients. Meanwhile, methodological benefits form the basis for further research on statin adjuvant therapy in schizophrenic patients.

Reference

1. Andrade, C. (2018). The Use of Statins for Antipsychotic Augmentation in Schizophrenia. *The Journal of Clinical Psychiatry, 79*(5).
2. Aslani, S., Razi, B., Imani, D., Mohammadi, K., Reiner, T., Željko, J., & Sahebkar, A. (2023). Effect of Statins on the Blood Lipid Profile in Patients with Different Cardiovascular Diseases: A Systematic Review with Meta-analysis of Randomized Clinical Trials. *Curr Med Chem, 30*(32).
3. Berthold, H. K., Berneis, K., Mantzoros, C. S., Krone, W., & Gouni-Berthold, I. (2013). Effects of simvastatin and ezetimibe on interleukin-6 and high-sensitivity C-reactive protein. *Scandinavian Cardiovascular Journal, 47*(1), 20–27.
4. Bushe, C. J., Taylor, M., & Haukka, J. (2010). Mortality in schizophrenia: a measurable clinical

endpoint. *Journal of psychopharmacology (Oxford, England)*, *24*(4), 17–25.
5. Challa, F., Seifu, D., Sileshi, M., Getahun, T., Geto, Z., Kassa, D., Alemayehu, M., Mesfin, M., Fekadu, A., & Woldeamanuel, Y. (2021). Serum level of highly sensitive C-reactive protein and IL − 6 markers in patients with treatment-resistant schizophrenia in Ethiopia: a comparative study. *BMC Psychiatry*, *21*(1), 4–11.
6. Chaudhry, I. B., Husain, N., Husain, M. O., Hallak, J., Drake, R., Kazmi, A., Rahman, R. ur, Hamirani, M. M., Kiran, T., Mehmood, N., Stirling, J., Dunn, G., & Deakin, B. (2013). Ondansetron and simvastatin added to treatment as usual in patients with schizophrenia: study protocol for a randomized controlled trial. *Trials*, *14*, 1–9.
7. Cho, M., Lee, T. Y., Kwak, Y. Bin, Yoon, Y. B., Kim, M., & Kwon, J. S. (2019). Adjunctive use of anti-inflammatory drugs for schizophrenia: A meta-analytic investigation of randomized controlled trials. *Australian and New Zealand Journal of Psychiatry*, *53*(8), 742–759.
8. Dawidowski, B., Górniak, A., Podwalski, P., Lebiecka, Z., Misiak, B., & Samochowiec, J. (2021). The Role of Cytokines in the Pathogenesis of Schizophrenia. *Journal of Clinical Medicine*, *10*(3), 262–268.
9. Feng, Z., Zhang, Y., You, X., Zhang, W., Ma, Y., Long, Q., Liu, Z., Hao, W., Zeng, Y., & Teng, Z. (2020). Effects of risperidone on blood levels of interleukin-6 in schizophrenia: A meta-analysis. *Medicine*, *99*(15), 19694.
10. Kim, S. W., Kang, H. J., Jhon, M., Kim, J. W., Lee, J. Y., Walker, A. J., ... & Berk, M. (2019). Statins and inflammation: new therapeutic opportunities in psychiatry. *Frontiers in psychiatry*, *10*, 103.
11. Lumbantoruan, S. D. (2019). *Hubungan Antara Fungsi Kognitif dan Kadar Interleukin-6 (IL-6) pada Orang dengan Skizofreni Suku Batak*. Sumatera: Universitas SUmatera Utara.
12. MacDowell, K. S., García-Bueno, B., Madrigal, J. L. M., Parellada, M., Arango, C., Micó, J. A., & Leza, J. C. (2013). Risperidone normalizes increased inflammatory parameters and restores anti-inflammatory pathways in a model of neuroinflammation. *International Journal of Neuropsychopharmacology*,*16*(1),121–135.
13. Madaan, V. (2009). Risperidone: a review of efficacy studies in adolescents with schizophrenia. *Drugs of today (Barcelona, Spain: 1998)*, *45*(1), 55–62.
14. McNeil, S., Gibbons, J., & Cogburn, M. (2022). *Risperidone*. Available: https://europepmc.org/article/NBK/nbk459313.
15. Meo, M. L., Machin, A., & Hasmono, D. (2021). Effect of Simvastatin in Serum Interleukin-6 Level in Patients with Acute Ischemic Stroke. *Folia Medica Indonesiana*, *56*(3), 165.
16. Neelamekam, S., Nurjono, M., & Lee, J. (2014). Regulation of interleukin-6 and leptin in schizophrenia patients: A preliminary analysis. *Clinical Psychopharmacology and Neuroscience*, *12*(3), 209–214.
17. Park, J. W., Park, K. H., Lee, J. E., Kim, Y. M., Lee, S. J., & Cheon, D. H. (2019). Antibody Microarray Analysis of Plasma Proteins for the Prediction of Histologic Chorioamnionitis in Women with Preterm Premature Rupture of Membranes. *Reproductive Sciences*, *26*(11), 1476–1484.
18. Postma, T. S., Lyliana G, N., Maya J L, S., Marc M, B., Peter, M., Erna van't, H., Selene R T, V., Marieke J H, B., & Iris E C, S. (2017). Statins as an Adjuvant Therapy for Psychotic Disorders: Current Evidence with a Systematic Overview of Double-Blind Placebo Controlled Trials. *Journal of Brain Disorders*, *1*(1), 12–19.
19. Riset Kesehatan Dasar (Riskesdas). (2018). *Persebaran Prevalensi Skizofrenia/Psikosis di Indonesia*. Jakarta: Kementrian Kesehatan RI.
20. Riskesdas. (2018). Laporan Provinsi Sulawesi Selatan Riskesdas 2018. In *Badan Penelitian Dan Pengembangan Kesehatan 110*, (9).
21. Saidah, S., Sonny, L. T., Lilik, H., Burhanuddin, B., Haerani, R., & Wempy, T. (2021). Levels of interleukin 6 as a predictor of metabolic syndrome in schizophrenic patients receiving combination therapy of typical and atypical antipsychotics. *Open Access Macedonian Journal of*

Medical Sciences, *9*, 600–607.
22. Shalehuddin, M., Adi, A. C., M, H. M., & Handajani, R. (2019). Relationship between Duration of Illness and Onset with PANSS and Interleukin-6 in Schizophrenia. *J Brain Res*, *2*(2), 109.
23. Shen, H., Li, R., Yan, R., Zhou, X., Feng, X., Zhao, M., & Xiao, H. (2018). Adjunctive therapy with statins in schizophrenia patients: A meta-analysis and implications. *Psychiatry Research*, *262*, 84–93.
24. Shuhaili, M. F. R. M. A., Samsudin, I. N., Stanslas, J., Hasan, S., & Thambiah, S. C. (2017). Effects of Different Types of Statins on Lipid Profile: A Perspective on Asians. *Int J Endocrinol Metab*, *15*(2), 1–12.
25. Tajik-Esmaeeli, S., Moazen-Zadeh, E., Abbasi, N., Shariat, S. V., Rezaei, F., Salehi, B., & Akhondzadeh, S. (2017). Simvastatin adjunct therapy for negative symptoms of schizophrenia: A randomized double-blind placebo-controlled trial. *International Clinical Psychopharmacology*, *32*(2), 87–94.
26. Talreja, O., Kerndt, C., & Cassagnol, M. (2022). Simvastatin. *StatPearls Publishing LLC*.
27. Ward, N. C., Watts, G. F., & Eckel, R. H. (2019). Statin Toxicity: Mechanistic Insights and Clinical Implications. *Circulation Research*, *124*(2), 328–350.
28. World Health Organization. (2017). *Mental health ATLAS 2017 state profile. Geneva: World Health Organization*. World Health Organization; WHO.