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Original Research

The Effect of Administering Omega-3 Supplements on Serum Lipopolysaccharide (LPS) Levels in Schizophrenia Patients Who Are Taking Atypical Antipsychotics in the Psychiatric Hospital of Prof HB Saanin Padang

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Abstracts

Introduction: Schizophrenia is a severe mental disorder that ranks among the top 10 major contributors to global disability. Schizophrenia is a disorder of brain function in the form of impaired perception, thoughts, feelings, cognitive processes, and behavior. They require long-term atypical antipsychotics for therapy, but they have secondary effects on food intake and cause intestinal dysbiosis, one of which is characterized by increased serum lipolysaccharide (LPS) levels. We aim to examine the impact of omega-3 supplementation on serum LPS levels in schizophrenia patients utilizing atypical antipsychotics. **Methods:** This research is an experiment with a randomized pretest-posttest control group design and a triple-blind study in Prof. HB Saanin Padang's psychiatric hospital and the Biomedic Laboratory, Faculty of Medicine, Andalas University, from July 2023 to February 2024. The research sample consisted of 15 individuals who received 1000 mg Omega-3 PUFA (180 mg EPA and 120 mg DHA) daily for 21 days, and another 15 individuals who served as the control group. We checked the serum LPS levels using ELISA in duplicate on days 0 and 22. We analyzed the data using the paired t-test. **Results:** There was a significant difference in serum LPS levels in schizophrenia patients taking atypical antipsychotics before and after being given omega-3 supplements in the inpatient ward of Prof. HB Saanin Mental Hospital Padang with $p = 0.02$ ($p < 0.05$). **Conclusion:** Omega-3 supplement 1000 mg/day can reduce serum LPS levels in schizophrenia patients who receive atypical antipsychotic therapy.

Keywords: Atypical Antipsychotics, Omega-3 PUFA, Lipopolysaccharide (LPS) levels, Schizophrenia, Mental Health

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INTRODUCTION

Schizophrenia is a chronic illness that causes the most disability in the world. Estimates place the global prevalence of schizophrenia patients in various age groups at 13.1-20.19 million. Most cases occur in Asia. In Indonesia, schizophrenia patient number 400,000, or 1.7 per 1000 people. The ninth rank with the highest number of schizophrenia patients is in West Sumatra Province, which is 50,608 people, and the city of Padang is the peak with a prevalence of 7.0 people [1 – 5].

Schizophrenia is a disorder of brain function in the form of impaired perception, feelings, thoughts, behavior, and cognition, making it difficult to distinguish between hallucinations and reality. In controlling symptoms, people with schizophrenia rely heavily on antipsychotics. There are two types of antipsychotics commonly used today, namely typical antipsychotics and atypical antipsychotics. AAtypical antipsychotics are currently the preferred therapy because they can simultaneously control negative symptoms, cognitive and mood disorders, and have limited extrapyramidal side effects. However, the use of atypical antipsychotics can lead to various cardiometabolic complications due to secondary effects on neurohormones that regulate appetite, and can also directly cause gut dysbiosis by completely inhibiting the growth of certain gut microbiota [6 – 9].

Gut dysbiosis is an alteration in the composition and abundance of the intestinal microbiota. This results in elevated levels of lipopolysaccharide (LPS) produced by pathogenic bacteria and reduced levels of short-chain fatty acids (SCFA), in addition to decreased expression of intestinal epithelial tight junctions. LPS crosses the intestinal epithelium via the paracellular route into the circulation, triggering a low-grade inflammatory reaction that is the underlying pathophysiology of many cardiovascular, immunologic, and neuropsychiatric diseases [10 – 14].

The prevalence of obesity and diabetes among individuals with schizophrenia exceeds that of the general population. Obesity is reported in about 50% of patients, glucose intolerance in 25% of patients, diabetes in 15% of schizophrenia patients, and the prevalence of metabolic syndrome in the adult population receiving atypical antipsychotic therapy is in the range of 37–63%. The emergence of these side effects is already apparent even at 12 weeks of atypical antipsychotic use, thus worsening quality of life and increasing relapse [2, 15, 16].

The dysbiosis caused by atypical antipsychotics must be addressed so that schizophrenia patients can recover without complications. The omega-3 effect on gut microbiota has been widely investigated, but the mechanism is less well defined. Omega-3 is an essential fatty acid that humans must obtain from food, which has benefits on gastrointestinal immunity, tolerance, and defense of gut microbiota. Several human studies have demonstrated that omega-3 supplementation can modulate gut microbiota, reduce LPS levels, increase SCFA, reduce atherogenic index, increase HDL, insulin sensitivity, and inflammation repair (hsCRP), and maintain gut wall integrity [17, 18, 19].

Building upon the aforementioned explanation, omega-3 emerges as a potentially beneficial nutrient in mitigating diseases linked to dysbiosis. Hence, researchers aim to investigate the impact of omega-3 supplementation on serum LPS levels among schizophrenia patients who are taking atypical antipsychotics in the inpatient ward of Prof. HB Saanin Mental Hospital Padang.

METHODS

The study employed an experimental design with a randomized pretest-posttest control group in July 2023 to February 2024 in 30 schizophrenia patients admitted to Prof. HB Saanin Mental Hospital Padang. The experimental group comprising 15 participants received omega-3 supplementation 1000 mg/day after breakfast, which contains 180 mg EPA and 120 mg DHA, for 21 days, while the control group of 15 people was also given a placebo. Examination of serum LPS

levels was carried out twice on day 0 (before treatment) and on day 22 (after treatment) at the Biomedical Laboratory of the Faculty of Medicine, Andalas University, using ELISA.

RESULTS

All data analysis was performed with SPSS for Windows. Serum LPS measurement results were presented as mean ± standard deviation (mean ± SD). Furthermore, data normality test was conducted using Shapiro-Wilk test, due to the small sample size and followed by homogeneity test using Levene test. In this study, LPS levels were normally distributed and homogeneous so that the research analysis used the t-paired test.

Characteristics of Research Subjects

Table 1. Characteristics of Schizophrenia Patients Taking Atypical Antipsychotics in the Inpatient Ward of Prof HB Saanin Mental Hospital Padang (n = 30)

Characteristics	Control Group (n=15)	Experimentgroup (n=15)
	Mean ± SD	Mean ± SD
Age (year)	34.1 ± 9.2	34.1 ± 9.3
Body weight (kg)	60.1 ± 8.8	58.3 ± 8.0
Height (cm)	158.6 ± 8.3	157.5 ± 6.2
BMI (kg/m^2)	23.9 ± 3.7	23.5 ± 3.4
Omega-3 food intake (mg/day)	687.9 ± 4.6	687.9 ± 4.6
Duration of atypical antipsychotic Therapy (month)	26.7 ± 22.7	26.9 ± 22.8

Characteristics	Control Group		Experimentgroup	
	n	%	n	%
Gender				
Male	9	30	9	30
Female	6	20	6	20
Education Level				
Elementary school	5	16.7	5	16.7
Junior high school	3	10.0	3	10.0
Senior high school	7	23.3	7	23.3
Smoking Habit				
Smoking	8	26.7	8	26.7
No smoking	7	23.3	7	23.3
Types of Atypical Antipsychotics				
Risperidon				
Clozapin	10	33.3	10	33.3
Risperidon+OLZ	1	3.3	1	3.3
Risperidon+Que	2	6.7	2	6.7
	2	6.7	2	6.7
Totally	15	50.0	15	50.0

Notes: BMI= Body Mass Index; Risperidon+OLZ = Combination of Risperidon and Olanzapine; Risperidon+Que = Combination of Risperidon and Quatiapine.

Table 1 explained that the average age in the experiment group was (34.1 ± 9.3) years and the control group had an average age of (34.1 ± 9.2) years. The average body weight in the experiment group was (58.3 ± 8.0) kg, slightly lower than the control group (60.1 ± 8.8) kg. The average height of the experiment group (157.5 ± 6.2) cm, slightly lower than the average height of the control group (158.6 ± 8.3) cm. The nutritional status of the experiment group was (23.5 ± 3.4) kg/m2, slightly lower than that of the control group (23.9 ± 3.7) kg/m2, but on average both were still in the normal nutrition category. The average duration of taking atypical antipsychotics in both groups was 26.9 ± 22.4) months. While the average intake of Omega-3 from food calculated from 24-hour Food Recall and analyzed with Nutrisurvey Indonesia in both study groups was (687.9 ± 4.6) mg/day.

Table 1 also shows that the gender of most respondents was male (60%), 30% in the experimental group and 30% in the control group. Female respondents amounted to 40%, 20% in the experiment group and 20% in the control group. The highest educational status of the respondents was high school (46.6%), followed by elementary school (33.4%) and junior high school (20%).

There were no respondents with no school or college education. More than half of the respondents smoked (53.4%) and the rest did not smoke (46.6%). The most common type of atypical antipsychotic consumed by schizophrenia patients was risperidone (66.6%), only some respondents consumed other types of antipsychotics or combined atypical antipsychotics.

Differences in Serum LPS Levels Before and After Treatment in Control and Experiment Groups

Table 2. Mean differences in serum LPS levels in both of the control group and the Omega-3 supplemented group PUFA supplementat 1000 mg/day for 21 days at Prof. HB Saanin Mental Hospital Padang Before and the experiment.

Table 2. Mean differences in serum LPS levels in both of the control group and the Omega-3 supplemented group PUFA supplementat 1000 mg/day for 21 days at Prof. HB Saanin Mental Hospital Padang Before and the experiment.

Serum LPS Level (EU/L)		Mean ±SD	SE	*p* value
Control (Plasebo) (n=15)	Before experiment	430.1 ± 53.5	13.8	$p = 0.005$
	After experiment	469.0 ± 47.5	12.3	
Omega-3 PUFA supplement 1000 mg/day for 21 days (n=15)	Before experiment	489.8 ± 56.8	14.7	$p = 0.02$
	After experiment	479.3 ± 69.4	17.9	

Note: test of differences in serum LPS levels before and after treatment was carried out using the t-paired test, significant ($p < 0.05$).

Table 2 shows that the average initial serum LPS level of the control group was (430.1 ± 53.5) EU/L. For 21 days, this group was given placebo and atypical antipsychotic therapy, then serum LPS levels were measured with an average of (469.9 ± 47.5) EU/L. Whereas in the experiment group, the mean initial LPS level was (489.8 ± 56.8) EU/L and the mean serum LPS level after being given Omega-3 PUFA supplement 1000 mg/day for 21 days was (479.3 ± 69.4) EU/L. It was found that the average serum LPS level of the control group after 21 days of atypical antipsychotic therapy was higher than the average initial serum LPS level, with $p = 0.005$ ($p < 0.05$). While in the experiment group, after being given Omega-3 PUFA supplement 1000 mg/day for 21 days, serum LPS levels after treatment were lower when compared to the average serum LPS levels before experiment, with $p = 0.02$ ($p < 0.05$).

DISCUSSION

Characteristics of Research Subjects

The results of this study indicate that in Indonesia, schizophrenia patients are more likely to be male in the adult age range. Although the reason for the gender difference in schizophrenia remains unrevealed, recent findings suggest that males exhibit a peak onset age between 21 and 25 years of age, whereas the age of onset in females is consistent with other studies reporting that 66%–87% of patients experience onset after the age of 40–50 years [20].

Despite the lack of a definitive explanation, there is a reciprocal relationship between educational status and the incidence of schizophrenia. Schizophrenia patients tend to have low educational status. Research suggests that not completing primary school and receiving low grades are correlated with an increased risk of schizophrenia [21, 22].

Schizophrenic patients also tend to have a high smoking habit. More than half of schizophrenia patients smoke. Smoking is a risk factor associated with the development of schizophrenia, and schizophrenia patients who smoke are more prone to experiencing heightened positive symptoms and diminished cognitive function and tend to behave aggressively than schizophrenia patients who are non-smokers. In addition, the harmful components present in cigarette smoke when ingested into the gastrointestinal tract

can lead to dysbiosis in the gastrointestinal microbiota through various mechanisms, including antimicrobial effects and modulation of the gut microbiota environment [23, 24].
Atypical antipsychotics are the current therapy of choice. Most schizophrenia patients consume risperidone, but some respondents take other types of antipsychotics or combined atypical antipsychotics. Atypical antipsychotics can alter the composition of the gut microbiota through neurohormonal mechanisms and directly inhibit the growth of some microbiota species [9].
Patients with schizophrenia who take atypical antipsychotics tend to have good nutritional status because their use has an agonist effect on neurohormone receptors (Serotonin 5-HT2c, muscarinic, and histamine H1), which increases food intake [25].

Effect of Atypical Antipsychotic Therapy on Serum LPS Levels

The mean baseline serum LPS level of the control group was (430.1 ± 53.5) EU/L. For 21 days, this group received daily atypical antipsychotic therapy and a placebo. On day 22, the mean serum LPS level of the control group increased to (469.9 ± 47.5) EU/L. Statistical tests showed a significant difference in the mean serum LPS levels before and after day 21 in the control group, with $p = 0.005$ ($p < 0.01$).
Atypical antipsychotics, which can directly inhibit some intestinal microbiota and damage the intestinal wall barrier, were responsible for the rise in serum LPS levels observed in the control group. In addition, the average daily intake of Omega-3 from food only amounted to (687 ± 4.61) mg/day; this amount is not sufficient from the recommended daily requirement of 1600 mg/day so that it cannot modulate the dysbiotic gut microbiota [26].

Differences in Serum LPS Levels in Experiment Groups

The mean initial serum LPS level in the experiment group was (489.8 ± 56.8) EU/L. After being given 1000 mg/day omega-3 PUFA supplement containing 180 mg EPA and 120 mg DHA for 21 days, the mean serum LPS level of the experiment group decreased to (479.3 ± 69.4) EU/L. Statistical tests showed a significant difference in the average serum LPS levels before and after being given Omega-3 PUFA supplements 1000 mg / day for 21 days in the experiment group, with $p = 0.02$ ($p<0.05$).
In the experiment group, the mean initial serum LPS level was (489.8 ± 56.8) EU/L. After being given a 1000 mg/day omega-3 PUFA supplement containing 180 mg EPA and 120 mg DHA for 21 days, the mean serum LPS level of the experiment group decreased to (479.3 ± 69.4) EU/L. In the experiment group, statistical tests showed a significant difference in the average serum LPS levels before and after being given Omega-3 PUFA supplements 1000 mg/day for 21 days, with $p = 0.02$ ($p<0.05$).
The drop in average LPS levels was because people got the recommended daily amount of Omega-3, which is 1600 mg/day. They got this from food (687 ± 4.61) mg/day plus supplements that gave them 1000 mg/day. Omega-3 is an unsaturated fatty acid that plays a role in repairing the intestinal wall barrier, increasing the synthesis of anti-inflammatory molecules such as butyrate, and modulating the gut microbiota so as to prevent LPS translocation to the circulation [25 – 27].
The findings of this study align with several studies conducted in adults, which have demonstrated general alterations in the gut microbiota following omega-3 supplementation. One such study involved the administration of pure omega-3 fatty acids (180 mg EPA and 120 mg DHA per capsule) daily for a duration of 2 weeks in obese patients. This intervention resulted in a reduction in the atherogenic index, elevation in HDL levels, enhanced insulin sensitivity, amelioration of inflammation (hsCRP), augmentation of Lactobacillus and Bifidobacterium populations, and a decline in gram-negative bacteria. Specifically, the decrease in Faecalibacterium often correlates with an increase in

Bacteroidetes and butyrate-producing bacteria belonging to the Lachnospiraceae family [27].

Omega-3 polyunsaturated fatty acids (PUFAs) exhibit beneficial effects by restoring microbiota composition and enhancing the production of anti-inflammatory compounds, such as short-chain fatty acids (SCFAs). Moreover, emerging evidence from animal model studies suggests that the interplay among gut microbiota, omega-3 fatty acids, and immunity contributes to maintaining gut wall integrity and modulating immune cell activity. Studies conducted in mice indicate that omega-3 fatty acids can alter the microbiota by promoting the production and secretion of intestinal alkaline phosphatase (IAP), which leads to a decrease in the abundance of lipopolysaccharide (LPS)-producing bacteria, consequently mitigating metabolic endotoxemia. Specifically, omega-3 supplementation has been shown to ameliorate intestinal barrier dysfunction and reduce PPAR-cho levels induced by intestinal ischemia and reperfusion injury in a Sprague-Dawley rat model. Human and animal research alike has underscored the capacity of omega-3 fatty acids to modulate the brain-gut axis through their influence on gut microbiota composition [28].

Noriega et al. (2016) examined the effect of omega-3s in improving various human diseases, including cardiometabolic, inflammation, and cancer. A diet of 600 mg omega-3 daily for 14 days in 45-year-old adult men decreased Faecalibacterium prausnitzii and Akkermansia spp. and increased some butyrate-producing bacteria. Some of the health benefits associated with omega-3 may be attributed in part to the augmentation of butyrate-producing bacteria. These discoveries could elucidate the mechanisms underlying the effects of omega-3 on certain chronic illnesses and could provide a foundation for patient care strategies [29].

Zhu X et al. (2021) investigated the therapeutic effects of omega-3 supplementation on the gut microbiota of individuals suffering from depression, cardiovascular disease, and inflammatory bowel disease. Their findings revealed that administering omega-3 containing 180 mg EPA and 120 mg DHA per day for 21 days resulted in an increase in the proportion of beneficial bacteria such as Lactobacillus, Helicobacter, and Ruminococcus and a decrease in the proportion of harmful bacteria such as Bacteroides, Clostridium, and Prevotella. Additionally, omega-3 supplementation led to elevated mucosal SIgA and serum IL-10 levels while decreasing serum levels of LPS, IL-1ß, and TNF-α [30].

CONCLUSION

Atypical antipsychotic therapy increases serum LPS levels in schizophrenia patients and Omega-3 PUFA supplementation of 1000 mg/day for 21 days can reduce serum LPS levels in schizophrenia patients taking atypical antipsychotics. The results indicated a notable disparity in serum LPS levels in schizophrenia patients taking atypical antipsychotics before and after being given omega-3 PUFA supplements in the inpatient ward of Prof HB Saanin Mental Hospital Padang with $p = 0.02$ ($p < 0.05$).

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CONFLICT OF INTEREST

There are no conflicts of interest in this research.

ETICHAL CLEREANCE

This research has been presented in front of the Ethics Committee of the Faculty of Medicine, Andalas University Padang with No. 38/UN.16.2/KEP-FK/2024 and has been approved for implementation. The research protocol contains attached information to respondents including reasons for participation, research objectives, time required,

risks and benefits of research. All consequences arising from the implementation of this study concerning intervention actions against respondents are the responsibility of the researcher.

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