RESEARCH ARTICLE

Effect of Omega-3 Adjuvant Therapy on Cognitive Improvement and Levels of Glial Cell Line-Derived Neurotrophic Factor (GDNF) in Schizophrenia Patients Receiving Risperidone Therapy

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ABSTRACT

Background: Schizophrenia is a disorder with severe and persistent psychotic manifestations accompanied by cognitive impairment. Treatment with atypical antipsychotic therapy (APG-2) provides only minimal benefit for the cognitive impairment of schizophrenia patients. Many efforts are currently being expanded to find new treatments that can serve as "co-treatments" to improve neurocognition from aspects of neurobiology and neuroplasticity. Several studies found that omega-3 fatty acids can improve cognitive function in schizophrenia patients.

Objective: The objective is to assess the impact of omega-3 adjuvant therapy on improving cognitive function and elevating glial cell line-derived neurotrophic factor (GDNF) levels in individuals diagnosed with schizophrenia who are undergoing risperidone treatment.

Method: A research study utilizing experimental analysis, including pre-tests and post-tests with non-random group selection, was conducted at Dadi Regional Special Hospital in South Sulawesi, Indonesia, between May and July 2023. Sample testing was carried out at the HUMRC Research Laboratory. The study involved 44 participants divided into two groups: a treatment group comprising 22 individuals who received 4 mg/day risperidone along with Omega-3 supplements for eight weeks and a control group of 22 individuals who received only 4 mg/day risperidone. Cognitive function was evaluated using the MoCA-Ina tool, while GDNF serum levels were determined through enzyme-linked immunosorbent assays (ELISA). Significance was assessed through the Chi-square, Wilcoxon, Mann-Whitney, Pearson and Spearman correlation tests.

Results: There was an improvement in cognitive function and a significant increase of GDNF serum levels in schizophrenia patients who received omega-3 adjuvant therapy over 8 weeks compared to individuals with schizophrenia who solely received the antipsychotic risperidone.

Conclusion: Supplementing standard risperidone therapy with omega-3 adjuvant can enhance cognitive function and elevate GDNF levels.

Keywords: Cognitive function, GDNF serum, Omega-3, Risperidone, Schizophrenia.

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INTRODUCTION

Schizophrenia is a disorder with severe and persistent psychotic manifestations accompanied by cognitive impairment and psychosocial disorders, in which there is deterioration of personal, social, and occupational functioning as a result of unusual perceptions and thoughts, disturbed emotions, and motor abnormalities.[1] The symptoms that occur in schizophrenia have a significant impact on the patients,

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families, and their social community.[2] Information provided by the World Health Organization (WHO) in 2018 indicates that approximately 23 million individuals worldwide are affected by schizophrenia. Data from the Indonesian Basic Health Research in 2018 shows that the prevalence of schizophrenia in Indonesia is 6.7 per 1000 households. This data has increased from 2013 data, which recorded a prevalence of schizophrenia patients at 1.3 per 1000 households.[3,4]

The current treatment of atypical antipsychotic, also called second-generation antipsychotic (APG-2), is expected to improve cognitive impairment because it works in the mesocortical pathway, which blocks serotonin (5HT2A) receptors more than dopamine (D2) receptors, which is different with first-generation antipsychotic (APG-1), which only act on mesocortical pathways that strongly block D2 receptors.[5] Risperidone accounts for nearly half of all atypical antipsychotics prescribed, based on recent reports. The choice of second-generation antipsychotic medications such as risperidone is based on their ability to improve positive symptoms, negative symptoms, and cognitive function while minimizing neuroleptic side effects compared to first-generation antipsychotic drugs (APG-1).[6-8]

However, it seems that APG-2 only provides minimal benefits for cognitive impairment in schizophrenia patients. Many efforts are currently being expanded to find new treatments that can serve as "co-treatments" to improve neurocognition from aspects of neurobiology and neuroplasticity.[2] Several experimental studies carried out by Hsu[9] and Wei Tang[10] in China reported that the administration of omega-3 fatty acids could enhance negative symptoms, cognitive function, and overall functioning in schizophrenia patients.[9,10]

Recently, numerous researchers have directed their efforts toward exploring the potential of nutritional therapy in addressing neurological and mental disorders. The objective is to enhance the influence of dietary components on brain function, neural plasticity, and psychological health.[11] The study carried out by Jamilian.[12] was randomized, double-blind, for 8 weeks, involving 60 schizophrenia patients split into two groups: one receiving omega-3 supplementation (1000 mg/day) (n = 30) and the other receiving a placebo (n = 30). Omega-3's efficacy in reducing overall psychopathological symptoms and total scores demonstrated significance compared to the placebo group, beginning at 4 and 6 weeks into the treatment, respectively (p <0.05). In this study, glial cell-derived neurotrophic factor (GDNF) levels were also measured, which plays a role in neural plasticity, which is very important for cognitive function. Research by Tang[13] in China showed that elevated serum GDNF levels correlated with improved cognitive abilities among individuals with schizophrenia, suggesting a potential neuroprotective role. GDNF might be pertinent to the dopaminergic and neurodevelopmental hypotheses of schizophrenia. A 2014 study by Niitsu,[14] in Japan, showed that higher levels of GDNF resulted in more severe attention deficits in schizophrenia patients.

This study represents a pioneering effort in Indonesia, particularly in Makassar, to investigate the potential benefits of omega-3 adjuvant therapy on cognitive function and serum GDNF levels in schizophrenia patients. Given the known association between schizophrenia and reduced levels of fatty acids in the brain, which can affect cognitive function, as well as the potential role of GDNF in schizophrenia pathology, exploring the integration of dietary omega-3 supplements in treatment strategies is deemed valuable. Moreover, considering the possibility that omega-3 supplementation could enhance the efficacy of standard antipsychotic medications by modulating neurotransmission, investigating its effects becomes even more pertinent.

With this background in mind, the research inquiry focuses on examining whether administering omega-3 adjuvant therapy can lead to improvements in cognitive function and an increase in GDNF levels in schizophrenia patients already undergoing risperidone therapy. The overarching objective is to assess the impact of omega-3 adjuvant therapy on cognitive function and serum GDNF levels in this patient population.

The research endeavors to accomplish several objectives. Firstly, it aims to evaluate and contrast the Montreal Cognitive Assessment Version - Indonesia (MoCA-Ina) scores among the control and treatment groups at three distinct time points: baseline, 4 and 8 week. Secondly, it seeks to verify and juxtapose the levels of glial cell-derived neurotrophic factor (GDNF) in schizophrenia patients within the control and treatment groups at both baseline and the eighth week. Finally, the study intends to delve into the relationship between GDNF levels and MoCA-Ina scores across both groups, exploring potential correlations. By addressing these aims, the research aims to shed light on the impact of omega-3 adjuvant therapy on cognitive function and serum GDNF levels in schizophrenia patients, thereby contributing to the advancement of treatment strategies for this complex psychiatric condition.

The hypothesis posited in this study suggests that schizophrenia patients receiving omega-3 adjuvant therapy alongside risperidone will exhibit an increase in MoCA-Ina scores and GDNF levels compared to those solely receiving risperidone. This hypothesis sets the stage for investigating the potential therapeutic effects of omega-3 supplementation in improving cognitive function and GDNF levels in schizophrenia patients, thereby contributing to advancements in treatment approaches for this complex disorder.

RESEARCH METHODS

The methodology employed in this study utilizes an experimental analysis approach, explicitly employing a pre-test and post-test research design with non-random group selection. This design allows for measuring variables before and after the treatment intervention, enabling researchers to assess changes over time within each group. The study was conducted at the psychiatric department of Dadi Regional Special Hospital, situated in South Sulawesi Province, from May to July 2023.

The study population consisted of hospitalized individuals diagnosed with schizophrenia who met specific inclusion criteria. The minimum sample size for each group was set at 22 individuals. To be included in the study, participants

had to meet various criteria, including being diagnosed with schizophrenia according to DSM V and ICD 10 criteria, being aged between 20 and 45 years, receiving a therapeutic dose of risperidone (4 mg/day), having a disease onset of ≤ 3 years, and having passed the acute phase (PANSS-EC < 15) with a total PANSS score ≤ 95. Additionally, participants needed to express willingness to participate in the research.

Exclusion criteria were also established, which included the presence of organic comorbidities, a history of drug consumption within six months prior to hospital admission, and the use of anti-inflammatory drugs or antibiotics. Moreover, dropout criteria were specified, such as irregular intake of the antipsychotic medication risperidone, refusal of research participation by the subjects, or mortality among the research subjects.

By delineating explicit inclusion, exclusion, and dropout criteria, the study ensures that participants are appropriately selected and that potential confounding factors are minimized. This rigorous approach enhances the study's internal validity and increases confidence in the accuracy and reliability of the results obtained.

The research tools employed in this study included an informed consent form, the MoCA-Ina scale, Risperidone medication at the therapeutic dose, omega-3 capsules, a blood sampling kit, and a GDNF ELISA kit. In this study, the study subjects were divided into two groups: The treatment group, which received risperidone along with omega-3 supplementation, and the control group, which received risperidone alongside a placebo. Data analysis was conducted using SPSS version 24.0. The data that has been processed will be presented in the form of tables, diagrams, and significant values. Approval was obtained from the Ethics Committee for Biomedical Research on Humans, Faculty of Medicine, Universitas Hasanuddin, to ensure ethical compliance. Prior to participation in the research, informed consent was obtained from each subject, and strict confidentiality regarding the identity of the research subjects was maintained.

RESULTS

In this study, 44 individuals diagnosed with schizophrenia were separated into two groups: A treatment group comprising 22 subjects and a control group consisting of 22 subjects, all meeting the inclusion criteria. Statistical descriptive analysis was conducted to present descriptive data on the frequency distribution of research participants. The subjects in this study were two women and the rest were men. The mean age of participants in the treatment group was 32 years, while in the control group, it was 34.64 years. Regarding education, it was shown that most subjects from both groups are junior and senior high school.

The study thoroughly examined participants' demographic characteristics to ensure the comparability between the treatment and control groups. The analysis revealed that a substantial majority of subjects in both groups were employed, comprising 81.8% of the total participants. Additionally, the predominant marital status among participants in both groups was married, accounting for 77.3% in each group. These findings suggest no significant disparities in employment status or marital status between the two groups, indicating initial comparability in these vital demographic factors.

Statistical tests were employed to confirm the homogeneity of the study participants further. The homogeneity test involved applying the T-independent test for age groups and the chi-square test for marital status, education, and employment. The results indicated that the *p-values* for all variables exceeded the threshold of 0.05 ($p > 0.05$). This implies no statistically significant differences between the treatment and control groups in terms of age distribution, marital status, education level, or employment status. The findings from Table 1 further support these conclusions, providing a clear overview of the demographic characteristics of participants in both groups and the results of the statistical tests conducted to assess homogeneity.

Table 2 displays the initial or baseline MoCA-Ina value measured in both groups. The treatment group had a mean baseline MoCA-Ina value of 17.91 ± 1.82, while the control

Table 1: Demographic characteristics of research subjects

Variable		*Kelompok*	
		Treatment n = 22	*Control n = 22*
Age (Mean ± SD)		32.00 ± 6.32	34.64 ± 8.58
Gender	Male	20	22
		90.9%	100.0%
	Female	2	0
		9.1%	0.0%
Education	Elementary school	5	4
		22.7%	18.2%
	Junior high school	7	7
		31.8%	31.8%
	Senior high school	7	7
		31.8%	31.8%
	Undergraduate	3	4
		13.6%	18.2%
Marital status	Married	17	17
		77.3%	77.3%
	Single	5	5
		22.7%	22.7%
Emplo yment	Employed	18	18
		81.8%	81.8%
	Unemployed	4	4
		18.2%	18.2%

Table 2: MoCA-Ina values and baseline GDNF levels in the treatment and control groups

Variable	*Treatment*	*Control*	*P*
Moca - Ina baseline	17.91 ± 1.82	17.32 ± 2.32	0.353[a]
GDNF baseline	4.16 ± 2.64	3.93 ± 3.01	0.549[b]

a. Independent t-test b. Mann Whitney test

group had a mean baseline MoCA-Ina value of 17.32 ± 2.32. Meanwhile, the baseline GDNF level in the treatment group of 4.16 appeared to be higher than the GDNF level within the control group, precisely 3.93, and following the execution of the Mann-Whitney test, the outcomes did not demonstrate significance, as indicated by a *p-value* exceeding 0.05 (Table 2).

Furthermore, to observe alterations in cognitive symptoms among both the treatment and control cohorts, the baseline Moca - Ina scores were analyzed at the 4 and 8 weeks, and assessments were conducted, revealing enhancements in both the treatment and control groups, as detailed in Table 3.

In Table 3, the MoCA-Ina scores measured at baseline, 4 and 8 weeks showed significant results in the treatment group. The mean MoCA-Ina score at the baseline was 17.91 ± 1.82; in the fourth week, it was 19.05 ± 1.70, and in the eighth week, it increased to a mean of 21.05 ± 1.68. Meanwhile, in the control group, when measured at baseline week, 4 and 8 week, there was an increase, but after being tested using the Friedman test, no significant results were obtained. Within the control group, MoCA-Ina scores rose from the baseline week to the 4 week; however, no additional increase was noted from the fourth week to the 8 week. When comparing the treatment and control groups, a significant value was observed in the 8 week for MoCA-Ina. Figure 1 displays a comparison of the rise in MoCA-Ina scores between the treatment group and the control group from baseline to the 4 and the 8 week.

Table 3: Comparison of MoCA-Ina values in the treatment and control groups baseline week, fourth week, and eighth week

Group	*Treatment*	*Control*	*p*
Moca - Ina week baseline	17.91 ± 1.82	17.32 ± 2.32	0.353[a]
Moca - Ina 4th week 19.05 ± 1.70 18.23 ± 1.77 0.125[b]			
Moca - Ina 8th week	21.05 ± 1.68	18.23 ± 1.77	0.000[a]
p	*<0.001[c]*	*0.319[d]*	

a. Independent t-test
b. Mann Whitney test
c. Repeated ANOVA test
d. Friedman test

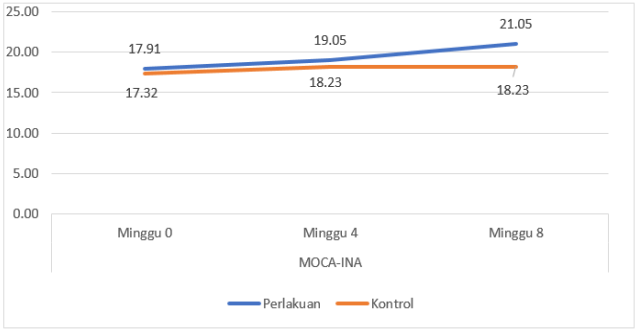

Figure 1: Comparison of MoCA-Ina improvement in the treatment and control groups

Both groups showed an uptick in MoCA-Ina scores, indicating cognitive enhancements. However, the treatment group exhibited a more pronounced improvement compared to the control group. Following eight weeks of omega-3 adjuvant therapy in the treatment group, there was a notable elevation in serum GDNF levels, increasing by 0.95 ng/mL from baseline to the eighth week. In contrast, the control group saw a smaller rise in GDNF serum levels, with an increase of only 0.88 ng/mL (Table 4).

At baseline, serum GDNF levels were compared between the treatment and control groups, revealing a significant increase in serum GDNF levels ($p < 0.05$) in the eighth week in the treatment group. Conversely, the increase in serum GDNF levels in the eighth week was not significant ($p > 0.05$) in the control group. Additionally, Table 5 illustrates the correlation

Table 4: Comparison of GDNF levels in the treatment and control groups at baseline and eighth week

Group	*Treatment*	*Control*	*p*
GDNF baseline	4,16 ± 2.64	3,93 ± 3.01	0.549[b]
GDNF 8th week	5,11 ± 2.76	4,81 ± 3.45	0.411[b]
p	*0.001[e]*	*0.249[f]*	

Table 5: Correlation between serum GDNF levels and Moca Ina in the treatment and control groups

		GDNF	
		r-value	*p*-value
Treatment	MOCA-INA	0,462	0.030[g]
Control		0,259	0.244[h]

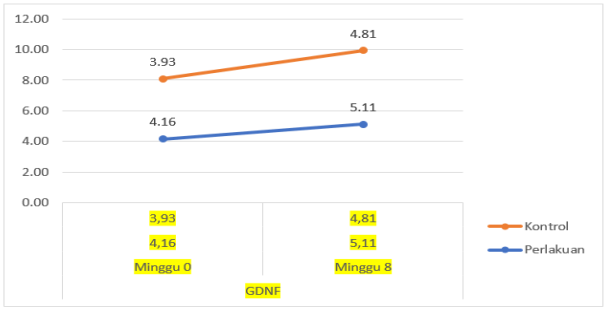

Figure 2: Comparison of the increase in GDNF levels in the treatment group and the control group

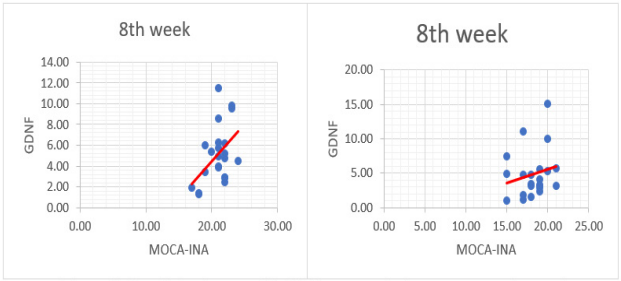

Figure 3: Correlation between MoCA-Ina scores in the treatment and control groups

between serum GDNF levels and MoCA-Ina values in both groups.

The findings from the Spearman correlation test revealed a significant correlation between MoCA-Ina and serum GDNF levels within the treatment group, indicating a moderate-strength positive relationship (p <0.05). No significant correlation was found between the total MoCA-Ina score and serum GDNF levels in the control group (p >0.05)(Figure 2). Figure 3 shows the correlation between GDNF scores and cognitive improvement.

DISCUSSION

This study aimed to investigate the effects of omega-3 adjuvant therapy on cognitive function, as measured by the MoCA-Ina assessment tool, and its potential association with serum GDNF levels in patients diagnosed with schizophrenia over an 8-week treatment duration. The initial step involved ensuring the comparability of the participants assigned to the treatment and control groups. Analysis revealed no significant differences in key demographic variables, such as age, education level, employment status, and marital status, between the two groups (p > 0.05). These findings indicate that the participants in both groups exhibited homogeneity in their baseline characteristics.

Homogeneity in demographic characteristics is essential in clinical studies as it helps to minimize confounding variables and ensures that any observed differences in outcomes can be more confidently attributed to the intervention being investigated. In this case, the absence of notable distinctions in demographic factors suggests that changes in cognitive function or serum GDNF levels observed during the study period are less likely to be influenced by factors such as age, education, or employment status. This homogeneity enhances the study's internal validity, strengthening the credibility of the results. It provides a solid foundation for subsequent analyses, allowing researchers to more accurately assess the specific effects of omega-3 adjuvant therapy on cognitive function and its potential relationship with GDNF levels in schizophrenia patients.

The average age of the research participants was 32.00 ± 6.32 in the treatment group and 34.64 ± 8.58 in the control group. This study included a higher number of male participants, as there was a more significant proportion of men hospitalized during the research period. According to theory, typically, schizophrenia tends to manifest at an earlier age in males than in females. Research indicates that more than half of schizophrenia patients are male, while only about a third are female.[2] Various theories can elucidate the disparities between sexes in schizophrenia. The hypothesis regarding schizophrenia suggests that gonadal hormones, like estrogen, may exert a neuroprotective effect, thereby mitigating the development of schizophrenia pathology in women. A notable correlation exists between estrogen deficiency during menopause and the severity of psychiatric symptoms in women. In men, there was also a documented inverse relationship between plasma estrogen levels and symptoms of schizophrenia. Schizophrenia is also linked to gender-specific associations with specific dopaminergic genes, such as catechol-O-methyltransferase and monoamine oxidase. Meanwhile, dopamine deficiencies and surpluses have been linked to the positive and negative symptoms commonly associated with schizophrenia.[15]

Regarding the highest level of education attained by schizophrenia patients in the treatment group, the breakdown was as follows: 31.8% completed high school, 31.8% completed middle school, 22.7% completed elementary school, and 13.6% attained a bachelor's degree. In the control group, the highest education distribution was as follows: 31.8% completed high school, 31.8% completed middle school, 18.2% completed elementary school, and 18.2% attained a bachelor's degree. From the latest education data above, it can be seen that individuals with schizophrenia tend to have a lower level of education. Underachievement academically prior to the age of 16, correlated with the onset of prodromal symptoms, could serve as a cognitive indicator preceding schizophrenia, potentially influencing educational outcomes later in life.[16]

In this study, the demographic characteristics of the participants were examined to assess their comparability between the treatment and control groups. The findings revealed that a significant proportion of participants, 81.8% in both groups, were employed, suggesting that the employment status was similar across both groups. Additionally, the predominant marital status among participants in both the treatment and control groups was married, with 77.3% of individuals in each group reporting this status. These findings suggest no significant disparities in employment or marital status between the two groups, indicating initial comparability in these vital demographic factors.

A homogeneity test was conducted on various demographic variables to further assess the similarity between the treatment and control groups. The test results indicated that the p-values for all variables exceeded 0.05 (p > 0.05), suggesting no statistically significant differences between the groups in terms of demographic characteristics such as age, gender, education level, income, or any other relevant variables. This finding supports the assertion that the participants in this study were homogeneous across both groups, meaning that any observed differences in outcomes between the treatment and control groups can be more confidently attributed to the intervention being studied rather than demographic variability. This homogeneity ensures the subsequent analyses' validity and reliability and strengthens the study findings' overall credibility.

In this study, cognitive improvement by assessing the improvement in MoCA-Ina scores in the comparison of the baseline week, fourth, and eighth week in the treatment group obtained significant results (p <0.05), and in the control group, the MoCA-Ina results were obtained in baseline week, fourth and eighth week were not significant. MoCA-Ina score improvement with a mean baseline week score of 17.91 with an interpretation of moderate cognitive impairment, a mean in the fourth week of 19.05 with an interpretation of mild cognitive impairment, and a mean in the eighth week, a mean of 21.05 with an interpretation of mild cognitive impairment.

This is by the study by Tang Wei,[10] which reported that omega-3 fatty acid treatment had beneficial effects on cognitive function, as reflected by significant improvements in the RBANS delayed memory factor used for cognitive evaluation.[10] The addition of omega-3 can improve clinical symptoms in schizophrenia patients.[17,18] The same results were reported in research by Satogami[19] in Japan, which obtained significant research results with an increase in brief assessment of cognitive in schizophrenia (BACS) scores. These results suggest that a decrease in omega-3 fatty acids is associated with cognitive impairment, impacting the patient's social functioning.[19]

This study observed that the MoCA-Ina value within the control group did not exhibit significance. However, there was a discernible rise in the MoCA-Ina value from the baseline week, averaging 17.32, to the fourth week, averaging 18.23, and continuing to the eighth week with a mean of 18.23. From the results of MoCA-Ina 's interpretation, it was found that moderate cognitive impairment improved to mild cognitive impairment. In research, Houthoofd.[20] proved that there were cognitive improvements in schizophrenia patients who were given risperidone. Previous research found that cognitive improvement with other modalities, namely music therapy in schizophrenia patients, could improve cognitive function.[21] Cognitive function encompasses a broad array of mental processes fundamental to our ability to perceive, understand, and interact with the world around us. These processes include attention, which allows us to focus on relevant information while filtering out distractions; memory, which enables us to retain and retrieve past experiences and information; language, which facilitates communication and expression of thoughts and ideas; perception, which involves interpreting sensory information from the environment; problem-solving, which involves finding solutions to complex problems by applying logical reasoning and creativity; and decision-making, which entails evaluating different options and choosing the most appropriate course of action based on our goals and preferences. Each cognitive ability is interconnected and relies on various neural networks and brain regions working together seamlessly. Furthermore, cognitive function is not static but can be influenced by genetics, development, education, lifestyle, and environmental factors. Understanding the complexities of cognitive function is essential for improving interventions and strategies to enhance cognitive abilities and mitigate cognitive decline associated with aging or neurological disorders.[29] Cognitive deficits, especially in memory abilities, are found in around 75 to 85% of schizophrenia patients. This has a negative impact on psychosocial functioning in schizophrenia.[9] DHA constitutes the primary omega-3 fatty acid present in the phospholipids of cell membranes within the cortical grey matter of the brain. Around 15% of the total fatty acids in the prefrontal cortex (PFC) of adult humans consist of DHA. Research indicates reduced levels of DHA in the brains of individuals diagnosed with schizophrenia.[10]

Alterations in phospholipid metabolism and fatty acid composition within distinct brain regions profoundly affect the physical characteristics of neuronal cell membranes. These changes can significantly influence fluidity and permeability, which are crucial for optimal neuronal function. Specifically, modifications in phospholipid metabolism can disrupt the delicate balance of lipids composing the membrane bilayer, potentially leading to changes in membrane fluidity. This altered fluidity can impact the activity of membrane-bound enzymes and the function of neurotransmission systems. Notably, receptors localized within specialized membrane microdomains known as lipid rafts may be susceptible to these alterations, as changes in membrane composition can affect their localization and signaling efficiency. Thus, the dynamic interplay between phospholipid metabolism, fatty acid composition, and neuronal membrane properties plays a pivotal role in regulating neuronal function and neurotransmission.[28] Supplementing with DHA can restore the DHA content within cell membranes.[9] One potential mechanism behind the positive impacts of omega-3 polyunsaturated fatty acids (PUFA) could involve bolstering the intracellular antioxidant defense system.[22] Research conducted across different stages of development (ultra-high risk, first episode, or chronic schizophrenia) consistently indicates that omega-3 PUFA supplementation can decrease oxidative stress levels.[23]

Upon analyzing serum GDNF levels, a notable rise was observed in the treatment group. The mean GDNF level before being given omega-3 treatment was 4.16 (± 2.64), increasing to 3.93 (± 3.01) after 8 weeks of being given omega-3. When examining GDNF levels in the control group, GDNF levels were found to be increased, but this was not significant in statistical tests. This is in line with Tang's[13] research in China, which showed that higher serum GDNF levels are correlated with better cognition.[24] This study showed a correlation between cognitive function and increased GDNF in the treatment group. There is research that correlates with increasing MoCA-Ina values and increasing GDNF levels on cognitive function in older people.[25] Increasing evidence suggests that GDNF levels might contribute to the development and advancement of the disease, similar to what is observed in Alzheimer's disease with cognitive decline. Research indicates a robust correlation between GDNF levels and cognitive impairment.[26] The production of GDNF is thought to participate in the survival and adaptability of neurons actively. Hippocampal neurogenesis facilitated by GDNF is thought to aid in alleviating cognitive impairment by enhancing the functionality of antioxidant mechanisms, thereby protecting against both oxidative stress and cognitive deficits.[27]

CONCLUSION

Schizophrenia patients who underwent omega-3 adjuvant therapy for 8 weeks exhibited more significant enhancements in cognitive function compared to those who did not receive omega-3 adjuvant therapy. The results showed that there was a higher increase in GDNF levels in schizophrenia patients who received omega-3 adjuvants compared to schizophrenia patients without omega-3 adjuvants. Furthermore, there was a moderate positive correlation between increasing GDNF levels and improving cognitive function in schizophrenia patients

who received omega-3 adjuvant therapy.

Specialist mental health clinicians may consider utilizing the findings of this study as guidance for the pharmacotherapy management of schizophrenia patients. This involves incorporating omega-3 as an adjunctive treatment to enhance cognitive function in patients. It is hoped that this research can be used as reference material for comprehensive management in improving cognitive impairment in schizophrenia patients who receive the antipsychotic risperidone. Theoretically, This study aims to contribute scientifically to understanding the impact of omega-3 supplementation on cognitive function and serum GDNF levels in schizophrenia patients undergoing treatment with the antipsychotic risperidone.

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