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Role of Omega-3 Polyunsaturated Fatty Acid in the Management of Major Depressive Disorder®

Nazia Yousef[1]*, Hammad Hassan[2], Zaheer Ahmed[1], Sofia Kausar[3] and Saima Kouser[1]

[1] Department of Environmental Design, Health and Nutrition Sciences, Allama Iqbal Open University, Islamabad, Pakistan

[2] DHQ Hospital Sialkot, Sialkot, Pakistan

[3] Department of Liver Transplant, Sheikh Zayed Hospital, Lahore, Pakistan

**Corresponding e-mail: Naziayousif19@gmail.com*

ABSTRACT

Background: *Patients with the major depressive disorder have prominently been reported with subnormal omega-3 polyunsaturated fatty acids (PUFAs) levels, including importantly low eicosapentaenoic acid and docosahexaenoic acid in cell plasma and dietary intake. However, more randomized controlled trials are needed to support its importance in the management of depression. Objective: To explore the role of omega-3 polyunsaturated fatty acid in the management of the major depressive disorder.* ***Materials and methods:*** *Total 70 patients of aged 20 to 40 years old, who were already diagnosed with depression and taking antidepressant treatment, were selected at Department of Psychiatry and Behavioral Sciences, King Edward Medical University Lahore, and were assigned into 2 groups, i.e. intervention and control, by simple random lottery method. For 12 weeks, the intervention group was advised to take one omega-3 (300 mg EPA, eicosapentaenoic acid and 200 mg DHA docosahexaenoic acid), or placebo (500 mg corn oil) capsules once daily with a meal. Beck depression inventory (BDI) scale was used to assess the depression. Demographic information was collected using a structured questionnaire. SPSS version 20 was used for data analysis. Chi-square test was used to check the association between depression and risk factors. Paired t-test was applied to measure the mean difference before and after the intervention.* ***Results:*** *Statistically significant role of omega-3 PUFAs 15.46 ± 4.98 (p=0.000) was found. And mean was found insignificant in the placebo group as 2.32 ± 4.43 (p=0.007).* ***Conclusion:*** *It is concluded that omega-3 polyunsaturated fatty acid has a statistically obvious role in reducing depression as an add-on treatment with anti-depressants in the intervention group as compared to the placebo group.*

Keywords: Depression, Omega-3 polyunsaturated fatty acids (PUFAs), Eicosapentaenoic acid (EPA), Decosahexonic acid (DHA), Randomized controlled trial (RCT)

This Clinical Trial has been registered.
(NCT03732378) @ www.clinicaltrials.gov

INTRODUCTION

Major depressive disorder (MDD), also simply known as depression, is a mental disorder present with low mood, loss of pleasure, feelings of guilt and thoughts of suicide, globally affecting the people of all ages, from all the communities. The World Health Organization estimates that more than 4.5% people throughout the world are affected by depression [1]. Currently, depression is a fourth leading cause of disability and till 2020 it will become second among 10 leading causes of disability, social and economic effects of depression and suicide is mounting in the present years [2].

Chiu reported that the prevalence of depression in Asia is 3.7% with exception of China and South Korea [3]. In Pakistan, depression rate is crucial, as latest studies show that the prevalence of depression 6%, 1.5% for schizophrenia, 1-2% of epilepsy and 1% of Alzheimer's disease [4]. Genders, family history, marital status, education level, economic status, body mass index, sleep duration, smoking was found as risk factors for depression [5-7]. A study conducted by Gadit and Mug ford concluded that among 3 capital cities of Pakistan (Karachi, Lahore, and Quetta), in Lahore prevalence rate of depression was high [8].

Omega-3 fatty acids are long-chain polyunsaturated fatty acids of plant and marine source, which are essential fatty

acids, meaning that these acids cannot be produced by the human body, and must be derived from dietary source [9]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two significant types of long chain omega-3 PUFAs in the human brain [10]. Polyunsaturated fatty acids (PUFAs) related to neuropsychiatric disorders include docosahexaenoic acid (DHA), the most abundant brain omega-3 fatty acid (40% of total mammalian brain fatty acids) and eicosapentaenoic acid (EPA) (only 1% of total brain fatty acids) [10,11].

It has been proposed that eicosapentaenoic acid (EPA) have prominent neuroprotective properties, like anti-oxidative activity and regulation of anti-inflammatory [12]. Climbing up affirmation propose that oxidative stress play a crucial role in the pathogenesis of many age-related psychiatric and neurodegenerative diseases like depression and dementia [13,14]. When the concentration of Reactive oxygen species (ROS) in the tissues become more than its antioxidant capacity, oxidative stress occurs [15]. Due to the huge utilization of brain and copious presence of polyunsaturated fatty acids (FAs), brain tissues are especially more prone to oxidative damage [16].

Etiology of depression is related to various endocrinological and metabolic disturbances, it has been reported that depression has elevated oxidative stress. There may also be iatrogenic such as drug-induced depression. Drugs related to depression include interferon therapy, beta-blockers, isotretinoin, contraceptives [17,18]. Omega-3 polyunsaturated fatty acids (PUFAs) due to its anti-oxidative activity may play a role in neuroprotection, anti-inflammatory and anti-apoptotic functions [19-24].

Polyunsaturated fatty acids (PUFAs) play a role in modulation of the structure and function of biological membranes, such as elasticity, membrane organization and ion, and therefore, may help in brain glucose uptake, neuronal function, an neurotransmission [9,25]. Different active pro or anti-inflammatory metabolites, such as eicosanoids, leukotrienes, and docosanoids are produced [26]. Polyunsaturated fatty acids (PUFAs) related to neuropsychiatric disorders include docosahexaenoic acid (DHA), the most abundant brain omega-3 fatty acid (40% of total mammalian brain fatty acids) and eicosapentaenoic acid (EPA) (only 1% of total brain fatty acids) [10,11].

It is consistently observed that erythrocyte levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were negatively associated with the risk of depression, analyzed that omega-3 polyunsaturated fatty acids (PUFAs) have promising effect in reducing the symptoms of major depressive disorder [27,28]. Previously several clinical trials investigated the effect of Omega-3 polyunsaturated fatty acids (PUFAs) in major depressive disorder, showing both positive, and negative results [29-32].

Most of the research into understanding the etiology and pathophysiology of depression has focused on genetic and environmental factors, while pharmacological treatment was based on the monoamine hypothesis of depression [33]. Selective serotonin reuptake inhibitors (SSRIs) are still broadly prescribed drugs for the treatment of depression, analyzed that depression remains treatment-resistant [34,35]. Combining Omega-3 fatty acids with selective serotonin reuptake inhibitors (SSRIs) has advantages in the treatment of depression [36,37].

Literature has shown that internationally many studies have been conducted to understand the prevalence, economic and social effects, pathophysiology, treatment, the relationship between omega-3 and depression. It has been suggested that a low level of omega-3 polyunsaturated fatty acids is related to increased risk of major depressive disorder, but few studies also oppose this association. A few studies have also been done in Pakistan on depression. But no study is reported till now about the significant role of omega-3 in the management of depression. The present study was aimed to evaluate the hypothesis that omega-3 polyunsaturated fatty acids (PUFA) and major depressive disorder are negatively associated.

This study was conducted at the psychiatry department of King Edward Medical University Lahore to explore the role of omega-3 polyunsaturated fatty acids in the management of the major depressive disorder.

MATERIALS AND METHODS

Study Design

The 12-week randomized, single-blind, placebo-controlled trial (RCT) was conducted at Department of Psychiatry and Behavioral Sciences, King Edward Medical University Lahore. From 19 May 2017 to 16 August 2017 one omega-3 capsule (300 mg EPA, eicosapentaenoic acid and 200 mg DHA docosahexaenoic acid) were given, or placebo (500 mg corn oil) [38-40].

Inclusion Criteria

Patient aged 20 to 40 years, were diagnosed according to the diagnostic and statistical manual of mental disorders, fourth edition text revision (DSM-iv-TR) for depression and taking an anti-depressant, were eligible for the study.

Exclusion Criteria

Patients were excluded if they were pregnant, lactating. Unstable medical or neurological conditions that can likely to interfere with the treatment of depression such as dementia, schizophrenia, epilepsy, history of allergy to omega-3 fatty acids, finfish or shellfish.

Data Collection and Evaluation

Subjects were assessed at the first visit according to inclusion and exclusion criteria. Information about demographics, dietary habits and risk factors such as age, gender, height, weight and family history of depression, dietary habits, education levels, marital status, cigarette smoking, supplementation and sleeping hours were obtained by using a structured questionnaire in the face to face interview in local and easy to understand language. BMI was calculated by using the equation BMI=kg/m^2.

Outcome Measurement

Evaluations of depression were performed by using Beck's inventory depression rating scale 21 items, at baseline, and after the intervention [41,42]. Ranking of Beck Depression Inventory (BDI) scale ranking is 1-10: Normal ups down, 11-16: Mild mood disturbance, 17-20: Borderline clinical depression, 21-30: moderate depression, 31-40: Severe depression, Over 40: Extreme depression.

Ethical Approval

Written approval (Reg.No.Psy/561/17) was taken from the head of the Department of Psychiatry and Behavioral Sciences, King Edward Medical University, Lahore. Informed consent had been taken from all study participants in written form after explaining the procedure of the study. This study was conducted according to the guidelines laid out in the Declaration of Helsinki.

Statistical Analysis

Data were analyzed through SPSS version 20.0 with 95% confidence interval. Frequency distribution and of demographic variables were checked. Chi-square test was used to check the relationship between depression and risk factors. Paired t-test was used to analyze the before and after intervention means difference. Results were presented in the tabular and graphical form.

RESULTS

Age, BMI, gender, family history, marital status, occupation, economic status, education level and sleeping hours were not significantly associated with depression, as illustrated in Table 1.

Table 1 Demographic characteristics

Variables	Patients	Control	p-value
Number	**30**	**31**	
Age (Years), Mean ± S.D	30.5 ± 6.92		0.968
BMI (Kg/m^2), Mean ± S.D	23.2 ± 1.8		0.91
Sex N (%)			
Female	34 (58.1%)		0.233
Male	27 (49.1%)		
Marital Status N (%)			
Married	37 (60.6%)		0.784
Unmarried	19 (33.0%)		
Divorced	3 (4.2%)		
Widow/Widower	2 (2.8%)		
Occupation			

Gov. Employ	7 (9.9%)	0.722
Private Job	11 (16.9%)	
Own Business	15 (23.9%)	
No Work/House Wife	19 (33.8%)	
Student	9 (14.1%)	
Family History		
Yes	11 (18.3%)	0.707
No	50 (81.7%)	
Education Level		
Uneducated	3 (4.2%)	0.76
Primary	6 (8.5%)	
Middle	13 (18.5%)	
High School	23 (32.4%)	
College	22 (31.0%)	
University	3 (4.2%)	
Monthly Income In PKR		
<20,000	16 (25.5%)	0.386
20,000-30,000	28 (45.1%)	
31,000-40,000	14 (22.4%)	
>50,000	3 (5.6%)	
Sleeping Hours/24 Hours		
<5 Hour	32 (53.5%)	0.617
6-8 Hours	29 (45.1%)	
BMI: Body Mass Index, Gov: Government, PKR: Pakistani Rupees		

DISCUSSION

The purpose of this study was to explore the role of omega-3 polyunsaturated fatty acids in the management of major depressive disorder and unveiled statistically significant role as the mean difference was 15.46 ± 4.98 (p=0.000). Placebo group means difference was 2.32 ± 4.43 (p=0.007). This finding is adjacent to the results of a randomized, double-blind, 12-week, placebo-controlled trial aimed to explore the effects of omega-3 supplementation in depression, in Korea. In this 12-week, parallel-group trial, (n=35) were assigned to take either 3 capsules of omega-3 PUFAs (1.140 mg of EPA + 600 mg of DHA; n=18) or placebo (n=17). Supplementation of omega-3 significantly reduced clinical global impression improvement scores as compared with intake of placebo [43].

Role of omega-3 PUFAs in depression may be due to the antioxidant activity of omega-3 PUFAs, this is closely matched to the studies, found that etiology of depression is related to various endocrinological and metabolic disturbances, it has been reported that depression has elevated oxidative stress [17,18]. Another previous study supported the role of inflammatory mechanisms in major depression was confirmed. (n=132) with chronic hepatitis C viral infection were tested to evaluate the role of genes (COX-2 and PLA-2) in the development of depression during interferon (IFN)-α treatment. Erythrocyte levels of the 3 main polyunsaturated fatty acids, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid of 63 patients were examined. Results suggested that probably by influencing the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels, genetic alteration in the COX-2 and PLA-2 genes, enhance the risk of IFN-α-induced depression [44].

Lower plasma levels of omega-3 polyunsaturated fatty acids and changed lipoprotein concentration have been reported in depression due to lipid metabolism disturbance [45,46]. Higher plasma levels of omega-3 polyunsaturated fatty acids (PUFAs) hinder the production of pro-inflammatory cytokines [47].

In contrary to the results of the current study, no indicative relationship was explored between any omega-3 polyunsaturated fatty acid level and residual depressive symptoms in older 130 outpatient aged from 60 to 86 years. Hamilton Depression Rating Scale (HDRS) scores>5 were used to define residual depressive symptoms. And fatty acids levels in erythrocyte membranes and in plasma were checked separately by gas chromatography [48]. Finding another study oppose the present study results, in which no association between polyunsaturated fatty acids intake and incidence of depressive symptoms was showed [49].

This may be due to the difference in demographic factors of participants and the small sample size of the current study. The present study explored no significant relationship between risk factors and depression. Mean age of participants was 30.5 ± 6.92. This finding was aligned with a previous study conducted in the Department of Psychiatry, Columbia University, New York, aimed to find the role of omega-3 polyunsaturated fatty acid supplementation and white matter changes in major depression. N=28 were treated with fish oil for 6 weeks [50]. The present study found females patients were more 34 (58.1%) than male patients 27 (41.9%). This finding was compatible with previous studies, concluded that females are more vulnerable to having depression as compared to males [51,52].

In this study family history was not statistically associated with depression ($p<0.707$) and this finding was incompatible to a previous double-blind placebo-controlled study, in which hypothesis was confirmed that serotonin transporter gene promoter polymorphism (5HTTLPR)-dependent low transcriptional activity of the human serotonin transporter gene is a genetically susceptible factor for depression. Total 45 white women, aged from 19 to 53 years (mean ± SD age, 26.3 ± 4.9), 24 healthy females with no family history of depression and 21 females with a positive family history of depression were studied [53].

In the current study, marital status was not significant with depression ($p<0.784$), finding contradict a review study examined that depression impacts marital status, ($p<0.01$) and, conversely, marital status effects the incidence of this disorder ($p=0.04$) [54]. Education level had no definite or statistical association with depression, however previous studies, concluded a clear negative relationship between depression and higher education levels. Higher educational level suggested being shielded against depression [55-57].

CONCLUSION

Role of Omega-3 polyunsaturated fatty acid as an add-on treatment with an antidepressant was significant and improved the Beck depression inventory (BDI) scores of depressive symptoms in the treatment group as compared to placebo. This suggests that the use of dietary omega-3 PUFAs can be prevented from depression.

Limitations

- A short period of time
- Single centered study
- Due to financial constraints, it was not possible to conduct the study on large scale, was dealt single-handedly and small sample size

DECLARATIONS

Conflict of Interest

It is affirmed that this manuscript is an honest, accurate, and transparent account of the study being reported, no important aspects of the study have been omitted. All authors and co-authors worked honestly.

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