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ORIGINAL PAPER

The effect of low-dose omega 3 fatty acids on the treatment of mild to moderate depression in the elderly: a double-blind, randomized, placebo-controlled study

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Abstract Due to the rise in the social and economic costs of depression, new antidepressant medication with fewer side effects should be found. Several studies have shown that an association exists between ω-3 polyunsaturated fatty acids (ω-3 PUFAs) and depression. However, this association has not been clear enough in the elderly with mild to moderate depression. Sixty-six inhabitants of Kahrizak Charity Foundation participated in this double-blind, randomized, placebo-controlled study. Each participant was $\geq$ 65 years of age, had a Mini Mental State Exam of $\geq$ 22, and had scores ranging from 5 to 11 on the Geriatric Depression Scale-15 (GDS-15). During the 6 months, the drug group was treated daily with one gram of fish oil capsule containing 300 mg of both eicosapentaenoic acid and docosahexaenoic acid. No significant differences were noted between the groups in regard to level of education, use of antidepressant drugs, alcohol, tobacco use, history of chronic diseases, age, body mass index (BMI), high-sensitive C-reactive protein (hs-CRP), total cholesterol, and GDS-15 scores at baseline. After adjusting for cholesterol, BMI, and history of thyroid dysfunctions, a statistically significant difference was seen in GDS-15 scores between both groups. Furthermore, treatment with ω-3 PUFAs was clinically more effective in treating depression in comparison with the placebo. In this study, low-dose ω-3 PUFAs had some efficacy in the treatment of mild to moderate depression in elderly participants.

Keywords ω-3 polyunsaturated fatty acids · Fish oils · Depression · Elderly

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Introduction

"Depression amplifies disability and lessens quality of life"; it is not a normal consequence of aging [1, 2]. Late-life depression tends to be a recurrent or persistent condition associated with increased office and emergency department visits, drug use, increase in the cost of medications, length of inpatient stay, and higher risk for drug abuse [3]. It is an independent risk factor for subsequent cognitive decline, which adversely impacts both medical and psychiatric morbidity and mortality [4–7], as well as the outcomes of comorbid diseases [8]. It can also increase the risk of subsequent development of diseases such as stroke [9], coronary artery disease [10], and diabetes [11, 12]. A recent study by Gallo et al. evaluated the consequences of major depression in an elderly patient population suffering from cancer. The authors found a decrease in the overall risk of death at 5 years was less in patients who received treatment for their depression in comparison with those with no treatment [13].

The problem of "subsyndromal depressive states" or minor depression is particularly important in the elderly population. These patients carry disease burdens similar to

major depression, including poorer health and social outcomes, functional impairment, family history of suicide, and higher treatment costs [14–17]. A study on elderly subjects with minor depression demonstrated a 5.5-fold increased risk of developing major depression by one year in comparison with subjects without depression [15].

"Despite the development of new antidepressant medications with improved side-effect profiles, it is estimated that 20–30% of those with MDD treated with antidepressant medication continue to experience residual depressive symptoms". In addition, 50% of those who have an episode of MDD will eventually have another [18]. Due to the rise in the social and economic costs of depression, there is a need for new antidepressant medication with fewer side effects. The ω-3 polyunsaturated fatty acids (ω-3 PUFAs) found in fish oil have been hypothesized to provide an alternative.

Several studies have shown that an association exists between ω-3 PUFAs and depression. McNamara et al. [19] found selective deficits in docosahexaenoic acid (DHA) levels in the postmortem orbitofrontal cortex of patients with major depression. Furthermore, animal models of mental illness have suggested that ω-3 fatty acids can affect brain processes such as mood and anxiety [20]. Finally, low levels of DHA predict low levels of cerebrospinal fluid 5-hydroxyindoleacetic acid, the major metabolite of serotonin, which is known to protect against depression [21]. Fish contain high concentrations of ω-3 PUFAs. Studies have indicated that frequent consumption of fish decreases the likelihood of depressive symptoms in comparison with infrequent consumption [22, 23]. Blood lipid analysis revealed lower concentrations of ω-3 PUFAs in depressed cases compared with non-depressed controls [24–27]. Additionally, some studies showed that consumption of ω-3 PUFA supplements was superior to placebos in the treatment of depression [28–30].

A great number of the world population, specifically the elderly, have low dietary intake of ω-3 PUFAs. Based on the 2003 report of the Food and Agriculture Organization of the United Nations (FAO), the consumption rate of fish and seafood in developed countries was 23 kg/capita/year, 13 kg/capita/year in developing countries, 5 kg/capita/year in Asia, and specifically 6.1 kg/capita/year in Iran [31]. In light of these facts, it seems plausible to study this effect in the elderly Iranian population. Although many studies have evaluated the effect of ω-3 PUFAs on depression, its effects on the elderly population need further investigation.

It is critical to use the lowest effective dose of a drug when treating the elderly. Higher doses of drugs are generally accompanied with more side effects. Side effects may lead to more intolerance and reduction in adherence to the treatment. Therefore, the outcome of treatment of the drug may be influenced by this factor. Thus, efforts were made to find the effect of low-dose ω-3 PUFAs on the treatment of mild to moderate depression in elderly residents of Kahrizak Charity Foundation (KCF).

Methods

This study investigated the treatment of depression with a low-dose ω-3 PUFAs in elderly residents of KCF. KCF is a private, non-governmental, non-profit, charitable organization where physically handicapped or elderly individuals with no financial resources are cared for free of charge. The study was initiated in December 2008 and concluded in June 2009.

The Ethical Committee of the Endocrinology and Metabolism Research Center of Tehran University of Medical Science approved the study in accordance with the Declaration of Helsinki. Approval was also received by the Ethical Committee of the KCF research center.

Participants and sampling

Sample size was calculated to detect an 80% power, a 95% confidence interval, and a 25% difference [37] between treatment and placebo groups on the measured Geriatric Depression Scale-15 (GDS-15) scores, taking into account a 10% loss rate. In order to obtain a more comparable sample, the two groups were matched by age (with 5-year interval), sex, and GDS-15 score groups (mild and moderate depression).

Details of the sampling process can be seen in Fig. 1. Among the 1,050 elderly residents of KCF, 353 residents were selected based on the study's inclusion and exclusion criteria, using their KCF medical profiles. The criteria were as follows: (1) Age $\geq$ 65, (2) No history of any end-stage diseases, Parkinson disease, or any unstable medical conditions, (3) No history of sea food allergies, (4) No consumption of fish oil or supplements enriched with ω-3 fatty acids 3 months prior to participation, (5) No history of psychiatric disorders with the exception of depression or anxiety, and (6) No diagnosis of mental retardation. Individuals with a reported history of dementia based on their KCF profiles were excluded from the study. Consent forms were obtained from the remaining individuals.

Each participant was administered a Mini Mental State Exam (MMSE) by a trained clinical psychologist in order to assess for dementia. Participants with scores of $\leq$ 21 were considered to have some grade of dementia based on the corrected MMSE scores for Iran and were not selected for the study [32].

The remaining 202 participants with MMSE scores of $\geq$ 22 were administered the GDS-15 by a trained clinical psychologist to assess for mood. One hundred and four participants with scores in the normal range (GDS-15

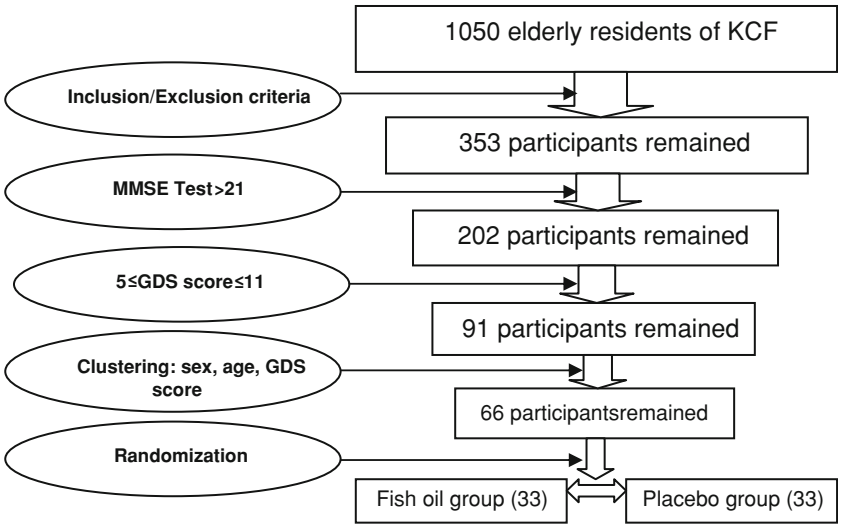

Fig. 1 Method of sampling

score < 5) and 7 participants whose scores were indicative of severe depression (GDS-15 score > 11) were excluded. Patients with dementia and also severe depression were referred to psychiatrists for treatment.

The remaining 91 participants were then clustered by their age groups (5-year intervals), sex, and GDS-15 score groups (mild and moderate depression). Sixty-six participants were matched one-to-one and the remaining participants were excluded from the study. The 66 participants were divided into the placebo and the drug groups using Random Number Generation Method (33 participants in each group).

After full written and verbal explanations about the study procedures, risks, and benefits, all participants signed written informed consent forms.

Study design and measures

The GDS has been tested and used extensively with the elderly population. The Short Form GDS (GDS-15) is preferred with patients who have short attention spans and/or feel easily fatigued, such as the physically ill and those with mild to moderate dementia. In a validation study comparing the Long and Short Forms of the GDS for self-rating of symptoms of depression, both were successful in differentiating depressed from non-depressed adults. With Short Form of the GDS, Scores of 0–4 are considered normal; 5–8 indicate mild depression; 9–11 indicate moderate depression; and 12–15 indicate severe depression, depending on age, education, and complaints [33, 34]. The GDS-15 Farsi version was used in this study. The Long and Short Forms of the GDS are excellent screening instruments used for major depression in the elderly residence of Iran. The Iranian version of GDS-15 has excellent reliability and validity as a screening instrument [35].

Two psychologists, not employed by KCF, assisted in the administration of the GDS-15 and the MMSE assessments. Each psychologist was assigned to administer one of the two assessments to all participants. In a pilot study, we randomly selected and obtained written consents from elderly residents of KCF for participation in the study. The participants met our inclusion criteria and were assessed twice at one-week intervals on both the GDS-15 and the MMSE in order to estimate the within-subject reliability of the tests. Pearson' correlation coefficients between the two successive scores were 0.97 and 0.96, respectively. The participants were not included in the study.

One hard gelatin capsule containing one gram of fish oil was used daily for the drug group. Each capsule contained cod liver oil, glycerol, water, and fish oil and was comprised of 180 mg eicosapentaenoic acid (EPA) and 120 mg DHA. The cod liver oil and fish oil were obtained from cold water fish.

The placebo was a hard gelatin capsule containing medium-chain triglycerides (MCTs) derivate from coconut oil, glycerol, and water, which appeared similar to the fish oil capsules of the drug group. Both fish oil and placebo capsules (manufactured by Zahravi Pharmaceutical Company) were similar in shape, color, and packaging. We used hard gelatin capsules to eliminate the odor and taste of the fish oil in order to keep our study blind.

Additional information was gathered before administering medication to the participants. These included the level of education, smoking, drug history, and any past medical and psychiatric history. Blood samples were taken to measure serum hs-C-reactive protein (hs-CRP) and total cholesterol. Samples were collected in the morning after 10 h of fasting. Additionally, their BMI (body mass index) was calculated by dividing weight by square of height (Kg/m^2).

In this double-blind study, the fish oil and the placebo capsules were contained in identical packaging. The capsules were coded with the letters A and B on the back of the packages, respectively.

An individual with limited medical knowledge was designated to administer the drugs to the participants based on each participant's code and the drug codes. This individual was blind to the contents of the capsules. In addition, the participants had no knowledge of the contents of the capsules and their designated codes. The drugs were given to the participants daily. Participants took the drugs under the supervision of the individual responsible for the administration of the drugs. The individual reported the drug intake of each participant. She was responsible to report whether any of the participants did not agree to take the drug and returned the drug to the research office. The participants were not coerced into taking the drugs and had a choice of not accepting the treatment. The staff was strictly responsible to report non-adherence to the drug treatment.

KCF has a total of 19 dormitories with about 20 to 25 rooms. Each dormitory has a 50- to 60-person capacity. The 66 participants did not live in one single dormitory. Rather, they lived separately among the other 1,050 residents. This condition helped to keep the study blind.

The participants were monitored for a total of 6 months. A trained nurse who was blind to the study performed weekly evaluations of drug consumption and side effects of the drugs. The nurse was not employed by the KCF. Evaluation and analysis of the reports provided by the staff enabled the control of processes and ensured the maintenance of the blindness of the study. Fortunately, no problems were observed that might have compromised the blindness during the course of the study.

During the study, participants who manifested an allergic reaction to ω-3 fatty acids and experienced acute MI, new stroke, delirium, loss of consciousness, unstable medical conditions, or death were excluded from the study.

At the end of the study, the participants were assessed with the GDS-15 test, similar to the beginning of the study. The clinical psychologist was blind to the drug groups of the participants. Participants who remained in a state of depression at the end of the study were referred to a psychologist.

Two trained nutritionists visited participants and completed a 3-day food recall both at the beginning and at the end of the study. All items provided on the food recall were estimated by household units and were converted to standard servings using the Iranian household units [36]. Nutritionist III (version 3. 5. 2, N-squared Computing, Salem, Ore) software was used to compute energy and nutrient intake.

Statistical methods

Statistical analyses were performed using SPSS software, release 17.0 (SPSS Inc., Chicago). Values less than 0.05 were considered significant. For non-parametric data evaluations, the chi-square and Fisher's exact tests were used. A *t* test was used to compare GDS-15 scores without categorization between the groups. A paired *t* test was used to compare the scores at the beginning and the end of the study in each group. A repeated-measure test and a two-way ANOVA were used to adjust for cholesterol, BMI, and history of thyroid dysfunctions to evaluate the effect of the treatment between the groups. The statistician was blind to the placebo and fish oil groups.

Results

Among the 66 participants in the study, 20 persons (30%) were men. Sex distribution in both groups was the same (10 men and 23 women in each group). Mean age in the drug group was 79.64 ± 7.39, similar to 79.73 ± 7.01 in the placebo group. No significant differences were observed regarding the level of education; use of antidepressant drugs; tobacco use; history of diabetes mellitus, hypertension, cardiovascular diseases, and stroke between the two groups (Table 1).

There was no history of chronic kidney diseases, chronic lung and liver diseases, immunologic disorders, and alcohol consumption in the participants. Additionally, there was a normal distribution in age, BMI, hs-CRP, total cholesterol, and primary GDS-15 test with no statistical differences between the groups (Tables 1, 2).

Outcome measures of the study are demonstrated in Table 2. Adjustments were made for cholesterol, BMI, and history of thyroid dysfunctions ($P < 0.2$) in order to decrease the effect of the factors influencing depression and its treatment between the fish oil and placebo groups. Subsequently, a significant statistical difference was seen in comparing both groups' GDS-15 scores. The indices of clinical response after categorizing the participants into four clinical groups (normal, mild, moderate, and severe depression) were investigated. There was a significant difference between the participants with a 25% increase in GDS-15 scores between the two groups.

Participants who did not take any antidepressant drugs were compared separately in both groups (Tables 1, 2). Then, similar outcomes were seen with all participants when comparing the fish oil and the placebo groups. In addition, differences in clinical response were more evident when participants who did not take antidepressant drugs were separated.

Table 1 Demographic information and initial evaluations between the groups

	All participants			Non-antidepressant		
	Fish oil group	Placebo group	*P*-value	Fish oil group	Placebo group	*P*-value
Gender, *n* (%)			–			0.99
Male	10(30.3)	10(30.3)		10(34.5)	9(34.6)	
Female	23(69.7)	23(69.7)		19(65.5)	17(65.4)	
Age, years(Mean ± SD)	79.64 ± 7.39	79.73 ± 7.01	0.95	80.03 ± 7.59	80.35 ± 7.42	0.87
Educational level, *n* (%)			0.78			0.61
Illiterate	25(75.8)	23(69.7)		23(79.3)	18(69.2)	
Elementary	6(18.2)	6(18.2)		4(13.8)	4(15.4)	
High school	2(6.1)	4(12.1)		2(6.9)	4(15.4)	
Tobacco use, *n* (%)			0.65			0.68
Never smoking or more than 10 years of cessation	28(84.8)	25(75.7)		24(82.8)	19(73.1)	
Less than 10 years of cessation	2(6.1)	3(9.1)		2(6.9)	3(11.5)	
Smoking	3(9.1)	5(15.2)		3(10.3)	4(15.4)	
History of disease, *n* (%)						
Diabetes mellitus	4(12.1)	5(15.2)	0.72	4(13.8)	4(15.4)	0.86
Hypertension	20(66.6)	22(66.7)	0.61	17(58.6)	18(69.2)	0.67
Cardiovascular diseases	13(39.4)	12(36.4)	0.8	12(41.4)	8(30.8)	0.41
Stroke	6(18.2)	3(9.1)	0.47	5(17.2)	2(7.7)	0.42
Thyroid dysfunctions	0(0.0)	5(15.2)	0.02	0(00.0)	4(15.4)	0.01
Antidepressant drugs history, *n* (%)			0.21			
SSRIs[a]	1(3)	5(15.2)				
TCAs[b]	3(9.1)	2(6.1)				
Body mass index, kg/m^2 (Mean ± SD)	25.69 ± 5.56	23.63 ± 5.52	0.14	26.03 ± 5.65	24.09 ± 3.66	0.14
Total cholesterol, mg/dl (Mean ± SD)	195.19 ± 33.10	179.67 ± 43.77	0.12	195 ± 34.21	180.41 ± 43.02	0.19
hs-CRP, mg/dl (Mean ± SD)	4.41 ± 5.89	3.86 ± 4.12	0.66	4.85 ± 6.16	3.38 ± 3.39	0.31

[a] Selective serotonin reuptake inhibitors

[b] Tricyclic antidepressants

Four participants from the fish oil group and seven from the placebo group used antidepressants drugs. Of these, one participant from the fish oil group and three participants from the placebo group were withdrawn from the study. There was no significant statistical difference between the remaining participants' GDS-15 change (*t* test, $P = 0.60$, $t = 0.54$). Participants took either tricyclic antidepressants or selective serotonin reuptake inhibitor antidepressant drugs. Due to the small sample size of the antidepressant drug users, it was not possible to evaluate these participants by adjusting for factors influencing depression and its treatment.

Twenty-one participants from the fish oil group had a history of diabetes, hypertension, cardiovascular diseases, and stroke. No differences were noted in comparing the GDS-15 scores of these participants with the scores of the other participants in the group ($P = 0.11$, $f = 2.69$, two-way ANOVA).

Four participants withdrew from the placebo group during the study. Three participants passed away during the study, two as a result of cardiac attack and one due to stroke. Another participant withdrew from the study due to vertigo. One participant from the drug group passed away due to stroke and was withdrawn from the study. There were no significant differences in demographic information and the initial evaluations as well as initial GDS-15 scores between participants who withdrew from the study and the others.

Table 3 lists all adverse effects observed during study in both groups. Gastrointestinal disturbances were the most common problem observed in the participants. Three cases of diarrhea, one new case of bloating and eructation, and one new case of reflux in the placebo group were observed. In comparison, one case of diarrhea, two new cases of bloating and eructation, and also one new case of reflux in the drug group were observed. These side effects were not severe and most decreased or settled approximately one month after beginning the study. One participant in the placebo group suffered from a new incidence of vertigo after using medication. No allergic reactions or skin problems were observed or reported in any of the

Table 2 Outcomes for participants with mild to moderate depression treated with one gram fish oil or placebo

	Fish oil group			Placebo group			*t*	*P*-value	*f*	*P*-value
	N	Mean	SD	*N*	Mean	SD		(without adjustment)		(with adjustment[a])
Geriatric depression scale-15										
Baseline										
All participants	33	7.24	1.95	33	7.21	1.83	0.70	0.95[b]	0.02	0.87[c]
Non-antidepressant	29	6.93	1.79	26	7.03	1.63	−0.23	0.81[b]	0.23	0.63[c]
Final										
All participants	32	6.00	2.92	29	6.91	3.98	0.91	0.36[b]	5.64	0.02[c]
Non-antidepressant	28	5.46	2.38	23	6.95	3.69	−1.67	0.10[b]	8.17	0.00[c]
Change										
All participants	32	−1.24	2.50	29	−0.30	2.77	−1.64	0.10[b]	5.35	0.03[d]
Non-antidepressant	28	−1.47	2.51	23	−0.08	3.05	−1.76	0.08[b]	7.96	0.00[d]
Fish oil group										
All participants	32						2.82	0.00[g]		
Non- antidepressant	28						3.07	0.00[g]		
Placebo group										
All participants	29						0.26	0.79[g]		
Non-antidepressant	23						0.13	0.89[g]		

	Fish oil group		Placebo group		*P*-value
	N	%	*N*	%	
Indicators of clinical response					
All participants					0.13[e]
Clinically improved	13	40.7	8	27.6	
No changed	17	53.1	14	48.3	
Clinically worsen	2	6.2	7	24.1	
Non-antidepressant					0.01[e]
Clinically improved	13	46.4	7	30.4	
No changed	15	53.6	10	43.5	
Clinically worsen	0	0	6	26.1	
≥25% decrease in GDS scores					
All participants	14	43.7	9	31	0.30[e]
Non-antidepressant	13	46.4	8	34.8	0.40[e]
≥25% increase in GDS scores					
All participants	2	6.2	7	24.8	0.04[f]
Non-antidepressant	2	7.1	7	30.4	0.06[f]
≥50% increase in GDS scores					
All participants	0	0	3	10.3	0.07[f]
Non-antidepressant	0	0	3	13	0.08[f]

[a] Adjusted for: thyroid dysfunctions, BMI, and serum cholesterol level

[b] *T* test

[c] Two-way ANOVA test

[d] Repeated-measure test

[e] Chi-square test

[f] Fisher's exact test

[g] Paired *t* test

participants. No difference in gastrointestinal side effects between participants who took antidepressants and those who did not was seen.

Table 4 lists the participants' medication use during the study. There were no significant differences between the two groups.

Table 3 Adverse events that occurred during the study

Adverse events	Fish oil group (frequency)	Placebo group (frequency)
CNS system	1	2
Visual system	–	–
Psychiatric events	–	–
Cardiovascular system	1	2
Respiratory system	1	–
Urogenital system	1	–
Skin	–	–
Gastrointestinal disturbance	4	5
Metabolic and endocrines	–	–
General (malaise/felt unwell)	1	3
Musculo-skeletal system	–	–

Table 4 Participants' medications during the study

	Fish oil group (frequency)	Placebo group (frequency)
ACE inhibitors	3	1
Angiotensin II receptor antagonists	0	1
Antihistamines	0	2
β-blockers	7	6
Benzodiazepines	3	2
Bronchodilators	1	1
Calcium channel blockers	3	2
Coumarins	1	0
Digitalis glycosides	2	2
Diuretics	5	3
Histamine H_2 antagonists	2	3
HMG-COA reductase inhibitors	2	3
Nitrates	0	1
NSAIDs	1	0

A summary of the dietary intake data can be seen in Table 5. An evaluation for energy, carbohydrate, protein, fat, saturated fatty acids, monounsaturated fatty acids, PUFAs, linoleic acid, and α-linolenic acid was done. There was no significant statistical difference in the intake of the above-mentioned substances between the two groups at the beginning and at the end of the study. Additionally, there were no differences between the baseline and the final assessment of the same dietary variables within each group. The medications being researched (fish oil and placebo) were not considered in the food records to keep the study blind.

Discussion

In this study, low-dose ω-3 PUFAs showed some efficacy in the treatment of mild to moderate depression in elderly participants.

There are some important factors to consider when treating the elderly. There is a high prevalence of chronic diseases such as hypertension, cardiovascular diseases, diabetes, hyperlipidemia, and other illnesses that may result from consuming multiple drugs with multiple side effects. Adherence to these drugs and tolerability to their side effects is an important factor in the treatment of the elderly. Therefore, finding drugs with lower doses and fewer side effects is necessary to improve elderly patients' adherence to treatment and to achieve better treatment outcomes. Astorg et al. [38] found that participants who consumed fatty fish or long-chain n-3 PUFAs higher than 0.10% of energy intake (approximately 250 mg/day in men and 200 mg/day in women) had significantly lower risks of any depressive episodes and recurrences. Some studies on dose ranges of ω-3 PUFAs in adults for the treatment of depression showed that lower doses of ω-3 PUFAs are more effective than higher doses [29, 39]. Furthermore,

Table 5 Dietary intakes at baseline and after the treatment

	Placebo group		Fish oil group	
	Before	6 months	Before	6 months
Energy (kcal/d)	1,719.46 ± 274.11	1,727.28 ± 222.91	1,709.85 ± 302.29	1,711.10 ± 283.19
Carbohydrate (%)	51.86 ± 3.71	52.69 ± 5.17	52.04 ± 2.47	52.74 ± 3.83
Protein (%)	13.04 ± 0.67	12.84 ± 1.41	13.25 ± 1.13	13.11 ± 2.35
Fat (%)	35.09 ± 3.63	34.46 ± 5.10	34.69 ± 2.57	34.14 ± 4.05
SFAs (g/d)[a]	20.23 ± 3.15	19.85 ± 3.68	19.65 ± 4.09	19.17 ± 4.92
MUFAs (g/d)[b]	27.90 ± 5.11	28.52 ± 3.96	26.76 ± 5.82	25.69 ± 6.36
PUFAs (g/d)	13.99 ± 2.64	13.80 ± 3.01	13.18 ± 3.28	13.01 ± 3.24
Linoleic acid (g/d)	13.01 ± 2.55	13.90 ± 3.12	12.30 ± 3.12	12.27 ± 3.23
α-Linolenic acid (g/d)	0.28 ± 0.05	0.27 ± 0.08	0.28 ± 0.05	0.28 ± 0.13

[a] Saturated fatty acids

[b] Monounsaturated fatty acids

gastrointestinal disturbances have been found to be the most common side effect of fish oil supplements. These can affect the patients' tolerance and adherence to the drug. Therefore, in order to find the lowest possible ω-3 PUFAs effective dose in the treatment of mild to moderate depression in the elderly, a dose of 300 mg EPA + DHA for 6 months was selected.

The risk of under dosing the sample was taken in the study. Based on the study results, it is safe to assume that these findings will be a guide for future studies to examine doses lower than 1 gram ω-3 PUFAs daily for the treatment of the elderly. It is highly recommended that future studies should be done on the basis of finding the appropriate treatment duration.

There are many factors that affect both the incidence and the treatment of depression. Most major chronic medical and neurological disorders and their treatments (i.e. stroke, diabetes, cancer, hypothyroidism, and heart complaints) increase the rates of depression [40–42]. In addition, low educational levels [43, 44], smoking [45–47], obesity [48, 49], low level of cholesterol [50], and higher concentrations of CRP [51–54] are also associated with depression. There is a bidirectional association between some of these factors and depression [40, 47, 49]. One of the strengths of this study was the consideration and evaluation of these factors. Inclusion and exclusion criteria were set for some psychological and also physical problems at the beginning of the study. Other factors had no significant difference between groups. Finally, the remaining factors with a p-value of less than 0.20 were adjusted comparing these factors between the groups. These factors served to increase the accuracy of the study to detect the effects of ω-3 PUFAs on elderly depression more precisely.

Appleton et al. [55] did not find clear evidence of a correlation between plasma concentrations of ω-3 PUFAs and depressed mood in a non-clinical population. Additionally, Rogers et al. [56] did not detect any effect of ω-3 PUFAs on the treatment of mild to moderate depression. Based on these findings, it can be hypothesized that ω-3 PUFAs are not effective in non-clinical populations of depression or that its effects are not clinically prominent. Samples were selected based on this hypothesis in order to evaluate mild to moderate depression in the elderly. The findings show that ω-3 PUFAs are effective in the treatment of mild to moderate depression in the Iranian-aged.

There was a decrease in GDS-15 scores in both groups at the end of the study. However, the fish oil group had a greater decrease in scores. The decrease in GDS-15 scores may be due to seasonal-related changes in mood in the participants. The study was initiated at the beginning of winter and was concluded at the end of spring. Depressive episodes in the fall/winter with remissions in the spring/summer are the major characteristics of seasonal-related changes in mood. Several biological hypotheses such as changing in circadian rhythms, neurotransmitter function, and molecular genetics are propounded for this problem [57, 58]. With due attention to the time of the study, it is probable that seasonal-related changes in mood were the cause of the decrease in GDS-15 scores in both groups after 6 months of the study. However, future studies can further evaluate this factor.

Five participants (7.5%) were withdrawn during the course of the study. There was no significant difference in the initial evaluation between the withdrawn participants and the others. Also, the rate of the withdrawn participants was under 10%. So it was decided not to perform a sensitive analysis for missed participants.

The effect of ω-3 PUFAs on the participant's depression was demonstrated more clearly when only evaluating the participants who did not take antidepressants. Use of antidepressants may be indicative of a more severe depression and may affect the study's depression evaluations. Additionally, no significant difference was noted between the two groups when comparing the GDS-15 scores of the participants who took antidepressant drugs. However, no conclusions may be drawn due to the very low number of antidepressant users in the study. Future studies may consider evaluating the effects of combination therapy with ω-3 PUFAs and antidepressant drugs in the elderly.

Some of the important aspects of the study include the shared environment, nursing, and medical care for all of the participants. All of the participants resided in the same place with similar climate, air pollution, food, sport, and rehabilitation equipment. In addition, because of KCF rules for accepting the elderly free of charge, the participants had nearly the same socioeconomic conditions. Clustering participants by age groups, sex, and GDS-15 score groups at the start of the study brought about more similarity between the groups. Another benefit of the study was excluding participants with dementia, thereby increasing the precision of the GDS-15 test. Previous blind studies have been compromised by the fish odor of drugs when compared with the placebos. This problem was limited by using oil-filled hard gelatin capsules and monitoring the daily intake of the capsules.

It is likely that one of the reasons that ω-3 PUFAs showed an effect on elderly depression more clearly was the low ω-3 intake in the routine diet of the participants at baseline. More studies are needed to evaluate the correlation between the effect of ω-3 PUFAs on the treatment of elderly depression and their routine consumption of ω-3.

There were some limitations in the study. An evaluation of depression through the study, for example at 4th, 8th, and 12th week of treatment, could have helped toward finding more details about the effects of fish oil as well as assessment of seasonal-related changes in mood on the

study. However, the inability to perform such evaluations serves as a limitation to the study.

A measure of any objective index of $n-3$ fatty acids status at either the baseline or the conclusion of the study was not done; however, in order to reduce this shortage, the monitoring of the consumption of the drug and the placebo consumption on a daily basis and under direct observation was increased. Furthermore, another nurse performed a weekly supervision of drug consumption and the associated side effects. In addition, food records were taken to lessen the mentioned shortage. Food record data showed no significant difference between energy and any type of fatty substances intake between the two groups at the beginning and at the end of the study. Any effective ω-3 PUFAs consumption between participants other than our given drugs could not be detected as well. The participants consumed less than three servings of fish during the 6-month course of the study based on the KCF food schedule. These validate that the placebo group did not consume effective ω-3 PUFAs and that the fish oil group consumed most of the given dosage of ω-3 PUFAs. However, there are some limitations. Although the dietary survey indicates similar intake of short-chain n-3 and n-6 fatty acids, differences in long-chain $n-3$ and $n-6$ fatty acid biosynthesis are highly variable. Therefore, we cannot consider the food records alone as a substitution for the measurement of objective index of ω-3 fatty acids status.

Using several types of depression assessments may strengthen the study design. It would be better to apply a clinician-rated test such as the Hamilton Depression Rating Scale in combination with the test used in this study. However, factors such as financial limitations existed. Additionally, the elderly become tired earlier than adults, especially the participants of this study who were of an average age of 80, and the accuracy of the test might be compromised. Only one test for depression evaluation could be selected. The GDS test is a self-rating scale but it can be given by interview and it has been validated in nursing homes [59]. The GDS test does not contain somatic symptoms, which might be due to medical illness. Also its format with simple response (yes/no) facilitates easier use by individuals [60]. These characteristics make the GDS test suitable for the elderly who are more affected by medical problems and impaired cognition. Therefore, this test was selected for this study. Because of the high rate of illiteracy in the participants, a test given by interview was better preferred.

In conclusion, in this study, low-dose ω-3 PUFA had some efficacy in the treatment of mild to moderate depression in elderly subjects. With due attention to good adherence of ω-3 PUFAs with the elderly and its minimal side effects, more studies are needed with dose finding patterns and larger samples to find the best range of low dose and the best duration of treatment. Some more studies are further needed to evaluate the effect of low-dose ω-3 PUFAs in severe elderly depression. Combination therapy of ω-3 PUFAs with antidepressant drugs in old ages should also be evaluated in the future studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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