DOI: 10.7860/JCDR/2016/19487.8597

Original Article

Obstetrics and Gynaecology Section

Effect of Citalopram in Combination with Omega-3 on Depression in Post-menopausal Women: A Triple Blind Randomized Controlled Trial

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ABSTRACT

Introduction: Depressive disorder is a common and disabling disorder that causes high rates of morbidity and mortality. Citalopram is an antidepressant drug, of the Selective Serotonin Reuptake Inhibitor (SSRI) class that has been used for geriatric depression since a long time ago. Prescription of omega-3 in geriatric depression has been increased recently; because of more favorable profile of their side effects. Some of the studies reported that omega-3 is effective in prevention or treatment of depressive disorders than Citalopram. However, there are contradictory studies too.

Aim: This study aimed to investigate the effect of a combination of omega-3 and citalopram in the treatment of women with post-menopausal depression.

Materials and Methods: This triple-blind randomized controlled trial was conducted on 60 women with post-menopausal depression who were referred to the Hamadan Fatemieh Hospital. After the participants completed the DSM-IV questionnaire and depression was confirmed by a psychiatrist, participants were assigned randomly into two-intervention and control groups. The patients in the control group received 20mg citalopram along with a placebo while patients in the intervention group received 20mg citalopram and 1g of omega-3. At baseline and at the end of the first, second, and fourth weeks, all of the participants answered the Beck's Depression Inventory (BDI). Descriptive statistics and t-test, repeated measures analysis of variance and Bonferroni post-hoc test was used to analyse the data.

Results: The depression score was 6.1±2.41 in intervention and 25.22±10.04 in control group, four weeks after intervention. A decreasing trend was observed in the mean depression scores of the intervention group during the study. Using repeated measures analysis of variance, a significant difference was observed between the mean depression scores of the two groups at the four measurement time-points ($p<0.001$). The mean depression scores of the intervention group were significantly lower than the control group either two weeks ($p< 0.001$) or four weeks after the treatments ($p< 0.001$).

Conclusion: Using omega-3, can reduce the severity of depression in post-menopausal women.

Keywords: Antidepressant drug, Depressive disorders, Menopause

INTRODUCTION

For most women, middle age –the ages between 45 to 55 years- is associated with menopause and the major life changes [1]. As menopause approaches, a woman's circulating oestrogen and progesterone decreases and multifaceted changes occur throughout the woman's body. Such changes can cause symptoms such as hot flashes, night sweats, vaginal dryness, mood swings, decreased libido, insomnia, fatigue, irritability, anxiety, depression, palpitations and arthralgia [2].

Depression is a very common disease that affects women more than men. It is estimated that lifetime incidence of depression is 1.5 to 3 times more in women than men [1]. Depression is defined as a depressed mood or loss of interest or motivation in all or more daily activities for a period of 2 weeks [3].

Post-menopausal depression has several aetiologies, including: a) experiencing previous periods of depression include Premenstrual Syndrome (PMS) or postpartum depression; b) experiencing menopause side effects such as hot flashes, night sweats and insomnia; c) stress; d) weight gain; and e) low socio-economic level [4]. Psychosocial problems such as insomnia and fatigue occur in 30 to 40% of post-menopausal women [5] and accounts for more than 20% of medical visits in women [6]. Depression is also a significant risk factor for development of osteoporosis, bone loss [7] and cardiovascular disorders [8] in post-menopausal women. A correlation has also been shown between depression and sexual abhorrence in post-menopausal women [9].

Like anxiety, depression affects the patients' relatives, because the patient induces a feeling of helplessness and despair to them [5].

Antidepressants are drugs used to treat clinical depression. Most antidepressants hinder the breakdown of serotonin or nor-epinephrine or both. A commonly used class of antidepressants are called Selective Serotonin Reuptake Inhibitors (SSRIs), which act on serotonin transporters in the brain to increase levels of serotonin in the synaptic cleft [10]. There are multiple classes of antidepressants which have different mechanisms of action. Another type of antidepressant is a Monoamine Oxidase Inhibitor (MAOI), which is thought to block the action of Monoamine oxidase, an enzyme that breaks down serotonin and nor-epinephrine. MAOIs are not used as first-line treatment due to the risk of hypertensive crisis related to the consumption of foods containing the amino acid tyramine [10,11].

Psychiatric medications carry risk of adverse effects, the occurrence of which can potentially reduce drug compliance. Some rebound or withdrawal adverse effects, such as the possibility of a sudden or severe emergence or re-emergence of psychosis in antipsychotic withdrawal, may appear when the drugs are discontinued, or discontinued too rapidly [12].

Antidepressant medications have many other side effects, including drowsiness, insomnia, restlessness, orthostatic hypotension, cardiac arrhythmias, digestive complications and weight gain [3].

In general, oestrogen therapy is the first step in the prevention and treatment of post-menopausal depression. Antidepressant medications such as Citalopram might be prescribed if symptoms of depression persist [13]. Citalopram is an antidepressant drug of the SSRI class that has side effect of antidepressant drugs [14]. Prescribing supplemental omega-3 is one of the treatment methods with minimal side effect [10]. Omega-3 fatty acids — also called ω-3 fatty acids or n-3 fatty acids —are Polyunsaturated Fatty Acids (PUFAs) with a double bond at the third carbon atom from the end of the carbon chain [15] that includes two essential fatty acids (including Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) [10]. A correlation has been shown between the low levels of omega-3 in plasma and some mental disorders [16]. Moreover, some of the studies have demonstrated promising results with omega-3 fatty acids as a treatment intervention for depressive and emotional disorders [17,18]. The effect of omega-3 on the level of serotonin in the cerebrospinal fluid [19] and the performances of cell membranes [20] has also been shown.

The women's life expectancy has increased in recent decades and more women experience the menopause period. On the other hand, depressed patients expend higher costs for their medical care including medication treatments. Few studies are also available on the effects of omega-3 on depression in post-menopausal women and in Iran also, no studies have been done in this region. Therefore, this study aimed to compare the effects of a combination of omega-3 and citalopram with citalopram monotherapy in the treatment of women with post-menopausal depression who were referred to the Hamadan Fatemieh Hospital.

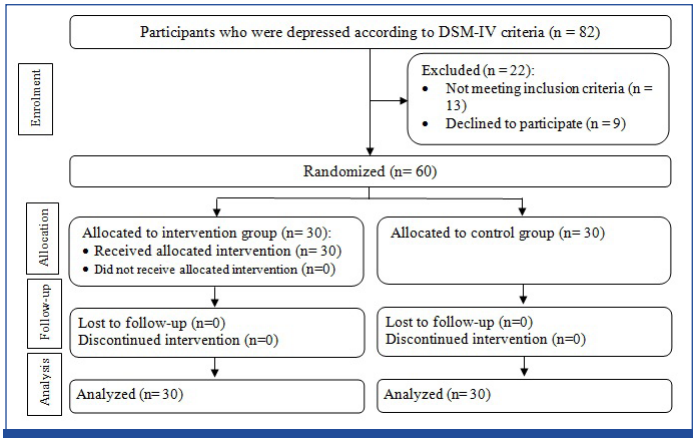
MATERIALS AND METHODS

This triple-blind randomized controlled trial was conducted on women with postmenopausal depression who were referred to the Hamadan Fatemieh Hospital from October 2013 to July 2014. Considering the prevalence of depression 11% [21], a power of 0.80, the Type I error of 0.05 and a possible attrition of 10%, we estimated that 30 experimental participants and 30 control participants will be needed to be able to reject the null hypothesis that the prevalence of depression for experimental and control participants is equal.

Inclusion criteria: Age range 65-45years, history of at least 12 months of amenorrhea, depression criteria according to the DSM-IV measure, earning a score higher than 10 on the Beck's Depression Inventory (BDI), confirmation of depression by the psychiatrist, having no history of hysterectomy, oophorectomy and radiation therapy, receiving no antidepressant medication during the past 6 months, having no sensitivity to herbs, not diabetic or with no cardiovascular disease, and a negative history of hormone therapy.

Exclusion criteria: Not consenting to the study, a depression score higher than 30 at follow-ups and any known drug side effects.

Participants were randomly allocated in the two groups using a permuted block randomization technique. Primarily, the six-block size of four was planned by a researcher who did not participate in sampling. Then, the sequence of blocks was determined using a table of random numbers. For blinding, a code was assigned to each participant and the codes were kept in two separate sealed envelopes of A and B. Then, one envelop was assigned to the intervention and the other one to the control group [Table/Fig-1]. Moreover, both medications were prepared in similar shapes and were coded by the pharmacist according to the allocation sequence.



[Table/Fig-1]: Flow chart on the participant recruitment and distribution in the study.

The study instrument included two parts: A demographic questionnaire (questions about participants' age, education level, age of menopause, age at the first and the last deliveries, and number of deliveries and abortions) and the BDI. The BDI-II included 21 questions, each answer being scored on a scale value of 0 to 3. Higher total scores indicate more severe depressive symptoms. Content validity of the instrument was confirmed by 10 faculty members in Hamadan Nursing and Midwifery faculty. The reliability of the instrument was assessed through the test-retest method. Accordingly, 15 patients answered the study instrument twice at an interval ten days. The test retest correlation coefficient was 0.86.

Procedure

All of the potential participants were recruited after answering the BDI for screening of depression and if their depression was confirmed by a psychologist. Then, the patients answered the demographic questionnaire and the psychologist prescribed them one of the predetermined medications according to the allocation sequence. In this way, participants in the control group received daily 20mg citalopram along with a placebo while patients in the intervention group received daily 20 mg citalopram and 1g of omega-3 for a week. The omega-3 drug was manufactured at the International Agensis in America and was prepared by Poorateb pharmaceutical companies in Iran.

Depression score, was evaluated using Beck questionnaire at the end of the first, second and fourth weeks. And in the follow-up periods the participants in both groups were examined by a psychiatrist. Neither the patients nor the physician, and the data analyser were aware of the type of intervention.

Ethical Considerations

The study protocol was approved by the Institutional Review Board and the Human Research Ethics Committee in the Hamadan University of Medical Sciences and registered in the clinical trial center (reg. IRCT 2013052113405N1). In addition, permissions were sought from the authorities in Fatemieh Hospital. All of the patients were informed about the design of the study but did not know which medication they will receive. All of the patients were assured about data confidentiality, safety of the study, and the voluntary nature of their participation. They also signed a written informed consent at the beginning of the study. We also observed all ethical issues in accordance with the last version of the Declaration of Helsinki.

STATISTICAL ANALYSIS

Data were analysed using SPSS-21.0. The Kolmogorov-Smirnov test was used to check the normal distribution of the data and the depression scores were normally distributed. Descriptive statistics (frequency, percentage, mean and standard deviation) were used

to describe the profile of the participants. The t-test was used to compare the mean depression scores between the two groups before treatment, one week, two weeks and four weeks after the treatments. Moreover, repeated measures analysis of variance (RM-ANOVA) was used to compare the depression scores across the four measurement time-points. As the Mauchly's test of sphericity did not indicate the data homogeneity, the Greenhouse-Geisser test was used. Bonferroni post-hoc test was used for two by two comparisons between the mean depression scores in the four measurements. Multivariate regression was performed to examine the role of different variables in postmenopausal depression. A p-value <0.05 was selected as statistically significant in all tests.

RESULTS

The mean age of the participants was 55.43 ± 6.66 years and their age ranged was from 75 to 46-year-old. No significant differences were observed between the demographic characteristics of the two groups except for their age and number of pregnancies [Table/Fig-2]. In the majority of the patients, menopause was started in ages over 45 years. More than 60% of the participants had an education level below high school, more than 80% experienced their first pregnancy at the age of 20 years or less, over 50% had more than 4 pregnancies and had no history of abortion.

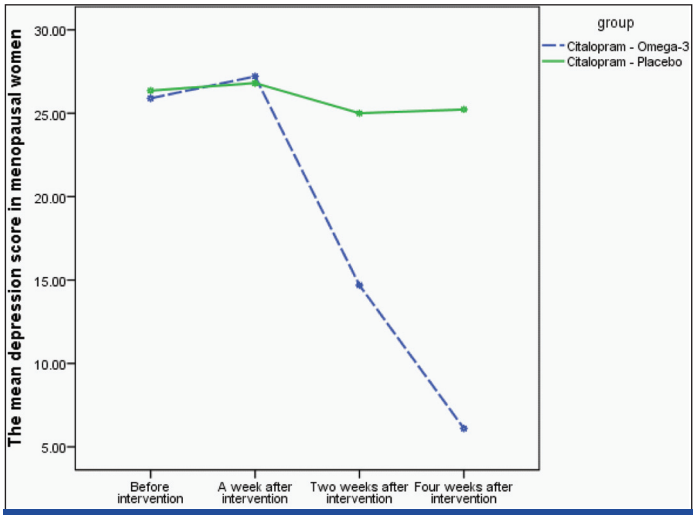
A decreasing trend was observed in the mean depression scores of the intervention group during the study. Using RM-ANOVA, a significant difference was observed between the mean depression scores of the two groups at the four measurement time-points [Table/Fig-3,4]. Using Bonferroni post-hoc test, no significant difference was found between the mean depression scores before and one week after the treatment in the intervention group. However, the differences were significant between intervention and control group in two and four week after intervention (p < 0.001).

In addition, independent t-test showed no significant differences between depression scores in the two groups before and also a week after the treatments (respectively p= 0.86 p= 0.88). But the mean depression scores of the intervention group were significantly lower than the control group in two weeks and four weeks after the treatments (p< 0.001) [Table/Fig-3].

Demographic characteristics of participants	Intervention Group (citalopram-Omega_3)* N= 30	Control Group (citalopram-Placebo)* N= 30	p-value
Age, year	55.17 ± 7.33	55.67 ± 6.06	0.51†
Education			
Illiterate	10 (33.3%)	10 (33.3%)	0.77‡
Less than diploma	18 (60.0%)	17 (56.7%)	
Diploma and higher	2 (6.7%)	3 (10.0%)	
Age at menopause, year	48.86 ± 4.34	48.09 ±4.95	0.62†
Age at first pregnancy, year	17.72 ± 7.26	16.93 ±2.86	0.50†
Age at last pregnancy, year	22.37 ±4.60	32.45 ±4.37	0.006†
Number of pregnancies	4.27 ± 2.54	6.09 ±2.38	0.009†
Number of abortions	0.55 ±0.73	0.70 ± 0.90	0.58†

[Table/Fig-2]: Comparison between the intervention and control groups in terms of demographic characteristics of participants.
* Greenhouse Geisser, †Independent t-test was used to compare Means

The mean depression scores were significantly higher in literate people (p = 0.02) and those with a history of more than four pregnancies (p= 0.01). No significant relationship was observed between other variables and the depression score [Table/Fig-5]. Moreover, multivariate regression was performed to examine the role of different variables in postmenopausal depression. However, none of the variables could significantly predict the postmenopausal depression (results are not presented here).



[Table/Fig-4]: Comparison between the mean of depression score of menopausal women in the two groups at 4 time periods.

Variables	Number (percent)	Mean ± SD	p-value
Age, year			
≤ 60	50 (83.3)	26.86 ± 9.84	0.71
> 60	10 (16.7)	22.50 ± 11.32	
Education			
The illiterate	20 (33.3)	30.60 ± 8.56	0.02*
Less than diploma	36 (60.0)	24.52 ± 10.50	
Diploma and higher	4 (6.7)	18.25 ± 4.92	
Age at menopause, year			
≤ 45	10 (16.7)	26.60 ±8.31	0.87
> 45	50 (83.3)	26.04 ± 10.53	
Age at first pregnancy, year			
≤ 20	49 (81.7)	26.46 ± 10.08	0.59
> 20	11 (18.3)	24.63 ± 10.74	
Age at last pregnancy, year			
≤ 30	28 (46.7)	24.21 ± 10.32	0.17
> 30	32 (53.3)	27.81 ± 9.82	
Number of pregnancies			
≤ 4	26 (43.3)	22.38 ± 9.99	0.01
> 4	34 (56.7)	29.00 ± 9.40	
History of abortion			
Yes	26 (43.3)	25.41 ± 9.48	0.53
No	34 (56.7)	27.07 ± 11.05	

[Table/Fig-5]: The relationship between the variables investigated with mean scores of depression in menopausal women.
* One-way ANOVA, the rest: t-test

	Group	Before intervention	A week after intervention	Two week after intervention	Four week after intervention	RM between groups*
Depression scores	Intervention	25.89 ± 10.56	27.20 ± 12.59	14.68 ± 8.19	6.10 ± 2.41	F = 30.75 p < 0.0001
	Control	26.35 ± 9.89	26.80 ± 9.30	25.00 ± 9.40	25.22 ± 10.04	
	t, df, p†	-0.17, 58, 0.86	0.14, 58, 0.88	-4.51, 58, < 0.0001	-9.98, 58, < 0.0001	

[Table/Fig-3]: Comparison between the intervention and control groups in terms of depression scores.
* Greenhouse Geisser, †Independent t-test was used to compare Means

DISCUSSION

This study showed that, more than two weeks of treatment with omega-3 (as a combination therapy) could effectively reduce the depression score in post-menopausal women. In a meta-analysis of randomized clinical trials, Grosso et al., found that the use of omega-3 PUFA is effective in patients with diagnosis of Major Depressive Disorder (MDD) and on depressive patients without diagnosis of MDD [22]. While Appleton et al., in their meta-analysis did not find sufficient evidence to determine the effects of n-3 PUFAs as a treatment for MDD [23]. Differences between the results of these two meta-analyses may be due to the difference in the number of imported articles; in Grosso et al., study, 11 trials conducted on patients with a MDD were included, while in Appleton et al., study there were 20 trials encompassing 26 relevant studies.

Results of some other relevant studies were similar to that of the present study, for instance. Saki et al., have compared the antidepressant effect of omega-3 and nortriptyline. They reported that the two medications were not significantly different in this regard [21]. Freeman et al., have also reported that eight weeks of treatment with omega-3, could significantly reduce the severity of depression in pre-menopausal women [17]. Su et al., Nemets et al., and Peet et al., have also investigated the effect of omega-3 on depression in menopausal women and reported that omega-3 was effective in reducing the severity of depression [24-26]. Depression is a major problem in perimenopausal ages and might be associated with many problems such as loss of energy, sleep disturbance, loss of appetite, weight loss, dizziness, muscle cramps, nausea, constipation or indigestion that are prevalent in these ages [27]. The magnitude of problem might also be increasing due to the increase in the life expectancy of Iranian women in the past two decades [28].

However, in a small study, Marangell et al., studied the effect of omega-3 on postpartum depression and reported that prescribing 2960 mg of EPA and DHA during the 34th to 36th weeks of pregnancy could not prevent postpartum depression [29]. Perhaps, the small sample size, lack of a control group and selecting the participants from a medical center had effects on the results. Marangell et al., also did not determine the optimal dose of the medication and perhaps started their treatment lately. It seems that the intervention would be more effective if the preventive doses of omega-3 starts earlier and continues for a longer period of time. In another study, Marangell et al., used DHA for the treatment of depression and reported that the treatment was not significantly effective [30]. Perhaps the dose used in the latter study was inadequate and used for a short duration. Moreover, Marangell et al., did not assess the patients' omega-3 levels. They also used only DHA while the intervention might be more effective in alleviation of depression if a combination of DHA and EPA is used.

None of the variables investigated in the present study showed a significant relationship with depression in post-menopausal women. This finding might be attributed to the limited number of variables investigated in the present study. A vast range of factors are associated with depression in this age group. Identification of these factors would help us not only to predict the risk of the disease, but also to design appropriate strategies for manipulating some modifiable risk factors and preventing the development of depression in these vulnerable ages. Then, the burden of psychological disorders would be decreased in the community.

LIMITATION

One of the limitations of current study is the small sample size. Thus, studies with larger sample size are recommended.

CONCLUSION

This study showed that using omega-3, can reduce the severity of depression in post-menopausal women. Considering the increasing number of women in menopausal ages and the high prevalence of health problems in this age group, prescribing complementary omega-3 might decrease the burden of depression in them. Integrating screening tests for measuring the levels of omega-3 in post-menopausal women and compensating it through complementary doses are suggested. Such strategies might be integrated in the primary health care services. Due to the small sample size of the present study and the inconsistencies between different studies, further investigations with larger sample sizes are suggested.

ACKNOWLEDGEMENTS

This study was supported by the research deputy of the Hamadan University of Medical Sciences. Therefore the authors would like to acknowledge the research deputy and the ethics committee of the university as well as the entire participant and the authorities and staff in the Fatemieh Hospital of Hamadan for their co-operation.

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FINANCIAL OR OTHER COMPETING INTERESTS: As Declared above.

Date of Submission: **Feb 02, 2016**
Date of Peer Review: **Apr 14, 2016**
Date of Acceptance: **Jul 06, 2016**
Date of Publishing: **Oct 01, 2016**