



# Omega-3 Fatty Acids plus Vitamin E Cosupplementation versus Vitamin E in Fibrocystic Breast Patient with Mastalgia: A Randomized Controlled Trial

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## Abstract

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**BACKGROUND:** Fibrocystic changes (FCCs) of the breast are a common breast condition. Mastalgia is the most common symptom of FCC; it usually causes fear of breast cancer and has negative effects on the quality of life.

**AIM:** The objective of the research was to establish the effect of cosupplementation of omega-3 plus Vitamin E on mastalgia in FCC patients, to evaluate its effect with that of Vitamin E only, and to determine the effect of omega-3 plus Vitamin E versus Vitamin E only on the radiological findings in FCC patients.

**METHODS:** This randomized controlled trial was conducted on 120 FCC patients with mastalgia. The participants were randomly assigned into three groups: Omega-3 plus Vitamin E group, Vitamin E only group, and control group. The new breast pain chart was used to assess the severity of mastalgia in the three groups before, through, and after intervention. Radiological assessment was done before and after the intervention.

**RESULTS:** After 3 months of the intervention, there was a statistically significant difference between the three groups regarding radiological results with  $p > 0.05$  and, after the 3<sup>rd</sup> month of interventions, there was a statistically significant difference between the groups regarding the new pain score with  $p > 0.001$ . The median of the new pain score premenstrual was 4.8, 2, and 2.5 in control, omega-3 plus Vitamin E, and Vitamin E only, respectively, but this difference was insignificant between the last two groups ( $p < 0.996$ ).

**CONCLUSION:** This study showed that Vitamin E and Vitamin E plus omega-3 were effective in relieving mastalgia in FCC patients. However, the addition of omega-3 was ineffective.

## Introduction

Fibrocystic changes (FCCs) of the breast are common benign conditions that affect more than half of women with incidence rate ranges between 45% and 70% in female reproductive life [1]. The prevalence of FCC in Egyptian females was estimated to be about 15% [2].

The etiology of FCC has not been established, but elevated estrogen levels, low progesterone levels, abnormal estrogen/progesterone ratio, increased prolactin, growth factor, insulin, and thyroid hormone levels have been implicated [3].

Many women with FCC have symptoms including swollen, tender breasts, and/or mass in one or both breasts. Mastalgia in FCC tends to fluctuate in severity throughout the month. It worsens just before the menstrual cycle, subsiding near the end. This pain is badly affecting the quality of life of FCC patients [4].

Women suffering from mastalgia have been found to have increase of the plasma levels of saturated fatty acid esters whereas unsaturated fatty acid esters were decreased. Fluctuation in this ratio affects the receptor sensitivity so prescription of essential fatty acids or the application of agents modifying the fatty acids ratio in plasma may offer benefits in the treatment of mastalgia. Vitamin E has been found to have an antioxidant effect with the ability to prevent the oxidation of unsaturated fatty acids and, therefore, decrease the unsaturated-saturated ratio of essential fatty acids and inhibit the receptors from becoming more susceptible to hormonal influence [5], [6], [7].

Our objectives were to identify the effect of omega-3 plus Vitamin E supplementation on mastalgia in patients with FCC and compare this effect with that of Vitamin E only on mastalgia in patients with FCC. Furthermore, one of the important objectives was to determine the effect of omega-3 plus Vitamin E supplementation versus Vitamin E only on the radiological findings in patients with FCC.

## Methods

### **Study design and setting**

It is a randomized controlled trial that was done in family medicine outpatient clinics, Kasr El-Ainy Hospital and in early detection and cancer prevention unit in National Cancer Institute from January 2019 to January 2020.

### **Inclusion criteria of patients**

Inclusion criteria were females aged 18–55 years who were diagnosed with FCC of the breast and are suffering from mastalgia ranging from mild to severe for at least 6 months.

### **Exclusion criteria of patients**

Pregnant and lactating women, patient who had a recent breast abscess or breast drainage, patient used omega-3 and Vitamin E supplementation before the trial, and postmenopausal women.

### **Sample size**

The sample size has been calculated using Epi Info version 7 software based on data from a previous study (Delfan *et al.*, 2015). The sample size was estimated to be 40 for each group, with 95% power and a significance level of 0.05.

### **Random allocation**

One hundred and twenty patients were assigned by simple randomization into three groups using sealed opaque envelopes that were distributed by a nurse who did not know the nature of the study.

The first group (Group A): Patients in this group received omega-3 capsules (1000 mg) once daily plus Vitamin E 400 mg once daily for three consecutive menstrual cycles.

The second group (Group B): Patients in this group received Vitamin E 400 mg once daily for three consecutive menstrual cycles.

The third group (Group C): Patients in this group were reassured and received analgesics only on demand.

The doses of omega 3 capsules and Vitamin E calculated based on previous literature who stated that this was an effective dose without any side effects [5].

### **Study tool**

A structured interviewing questionnaire for patients was constructed and filled in the clinics by

doctors of the research team who take full medical history and examine the patients to cover the following items:

#### *Sociodemographic data*

Patient code number, age, residency, occupational, educational, and marital status.

#### *General medical data*

To exclude any medical problem which can interfere with the study? Medical history, history of past illness, history of breast cancer, history of recent breast abscess, family history of breast cancer, and present history including duration and severity of breast pain, breast masses, and nipple discharge.

#### *Reproductive health data*

It included menstrual history (the age at first menses, duration, amounts, regularity of menstrual cycle, and history of premenstrual symptoms), obstetric history which included: (The woman age at first pregnancy and the total number of pregnancies), gynecological history (vaginal bleeding, vaginal discharge, and pelvic pain), and contraceptive history (use and type).

#### *Complete general examination*

It included anthropometric measurements and calculating body mass index (BMI). Moreover, a clinical breast examination included breast masses (either unilateral or bilateral, numbers, locations, and its size) and nipple discharge.

#### *New breast pain score*

It is the chart that was used to assess the pain score in the patient [8]. Approval was taken by email from the authors. In the new breast pain chart, the patient trained by the research team how to score the pain severity daily in the form of a visual linear analog scale score. The patient recorded pain score also during her menstruation on a separate part of the chart, making this chart more favorable than other breast pain charts. Hence, our patients were requested to record their pain experience using a 10 cm visual analog scale as mild (1–4 cm), intermediate (5–7 cm), and severe (8–10 cm) and to plot the number in the chart that was given to them to assess the pain. The patients were reminded weekly to plot the score and to record any new symptoms they felt.

The patients were asked to register the daily occurrence of other symptoms and the changes in breast tenderness and pain. The groups were assessed after the end of the menstrual cycle for three consecutive menstrual cycles.

### Breast ultrasonography or mammography

Radiologists responsible for the assessment outcome were blinded to which group the patient was in. Breast ultrasound was done to patients younger than 40 years old before and after the intervention, while mammography and ultrasound were done before and after the intervention, to all patients who are 40 years old or older. Imaging was done before the intervention to diagnose the FCC in the breast and to exclude other breast diseases.

### Statistical analysis of data

Data management and statistical analysis were performed using the Statistical Package for the Social Sciences version 24.

Numerical data were summarized using means and standard deviations or medians and ranges. Data were explored for normality using the Kolmogorov–Smirnov test and the Shapiro–Wilk test. Categorical data were summarized as percentages. Comparisons between the three groups concerning normally distributed numeric variables were done using the one-way ANOVA. Non-normally distributed numeric variables were compared by the Kruskal–Wallis test followed by the Dunn *post hoc* test. For categorical variables, differences were analyzed with Chi-squared test and Fisher's exact test when appropriate. All p values are two sided.  $p \leq 0.05$  was considered statistically significant.

### Ethical considerations

The current study was revised and approved by the Scientific Research Ethical Committee of the Faculty of Medicine, Cairo University. The approval number is N-126-2019. Informed consent was obtained from each participant before they were enrolled in the study after explaining the aim and the objectives of the study to the participants ensuring the confidentiality of the data.

## Results

There was no statistically significant difference between the studied groups regarding age and BMI. The three groups were matched regarding sociodemographic characteristics including residence, occupation, and education ( $p > 0.05$ ), as shown in Table 1.

The relation of radiological results between the three groups before intervention was insignificant, with most of the patients having focal FCC, as shown in Table 2.

The relation between the three groups regarding the radiological results after intervention was significant ( $p > 0.05$ ); 35% in Vitamin E only group

**Table 1: Baseline characteristics of the studied groups**

Items	Control		Omega 3 plus Vitamin E		Vitamin E		p value
Age	Mean $\pm$ SD		Mean $\pm$ SD		Mean $\pm$ SD		
	34.6 $\pm$ 8.5		30.4 $\pm$ 7.7		32.3 $\pm$ 7.7		0.062
BMI	Mean $\pm$ SD		Mean $\pm$ SD		Mean $\pm$ SD		
	25.9 $\pm$ 4.1		25.9 $\pm$ 4.1		26.8 $\pm$ 3.8		0.481
	No	%	No	%	No	%	
Residency							
Urban	30	75.0	26	65.0	32	80.0	0.303
Rural	10	25.0	14	35.0	8	20.0	
Marital status							
Single	7	17.5	10	25.0	8	20.0	0.940
Married	30	75.0	27	67.5	30	75.0	
Widow	2	5.0	1	2.5	1	2.5	
Divorced	1	2.5	2	5.0	1	2.5	
Education							
No	7	17.5	4	10.0	1	2.5	0.280
Med	15	37.5	17	42.5	19	47.5	
High	18	45.0	19	47.5	20	50.0	
Occupation							
Working	23	57.5	20	50.0	26	65.0	0.398
Not working	17	42.5	20	50.0	14	35.0	

SD: Standard deviation, BMI: Body mass index, No: Number,  $p \leq 0.05$  is considered statistically significant, analysis done by ANOVA test for age and BMI, analysis done by Chi-square test for residency, marital status, education, and occupation.

had focal area of thick parenchyma after intervention, while, in the control group, 45% had focal FCC as demonstrated in Table 3.

There was an insignificant difference between the three groups regarding the average pain score before intervention, as shown in Table 4.

There was a significant correlation between the control group and omega-3 plus Vitamin E group regarding the average pain score in the premenstrual, menstrual, and postmenstrual periods in the 3<sup>rd</sup> month of the intervention, also there was a significant correlation between the control group and Vitamin E only group regarding average pain score in the premenstrual, menstrual, and postmenstrual periods, but there was an insignificant correlation between omega-3 plus Vitamin E group; this is shown in Table 5.

## Discussion

One of the important objectives of the current study was to determine the effect of omega-3 plus Vitamin E supplementation versus Vitamin E only on the radiological findings in patients with FCC. To the best of our knowledge, it is the first study to compare the radiological changes in patients with FCC before and after omega-3 plus Vitamin E supplementation.

There was no statistically significant difference between the studied groups regarding the radiological results before intervention with most patients having focal FCC. However, there was a statistically significant difference between the studied groups regarding radiological results after intervention with 35.5% of patients in the three groups becoming normal and 27.5% and 22% of patients in omega-3 plus Vitamin E and Vitamin E only groups having focal FCC.

However, these results were not in agreement with the study of Meyer *et al.* in 1990 [9] which

**Table 2: Pre-intervention radiology results of the studied groups**

Pre-intervention	Control		Omega 3 plus Vitamin E		Vitamin E		p value
	No	%	No	%	No	%	
Radiology result							
Focal area of thick parenchyma	2	5.0	4	10.0	4	10.0	0.538
Cluster of small cysts or discrete single cyst	19	47.5	12	30	14	35.0	
Focal fibrocystic changes as solid mass or thin-walled cysts	19	47.5	24	60.0	22	55.0	

No: Number,  $p \leq 0.05$  is considered statistically significant, analysis done by Chi-square test.

**Table 3: Radiology results after intervention in the three groups**

After intervention	Control		Omega 3 plus Vitamin E		Vitamin E		p value
	No.	%	No.	%	No.	%	
Radiology result							
Normal	4	10.0	5	12.5	4	10.0	0.05
Focal area of thick parenchyma	2	5.0	9	22.5	14	35.0	
Cluster of small cysts or discrete single cyst	17	42.5	15	37.5	13	32.5	
Focal fibrocystic changes as solid mass or thin-walled cysts	17	42.5	11	27.5	9	22.5	

No: Number,  $p \leq 0.05$  is considered statistically significant, analysis done by Chi-square test.

investigated the role of Vitamin E in the treatment of benign breast disease on 105 women. Breast examinations and mammography were done, after each treatment, at approximately the same phase of the patients' menstrual cycle. The study concluded that no significant subjective or objective effects were observed after treatment.

**Table 4: The average pain score of the studied groups before intervention**

Average pain score	Control Median	Omega 3 plus Vitamin E Median	Vitamin E Median	p value
Premenstrual	5.5	7	7	0.061
Postmenstrual	3.5	3	3	0.294
During menstruation	3	2	2.8	0.081
Worst pain before intervention	8	8	8	0.052

The current study illustrated that there were no statistically significant differences between the studied groups regarding pain at different intervals of menstruation when evaluated before intervention. However, there was a significant difference between the three studied groups after intervention, which was detected between the control group and omega-3 plus Vitamin E group and control group and Vitamin E group only regarding average pain score in the 3<sup>rd</sup> month of intervention. However, there is insignificant relation between omega-3 plus Vitamin E group and Vitamin E only group in average pain score after intervention.

**Table 5: The average pain score of the studied groups after intervention**

Average pain score	Control group Median	Omega 3 plus Vitamin E Median	Vitamin E Median	p value
1 <sup>st</sup> month premenstrual	5	5	5	0.434
Postmenstrual	3	2	3	0.076
During menstruation	2	2	2	0.159
Worst pain in the 1 <sup>st</sup> month	7	7	7	0.256
2 <sup>nd</sup> month premenstrual	4.5	4	4	0.604
Postmenstrual	2	2	2	0.147
During menstruation	2 <sup>a</sup>	1 <sup>a</sup>	2	0.009
Worst pain in the 2 <sup>nd</sup> month	7	6	6	0.077
3 <sup>rd</sup> month premenstrual	4.8 <sup>a-b</sup>	2 <sup>a</sup>	2.5 <sup>b</sup>	0.001
Postmenstrual	2 <sup>a-b</sup>	1 <sup>a</sup>	1 <sup>b</sup>	<0.001
During menstruation	2.3 <sup>a-b</sup>	1 <sup>a</sup>	1 <sup>b</sup>	<0.001
Worst pain in the 3 <sup>rd</sup> month	7 <sup>a-b</sup>	5 <sup>a</sup>	5 <sup>b</sup>	<0.001

min: Minimum, max: Maximum,  $p \leq 0.05$  is statistically significant, the analysis was done by Kruskal-Wallis test followed by Dunn test; similar letters in the same row are statistically significant.

These results were also consistent with the study of Jaafarnejad *et al.* in 2013 [10] which investigated the effect of Vitamin E compared to fish oil on the severity of mastalgia in 70 women aged 15–49

years, and the results showed no significant differences between the two groups.

However, the finding does not agree with the study of Delfan *et al.*, 2015 [5], which was a double-blind, randomized clinical trial conducted in Iran on 88 patients with mastalgia aged between 20 and 55 years. They found that Vitamin E plus omega free fatty acids are more effective than the use of Vitamin E alone in decreasing mastalgia. They used the Cardiff Breast Score in the assessment of mastalgia, while we used the new breast pain score.

The present study illustrated the effectiveness of omega-3 plus Vitamin E group in improving mastalgia as there was statistically significant improvement when comparing pre- and post-intervention pain scores in omega-3 plus Vitamin E group.

However, Kashanian *et al.*, 2015 [11], investigated the effect of omega-3 fatty acids on premenstrual syndrome and reported that omega-3 fatty acids decreased breast tenderness and affected some other symptoms.

The study of Vaziri *et al.*, 2014 [12], compared the effects of a flaxseed diet and omega-3 fatty acids supplementation on the treatment of cyclical mastalgia. The study demonstrated that the flaxseed bread diet was a more effective approach in decreasing cyclical mastalgia.

The present study illustrated the effectiveness of Vitamin E in improving mastalgia as there was a statistically significant improvement when comparing pre- and post-intervention pain scores in Vitamin E only group.

These results agreed with the study of Hajizadeh *et al.* in 2019 [13]. The meta-analysis showed significant differences between Vitamin E and placebo in the severity and duration of cyclic mastalgia as Vitamin E reduces both the severity and the duration of the disorder compared to placebos, which only reduce its severity and can, therefore, be considered treatment with minimum side effects.

Furthermore, Muralidhar *et al.* in 2016 [14] reported that women treated with Vitamin E for 3 months

showed a decrease in the severity of pain as measured by a numerical pain rating scale. The biochemical analysis also showed a significant decrease in oxidative stress markers.

The study of Shobeiri *et al.* in 2015 [15] was performed to clarify the effects of Vitamin E as a safe treatment for cyclic mastalgia among fertile women. This study was conducted on 150 women with cyclic mastalgia. The severity and duration of breast pain were measured according to both the Cardiff Breast Pain Chart and the visual analog scale. The efficacy demonstrated by the Vitamin E recipient case group was superior to that of the group that received a placebo.

These results agree with the study of Pruthi *et al.* in 2010 [16] which investigated the effect of Vitamin E compared to placebo on the severity of mastalgia and showed that Vitamin E has a greater effect than placebos.

In the same manner, Parsay *et al.* in 2009 [7] investigated the effect of a twice-daily administration of Vitamin E over 4 months and compared it to the administration of placebos on the severity of mastalgia in 150 women and found a significant reduction in the severity of mastalgia in the intervention group in the 2<sup>nd</sup> month.

### Limitations of the study

Illiterate patients had difficulty completing the questionnaire; this was overcome by more explanation to them and asking them to put dashes instead of numbers.

Some patients dropped out and could not attend at regular follow-up times; this was overcome by contacting these females by phone calls and rescheduling another visit.

### Conclusion

We conclude that Vitamin E and Vitamin E plus omega-3 were effective in improving FCC, which was obvious in radiological results, also they were effective in relieving mastalgia in FCC than reassurance, but the comparison between Vitamin E and Vitamin E plus omega-3 was not significant, which means that addition of omega-3 was ineffective.

### Recommendations

Proper assessment and management of breast pain in primary health care to improve patients' quality of life are recommended. It is also recommended

to use the new breast pain score in primary health-care clinics. The reassurance of patients and Vitamin E supplementation has a positive effect in breast pain management. Further studies on the effect of Vitamin E and omega-3 on a large number of patients complaining of mastalgia, using different doses, are recommended.

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