Effects of Melatonin Supplementation on Clinical Symptoms and Paraclinical Outcomes in Women Diagnosed With Fibrocystic Breast Disease: An Interventional Study

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Abstract- Fibrocystic breast disease is the most common benign breast disease in women, and it is necessary to investigate the most effective treatment method to reduce its symptoms. Therefore, the study was conducted to investigate the effect of melatonin supplementation on clinical symptoms and paraclinical outcomes in women diagnosed with fibrocystic breast disease. Investigating the Effects of melatonin supplementation on clinical symptoms and paraclinical outcomes in women diagnosed with fibrocystic breast disease. The present study is a controlled intervention-placebo treatment conducted on women suffering from fibrocystic breast disease aged 18-40. This interventional study was conducted on 66 patients (33 in the intervention group and 33 in the control group). Melatonin supplement of 3 mg was administered to the intervention group and a placebo to the control group for 12 weeks. Patient information, symptoms, and paraclinical outcomes were recorded at the beginning of the study before the intervention and 12 weeks after the intervention. After collecting the data, we analyzed it using SPSS version 16 software and appropriate statistical tests. The findings of this study showed that melatonin administration in patients with fibrocystic breast disease reduced anxiety, depression, improved sleep quality, increased TAC (Total Antioxidant Capacity), and decreased MDA (Malondialdehyde). However, both study groups did not have statistically significant differences in the average pain and hs-CRP before and after the intervention. According to the findings of the study and the identification of the positive effect of melatonin on laboratory indicators and symptoms in patients with fibrocystic breast disease, it is recommended to prescribe melatonin in addition to standard treatment to witness a better and faster recovery, and in this way, the quality of life of patients can be increased.

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Introduction

Fibrocystic breast disease is the most common benign breast disease in women, primarily affecting women between the ages of 20 and 50 (1). The exact pathogenesis of this disease is unknown. However, hormonal imbalance, particularly an increase in the ratio of estrogen to progesterone, plays a vital role in the development and progression of this condition (2). Estrogen hormone causes epithelial cell proliferation and differentiation and increases mitosis, while progesterone acts on the opposite. As a result of the monthly changes in these two hormones and the disruption of their balance in women, fibrocystic breast changes are created (3).

This disease is among the most common reasons women visit the general surgery clinic (4). Studies have demonstrated that oxidative stress and inflammatory

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factors are increased due to increased proliferation, differentiation, and mitosis of mammary gland epithelial cells (5,6). The incidence of benign breast disease has demonstrated a notable clinical association with breast cancer and the use of estrogen and anti-estrogen therapies. According to studies, the prevalence of benign breast lesions increases 1.7 times in postmenopausal women who receive estrogen and progestin for more than eight years. It has also been reported that a combination of estrogen and progesterone used as therapy is associated with a 74% risk of benign breast disease (7).

Fibrocystic changes are associated with symptoms of heaviness, chest pain, and fullness in the chest area. These symptoms increase before menstruation and decrease after this period. Most women suffering from fibrocystic disease say they feel more pain when angry. This pain remains in the breast tissue, and shoulder and arm pain cannot be related to this disease. Periodic mastalgia is the most common symptom of fibrocystic changes in the breast, causing complaints for most women. Fibrocystic changes can sometimes result in asymptomatic masses that are soft, movable, and compressible.

However, the most frequent symptom is tenderness and diffuse pain in both breasts, as well as discharge from the nipple from time to time. These lumps may be touched singly or multiple times, change size due to hormonal fluctuation, and even temporarily disappear. Due to the enlargement of cysts in the period preceding menstruation (as a result of hormonal changes), most women experience more severe breast pain and swelling 12-14 days before their period (8-10). Mastalgia can cause anxiety and fear of malignancy in women suffering from this disease. It can also affect the work, social, and educational functioning of patients, thus reducing their quality of life and self-care (11-13).

Several studies have shown the relationship between mastalgia and psychological disorders such as depression and anxiety and reduced sleep quality. The prevalence of depression, anxiety, and sleep disorders in patients with fibrocystic breast disease has been reported as 76.2%, 66.4%, and 58.3%, respectively, which is significantly higher than the general population (14). For mastalgia patients, lifestyle changes and reassurance are the first options. Other suggestions are the use of a supportive bra and changing the dose of the hormone replacement therapy regimen. Painkillers such as aspirin and ibuprofen are suitable treatment options (15,16). Despite the lack of proven efficacy in previous studies, evening primrose oil is recommended as a supportive measure if pain persists despite treatment. A period of 3 to 6 months is the recommended deadline for observing the desired effect (17).

Hormone therapy may balance hormone levels and reduce breast pain. physician may recommend oral contraceptives containing synthetic estrogen, progesterone, or both. Research has also shown that progesterone gel can reduce cysts. Certain supplements may reduce pain associated with fibrocystic breast disease. According to the findings of some studies, people who consumed primrose oil or vitamin B6 reported a reduction in pain intensity one, two-, and three-months following treatment (18,19).

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced and secreted by the pineal gland. This molecule is a very strong antioxidant (20,21). Melatonin's effect on the quality of life and oxidative stress markers in MS patients was investigated in a study conducted by Raygan *et al.*, in Iran. The administration of 5 mg of melatonin every day for 90 days to multiple sclerosis patients resulted in improved quality of life and oxidative stress markers in the patients (22). In another study, the daily consumption of 10 mg of melatonin in diabetic patients with coronary artery disease after 12 weeks caused a significant improvement in oxidative stress biomarkers (total antioxidant capacity of plasma and malondialdehyde), inflammatory factors, and mental health parameters such as depression and anxiety (23). Alamdari *et al*., in Iran investigated the effect of melatonin on antioxidant capacity in obese women. Their results demonstrated that melatonin supplementation with a daily dose of 6 mg in obese women after 40 days led to a significant improvement in inflammation and oxidative stress biomarkers (MDA and TAC) (24). A study conducted by Kozirog *et al*., examined melatonin's effects on antioxidant capacity and metabolic factors in metabolic syndrome patients. The addition of melatonin at a daily dose of 5 mg to patients with metabolic syndrome significantly improved oxidative stress biomarkers after 2 months; however, no significant changes were observed in hs-CRP levels (25).

Despite the considerable prevalence of fibrocystic breast disease among women and its extensively documented influence on their quality of life, there exists a significant gap in comprehending efficacious treatment methodologies. While disturbances in hormonal equilibrium have been associated with the origin of this condition, a comprehensive therapeutic approach that not only alleviates physical symptoms but also addresses psychological distress and oxidative

stress remains elusive. Present treatments primarily center on symptom control, often neglecting the underlying factors contributing to the ailment.

The impetus behind this study stems from the necessity for a more comprehensive and efficient treatment paradigm for fibrocystic breast disease. The investigation into melatonin supplementation as a potential intervention arises from the multifaceted functions of melatonin as an antioxidant, a regulator of hormonal equilibrium, and an influencer of psychological well-being. Through the exploration of melatonin's effects on clinical symptoms, psychological well-being indicators, and analytical outcomes in women diagnosed with fibrocystic breast disease, our objective is to bridge the existing gap in knowledge and offer insights into a novel therapeutic avenue that could amplify the quality of life for these individuals.

Apprehending the potential advantages of melatonin supplementation in alleviating fibrocystic breast disease symptoms holds significance not solely for enhancing patient care, but also for furthering our comprehension of the interplay among hormonal imbalances, oxidative stress, and psychological well-being within the context of this condition. By shedding light on these relationships, our study aspires to contribute valuable insights that may inform the formulation of more tailored and efficacious treatment approaches for women grappling with fibrocystic breast disease.

Materials and Methods

The present study is a controlled intervention-placebo treatment conducted on women suffering from fibrocystic breast disease aged 18-40. The initial sampling was done by the "convenient" method from the general surgery clinic affiliated with the social security organization of Isfahan province, Iran, between April and December 2022, among the patients referred for treatment of the disease. For this purpose, women suffering from fibrocystic disease with a history of at least six months were identified. After determining the time, an appointment was made.

In these meetings, the research objectives were explained to women diagnosed with fibrocystic breast disease. If they agreed verbally, written consent was also taken. As part of the first meeting, trained experts in the women's clinic of the selected centers recorded the height and weight of the women. The study participants were all women with fibrocystic disease who were referred to the surgical clinic and met the study criteria. Inclusion criteria included women with fibrocystic breast disease aged 40-18 years. Exclusion criteria consisted of proof of breast cancer, receiving Tamoxifen, Danazol, and Bromocriptine drugs in the last three months, having any active infection, and taking any supplements (vitamins, minerals) in the past three months. The diagnosis of fibrocystic disease was based on both clinical and paraclinical findings. According to similar studies, The sample size was calculated according to similar studies and considering the type 1 error of 0.05 and the test power of 80%, as well as the mean change (d) equal to 2.9 and the standard deviation of 1.1 for each group of 30 people. (26). This study included 66 patients diagnosed with fibrocystic breast disease (33 in the intervention group and 33 in the control group). Study participants were randomly divided into receiving melatonin supplement or placebo for 12 weeks.

For the randomization process, women suffering from fibrocystic breast disease were initially stratified based on two criteria: BMI and age. Participants were categorized into four subgroups: those with a BMI greater than 25 and age greater than 30 years, those with a BMI greater than 25 and age less than 30 years, those with a BMI less than 25 and age greater than 30 years, and those with a BMI less than 25 and age less than 30 years. Within each subgroup, participants were randomly assigned to either the treatment group receiving a melatonin supplement or the control group receiving a placebo (containing starch).

The randomization was performed using a computer-generated randomization sequence to ensure equal chances of assignment to either group, thus maintaining allocation concealment. An independent statistician, who was not involved in the study, generated the randomization sequence. To ensure the integrity of the allocation process, the sequence was concealed using sealed, opaque, and sequentially numbered envelopes. These envelopes contained the group assignments and were opened only after the participant’s information had been recorded.

For 12 weeks, melatonin supplement of 3 mg (OPD Pharma, Damavand, Iran), two tablets an hour before sleep, was used. Additionally, a placebo capsule containing starch that resembled melatonin supplement in color, shape, and other characteristics was used for 12 weeks. Patients' supplement follow-up was controlled once a week through a telephone call by a trained expert. In cases where the patients did not consume the supplement, they were excluded from the study.

A trained expert evaluated anthropometric indices at the beginning and 12 weeks after the intervention.

Weight was measured in a fasting state, without shoes, with minimal clothes, and using a Seca (Hamburg, Germany) digital scale with 0.1 kg accuracy. Height was measured with a tape measure with 0.1 cm accuracy. The BMI was calculated by dividing the weight by height squared. The visual analog scale (VAS) method was used to determine pain intensity (27). In this method, a graduated ruler is used. The patient is asked to rate his pain intensity from 0 to 10. Zero indicates no pain, 1-3 indicates mild pain, 4-6 moderate pain, and 7-10 indicates severe pain. Previous studies show the validity and reliability of persion version of this tool (28).

Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Pittsburg Sleep Quality Index (PSQI) were used to determine mental health parameters such as depression, anxiety, and sleep quality. The Beck Depression Inventory (BDI) is used to assess the level of depression in individuals aged 13 and older. This questionnaire contains 21 questions with four options. Each question is scored from 0 to 3. Finally, a score of 0 to 13 is equivalent to the absence of depression, a score of 14 to 19 for mild depression, a score of 20 to 28 for moderate depression, and a score of 29 to 63 for severe depression (29). The Beck Anxiety Inventory (BAI) consists of 21 questions with four options, and each question is scored from 0 to 3. If the total score is 0 to 7, it indicates the absence of anxiety. A score between 8 and 15 is considered mild, 16 to 25 moderate, and 26 to 63 severe (30).

The Pittsburgh sleep quality index (PSQI) has seven scales and 19 questions with four options. The range of scores obtained will be from 0 to 21. The higher the score, the lower the person's sleep quality (31). The validity and reliability of the Persian equivalent of these questionnaires have been examined in previous studies (32,33).

For biochemical evaluation, 10 ml of fasting blood samples were taken from the patients at the beginning and 12 weeks after the intervention in the laboratory of Shariati Hospital. The ELISA device was used to measure serum levels of inflammatory factor serum hs-CRP in ng/ml. The plasma antioxidant capacity was determined using the Benzie and Strain method by colorimetry using the Cusabio Biotech co-kit (Wuhan, China). In addition, malondialdehyde was determined by the TARS method based on the reaction of MDA with thiobarbituric acid at 535 nm.

Statistical analysis used

Data normality was determined using a one-sample Kolmogorov Smirnov test as part of the data analysis. As a result of confirming normality, parametric methods such as the Student T-test and variance analysis were used to analyze the data. In the case of non-normality, the Kruskal-Wallis and Mann-Whitney tests were used. The chi-square and Fisher's exact test were used to check the qualitative variables. The software used in this research is IBM SPSS v.16. The significance level of the tests was considered less than 5%.

Results

The data obtained from 66 female patients in the age range of 18 to 40 years were analyzed. Demographic information, including average age, height, weight, and BMI for both groups, revealed no statistically significant difference (P>0.05) (Table 1).

Table 1. Mean and standard deviation of age, height, weight, and BMI in patients of two study groups

Variable	Group	Number	Mean	Standard deviation	*P*
Age (year)	Intervention	33	36.12	5.50	0.667
	Control	33	37.27	3.35	
height (cm)	Intervention	33	159.73	6.38	0.216
	Control	33	157.39	4.98	
weight (kg)	Intervention	33	66.76	8.39	0.888
	Control	33	64.91	8.33	
BMI (kg/m2)	Intervention	33	26.22	3.39	0.682
	Control	33	26.25	3.59	

There was no statistically significant difference between the average pain before and after the intervention in the patients of the two study groups (P>0.05). There was no statistically significant

difference between the average anxiety before and after the intervention in the patients of the two study groups (P>0.05). It was found that anxiety in the intervention group decreased by 4.7 units, whereas that of the control group decreased by 0.67 units, a statistically significant difference (P=0.015). In other words, melatonin significantly reduced anxiety among patients in the intervention group. In both study groups, the average depression before and after the intervention did not differ statistically significantly (P>0.05). There was, however, a significant difference between the intervention group and the control group in terms of depression changes, which was statistically significant (P=0.009).

There was no statistically significant difference in the average sleep quality before the intervention in the patients of the two study groups (P>0.05). However, it was found that the sleep quality 12 weeks after the intervention was 2.42 in the intervention group and 4.03 in the control group, which was statistically significant (P=0.001). In other words, the sleep quality score decreased by 2.18 units in the intervention group, while it decreased by 0.24 units in the control group, which was statistically significant (P<0.001).

Melatonin could improve sleep quality in patients with fibrocystic breast disease. In both study groups, the average TAC before and after intervention did not differ statistically significantly (P>0.05). However, TAC changes increased by 0.1 units in the intervention group and by 0.01 units in the control group, which was statistically significant (P<0.001). In the two study groups, the average hs-CRP before and after intervention did not differ statistically significantly (P>0.05). Patients in the two study groups did not have statistically significant differences in average MDA before intervention (P>0.05). However, 12 weeks after the intervention, MDA was 7.85 mol/l in the intervention group and 8.87 mol/l in the control group, indicating statistical significance (P<0.001). Thus, MDA changes decreased by 1.11 units in the intervention group and by 0.08 units in the control group, which was statistically significant (P<0.001) (Table 2).

Table 2. Pain, Anxiety, depression, Sleep quality and biomarkers of oxidative stress at baseline and 12 weeks after the intervention in in women diagnosed with fibrocystic breast disease

Variable	Measurement scale	Time	Group		*P*
			Intervention	Control	
			SD ± Mean	SD ± Mean	
Pain	Vas score	Before intervention	3.67±1.82	3.39±2.23	0.659
		12 weeks after the intervention	1.82±1.28	2.21±1.38	0.249
		Changes	-1.85±2.52	-1.18±2.50	0.252
Anxiety	Beck Anxiety Inventory	Before intervention	17.45±14.27	18.00±15.01	0.887
		12 weeks after the intervention	12.76±10.60	17.33±13.62	0.129
		Changes	-4.70±7.90	-0.67±2.81	0.015
Depression	Beck Depression Inventory	Before intervention	15.27±10.81	15.42±13.40	0.325
		12 weeks after the intervention	11.88±8.07	14.36±13.72	0.753
		Changes	-3.39±6.26	-1.06±5.20	0.009
Sleep quality	Pitssburge sleep Quality Index	Before intervention	4.61±1.61	4.27±2.41	0.392
		12 weeks after the intervention	2.42±1.37	4.03±2.11	0.001
		Changes	-2.18±2.08	-0.24±0.86	<0.001
TAC	mmol/l	Before intervention	1.28±0.23	1.31±0.30	0.295
		12 weeks after the intervention	1.37±0.29	1.32±0.28	0.220
		Changes	0.10±0.12	0.01±0.11	<0.001
hs-CRP	ng/ml	Before intervention	2.74±1.17	3.00±1.05	0.559
		12 weeks after the intervention	1.46±1.03	1.89±1.01	0.053
		Changes	-1.29±0.76	-1.11±0.52	0.686
MDA	μmol/l	Before intervention	8.96±1.01	8.95±0.86	0.985
		12 weeks after the intervention	7.85±0.60	8.87±0.79	<0.001
		Changes	-1.11±1.20	-0.08±0.28	<0.001

Discussion

This study investigated the effect of melatonin supplementation on clinical symptoms and paraclinical outcomes in women with fibrocystic breast disease in selected centers. The present study findings showed that

the average pain and hs-CRP before and after the intervention in the patients of the two study groups did not have a statistically significant difference. However, melatonin significantly reduced anxiety in the intervention group. Also, melatonin reduced depression and improved sleep quality in the intervention group.

In the melatonin intervention group, changes in oxidative stress biomarkers such as TAC, MDA, and the inflammatory marker hs-CRP were also statistically significant. There is no study on the effect of melatonin supplementation on clinical symptoms and mental health parameters such as depression, anxiety, sleep quality, biomarkers of oxidative stress, and inflammatory factors in women suffering from fibrocystic breast changes (based on our search).

However, the effect of this supplement on inflammatory profiles, oxidative stress, and fluid parameters has been investigated in patients with other diseases, such as type 2 diabetes, multiple sclerosis, and obesity (34). In a study conducted by Raygan *et al*., investigating the effect of melatonin in MS patients, melatonin supplementation with a daily dose of 5 mg after 90 days led to improved life quality and oxidative stress markers in them (23). Another study showed that daily consumption of 10 mg of melatonin for 12 weeks caused a significant improvement in oxidative stress biomarkers (total plasma antioxidant capacity and malondialdehyde) and inflammatory factors and psychological health parameters such as depression and anxiety in diabetic patients with coronary artery disease (23).

Although the patients studied in the above study are not the same as in the present one, the findings regarding the effect of melatonin on improving oxidative stress (total plasma antioxidant capacity and malondialdehyde) and psychological health in depression and anxiety are consistent with this study. In our study, there was no difference in hs-CRP between the two intervention and control groups due to receiving drugs except melatonin in the routine treatment of disease symptoms in patients with fibrocystic breasts.

Also, in a study conducted by Ghaderi *et al*., to investigate the effect of melatonin on mental health indicators, melatonin at a daily dose of 10 mg in patients under maintenance treatment with methadone caused an increase in sleep quality and a noticeable reduction in anxiety and depression scores (1). Our findings are in agreement with those of the study mentioned above. Our study found that melatonin significantly improved sleep quality and decreased anxiety and depression scores. Alamdari *et al*., investigated the effect of melatonin on blood pressure and antioxidant capacity in obese women, concluding that melatonin supplementation at a daily dose of 6 mg in obese women after 40 days led to a significant improvement in inflammatory factors and oxidative stress biomarkers (MDA and TAC) (24). Even though the patients in the above study were not the same as those in the present study, those findings are consistent with ours. Therefore, it can be concluded that melatonin administration significantly improves oxidative stress biomarkers (increased TAC and decreased MDA).

Despite the positive outcomes, the absence of significant changes in pain and hs-CRP levels requires further discussion. Pain and hs-CRP are vital indicators of inflammation and overall health, and their persistent levels may reflect underlying factors not addressed by the intervention. Importantly, the *P* for hs-CRP was 0.053, close to the significance threshold, suggesting a trend towards significance that could become clear with a larger sample size or a longer intervention duration. Previous research has demonstrated that while some interventions can reduce inflammatory markers, responses can be highly individualized and influenced by baseline levels and other comorbidities (35). For example, Ridker *et al*., found that while statin therapy significantly reduced hs-CRP levels, the extent of reduction varied widely among individuals (36). Moreover, the chronic nature of pain and its multifactorial etiology may necessitate more intensive or prolonged interventions to achieve significant changes (37). Future research should investigate the factors contributing to the variable responses in pain and hs-CRP, potentially incorporating more personalized approaches to optimize outcomes. This could involve stratifying participants based on baseline inflammation levels or including adjunct therapies targeting specific inflammatory pathways. Additionally, examining the long-term effects of the intervention might reveal delayed benefits not immediately apparent within the study's timeframe.

The findings of the present research should be evaluated along with its limitations. The small sample size was one of the most substantial limitations of this research. Of course, conducting a study with a larger sample size will lead to better conclusions, so this study should be carried out with a larger sample size to increase the generalizability coefficient of the findings.

Our study showed that administering melatonin to patients with fibrocystic breast disease reduced anxiety and depression, improved sleep quality, increased antioxidant capacity, and decreased MDA. However, the

average pain and hs-CRP before and after the intervention in the patients of the two study groups did not have a statistically significant difference. Based on the study's results and identification of melatonin's positive effects on laboratory indicators and symptoms in patients with fibrocystic breast disease, it is recommended to prescribe melatonin in addition to standard treatment to witness a better and faster recovery for patients. In this way, patients' quality of life can be enhanced.

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