Original Article

The Effect of Melatonin on the Sexual Function among Postmenopausal Women: A Randomized Placebo-Controlled Trial

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ABSTRACT

Background: Menopause is associated with alterations in women's behaviors and sexual function. Altered sexual function can in turn causes serious health problems for women and negatively affect their marital relationships. **Objective:** This study aimed to investigate the effects of melatonin on the sexual function of postmenopausal women. **Methods:** This randomized double-blind placebo-controlled clinical trial was made in 2012–2013 on 240 postmenopausal women who aged 40–60 and referred to public obstetrics and gynecology clinics affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. Participants were randomly divided into a melatonin and placebo group. Women in the melatonin and the placebo groups, respectively, received melatonin (3-mg tablets) and placebo for 3 consecutive months. Before and every 1 month during the intervention, participants' sexual function was assessed using Female Sexual Function Index. The repeated measures analysis of variance, the least significant difference, the independent sample *t* test, the Chi-square, and Fisher's exact tests were done for data analysis. **Results:** Sexual function mean score in the melatonin and placebo groups significantly increased from 12.49 ± 7.07 to 20.72 ± 8.57 and from 12.11 ± 7.82 to 15.55 ± 9.06, respectively. Yet, the amount of increase in the melatonin group was significantly higher than the placebo group. Moreover, there were significant differences between the groups regarding the variations of sexual function mean score across the four assessment points ($P < 0.001$). In addition, except for the baseline assessment point, the mean score of sexual function in the melatonin group was significantly greater than the control group at all other assessment points ($P < 0.05$). **Conclusion:** Melatonin significantly improves sexual function among postmenopausal women.

KEYWORDS: *Melatonin, Menopause, Sexual desire, Sexual function, Sexual satisfaction, Women*

INTRODUCTION

Menopause is one of the most critical stages in women's lives. Menopause is the permanent cessation of menstruation due to the lack of ovarian follicular maturation, and consequently, a decrease in the production of estrogen for at least 1 year.[1] The average menopause age is between 50 and 52.

Menopause and lack of estrogen are associated with different changes in the body and a wide variety of health problems such as hot flashes, atrophic changes in the genitourinary system, mood and behavior changes, and reduction in sexual desire.[2] Moreover, during menopause, several histological changes occur in the vagina which include a reduction in surface vaginal epithelium, loss of flexibility in the vaginal walls, and

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a decrease in the volume of vaginal lubrication. These changes can lead to sexual problems such as dyspareunia and decreased libido.[3] A study reported that only about 58.9% of postmenopausal women had a satisfactory quality of life in terms of sexual function.[2]

Hormone replacement therapy is one of the treatment modalities for menopausal problems. However, it is accompanied by different complications such as vaginal bleeding, increased risk for breast cancer, and a delay in the diagnosis of malignancies due to the erroneous attribution of malignancy-related vaginal bleeding to hormone replacement therapy.[4] Besides, there are considerable controversies regarding the effectiveness of hormone therapy in preventing and treating postmenopausal sexual dysfunction.[3,5,6] Thus, other treatment modalities, such as melatonin, were used as alternative methods in previous studies.[7-9]

Melatonin is produced endogenously from amino acid tryptophan in the pineal gland. During the day, the level of melatonin in the blood is quite low; however, in the evening, serotonin is converted to melatonin, and thus, the rhythmic secretion of melatonin starts. Melatonin plays an important mediating role in the body.[10,11]

There are only a few studies into the impacts of melatonin on sexual function. Previous studies also highlighted the need for more research into whether melatonin can affect sexual function in women.[7,9]

Objectives

This study aimed to investigate the effects of melatonin on the sexual function of postmenopausal women.

Methods

Participants

This double-blind randomized clinical trial was conducted from January 2012 to August 2013 on 240 postmenopausal women referred to public obstetrics and gynecology clinics affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. Study population consisted of postmenopausal women who aged 40–60 and complained of sexual dysfunction.

Sample size was calculated using the results of Moghassemi *et al*.' study. They reported that the mean scores of sexual function in their control and intervention groups were 23.11 ± 7.61 and 25.66 ± 4.87, respectively.[6] Consequently, considering a power of 80% and a type I error of 0.05, we estimated that 98 women were needed for each study group. Sample size calculation formula was $n=2\sigma^2([z_{1-\alpha/2}+z_{1-\beta}]^2/[\mu_1-\mu_2]^2)$. However, allowing for a 20% dropout and considering an effect size of 46.1%, we estimated that 240 women were needed (120 in each group). Thus, for primary intention-to-treat analysis, the data from 240 participants were available.

After a public announcement in all healthcare centers located in Shiraz city, Iran, 680 postmenopausal women volunteered to participate in the study. In the announcements, volunteers had been asked to refer to Motahhari Medical Center, Shiraz, Iran. All volunteers were evaluated regarding the inclusion criteria which were a Goldberg General Health Questionnaire (GHQ) score >23, Female Sexual Function Index (FSFI) score >28, follicle-stimulating hormone serum level above 40 IU, no history of hormone replacement therapy, no history of using soya, its products, and vitamin supplements during the last 3 months before the study, no use of sedatives, antidepressants, sleeping pills, and antihypertensive drugs, high health status as determined through physical examinations, and no history of liver, kidney, and gastrointestinal diseases. Women were excluded if they failed to take prescribed medications for any reason, were unwilling to continue participation in the study, and showed allergic reaction to melatonin or the placebo.

Data collection

Data were gathered through interviewing participants using a demographic and clinical characteristics questionnaire, Goldberg GHQ, FSFI, and a form for documenting drug side effects. The items of the demographic and clinical characteristics questionnaire were age, length of marriage, menarche and menopause age, weight, and systolic and diastolic blood pressures.

GHQ was used to evaluate women's general health before the intervention with the aim of excluding women with low general health status. This questionnaire consists of 28 items in the four dimensions of anxiety, depression, somatic symptoms, and social dysfunction. Each item is followed by the four choices of "Not at all," "No more than usual," "Rather more than usual," and "Much more than usual," which are scored 0, 1, 2, and 3, respectively. Higher scores signify lower general health status.[12] The Cronbach's alpha values of GHQ and its anxiety, depression, somatic symptoms, and social dysfunction dimensions have been reported to be 0.94, 0.96, 0.90, 0.89, and 0.78, respectively.[13,14]

FSFI comprises nineteen items and assesses the following six domains of sexual function: desire (items 1, 2), arousal (items 3–6), lubrication (items 7–10), orgasm (items 11–13), satisfaction (items 14–16), and pain (items 17–19). The score of each item ranges from 0 or 1 to 5. The score of each domain is calculated through summing up the scores of the items of that domain and multiplying the sum score by a domain

factor. The domain factors of the aforementioned six domains are 0.6, 0.3, 0.3, 0.4, 0.4, 0.4, respectively. Accordingly, the score of each FSFI domain ranges from 0 or 1 to 6 and the total FSFI score ranges from 2 to 36. Total FSFI scores of >28 signify sexual dysfunction. Respondents are asked to answer FSFI items based on their sexual feelings and function during the past 4 weeks. The Cronbach's alpha of FSFI was reported to be 0.70.[15]

Randomization

Based on an allocation ratio of 1:1 and the sample size of the study, numbers 1–240 were written on small slips of paper, and the slips were placed in a box, and then, they were mixed. After that, slips were randomly drawn and their numbers were consecutively written in one of the A or B lists. Finally, the lists were used for random assignment. Three researchers were responsible for preparing medications, implementing the intervention, and performing the interviews and physical and mental assessments. All of them together with all participating women were blind to group assignment. One of the researchers, who was aware of the types of the intervention, packed the medications similarly. The second researcher, who was unaware of the contents of the packages, delivered the packages to participants. The third researcher who was unaware of the types of the intervention, interviewed the participants, performed assessments, and collected the data.

Intervention

Women in the intervention group were provided with 3-mg melatonin tablets (manufactured by Poura Teb Company under the license of Nature Made Company, U.S.) while their counterparts in the control group were given placebo tablets that were similar to melatonin tablets in shape and color (produced by the School of Pharmacy at Shiraz University of Medical Sciences). The ingredients of placebo tablets were lactose, avicel, and magnesium stearate. The prescription dose of melatonin was determined based on the results of previous studies.[16,17] At the beginning of the study, women in both groups were provided with a thirty-tablet pack (containing either melatonin or placebo) and were asked to take one tablet per night at 18:00–21:00 for a whole month. At the end of the month, they were asked to refer to the study setting for receiving a new thirty-tablet pack of medications and also for completing FSFI. Study intervention lasted for 3 consecutive months, and consequently, women used three thirty-tablet packages – ninety tablets in total. Before providing them with new packages, we required them to return tablets they had not taken during the previous month. Because of the probable effects of diet and nighttime lighting on serum levels of melatonin, all participants were asked to consume a regular diet and sleep in completely dark rooms. Furthermore, women in both groups were provided with the same instructions about the intervention. Study questionnaires were completed by the participants four times, i.e., before and at the end of each month of the intervention. To reduce attrition rate, we called participants at the end of each week during the intervention to remind them of the medication plan and the date of their next visit.

Ethical considerations

The present study was approved by the Medical Research Ethics Committee of Shiraz University of Medical Sciences (approval code: 90-5880). Besides, the study was registered at Iranian Registration for clinical trials (registration code: IRCT201201041548N13). At the beginning of the study, we provided participants with comprehensive information about the objectives of the study, sexual dysfunction, melatonin and its benefits and possible side effects, type and length of the intervention, and follow-up assessments. Therefore, they could consciously decide whether or not to take part in the study. Then, they were asked to sign an informed consent form. We also provided them with our phone numbers, and hence, they could call and ask us their questions, if any, about the research. They were assured of the confidentiality of their data.

Data analysis

Descriptive statistics were used to summarize and present the data. The Kolmogorov–Smirnov test was done to examine the distribution of the main study variables. Results showed that the distribution of all variables was normal. Accordingly, the independent-sample *t*-test was run for between-group comparisons regarding baseline demographic and clinical characteristics and FSFI scores. The Chi-square and Fisher's exact tests were also used to compare the groups respecting the side effects of treatments. The repeated measures analysis of variance (ANOVA) was conducted to investigate the effects of melatonin on sexual function across the four assessment points. As Mauchley's test showed that sphericity was not assumed (χ^2 = 60.78: P < 0.001), degrees of freedom were corrected using Greenhouse Geisser estimates (epsilon = 0.818). The least significant difference (LSD) *post hoc* test was also used for pairwise between-group comparisons. The coefficient of variation was used to compare the primary and secondary outcomes in both groups. Finally, the analysis of covariance was performed to reduce the effects of confounders (such as last menstruation, menopause age, body mass index, and age). Significance level was set at <0.05.

Results

Initially, 240 women were recruited to the study, 41 of them were excluded due to loss to follow-up, failure to receive treatments, experience of side effects, or other causes. Therefore, 199 completed the study [Figure 1]. There were no significant differences between the groups at baseline regarding women's clinical and demographic characteristics [$P > 0.05$; Table 1] as well as the mean scores of sexual function and its domains ($P > 0.05$) [Tables 2 and 3].

Table 2 presents the sexual function mean scores of women. During the course of the study, sexual function mean scores increased in both groups [Figure 2]. Repeated measures ANOVA revealed that within-group increase in sexual function mean score over the time was statistically significant in both groups ($P < 0.001$). Yet, the amount of increase in the sexual function mean score of women in the melatonin group was significantly greater than that of the placebo group (8.23 ± 1.50 vs. 3.44 ± 1.24; $P < 0.001$). Repeated measures ANOVA also revealed significant between-group difference regarding the variations of sexual function mean scores over time ($P < 0.001$). Moreover, the results of LSD *post hoc* test illustrated that except for the baseline assessment point, the mean score of sexual function in the melatonin group was significantly greater than the control group at all other assessment points. The interaction of time and group was also significant [$P < 0.001$; Table 2].

Table 1: Comparing the groups respecting participant's demographic and clinical characteristics

Variable	Groups[a] (mean±SD)		*P*[b]
	Intervention	Control	
Age (years)	52.85 ± 4.26	53.39 ± 4.22	0.162
Length of marriage (year)	34.15 ± 6.71	34.99 ± 6.59	0.164
Menarche age (years old)	13.30 ± 1.56	13.60 ± 1.35	0.061
Time passed from the last menstruation (month)	56.18 ± 42.85	53.77 ± 44.65	0.335
Menopause age (years)	48.12 ± 4.04	48.88 ± 4.44	0.082
Weight (kg)	65.66 ± 10.11	65.10 ± 10.77	0.312
Systolic blood pressure (mmHg)	113.98 ± 15.50	111.79 ± 14.56	0.131
Diastolic blood pressure (mmHg)	72.25 ± 9.19	71.38 ± 9.03	0.228
BMI (kg/m^2)	26.66 ± 3.77	26.49 ± 4.25	0.370
Follicle-stimulating hormone	89.85 ± 44.70	88.67 ± 40.39	0.423

[a]Data are presented as mean±SD, [b]The independent-sample *t*-test. SD: Standard deviation, BMI: Body mass index

The results of the repeated measures ANOVA also illustrated that the mean scores of all sexual function domains in the melatonin group significantly increased during the study ($P < 0.05$). However, the variations of the scores in the placebo group were small and insignificant ($P > 0.05$). Moreover, repeated measures ANOVA indicated significant between-group differences regarding the variations of the mean scores of all sexual function domains across the four assessment time points [$P < 0.01$; Table 3]. Pairwise comparisons using the LSD *post hoc* test also showed that between-group differences regarding the mean scores of the arousal and sexual satisfaction domains were significant at the second, third, and fourth time points, while between-group differences regarding the mean scores of the desire, lubrication, orgasm, and pain domains were

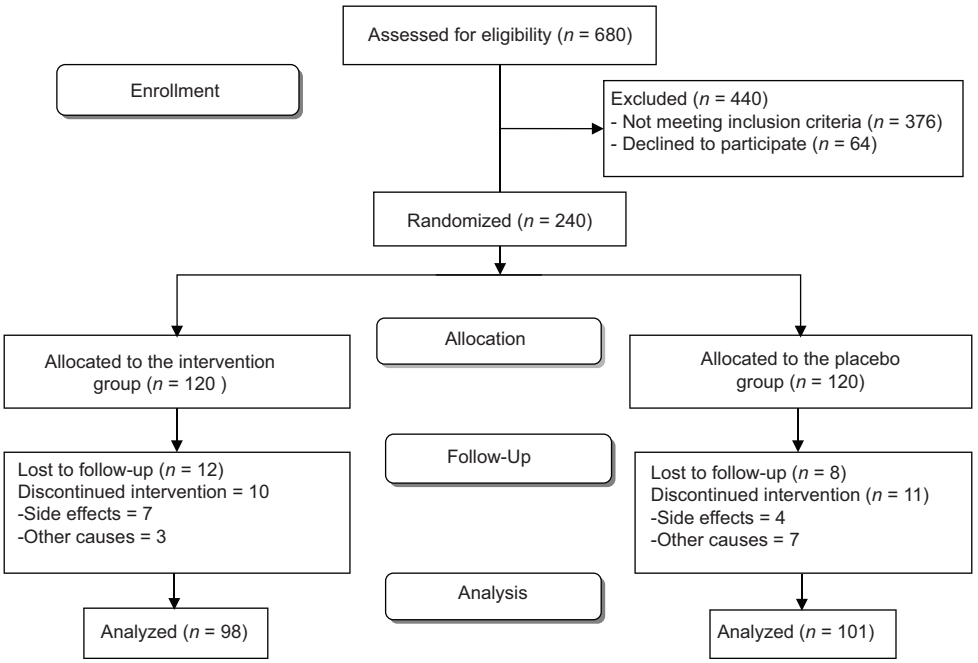

Figure 1: The study flow diagram

Table 2: Participant's sexual function mean scores at different assessment time points

Groups	Time of assessment				Time[b]	Groups[b]	Time × groups[b]
	Before	1 month after	2 month after	3 month after			
Intervention	12.49 ± 7.07[a]	16.19 ± 8.27	18.35 ± 8.32	20.72 ± 8.57	<0.001	<0.001	<0.001
Placebo	12.11 ± 7.82	13.32 ± 8.49	13.91 ± 8.88	15.55 ± 9.06			
P	0.360	0.009	<0.001	<0.001			

[a]Data are presented as mean±SD, [b]Repeated measures ANOVA. ANOVA: Analysis of variance, SD: Standard deviation

Table 3: Comparison of changes in the scores for sexual function domains in the two groups

Domains	Time of assessment[a]				Time	Group	Time × group[b]
	Before	1 month after	2 months after	3 months after			
Desire							
Intervention	1.65 ± 0.77[a]	2.25 ± 0.98	2.56 ± 1.04	2.91 ± 1.21	<0.001	<0.001	0.005
Control	1.74 ± 0.90	1.10 ± 0.98	2.17 ± 1.10	2.26 ± 1.12			
Arousal							
Intervention	2.00 ± 1.49	2.44 ± 1.60	2.81 ± 1.67	3.16 ± 1.60	<0.001	0.001	0.002
Control	1.77 ± 1.44	1.89 ± 1.51	1.95 ± 1.60	2.34 ± 1.61			
Lubrication							
Intervention	1.76 ± 1.52	2.50 ± 1.83	2.95 ± 1.91	3.52 ± 1.89	<0.001	<0.001	0.003
Control	1.64 ± 1.59	1.91 ± 1.82	2.17 ± 2.02	2.51 ± 2.02			
Orgasm							
Intervention	2.10 ± 1.60	2.69 ± 1.80	3.17 ± 1.75	3.46 ± 1.77	<0.001	0.002	0.003
Control	1.87 ± 1.61	2.33 ± 1.89	2.30 ± 1.87	2.62 ± 1.85			
Sexual satisfaction							
Intervention	2.74 ± 1.40	3.25 ± 1.52	3.65 ± 1.40	3.86 ± 1.55	<0.001	<0.001	<0.001
Control	2.78 ± 1.59	2.68 ± 1.52	2.86 ± 1.60	2.94 ± 1.57			
Pain							
Intervention	2.20 ± 1.79	2.92 ± 1.98	3.28 ± 2.12	3.78 ± 2.08	<0.001	<0.001	0.015
Control	2.21 ± 2.01	2.37 ± 2.12	2.52 ± 2.26	2.84 ± 2.17			

[a]Data are presented as mean±SD, [b]Repeated measures ANOVA. ANOVA: Analysis of variance, SD: Standard deviation

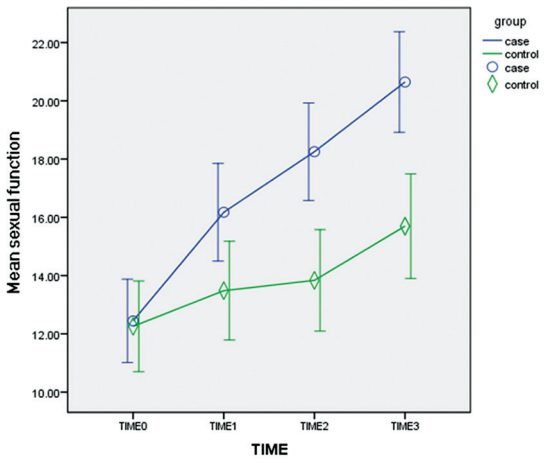

Figure 2: Comparing the mean score of sexual function in melatonin and placebo groups during the four consecutive measurements

statistically significant only at the third and the fourth assessment time points; [$P < 0.05$; Table 3].

Overall, fourteen women from the melatonin group (11.67%) and ten from the placebo group (8.33%) complained of problems such as drowsiness, nausea, vomiting, and headache, which are the known side effects of melatonin. Most importantly, bleeding and spotting were reported only by four participants from the melatonin group. The results of the Chi-square and the Fisher's exact tests illustrated no significant between-group difference regarding treatment side effects [$P > 0.05$; Table 4].

Discussion

The results of the present study showed that melatonin significantly improved postmenopausal women's sexual function. The results also revealed significant differences between the two groups in terms of the mean scores of all sexual function domains.

Various factors including sex education, economical status, and depression can affect sexual function.[18] Evidence also suggests that melatonin affects mammals' sexual function through the central serotonergic system.[19] Probably, melatonin improves sexual function in mammals by lowering the arousal threshold through moderating the sensitivity of central 5-hydroxytryptaminergic receptors.[9] Moreover, melatonin acts as a functional mediator in the reproductive system and transfers environmental signals

Table 4: Frequency distributions of melatonin side effects at the end of intervention

Complications	Group		*P*
	Intervention, *n* (%)	Control, *n* (%)	
Headache and dizziness	2 (1.67)[a]	2 (1.67)	0.689[b]
Nausea and vomiting	5 (4.17)	2 (1.67)	0.223[b]
Drowsiness	9 (7.5)	6 (5)	0.212[c]
Bleeding and spotting	4 (3.33)	0	0.061[b]
Heartburn	0	3 (2.50)	0.123[b]
Tingling of extremities	0	3 (2.50)	0.123[b]
Feeling full	2 (1.67)	0	0.249[b]
Constipation	1 (0.83)	1 (0.83)	0.751[b]
Diarrhea	0	1 (0.83)	0.500[b]
Flatulence	2 (1.67)	0	0.249[b]

[a]Data are presented as Frequently distribution, [b]Fisher's exact test, [c]Chi-square test. SD: Standard deviation

to the reproductive axis. This activity together with the effects of melatonin on psychological moods can explain the improvement in sexual function.[17] Given the adverse effect of sleep disturbances on sexual function,[3,20,21] positive effects of melatonin on sexual function can also be due to its positive effects on sleep quality and duration.[22,23] Other possible mechanisms for positive effects of melatonin on sexual function include the reduction of oxidative stress and the prevention of cell apoptosis in the central nervous system which eventually delay its aging process.[24] Most of our participants were willing to continue using melatonin because they believed it gave them more energy, vitality, and power for doing their daily activities and alleviated their muscular pains and depression.

The present study showed increases in sexual function mean score in both groups. However, the amount of increase in the melatonin group was significantly higher than the placebo group. Babaei *et al*. also found an improvement in the sexual function of diabetic male rats after receiving melatonin.[9] Kirecci *et al*. reported that decreased plasma level of melatonin can lead to premature ejaculation. They found that selective serotonin reuptake inhibitors increased the plasma level of melatonin and treated premature ejaculation, probably through both central and peripheral mechanisms.[19] Increases in the mean score of sexual function among women in the placebo group may be attributed to the psychological effects of placebo.

Study findings also showed significant between-group differences regarding the mean scores of all six domains of sexual function, denoting the effectiveness of melatonin in improving all six domains. Sexual responses depend on the temporal sequence and the coordination of different sexual function phases. Studies showed that any changes in one of the sexual function domains can affect other domains.[18,25-27] Clinical observations also revealed that if a woman receives desirable sexual stimulations leading to her sexual excitement, she will have greater "desire" for sexual activity.[28] Therefore, melatonin may directly and indirectly be responsible for improving all six domains of sexual function in women through different mechanisms such as increasing sexual desire and improving mood and behavior. A study showed significant decreases in the production and the serum level of melatonin after menopause as well as a significant correlation between serum level of melatonin and the levels of depression and anxiety.[7] Another study also showed that nocturnal melatonin therapy for 6 months improved menopause-related depression.[29] Accordingly, significant improvement in postmenopausal women's sexual function in the present study can also be attributed to the probable effects of melatonin on anxiety and depression. Improvement in the mean score of the pain domain in the present study can also be due to the fact that melatonin can improve vaginal lubrication. Tamura *et al*. also reported that melatonin can change the production of steroids in granulosa cells in the ovaries of some mammals (such as hamsters and human beings), and hence, it can improve sexual function by improving vaginal lubrication and reducing vaginal atrophy.[30]

Conclusion

Melatonin is effective in significantly improving different aspects of sexual function among postmenopausal women. Yet, further research is still needed to determine the precise mechanisms by which melatonin improves postmenopausal women's sexual function. One of the limitations of the present study was its relatively short follow-up period. Thus, future studies are recommended to evaluate the therapeutic effects and the probable side effects of long-term melatonin therapy among postmenopausal women.

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Conflicts of interest

There are no conflicts of interest.

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