RESEARCH ARTICLE

Effects of Melatonin on Some Bone Mineralization Biomarkers for Overweight or Obese Perimenopause Women; A Possible Role in Osteoporosis Treatment

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ABSTRACT

Background: Melatonin has shown to play an important role in many physiological functions, but its effects on bone metabolism were not well defined in humans**.**

Objective: Evaluation of the effects of oral melatonin used for two months on bone mineralization biomarkers for women in perimenopause.

Methods: Interventional double-blind placebo-control study, in which 60 women in perimenopause (age range 46–48) assigned in either control (n = 30) or study (n = 30) group. The last group received 3 mg tablet of melatonin once a day at night for two months. Parameters measured were serum osteocalcin, 25(OH) vitamin D, calcium, and C-terminal telopeptide of type 1 collagen (CTX-1).

Result: Melatonin led to significant rise ($p < 0.05$) in osteocalcin, serum vitamin D, serum calcium, and CTX-1 as compared with control values.

Conclusion: Melatonin showed positive effects on bone health by a significant increase in some bone mineralization biomarkers.

Keywords: C-terminal telopeptide of type 1 collagen (CTX-1), Melatonin, Osteocalcin, Perimenopause women.

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INTRODUCTION

Osteoporosis and insomnia are the major problems among women in perimenopause, especially due to decrease the level of estrogen and melatonin.[1,2] A decline in the levels of these hormones in perimenopause and postmenopausal women can significantly causing vasomotor symptoms (e.g., hot flashes, vaginal dryness, sexual dysfunction, mood disturbances, anxiety, and restlessness) in addition to fatigue and poor concentration.[3] These symptoms gradually disappear in most women during menopausal transition but, in other women, comorbidities develop associated with greatest reduction in melatonin level and persistent bone loss.[4] These fluctuations of hormones during premenopausal period leading to change in the level of bone turnover markers (osteocalcin, OC for bone formation, and CTX-1 for bone resorption) in serum.[5] The vasomotor symptoms negatively affect daily functioning and habits leading many women to seek for pharmaceutical options, such as, hormone therapy or non-pharmaceutical options, like vitamins to normalize sleep pattern,[6] many over the counter options, nutritional supplements, like melatonin, etc., are available to improve the physical symptoms and bone health of women in peri and menopause.[7]

Melatonin is an endogenous hormone synthesized from serotonin in the pineal gland in response to darkness, with level beginning to rise reaching peak at about 2:00 am.[8] Light

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exposure turns off the secretion of melatonin and inhibits its nocturnal elevation in plasma.[9] In recent years, human and animals researches examine melatonin efficacy on treating symptoms associated with menopause including its effect on bone by inducing osteoblast to promote bone formation or by inhibiting bone resorption through its action on osteoclasts[10-12]; the mechanisms underlying the symptoms of perimenopause and bone loss in those women may be because of hormonal imbalance demonstrated as changes in the level of estrogen, follicle stimulating hormone (FSH), and progesterone.[13,14]

AIM OF STUDY

To investigate the effect of daily melatonin supplement for women in perimenopause given for 2 months on bone markers and correlation between them.

METHODS

This double-blind controlled study enrolled for one year from October 2018 to end of September of 2019; sixty apparently healthy women in perimenopause and recently in menopause that fulfilled the criteria of study; they are randomly divided into two groups; control group (n = 30) received placebo and study group (n = 30) received melatonin, in dose 3 mg daily at night for two months.

Inclusion Criteria

- Age range 37 to 55 years old
- Has at least one symptoms of perimenopause, especially irregular periods and/or no more 12 months passed on last cycle to be classified as in menopause, these symptoms include[15]:
  - Irregular periods
  - Hot flashes
  - Breast tenderness
  - Worse premenstrual syndrome
  - Lower sex drive
  - Fatigue
  - Vaginal dryness; discomfort during sex
  - Urine leakage, when coughing or sneezing
  - Urinary urgency (an urgent need to urinate more frequently)
  - Mood swings
  - Trouble sleeping
- Body mass index > 25 (overweight or obese)
- Has no diabetes mellitus, rheumatoid arthritis, hypertension or not, on vitamin D supplement
- Participants instructed not to use any supplements during the study period, otherwise, excluded
- Parameters measured were serum osteocalcin, 25(OH) vitamin D, calcium, and CTX-1, by blood sample drawn at after the first visit and after 2 months (Figure 1).

Data Analysis

Include t test, ANOVA, and Qi square analysis, correlation.

RESULTS

Demographic Data of the Patients

As shown in Table 1, there were no significant ($p < 0.05$) differences between control and study group.

Bone Mineralization Biomarkers

Osteocalcin

Osteocalcin raised significantly ($p < 0.05$) in study group after using melatonin for 2 months, as compared with its baseline value (28 ± 8.67 for study after treatment *vs.* 19.6 ± 7.33 for baseline); and also, it was significantly ($p < 0.05$) higher than values of control group (28 ± 8.67 after treatment for study group *vs.* 17.6 ± 6.02 for control), as shown in Table 2.

Table 1: Demographic data of patients in the study groups; some of the data expressed as mean ± standard deviation

	Control group (n = 30)	*Study group (n = 30)*	*p values*
Age (years)	45.7 ± 4.4	45 ± 4.9	0.562
Weight (kg)	97 ± 10.4	94.9 ± 13.6	0.324
Height (cm)	163.6 ± 5.7	160.6 ± 6.5	0.063
Body mass index (kg/m^2)	36.4 ± 4.8	37.1 ± 6.56	0.648
Obesity ratio	28 (93.3%)	26 (86.7%)	0.667

p-values <0.05 considered as significant values

In age (45.7 ± 4.4 *vs.* 45 ± 4.9; p-value = 0.562); weight (kg) = (97 ± 10.4 *vs.* 94.9 ± 13.6; p-value = 0.517); height (cm) = (163.6 ± 5.7 *vs.* 160.6 ± 6.5; p-value = 0.063); body mass index (kg/m^2) = (36.4 ± 4.8 *vs.* 37.1 ± 6.56; p-value = 0.648); obesity ratio = 28 (93.3%) control *vs.* 26 (86.7%) study group

Table 2: Comparison of bone mineralization biomarkers in both study groups, before and after treatment; values are expressed as mean ± standard deviation

	Control group (n = 30)		*Study group (n = 30)*		
	Before treatment	*After treatment*	*Before treatment*	*After treatment*	*p values*
Osteocalcin (ng/mL)	16.5 ± 5.63	17.6 ± 6.02	19.6 ± 7.33	28 ± 8.67*[a]	0.00001
Serum vit. D (ng/mL)	19 ± 5.11	19.7 ± 4.94	19.6 ± 7.07	23.8 ± 9.23*[a]	0.027
Serum calcium (mg/dL)	7 ± 1.91	7.2 ± 1.84	7.8 ± 3.64	9.2 ± 2.1*[a]	0.004
CTX-1 (ng/mL)	20.1 ± 6.66	19.5 ± 6.34	22.8 ± 10.45	27.3 ± 18.4*[a]	0.039

*significant ($p < 0.05$) as compared to its before treatment values; [a]significant ($p < 0.05$) as compared to control value

Table 3: Correlations coefficient for study parameters

Parameters	*Age*		*Osteocalcin*		*Vitamin D*		*Calcium*		*CTX-1*		*BMI*	
r value	*p value*	*r value*	*p value*	*r value*	*p value*	*r value*	*p value*	*r value*	*p value*	*r value*	*p value*	*r value*
Age	1	1	-0.069	0.598	-0.194	0.139	0.051	0.698	0.198	0.127	0.039	0.769
Osteocalcin	-0.069	0.598	1	1	-0.224	0.082	-0.186	0.151	-0.256	0.045*	-0.075	0.568
Vitamin D	-0.194	0.139	-0.224	0.082	1	1	0.215	0.098	0.207	0.109	0.293	0.022*
Calcium	0.051	0.698	-0.186	0.151	0.215	0.098	1	1	0.217	0.092	-0.022	0.868
CTX-1	0.198	0.127	-0.256	0.045*	0.207	0.109	0.217	0.092	1	1	0.103	0.433
BMI	0.039	0.769	-0.075	0.568	0.293	0.022*	-0.022	0.868	0.103	0.433	1	1

*p-value < 0.05 considered as significant

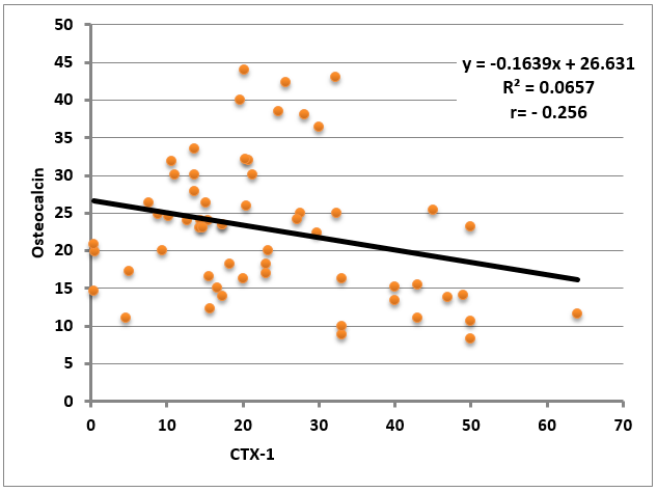

Figure 1: Scattered diagram show correlation between osteocalcin and CTX-1

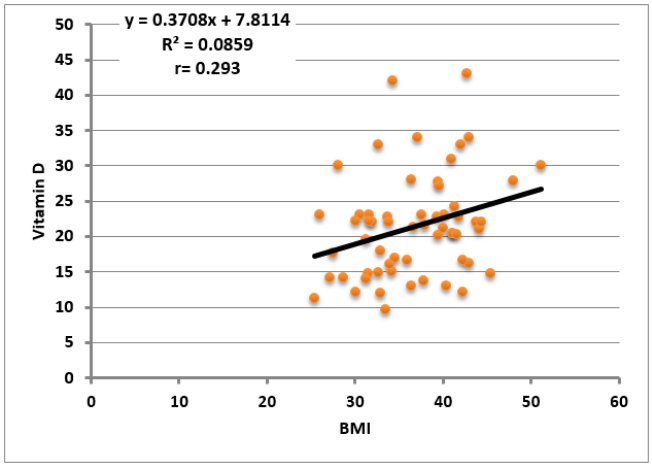

Figure 2: Scattered diagram show correlation between vitamin D and BMI

Serum Vitamin D

Serum vitamin D raised significantly ($p < 0.05$) in study group after using melatonin for 2 months as compared with its baseline value (23.8 ± 9.23 for study after treatment *vs.* 19.6 ± 7.07 for baseline); and also, it was significantly ($p < 0.05$) higher than values of control group (23.8 ± 9.23 after treatment for study group *vs.* 19.7 ± 4.94 for control), as shown in Table 2.

Serum Calcium

Serum calcium raised significantly ($p < 0.05$) in study group after using melatonin for 2 months as compared with its baseline value (9.2 ± 2.1 for study after treatment *vs.* 7.8 ± 3.64 for baseline); and also, it was significantly ($p < 0.05$) higher than values of control group (9.2 ± 2.1 after treatment for study group *vs.* 7.2 ± 1.84 for control), as shown in Table 3.

Correlation of Measured Parameters

Osteocalcin

The bone formation marker inversely correlated with bone resorption marker CTX-1.

Vitamin D and BMI

Vitamin D and BMI are positively correlated with each other (r = 0.293, p-value = 0.022), while osteocalcin is negatively associated with CTX-1 (r = -0.256, p-value = 0.045) (Figure 2).

DISCUSSION

Few studies about the women in perimenopause, their health status, and symptoms because many of these women are busy with work and neglect their health. Treatments help to alleviate some of their symptoms, mainly bone loss are usually temporary and associated with side effects, so those women seek for alternative methods to relieve menopausal symptoms, like yoga or herbal therapies, alternative medications like melatonin aimed to treat many of menopausal symptoms, restore the hormonal changes, and modulate bone markers.[16-18,]

Melatonin is neuroendocrine hormone produced by the pineal gland and has many biological effects, including bone remodeling, antiaging, sleep regulation, and antioxidative agent.[19] Despite the importance of melatonin in these biological functions, its role in diminishing osteoporosis in women in perimenopause is not fully understood.[20]

In this research, melatonin is an oral supplement used for 2 months for women in perimenopause to study its effect on biochemical markers related to bones mineralization for study group, and compared to placebo, this method is similar to method done by Falah *et al.* and Jubran *et al.*[21,22]

Melatonin administration was able to provide a rapid increase in the serum concentration of bone markers: osteocalcin, vitamin D, calcium, and CTX-1 significantly ($p < 0.05$) compared to control group. This is the principal endpoint in our research, and these results were different from results of many studies that found the use of melatonin

has no effect on the level of osteocalcin and other measured markers.[23-25]

In the present article, we will look at the recent evidence of the effect of melatonin on bone; it can decrease bone resorption and improve its remodeling by several mechanisms, the first by promoting of osteoblast proliferation and synthesis of osteoprotegerin, this osteoprotegerin prevents the binding of osteoclast differentiation factor (RANKL) to its receptor, which inhibits the differentiation of osteoclasts,[26,27] second mechanism is that melatonin has indirect regulation on bone metabolism, such as, estrogen, calcitonin, and parathyroid hormone (PTH), and the third mechanism is that the ability of melatonin on production of antioxidant for neutralization of osteoclasts superoxide anions that are needed for degradative process.[28]

There was a positive association between serum vitamin D and body mass index in women during perimenopause stage, this finding is unlike finding published in many studies.[29-32]

It seems BMI may be associated with the serum level of vitamin D during perimenopause in way different in other age stages, which may have some similarity to finding to Zhang *et al.* (2015), may be related to the state of visceral fat composition, where overweight or obese perimenopause women showed higher vitamin D level.

This probably related to changes in visceral fat composition due to melatonin supplementation.[33-35] These changes may lead to reduce trapping or sequestering of vitamin D in adipose tissue in obese women restoring the positive association of BMI and serum vitamin D.[36]

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