RESEARCH PAPER

Effect of Melatonin on bone health and quality of life In Postmenopausal women

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Abstract

Background: Menopause is associated with hormonal changes that may adversely affect bone health and quality of life. Melatonin has been suggested to play a role in bone metabolism and symptom control in postmenopausal women. This study aimed to evaluate the effect of melatonin on bone health and quality of life among postmenopausal women.

Methods: This randomized controlled trial was conducted at the Department of Physical Medicine and Rehabilitation, BSMMU, Dhaka, from September 2023 to October 2024. Sixty naturally postmenopausal women aged ≥45 years with normal BMD or osteopenia were randomized into melatonin and control groups. The intervention group received melatonin 3 mg daily with calcium and vitamin D supplementation, while the control group received calcium and vitamin D only. BMD was assessed by DXA and quality of life by the MENQOL questionnaire. Fifty-seven participants completed the study.

Results: Baseline sociodemographic and clinical characteristics were comparable between the groups. After 6 months, lumbar bone density and right femoral neck density differed significantly between the groups ($p=0.001$ and $p=0.014$, respectively), while left femoral neck density showed no significant difference ($p=0.119$). MENQOL assessment demonstrated no significant differences in vasomotor, psychosocial, or sexual domains; however, the physical domain showed significant improvement in the melatonin group ($p=0.042$).

Conclusion: Melatonin supplementation was associated with favorable effects on bone health and physical aspects of quality of life among postmenopausal women. Larger studies with longer follow-up are recommended to confirm these findings.

Keywords: Melatonin, Postmenopausal Women, Bone Mineral Density, Quality of Life, MENQOL, Osteopenia.

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INTRODUCTION

The reproductive health of a female undergoes transformations over the course of her lifespan. The process of menopausal transition is characterized by individual variability in terms of duration and symptomatology. However, the majority of women will undergo a progression from consistent menstrual cycles to irregularity and eventual cessation of menstruation [1]. Although menopause is a natural physiological process, it is frequently accompanied by bone loss resulting to osteoporosis and fracture [2]. A large proportion of postmenopausal women suffered from menopausal symptoms. The most common menopausal complaints reported by the postmenopausal women were sleep disturbances, muscle or joint pain, hot flushes and night sweats. Sexual life was also affected by menopause. Moreover, postmenopausal women suffered from depression and anxiety [3]. Osteopenia develops invisibly; if not diagnosed and treated in a timely manner, it can lead to osteoporosis and future fractures [4]. Similar to osteoporosis, osteopenia primarily affects

postmenopausal and perimenopausal women over the age of 60 [4,5]. Occasionally, it manifests as bone tissue deterioration and destruction of bone structure [5]. Osteoporosis affects 9 million Americans and osteopenia 50 million. By 2030, osteoporosis will affect 11.9 million and osteopenia 64.3 million [6]. Osteopenia affects almost half of U.S. women over 50, 3.4 times more than osteoporosis [7]. In a previous study conducted in Bangladesh, prevalence of osteopenia and osteoporosis was seen in 33.0% and 8.0% of patients respectively concerning BMD proximal femur and spine DXA [8]. Unless a fracture occurs, bone loss typically progresses gradually and unobserved during the osteopenic period. Dual Energy X-ray Absorptiometry (DXA) can be used as a baseline bone mineral density (BMD) assessment for diagnosis and future monitoring. Typically, pharmacological treatment is delayed or given "watchful waiting" until the transition to osteoporosis is diagnosed (T-score -2.5 or less at the femoral neck/spine); or if there is a history of a previous hip or vertebral fracture; or if the T score is between -1.0 and -2.5 at the femoral neck/spine and the 10-year risk of hip fracture 3% or 10-year risk of major osteoporosis related fracture [9]. Thus, osteopenia is frequently accompanied by substantial treatment uncertainty during the period of maximum fracture risk [7]. The combination of calcium and vitamin D reduces the risk of hip and other fractures only marginally [10,11]. The majority of extant pharmaceutical treatments for bone loss are treatment-oriented rather than preventative and primarily aim to prevent further bone loss rather than promote new bone formation.

Most treatment regimens for this skeletal system (bisphosphonates, parathyroid hormone, raloxifene, calcitonin, and strontium ranelate) inhibit osteoclasts to reduce bone resorption, thereby increasing bone density and improving bone bearing capacity [5,12]. Although these are currently accepted treatment options, their adverse effects, such as the increased risk of mandible necrosis and subtrochanteric or femoral shaft fractures, hot rashes, deep venous thrombosis, and osteosarcoma, affect their efficacy [13-18]. These adverse events may affect adherence and absorption, resulting in decreased drug efficacy. These findings indicate the need for the development of new strategies to prevent or rectify bone loss [5].

Objective

The objective of this study was to assess the effect of melatonin on bone health and quality of life in post-menopausal women.

METHODOLOGY & MATERIALS

This randomized controlled trial was conducted in the Department of Physical Medicine and Rehabilitation, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from September 2023 to October 2024. A total of 60 naturally postmenopausal women aged ≥45 years with normal bone mineral density (BMD) or osteopenia (T-score -1 to -2.5) were enrolled using purposive sampling. Participants with osteoporosis, surgical or radiation-induced menopause, chronic rheumatological diseases, impaired liver or renal function, uncontrolled hypertension, drug abuse, or use of medications affecting bone metabolism were excluded. Participants were randomized into two groups by lottery allocation. Group A (melatonin group, n=30) received melatonin 3 mg at bedtime daily for 6 months in addition to calcium 1000 mg and vitamin D3 400 IU supplementation, while Group B (control group, n=30) received only calcium and vitamin D3 supplementation. Both groups were advised to perform at least 30 minutes of brisk walking daily. Three participants were lost to follow-up, resulting in 57 participants completing the study. Baseline demographic, clinical, and anthropometric data were collected using a semi-structured questionnaire. Clinical assessments were performed at baseline, 3 months, and 6 months. The primary outcome was quality of life, assessed using the validated Menopause-Specific Quality of Life (MENQOL) questionnaire, which evaluates vasomotor, psychosocial, physical, and sexual domains. Secondary outcome was bone mineral density, measured at baseline and 6 months using dual-energy X-ray absorptiometry (DXA) at the lumbar spine (L1–L4), right hip, and left hip. Adverse events and treatment compliance were monitored during follow-up visits and through telephone communication when necessary.

Data were collected through face-to-face interviews and clinical examinations and were analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation or median (range), while categorical variables were presented as frequencies and percentages. Appropriate parametric and non-parametric tests, including paired and unpaired t-tests and Mann–Whitney U tests, were used for comparison. A p-value <0.05 was considered statistically significant. Ethical approval was obtained from the Institutional Review Board of BSMMU, and written informed consent was obtained from all participants.

RESULTS

Table 1: Sociodemographic characteristics (N=57)

Variables	Group A (n=29)	Group B (n=28)	p-value
Age (in years) (Mean±SD)	55.06±7.35	54.50±8.15	[t]0.778[ns]
45-60 years	24 (82.75)	22 (78.57)	[c]0.739[ns]
61-75 years	5 (17.25)	6 (21.43)	
Marital status			>[f]0.99[ns]
Married	30(100)	30 (100)	
Unmarried	0 (0)	0 (0)	
Education			[c]0.716[ns]
Primary	22 (75.86)	21 (73.3)	
SSC	1 (3.44)	1 (3.3)	
HSC	1 (3.44)	0 (0)	
Illiterate	5 (17.24)	6 (23.3)	
Occupation			[c]0.495[ns]
Service	1 (3.3)	2 (6.7)	
Housewife	29 (96.7)	27 (90)	
Unemployed	0 (0)	1 (3.3)	
BMI (kg/m^2) (Mean±SD)	26.92±1.44	27.27±1.86	[t]0.420[ns]

Data presented as frequency and percentage over the columns and Mean±SD over the rows Chi-square test was done for qualitative variables.
Fisher exact test was done for qualitative variables in 2/2 table, where the expected value was <5 in ≥20% of cells. An unpaired t-test was done for normally distributed quantitative variables.

Table 1 compared the sociodemographic characteristics between Group A and Group B, total consisting of 57 participants. The mean age of participants in Group A was 55.06±7.35 years, while in Group B, it was 54.50±8.15 years, with no significant difference between the groups (p=0.778). The majority of participants in both groups were aged 45-60 years, married, and primarily housewives, with no significant differences in marital status (p>0.99), education level (p=0.716), or occupation (p=0.495). Additionally, there was no significant difference in BMI between the groups, with Group A having a mean BMI of 26.92±1.44 kg/m² and Group B 27.27±1.86 kg/m² (p=0.420). Overall, the groups were well-matched in terms of age, marital status, education, occupation, and BMI.

Table 2: Clinical findings of the study participants (N=57)

Variable s	Group A (n=29)	Group B (n=28)	p-value
	Mean±SD	**Mean±SD**	
Pulse (bpm)	79.13±6.50	77.90±9.56	[t]0.561[ns]
	Median (IQR)	**Median (IQR)**	
SBP (mmHg)	120 (120-130)	120 (117.50-130)	[u]0.556[ns]
DBP (mmHg)	80 (70-80)	80 (70-90)	[u]0.616[ns]

Data presented as Mean±SD and Median (IQR) over the rows
An unpaired t-test was done for normally distributed quantitative variables
A Mann Whitney U-test was done.

This study found no significant differences in vital signs between the groups. Group A had a mean pulse rate of 79.13±6.50 bpm, and Group B had 77.90±9.56 bpm (p=0.561). Median systolic blood pressure was 120 mmHg in both groups, and median diastolic blood pressure was 80 mmHg, with no significant differences (p=0.556 and p=0.616, respectively). Overall, vital signs were similar between the two groups (Table 2).

Table 3: Comparison of the lumbar density after 6 months between two groups (N=57)

Variables	Group A (n=29)	Group B (n=28)	p-value
	Median (IQR)	**Median (IQR)**	
Lumbar Density after 6 months	-2.10 (- 2.30 to - 1.60)	-1.05 (- 1.92 to 0.27)	**[u]0.001[s]**

Data presented as Median (IQR) over the rows

Mann Whitney U-test was done for non-normally distributed quantitative variables.

After six months, remarkable change was seen in lumbar bone density between the two groups. Group A had a median lumbar density of -2.10 (IQR: -2.30 to -1.60), which was lower compared to Group B, which had a median lumbar density of -1.05 (IQR: -1.92 to 0.27). The p-value of 0.001 indicates that this difference was statistically significant, suggesting that Group A continued to have lower lumbar bone density than Group B after the six-month period (Table 3).

Table 4: Comparison of femoral neck (right) density after 6 months between two groups (N=57)

Variables	Group A (n=29)	Group B (n=28)	p-value
	Median (IQR)	Median (IQR)	
Femoral neck (right) density after 6 months	-0.20 (-0.60 to 0.35)	0.65 (- 0.12 to 1.57)	**^{u}0.014^{s}**

Data presented as Median (IQR) over the rows Mann Whitney U-test was done

After six months, the femoral neck density in the right hip continued to show a significant difference between the two groups. Group A had a median density of -0.20 (IQR: -0.60 to 0.35), while Group B had a higher median density of 0.65 (IQR: -0.12 to 1.57). The p-value of 0.014 indicates that this difference remained statistically significant, with Group B maintaining a significantly higher femoral neck density compared to Group A after the six-month period (Table 4).

Table 5: Comparison of femoral neck (left) density after 6 months between two groups (N=57)

Variables	Group A (n=29)	Group B (n=28)	p-value
	Median (IQR)	Median (IQR)	
Femoral neck (left) density after 6 months	-0.10 (-0.55 to 0.85)	0.55 (-0.10 to 1.77)	^{u}0.119^{ns}

Data presented as Median (IQR) over the rows Mann Whitney U-test was done

After 6 months, the femoral neck (left) density did not show a statistically significant difference between Group A and Group B. Group A had a median density of -0.10 (IQR: -0.55 to 0.85), while Group B had a median density of 0.55 (IQR: -0.10 to 1.77), with a p-value of 0.119. This suggests that although Group B had a higher median density, the difference was not significant after 6 months of the intervention (Table 5).

Table 6: Comparison of quality of life between two groups at the baseline

Variables	Group A (n=29)	Group B (n=28)	p-value
Vasomotor	6.50 (4-8.25)	5 (4-7)	^{u}0.190^{ns}
Psychosocial	8 (6-12)	9 (6- 9.25)	^{u}0.771^{ns}
Physical	28 (22.50-9.25)	24.50 (20-28.50)	^{u}0.164^{s}
Sexual	7 (5-10)	7 (5-8)	^{u}0.764^{ns}

Data presented as Median (IQR) over the rows Mann Whitney U-test was done

The median vasomotor score for Group A was 6.50 (IQR: 4-8.25), while Group B had a median of 5 (IQR: 4-7), with a non-significant p-value of 0.190. The psychosocial score for Group A was 8 (IQR: 6-12) compared to Group B's 9 (IQR: 6-9.25), yielding a p-value of 0.771, indicating no significant difference. The physical score was slightly higher in Group A at 28 (IQR: 22.50-39.25) compared to 24.50 (IQR: 20-28.50) in Group B, with a non-significant p-value of 0.164. Both groups had a median sexual score of 7, with Group A's IQR at 5-10 and Group B's at 5-8, resulting in a non-significant p-value of 0.764 (Table 6).

Table 7: Comparison of quality of life between two groups after 6 months

Variables	Group A (n=29)	Group B (n=28)	p-value
Vasomotor	5 (3-7)	4 (3.25-6)	^{u}0.558^{ns}
Psychosocial	7 (5-10)	8 (5-8)	^{u}0.981^{ns}
Physical	15 (11-28.50)	22 (17.25-26)	**^{u}0.042^{s}**
Sexual	6 (4-8.50)	6 (5- 6.75)	^{u}0.890^{ns}

Data presented as Median (IQR) over the rows Mann Whitney U-test was done for non-normally distributed quantitative variables

Group A and Group B manifest no notable differences in Vasomotor (p = 0.558), Psychosocial (p = 0.981), or Sexual symptoms (p= 0.890). However, Group A had significantly better Physical outcomes than Group B (p = 0.042) (Table 7).

DISCUSSION

Osteoporosis is a significant economic burden, with mortality risks from hip fractures. Melatonin is vital for bone health, promoting bone formation, inhibiting bone loss, and offering antioxidant protection. Recent discoveries about its effects on mitochondrial receptors highlight its potential for further research. Due to its broad benefits, melatonin is a promising option for slowing bone loss in at-risk populations, such as the elderly and postmenopausal women.

In the comparison of sociodemographic characteristics between Group A and Group B, both groups were found to be well-matched in terms of age, marital status, education, occupation, and BMI, with no statistically significant differences observed. Our findings were almost similar with Kotlarczyk et al., as they found significant difference regarding age of two groups [19].

Clinical findings further supported the similarity between the groups, as no significant differences were found in pulse rate, systolic, or diastolic blood pressure between the two groups at baseline. This homogeneity in vital signs reinforces the comparability of the two groups at the study's outset.

When examining lumbar density, a significant difference was observed between the groups both at baseline and after six months, with Group A consistently showing lower lumbar bone density compared to Group B. This difference suggests that Group B may have had better baseline bone health. However, within-group comparisons revealed no statistically significant changes in lumbar density from baseline to six months for either group, indicating that the intervention may not have had a substantial impact on lumbar bone density within the duration of the study. The analysis of femoral neck density revealed significant differences between the groups at baseline and after six months, particularly in the right femoral neck. Group B consistently showed higher femoral neck density compared to Group A, which was statistically significant at both time points. Within-group analyses showed improvements in femoral neck density for both groups over time, particularly in Group A, which initially had lower density. This suggests that, while Group A had lower bone density at baseline, there was some degree of improvement in response to the intervention.

In contrast, the research on melatonin supplementation in perimenopausal and postmenopausal women highlights melatonin's potential benefits for both bone health and quality of life. Kotlarczyk et al., found that while melatonin supplementation did not lead to significant changes in bone density or bone turnover markers, it did improve physical symptoms associated with perimenopause and reduced menstrual cycling frequency [19]. This suggests that melatonin might help alleviate some of the physical discomforts associated with hormonal changes during perimenopause, even if it does not directly affect bone density in the short term.

The adherence to medication and exercise was also analyzed, showing that both groups had high levels of adherence, with no statistically significant differences between the groups after three and six months. This indicates that adherence was consistent across the groups, which is an important factor when considering the overall impact of the intervention on bone density and quality of life.

Finally, the comparison of quality of life showed no significant differences between the groups at baseline in terms of vasomotor, psychosocial, physical, and sexual domains. After 6 months, no significant differences in Vasomotor (p = 0.558), Psychosocial (p = 0.981), or Sexual symptoms (p
= 0.890) was observed. However, Group A had significantly better Physical outcomes than Group B (p = 0.042). This suggests that, despite the differences in bone density, the

overall quality of life as measured by these variables remained comparable between the two groups throughout the study.

Toffol et al., expanded on this by examining the relationship between melatonin levels and various health outcomes in perimenopausal and postmenopausal women [20]. Their findings showed that postmenopausal women had lower nighttime melatonin levels, and longer melatonin secretion was linked to better quality of life in perimenopausal women. This points to a potential role for melatonin in improving overall well-being during menopause, possibly through its effects on mood, sleep, and circadian regulation. Further, the studies by Amstrup, Sikjaer, Heickendorff, et al., and Maria et al., provide more direct evidence of melatonin's positive impact on bone health [2,21]. Amstrup's showed that one year of melatonin supplementation led improvement in bone mineral density (BMD) at the femoral neck and spine, particularly with a higher dose of 3 mg/day [21]. This suggests that melatonin could play a protective role against fractures, especially in postmenopausal women with osteopenia. Maria et al., took this a step further by combining melatonin with other bone-supporting supplements, resulting in significant increases in BMD in the lumbar spine and femoral neck, along with improvements in mood and sleep quality [2]. Their studies proved that this combination promotes bone formation and inhibits bone resorption, offering a comprehensive approach to managing bone health and improving quality of life.

The melatonin research highlights the molecule's potential to influence both bone density and quality of life, especially when combined with other supplements. This suggests that melatonin would be a useful option to intervention regimens for improving bone health and overall well-being in populations at risk of osteoporosis, particularly postmenopausal women.

In summary, while there were significant differences in bone density of both right and left femoral necks at the beginning and after 6 months of study in Group A, also significant improvement of physical domain in quality of life over the six-month period. The findings highlight the need for longer-term studies to assess the impact of interventions on bone density and quality of life and suggest that additional factors may need to be considered to achieve meaningful improvements in these areas.

Limitations of the study

The study's findings may not be generalizable due to the limited number of participants The six-month duration may be insufficient to observe long-term changes in bone density and quality of life. The study participants varied in terms of the prevalence of menopausal symptoms, which may have affected the results. The study did not account for other factors affecting quality of life and sleep quality, such as physical activity, diet, and psychological well-being. Medication and exercise adherence were self-reported, which may introduce bias.

Conclusion

In conclusion, while this study identified significant differences in bone density with improvement in physical domain of quality of life, the melatonin studies emphasize the potential for melatonin to positively impact both areas. Melatonin's role in improving physical symptoms and enhancing bone density suggests that it could be a key therapeutic agent in managing bone health and improving quality of life in aging populations. The consistent findings across multiple studies warrant further research into melatonin's mechanisms and its long-term benefits for bone health and postmenopausal quality of life.

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Conflicts of interest

There are no conflicts of interest.

References

1. Mansfield PK, Carey M, Anderson A, Barsom SH, Koch PB. Staging the menopausal transition: Data from the TREMIN Research Program on Women's Health. Women's

Health Issues. 2004;14(6):220–226. doi:10.1016/j.whi.2004.08.002.

2. Maria S, Swanson MH, Enderby LT, D'Amico F, Enderby B, Samsonraj RM, et al. Melatonin-micronutrients Osteopenia Treatment Study (MOTS): a translational study assessing melatonin, strontium (citrate), vitamin D3 and vitamin K2 (MK7) on bone density, bone marker turnover and health related quality of life in postmenopausal osteopenic women following a one-year double-blind RCT and on osteoblast-osteoclast co-cultures. Aging. 2017;9(1):256–285. doi:10.18632/aging.101158.
3. Vishwakarma G, Ndetan H, Das DN, Gupta G, Suryavanshi M, Mehta A, et al. Reproductive factors and breast cancer risk: A meta-analysis of case–control studies in Indian women. South Asian Journal of Cancer. 2019;08(02):080–084. doi:10.4103/sajc.sajc_317_18.
4. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporosis International. 2006;17(12):1726–1733. doi:10.1007/s00198-006-0172-4.
5. Bao T, Zeng L, Yang K, Li Y, Ren F, Zhang Y, et al. Can melatonin improve the osteopenia of perimenopausal and postmenopausal women? A meta-analysis. International Journal of Endocrinology.2019;2019:1–9. doi:10.1155/2019/5151678.
6. Maria S, Witt-Enderby PA. Melatonin effects on bone: potential use for the prevention and treatment for osteopenia, osteoporosis, and periodontal disease and for use in bone-grafting procedures. Journal of Pineal Research. 2014;56(2):115–125. doi:10.1111/jpi.12116.
7. Pfister AK, Welch CA, John M, Emmett MK. Changes in nonosteoporotic bone density and subsequent fractures in women. Southern Medical Journal. 2016;109(2):118–123. doi:10.14423/SMJ.0000000000000410.
8. Halder D, Ali Y, Faysal JR, Nayeem F, Rouf A, Tasnim N. Pattern of bone mineral density in postmenopausal women in a tertiary care centre of Bangladesh. Bangladesh Journal of Medicine. 2023;34(2):121–125.
9. Watts NB, Lewiecki EM, Miller PD, Baim S. National Osteoporosis Foundation 2008 clinician's guide to prevention and treatment of osteoporosis and the World Health Organization Fracture Risk Assessment Tool (FRAX): what they mean to the bone densitometrist and bone technologist. Journal of Clinical Densitometry. 2008; 11(4): 473–477. doi:10.1016/j.jocd.2008.04.003.
10. Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, et al. Calcium intake and risk of fracture: systematic review. BMJ. 2015;351:h4580. doi:10.1136/bmj.h4580.
11. Avenell A, Mak JC, O'Connell DL. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database of Systematic Reviews. 2021;(6). doi:10.1002/14651858.CD000227.pub4.
12. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden: A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of Osteoporosis. 2013;8(1–2):136. doi:10.1007/s11657-013-0136-1.
13. Park KH, Kang JW, Lee EM, Kim JS, Rhee YH, Kim M, et al. Melatonin promotes osteoblastic differentiation through the BMP/ERK/Wnt signaling pathways. Journal of Pineal Research. 2011;51(2):187–194. doi:10.1111/j.1600-079X.2011.00875.x.
14. Rutkowski JL. Combined use of glucocorticoids and bisphosphonates may increase severity of bisphosphonate-related osteonecrosis of the jaw. The Journal of Oral Implantology. 2011;37(5):505. doi:10.1563/1548- 1336-37.5.505.
15. Torres J, Tamimi F, García I, Cebrian JL, López-Cabarcos E, Lopez A. Management of atrophic maxilla in severe osteoporosis treated with bisphosphonates: a case report. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2008;106(5):668–672. doi:10.1016/j.tripleo.2008.03.008.
16. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. Journal of Oral and Maxillofacial Surgery. 2004;62(5):527–534. doi:10.1016/j.joms.2004.02.004.

17. Grady D, Ettinger B, Moscarelli E, Plouffe L, Sarkar S, Ciaccia A, et al. Safety and adverse effects associated with raloxifene: Multiple outcomes of raloxifene evaluation. Obstetrics & Gynecology. 2004;104(4): 837–844. doi:10.1097/01.AOG.0000137349.79204.b8.
18. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1–34) for 2 years and relevance to human safety. Toxicologic Pathology. 2002; 30(3): 312–321. doi:10.1080/01926230252929882.
19. Kotlarczyk MP, Lassila HC, O'Neil CK, D'Amico F, Enderby LT, Witt-Enderby PA, et al. Melatonin osteoporosis prevention study (MOPS): a randomized, double-blind, placebo-controlled study examining the effects of melatonin on bone health and quality of life in perimenopausal women: Melatonin effects in perimenopausal women. Journal of Pineal Research. 2012;52(4):414–426. doi:10.1111/j.1600-079X.2011.00956.x.
20. Toffol E, Kalleinen N, Haukka J, Vakkuri O, Partonen T, Polo-Kantola P. Melatonin in perimenopausal and postmenopausal women: associations with mood, sleep, climacteric symptoms, and quality of life. Menopause. 2014;21(5):493–500. doi:10.1097/GME.0b013e3182a6c8f3.
21. Amstrup AK, Sikjaer T, Mosekilde L, Rejnmark L. The effect of melatonin treatment on postural stability, muscle strength, and quality of life and sleep in postmenopausal women: a randomized controlled trial. Nutrition Journal. 2015;14:102. doi:10.1186/s12937-015-0093-1.