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REVIEW

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Melatonin and the health of menopausal women: A systematic review

Yulia Treister-Goltzman[1,2] | **Roni Peleg**[1,2]

[1]The Department of Family Medicine and Siaal Research Center for Family Practice and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[2]Clalit Health Services, Southern District, Beer-Sheva, Israel

Correspondence
Yulia Treister-Gotzman, The Department of Family Medicine and Siaal Research Center for Family Practice and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
Email: yuliatr@walla.co.il

Abstract

Melatonin is involved in multiple changes that characterize the aging and can potentially be a safe and effective treatment for menopausal women. The aim of this study was to carry out a systematic review of the medical literature on the health benefits of oral melatonin administration on menopausal women. The electronic databases PubMed, Scopus, and Web of Science were searched systematically on interventional studies that evaluated the association between oral melatonin administration and the health of menopausal women. Risk for bias was assessed for randomized, controlled studies by the RoB v.2 tool and for non-randomized trials by the ROBINS-I tool. Twenty-four studies on melatonin treatment in various aspects of women's health were included in the final systematic review. The studies included 1,173 participants. No evidence was found for an independent effect of melatonin on hemodynamic measures or markers of glucose metabolism. There is some evidence that very low-density lipoprotein and triglycerides levels increase during melatonin administration. There is a fair amount of evidence that melatonin treatment has a favorable effect on bone density and BMI. Melatonin treatment improves EEG patterns and subjective sleep quality in postmenopausal women with preexisting sleep impairment. In a dose of 3 mg and above, melatonin improves climacteric symptoms in one or more domains. The vast majority of the studies had a low risk for bias. In light of multiple health benefits and an excellent safety profile, melatonin administration should be considered in menopausal women.

KEYWORDS

body weight, lipids, melatonin, menopause, perimenopausal bone loss, sleep, symptoms

1 | INTRODUCTION

Aging is associated with disruptions in the circadian system and a decrease in melatonin secretion. Toward the fifth decade of life, characteristic changes in the architecture of sleep and corresponding EEG changes occur.[1] These changes have ramifications for mental and physical health, and for the immune, metabolic, endocrine, and cardiovascular systems.[1,2] The pineal hormone has a direct influence on almost every organ in the body. It regulates the immune system, prevents neuronal over-excitation, has analgesic properties, supports bone health, and participates in metabolic and antioxidant processes.[3] In women, chronologic aging is associated with reproductive aging. Changes and fluctuations in ovarian hormones and gonadotropins cause cessation in reproductive function and affect many other estrogen-dependent

physiologic processes. Women experience changes in body structure, image, and functioning. Immuno-metabolic changes during menopause lead to fat tissue redistribution, and abdominal adiposity, a central component of the metabolic syndrome.[4] Hormonal perturbations lead to sleep problems.[1,2] Vaso-motor symptoms, characteristic of that period also contribute to decreased sleep quality. Sleep problems increase appetite, especially in the evening, decrease physical activity, and lead to weight gain. Emotional problems during menopause have a bi-directional association with sleep quality.[2] In light of health concerns associated with hormone replacement therapy (thromboembolic and cardiovascular events, and malignancy), there is an emerging need for other treatments for metabolic, emotional, nutritional, and sleep disturbances in peri- and postmenopausal women. Since melatonin is involved in all these processes and it has a good safety profile, it has potential as a drug with multiple health benefits for menopausal women.

The aim of this study was to carry out a systematic review of the medical literature on potential health benefits of oral melatonin administration on peri- and postmenopausal women.

2 | MATERIALS AND METHODS

2.1 | Search strategy for identification of studies

The electronic databases PubMed, Scopus, and Web of Science were searched systematically in February 2021 to identify interventional studies that related to the health effects of melatonin treatment in postmenopausal women, without limiting by date or language of publication. Two investigators (YTG and RP) conducted the search of relevant studies according to predetermined inclusion and exclusion criteria. The search was conducted with the keywords "melatonin" and "menopausal." We decided to restrict our review to studies in which the only intervention was oral melatonin administration. This determination was made to assure a relatively uniform drug formulation and in light of the dearth of trials that focus on treatment with parenteral melatonin or melatonin agonists. The inclusion criteria were as follows: (1) the study evaluated the association between oral melatonin administration and menopausal women's health, and (2) original research. The exclusion criteria were as follows: (1) the study was not original research (review articles, case reports, book chapters), (2) the study was not interventional, and (3) the intervention did not include oral melatonin, but light deprivation, a melatonin agonist, or parenteral melatonin. If the study examined a combination of melatonin with other drugs, it was included in the review only if there was a group with melatonin treatment only, (4) the study population was not peri- and postmenopausal women and (5) the study was conducted on a population with a specific disease (oncologic, etc)

In the first stage, all abstracts were reviewed independently by the two investigators who included or excluded them from the study. In the second stage, the two investigators read the full texts of all the articles that were selected in the first stage and went over the bibliographies to identify additional papers. If there was a disagreement as to whether a paper should be included the final decision was reached by joint discussion.

2.2 | Data collection

The following data were collected the following: author and year of publication, study type, number of participants, mean age, dosage, duration and other details of melatonin administration, main outcome measures, and findings.

2.3 | Assessment of risk of bias

For the purpose of risk of bias assessment, the studies were divided into two groups: randomized controlled trials (RCT) and non-randomized intervention trials (NRT). For the first group of studies, we used the RoB v.2 tool.[5] This tool was developed by the Cochrane Statistical Methods and Cochrane Bias Methods groups and is widely used including in Cochrane reviews. Bias domains included in this tool are randomization, deviation from intended interventions, missing data, measurement of outcomes, and selection of reported result. For the second, NRT, group the ROBINS-I tool was used.[6] This tool was developed by Cochrane Bias Methods group and leading international epidemiologists and methodologists to compare the health effects of two or more interventions. Due to the fact that most of the NRT in our review included only one intervention group, we adapted this tool for our study. The adapted tool assessed six bias domains: confounding, selection of participants, deviation of intended interventions, missing data, measurement of outcomes, and selection of reported result. Based on bias risk in all domains, the risk for bias for each study was judged as low/high/some concerns for RCT and low/moderate/serious/critical/no information for NRT.

3 | RESULTS

Of 505 articles identified through the literature search, 24 studies on melatonin treatment in various aspects of women's health, with a total 1,173 participants, were included in the systematic review (Figure 1). Eighteen of the included studies were RCT and six NRT. The mean age of participants ranged from 49.5-62.5 years. The studies were related to

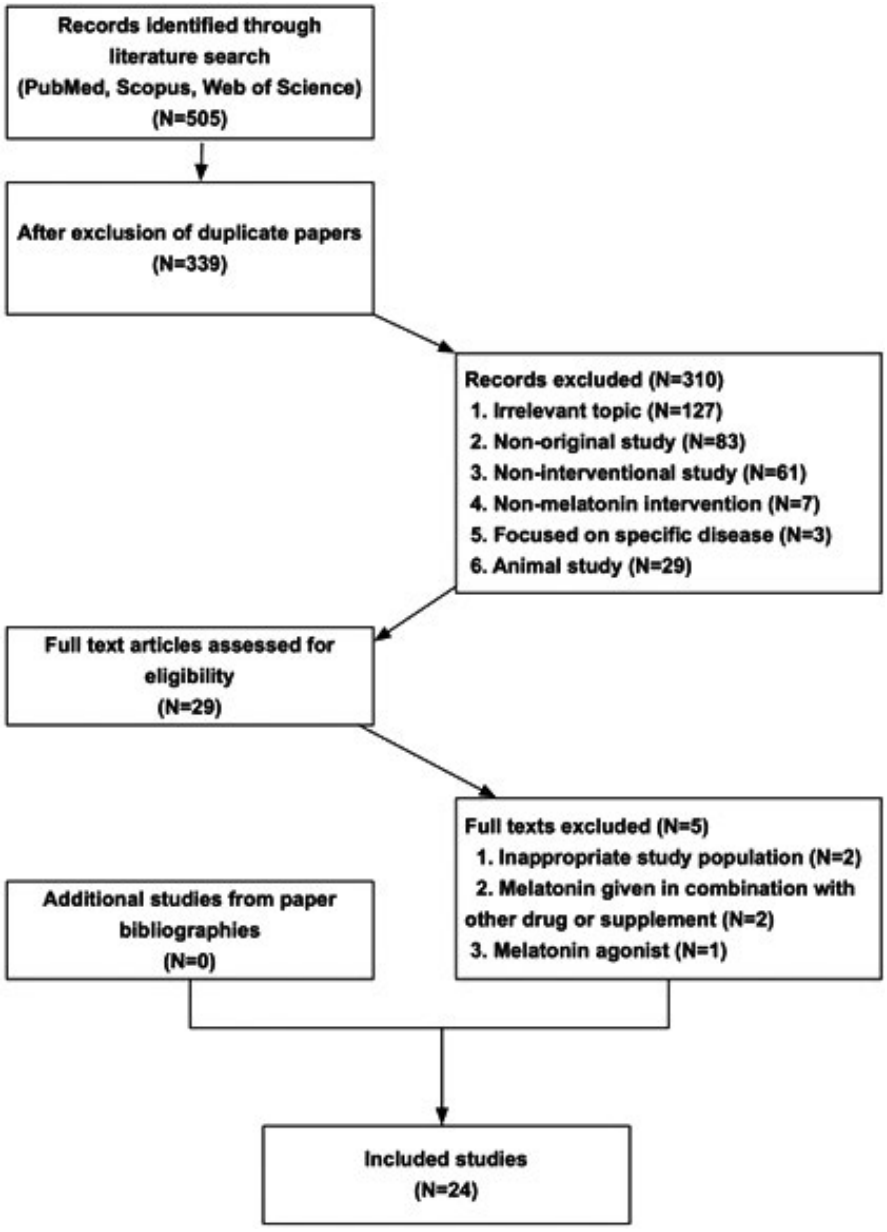

FIGURE 1 Flowchart of review process

different aspects of physiologic, physical, and mental health. Melatonin dosages varied from 1 mg-100 mg and the duration of treatment from a single administration to 12 months. The most popular dose was 3 mg.

The summary of studies on melatonin effects on menopausal women's health is presented in Table 1.

3.1 | Melatonin's effect on hemodynamic measures

Four RCT focused on the effect of melatonin on hemodynamic measures.[7-10] Three studies involved a one-time administration of 1mg of melatonin to women without a diagnosis of hypertension.[7-9] Two of them[7,8] found a positive effect on systolic and diastolic blood pressure, a decrease in norepinephrine, and an increase in nitric oxide level among women on hormone replacement therapy only. A third study[9] found a positive effect on endothelial-dependent vasodilatation in the brachial artery. The results of the fourth study, in which 1 or 3 mg of melatonin was administered for 12 months, did not show any effect on hemodynamic measures.[10] This study did not assess hypertension at baseline. In summary, there is insufficient evidence for an independent effect of melatonin on hemodynamic measures among menopausal women.

3.2 | Melatonin's effect on cortisol levels and markers of glucose homeostasis

Four RCTs focused on melatonin's effect on cortisol, leptin, and markers of glucose homeostasis.[11-14] In all studies, the participants had normal blood glucose levels at study inception. Three studies[11-13] involved a single administration of

TABLE 1 Studies included in the meta-analysis on melatonin effects on menopausal women's health

Study	Design	Description of participants	Details of melatonin treatment
A. Studies on influence of melatonin administration on physiologic functions and measurements			
Cagnacci et al, 2000[7]	Randomized, controlled, double-blind, cross-over study	31 postmenopausal women, 13 on HRT. 53 ± 1.5 years	1 mg of melatonin once daily between 2 PM and 6 PM
Cagnacci et al, 2001[8]	Randomized, controlled, double-blind, cross-over study	23 postmenopausal women, 12 on HRT. 52 ± 1.7 years	1 mg of melatonin once between 2 PM and 3 PM
Modena et al, 1998[9]	Randomized, controlled, double-blind, cross-over study	18 postmenopausal women 53.2 ± 4.2 years	Single administration of 1 mg of melatonin or placebo
Cagnacci et al, 1997[11]	Randomized, controlled, double-blind, cross-over study	7 postmenopausal women 54-62 years	Single administration of 100 mg of melatonin at 8 AM, with or without estrogen supplement
Cagnacci et al, 2001[12]	Randomized, controlled, double-blind, cross-over study	22 postmenopausal women, 14 on HRT. 52-61 years	Single administration of 1 mg of melatonin at 8.30 AM.
Cagnacci et al, 2002[13]	Randomized, controlled, double-blind, cross-over study	36 postmenopausal women. 55.4	Single administration of 1 mg of melatonin given at 8.30 AM, 10.30 AM, or 3.30 PM.
Wakatsuki et al, 2000[15]	Open-labeled, interventional study	15 postmenopausal women. Mean age 52 years (range 48-55)	6 mg of melatonin between 9 and 10 PM for two weeks
Wakatsuki et al, 2001[16]	Open-labeled, interventional study	15 postmenopausal women Mean age 52 years (range 48-55)	6 mg of melatonin between 9-10 PM for two weeks
Tamura et al, 2008[17]	Open-labeled, interventional study	10 peri- and postmenopausal women. Mean age 52 years (range 42-65)	1 mg of melatonin at 9 PM for one month
Parandavar et al, 2018[18]	Randomized, double-blind, placebo-controlled	240 postmenopausal women. 53.2 ± 4.2 years	3 mg of melatonin between 6-9 PM for three months
Sagan et al, 2017[19]	Open-labeled, controlled, interventional study	90 postmenopausal women 46-67 years	2.5 mg of melatonin one hour before bedtime for four weeks
Staikou et al, 2012[24]	Randomized, controlled, double-blind study	23 women, 11 of them postmenopausal No data on age	Single administration of 6 mg of melatonin at 9 AM
Amstrup et al, 2015[20]	Randomized, controlled, double-blind study	81 osteopenic postmenopausal women62.5 ± 4	1 mg or 3 mg at bedtime for 12 months
Amstrup et al, 2016[14]	Randomized, controlled, double-blind study	81 osteopenic postmenopausal women 62.5 ± 4	1 mg or 3 mg at bedtime for 12 months
B. Studies on influence of melatonin administration on clinical outcomes (with or without physiologic functions and measurements)			
Kripke et al, 2006[26]	Randomized, controlled trial	20 postmenopausal women 51-69 years	0.5 mg 2-3 hours before bedtime or 0.5 mg upon morning awakening for four weeks
Parandavar et al, 2017[30]	Randomized, double-blind, placebo-controlled	240 postmenopausal women 53.2 ± 4.2 years	3 mg of melatonin between 6-9 PM for three months
Parandavar et al, 2014[29]	Randomized, double-blind, placebo-controlled	240 postmenopausal women 53.2 ± 4.2 years	3 mg of melatonin between 6-9 PM for three months
Walecka-Kapica, 2014[23]	Open-labeled, interventional study	56 postmenopausal and 25 young women 56.9 ± 5.3 years (postmenopausal group)	5 mg of melatonin at 9 PM for 24 weeks
Secreto et al, 2004[28]	Randomized, controlled, double-blind study	262 postmenopausal women Mean age 52 years (range 50-57)	3 mg of melatonin in the evening hours for three months
Madaeva et al, 2020[25]	Open-labeled, interventional study	21 perimenopausal women 51.2 ± 4.7 years	3 mg of melatonin 30 minutes before bedtime for three months

Outcome	Main findings
Internal carotid artery pulsatility index, index of downstream resistance to blood flow, BP[a] and catecholamine levels	In women on HRT[b] only, melatonin administration reduced systolic, diastolic, mean BP[a], resistance to blood flow in the internal carotid artery, and norepinephrine levels
Internal carotid artery pulsatility index, BP[a], and levels of nitric oxide	Only in women on HRT[b], melatonin reduced internal carotid artery flow, systolic and diastolic BP, and increased nitric oxide level
Brachial artery diameter and flow	Melatonin had a positive effect on endothelial-dependent vasodilation
Cortisol levels	Melatonin induced a marked increase in daytime cortisol levels that disappeared during estrogen administration
C-peptide, oral glucose tolerance test.	Melatonin reduced glucose tolerance and insulin sensitivity in all women
Leptin levels	Leptin levels were not significantly modified by melatonin, independent of HRT[b]
Lipid profile, apolipoproteins, LDL[c] activation	Melatonin significantly increased levels of TG[d], but did not alter HDL[e] or LDL[c] level, reduced LDL[c] susceptibility to oxidative modification
Lipid profile, apolipoproteins, activity of lipoprotein lipase, hepatic TG[d] lipase, lecithin cholesterol acyltransferase	Melatonin significantly increased levels of TG[d], and VLDL[f], Apolipoproteins C2, C3, and E, inhibited lipoprotein lipase.
Lipid profile	Melatonin treatment significantly increased serum concentrations of HDL[e] only
Lipid profile	Only TG[d] level increased significantly in the melatonin group
Lipid peroxidation (LPO) as measured by the concentration of malondialdehyde+4 -hydroxyalkenals	Melatonin reversed increased serum LPO only in the sub-group of former smokers
EEG[g] theta to alpha power ratio at twelve recording sessions	No EEG[g] changes in postmenopausal women, possible awaking effect in reproductive women
BMD[h] by DXA[i], QCT[j], high-resolution peripheral QCT[j], calciotropic hormones and bone markers	Femoral neck BMD[h] increased significantly in response to melatonin in a dose-dependent manner. Trabecular thickness in tibia increased in the melatonin group and mineral density in the spine increased significantly only in the 3 mg group
Body composition: fat and lean mass by DXA[i], BMI[k], levels of leptin, adiponectin and insulin, lipid profile and markers of glucose homeostasis.	In the melatonin group, fat mass decreased and lean mass increased significantly. Adiponectin increased borderline to significantly in the melatonin group. No changes in leptin, insulin, lipid profile, or markers of glucose homeostasis.
Depression, hot flashes and physical symptoms inventory, LH[l] level	Melatonin led to LH[l] suppression, with no effect on hot flashes, mood, and sleep
Sexual function (female sexual function index)	Significant increase in mean sexual function score and in each domain
Climacteric symptoms (Green climacteric scale)	Significant decrease in overall climacteric score and in various dimensions
Quality of sleep (ISI), BMI[k], Waist/Hip ratio	Significant improvement in quality of sleep and decrease in BMI[k]
Menopausal symptoms on Green climacteric scale	No advantage for melatonin over placebo
Subjective severity of insomnia (ISI[m]) and polysomnographic pattern	Improvement in ISI[m] and polysomnographic sleep latency, overall sleep efficiency and REM sleep, decrease in sleep fragmentation

(Continues)

Study	Design	Description of participants	Details of melatonin treatment
Kotlarczyk et al, 2012[21]	Randomized, controlled, double-blind study	19 perimenopausal women 49.5 years (range 45.1-54.5)	3 mg melatonin at bedtime for six months
Chojnacki et al, 2018[22]	Randomized, controlled, double-blind study	60 postmenopausal women 51-64 years, placebo: 56.2 ± 4.1 years, melatonin: 57.3 ± 6.4 years	3 mg in the morning and 5 mg in the evening for 12 months
Bellipanni et al, 2005[27]	Randomized, controlled, double-blind study	139 peri- and postmenopausal women 42-62 years	3 mg between 10-11 PM for 6 months
Amstrup et al, 2015[10]	Randomized, controlled, double-blind study	81 postmenopausal women 62.5 ± 4 years	1 mg or 3 mg at bedtime for 12 months

[a]Blood pressure
[b]Hormone replacement therapy
[c]Low-density cholesterol
[d]Triglycerides
[e]High density cholesterol
[f]Very low-density cholesterol
[g]Electroencephalography
[h]Bone mineral density
[i]Dual X-ray absorptiometry
[j]Quantitative computed tomography
[k]Body mass index
[l]Luteinizing hormone
[m]Insomnia severity index.

melatonin, in one 100 mg,[11] and in the other two 1 mg.[12,13] In the study in which 100 mg was given,[11] there was an increase in daytime cortisol levels. In the second study,[12] there was reduced glucose tolerance and insulin sensitivity. In the third study,[13] there was no effect on leptin levels. In another study,[14] 1 mg or 3 mg of melatonin was administered for 12 months. Melatonin-induced adiponectin increased with borderline significance, but there were no changes in leptin, insulin, or markers of glucose homeostasis. In summary, there is no conclusive evidence on melatonin's effect on cortisol levels and markers of glucose metabolism in menopausal women with normal blood glucose levels.

3.3 | Melatonin effect on lipid profile

Six studies investigated melatonin's effect on lipid profile and oxidation.[14-19] An NRT,[15,16] in which 6 mg of melatonin was administered for two weeks, found significant increases in the levels of triglycerides (TG), very low-density lipoproteins (VLDL), apolipoproteins C2, C3, and E (Apo C2, C3, and E), and inhibition of lipoprotein lipase. There was no effect on the level of high-density lipoprotein (HDL) and low-density lipoprotein (LDL). An RCT[18] also showed increased TG levels after three months with a daily administration of 3 mg. In contrast, in an NRT,[17] in which postmenopausal women received 1 mg of melatonin for one month in an open-labeled study, there was no effect on VLDL, LDL, or total cholesterol (TC). In an RCT,[14] there was no difference in TC, HDL, LDL, and TG between women who received 1 mg or 3 mg melatonin for one year, and placebo. In an NRT,[19] increased serum lipid peroxidation was reversed, but only in former smokers. In conclusion, there is some evidence that VLDL and TG increase during melatonin administration at a dose of 3-6 mg, without any effect on LDL or TC.

3.4 | Melatonin's effect on bone density and body composition

Two RCTs[20,21] investigated the effect of melatonin on bone density (BMD) composition. In one study[20] in which 1 or 3 mg of melatonin was given for a year, there was a significant increase in femoral neck BMD and trabecular thickness in the tibia, while mineral density of the spine increased significantly in the 3 mg group only. In the second study,[21] where 3 mg of melatonin was given for six months, there were no significant changes in markers of bone density or

Outcome	Main findings
Menopausal symptoms, sleep quality, and bone density	No significant change on BMD[h] or bone turnover markers, however the ratio of bone resorption/ bone formation markers trended downwards. Melatonin significantly improved subjective physical symptoms of menopause. No influence on sleep quality
Menopausal symptoms (Kuperman index), BMI[k] and female hormones	In the melatonin group the value of Kuperman index and BMI[k] decreased significantly, no change in female reproductive hormones
Menopausal symptoms, thyroid function, prolactin, female hormones	Abrogation of menopause-related depression, decrease in gonadotropins only in younger women (43-49 years).
Postural balance (by stadiometer), muscle strength (by dynamometer chair), quality of life, Quality of sleep (Pittsburgh Sleep quality index), BP[a], and heart rate	Melatonin did not affect muscle strength or balance, nor quality of life, sleep or hemodynamic measures. In patients with insomnia at baseline, there was a trend toward sleep improvement

bone turnover, but there was a downward trend in ratio of bone resorption/bone formation markers. In an RCT,[10] melatonin did not have a significant effect on muscle strength or balance. In another RCT,[14] there was a significant decrease in fat mass and increase in lean mass, but the BMI did not change. In contrast, in an RCT[22] in which 8 mg of melatonin was given for 12 months, and in an NRT[23] in which 5 mg of melatonin was given for 24 weeks, there was a significant reduction in BMI, especially in obese women.[23] Thus, there is evidence that treatment with melatonin at a dose of 3 mg or higher for at least six months has a favorable effect on BMD. At a dose of 5-8 mg for 6-12 months, melatonin was associated with decreased BMI.

3.5 | Melatonin's effect on sleep

Two studies investigated EEG changes during sleep after melatonin administration. In a double-blind study of a single administration of 6 mg of melatonin,[24] there were no changes in the EEG pattern of participants in the melatonin group. The results of an open-labeled study in which 3 mg of melatonin was administered for three months to women with sleep impairment[25] showed improved polysomnographic sleep latency, overall sleep efficiency, and REM sleep, and reduced sleep fragmentation. The same study found improvement in subjective measures of insomnia severity. Women with sleep impairment who were treated with 5 mg of melatonin for 24 weeks in an NRT study[23] reported significantly improved sleep quality. In an RCT on the effect of 1mg or 3 mg of melatonin for 12 months,[10] a trend toward sleep improvement was seen only in patients with baseline insomnia. In RCTs where inclusion criteria did not include sleep impairment,[21,26] an administration of 0.5 mg of melatonin for four weeks and 3 mg of melatonin for six months, respectively, did not affect subjective sleep quality. In summary, melatonin treatment improves the EEG pattern and subjective sleep quality only in menopausal women with preexisting sleep impairment.

3.6 | Melatonin's effect on sex hormones and menopausal symptoms

Treatment with 0.5 mg of melatonin for four weeks in an RCT study suppressed LH.[26] In another RCT, treatment with 3 mg of melatonin for six months led to reduced LH in younger perimenopausal women (43-49 years) and to

reduced FSH in women with low basal melatonin levels.[27] There was no significant change in 17β estradiol and FSH in another RCT.[22] Melatonin did not affect hot flashes and mood in postmenopausal women with those symptoms.[26] In an RCT, administration of 3 mg of melatonin for three months did not affect the overall Green Scale climacteric symptom score, or psychological and somatic symptoms separately.[28] In this study, women were included regardless of the extent of their troublesome menopausal symptoms at baseline. There was no effect of 1mg or 3 mg of melatonin on psychological or mental well-being, or overall quality of life among postmenopausal women with heterogeneous degrees of initial impairment in an RCT.[10] In another RCT,[29] women with severe climacteric symptoms at baseline were treated with 3 mg of melatonin for three months leading to significant improvement in climacteric symptoms in four domains: psychological, somatic, vasomotor, and sexual. In another RCT,[21] administration of 3 mg of melatonin daily for six months did not affect psychosocial, vasomotor, and sexual domains scores, but was associated with a significant improvement in the physical domain score among women with different degrees of menopausal symptoms. There was a significant improvement in psychological, vasomotor, and physical symptoms when 8 mg of melatonin was given daily for 12 months in postmenopausal women with menopausal symptoms of average severity in an RCT.[22] Another study reported a significant improvement in mood and mitigation of depression in the melatonin group after treatment with 3 mg daily for six months among peri- and postmenopausal women with different degrees of climacteric symptoms.[27] A significant improvement in overall sexual function and in each of the domains of desire, arousal, lubrication, orgasm, sexual satisfaction, and pain, was found with 3 mg daily treatment of melatonin compared to placebo in an RCT.[30] In summary, although there is no conclusive evidence for the regulation of sex hormones by melatonin, in most high-quality studies, there was significant improvement in one or more climacteric symptom scores with the administration of 3 mg of melatonin or more for three months or more, regardless of the initial degree of climacteric symptoms.

3.7 | Safety

Six of the included studies[7-9,11-13] did not report any adverse effects after a single administration of melatonin. Among the studies with more prolonged melatonin administration, one NRT[23] and one RCT[22] found morning fatigue in patients treated with melatonin, without requiring discontinuation, in RCTs[18,28,30] bleeding, spotting, drowsiness, nausea, vomiting, and headache were observed in a few patients in the melatonin group, but without a significant difference from the placebo group. In one study,[20] diarrhea and a hangover effect were observed in two participants in the melatonin group. No adverse events were noted in the remaining studies.

3.8 | Risk of bias of the included studies

As shown in Table 2, all but one of 18 RCTs had a low risk for bias. In one RCT,[27] there was some concern for bias. Four NRTs[15-17,25] had a low risk for bias, and two[19,23] had a moderate risk for bias (Table 3). Thus, none of the studies was excluded on the basis of quality. At the same time, it is worth noting that while many of the RCTs had a low overall risk for bias, there was some concern about missing values.[10,14,18,20,24,27-30] Intention to treat analyses were not performed in these studies,[18,24,28,30] and no data were presented on the exact distribution of dropout cases among study groups in study by Bellipanni et al[27] Although dropout cases were negligible in most studies, given the small number of participants, it could have affected the outcomes, mainly reducing the effect size. Another issue of some concern was adherence to intervention, as some of the studies did not report the percent of melatonin/placebo pills that were actually taken by the participants.[18,21,22,27,29,30] For NRTs, there was a moderate risk for bias in confounding and selection domains due to the selection of patients from a specific environment,[19] due to the assessment of potential confounders based on questionnaires,[19] because the participants' chronic diseases were not taken into account,[17] and because other interventions were implemented, such as a special diet in addition to the main intervention,[23] and no information on actual adherence to the intervention was presented in the studies.[17,19,25]

4 | DISCUSSION

Disruptions in the circadian system in menopausal women compound hormonal alteration leading to multiple physiological and physical changes. Melatonin is considered a pleiotropic hormone that is involved in and controls most of these changes.[31] The aim of this systematic review was to conduct a scientific investigation of the beneficial effect of oral melatonin on women's health and their bothersome symptoms. The results show that although multiple effects have been attributed to melatonin, only a few of these are supported by good scientific evidence in postmenopausal women. We did not find consistent evidence for the effects of melatonin on hemodynamic measurements, insulin sensitivity or glucose homeostasis. No effect was found on TC, HDL, and LDL levels. In contrast, the finding of increase in TG and VLDL levels was replicated in several high-quality studies, in which the daily dose of melatonin was 3 mg and higher. A dose of 3 mg and higher also had favorable effect on BMD. At a dose of 5-8 mg

TABLE 2 Risk of bias assessment in randomized trials (RoB 2)

Study	Domain 1(randomization)	Domain 2 (deviations from the intended intervention)	Domain 3 (missing outcome data)	Domain 4 (measurement of the outcome)	Domain 5 (selection of the reported result)	Overall risk of bias
Cagnacci et al, 2000[7]	L	L	L	L	L	L
Cagnacci et al, 2001[8]	L	L	L	L	L	L
Modena et al, 1998[9]	L	L	L	L	L	L
Cagnacci et al, 1997[11]	L	L	L	L	L	L
Cagnacci et al, 2001[12]	L	S	L	L	L	L
Cagnacci et al, 2002[13]	L	L	L	L	L	L
Parandavar et al, 2018[18]	L	S	S	L	L	L
Staikou et al, 2012[24]	L	L	S	L	L	L
Amstrup et al, 2015[20]	L	L	S	L	L	L
Amstrup et al, 2016[14]	L	L	S	L	L	L
Kripke et al, 2006[26]	L	L	L	L	L	L
Parandavar et al, 2017[30]	L	S	S	L	L	L
Parandavar et al, 2014[29]	L	S	S	L	L	L
Secreto et al, 2003[28]	L	S	S	L	L	L
Kotlarczyk et al, 2012[21]	L	S	L	L	L	L
Chojnacki et al, 201[22]	S	S	L	L	L	L
Bellipanni et al, 2005[27]	S	S	S	L	L	S
Amstrup et al, 2015[10]	L	L	S	L	L	L

Abbreviations: L, Low; H, High; S, Some concerns.

TABLE 3 Risk of bias assessment in non-randomized intervention studies (ROBINS-I)

Study	Domain 1: confounding	Domain 2: selection	Domain 3: deviation from intervention	Domain 4: missing data	Domain 5: measurement of outcomes	Domain 6: selection of reported result	Overall risk of bias
Wakatsuki et al, 2000[15]	L	L	L	L	L	L	L
Wakatsuki et al, 2001[16]	L	L	L	L	L	L	L
Tamura et al, 2008[17]	L	M	L	M	L	L	L
Sagan et al, 2017[19]	M	M	L	M	L	L	M
Walecka-Kapica, 2014[23]	M	M	L	L	M	M	M
Madaeva et al, 2020[25]	M	L	L	M	L	L	L

Abbreviations: L, Low risk of bias; M, Moderate risk of bias.

for 6-12 months, melatonin administration was associated with a decrease in BMI, with a stronger association in overweight/obese women. The classic indication for melatonin administration is insomnia. Although there is still no unequivocal conclusion as to its clinical efficacy for this indication, high-quality studies and a meta-analysis demonstrated its effectiveness and safety in middle-aged and older individuals.[32,33] Our study also showed that melatonin treatment improves EEG pattern and subjective sleep quality in menopausal women with preexisting sleep impairment. Additionally, most of the high-quality studies included in our systematic review found that melatonin treatment at a dose of 3 mg and higher improved climacteric symptoms in one or more domains. The only systematic review that investigated melatonin's effect on menopausal women that was conducted before the present review focused exclusively on melatonin's effect on BMD and included three studies that yielded similar results.[34]

4.1 | Strengths and limitations

The present study is the first systematic review to assess the effect of melatonin treatment on menopausal women. A large number of articles with a respectable number of participants were identified. Some individual studies involved a small number of patients, with varying doses, time, and duration of melatonin administration. Although all of the studies involved menopausal women, the age and inclusion criteria of the studies varied, with some including the general population of menopausal women and other menopausal women with specific climacteric complaints. However, in analyzing the results we related to and discussed all these differences.

4.2 | Future perspectives

Although the findings of our review are encouraging, they demonstrate an urgent need for a well-organized, large-scale RCT on melatonin treatment for menopausal women. Our review highlights the main drawbacks of previous studies, including the small number of participants, missing data, and a lack of transparency while reporting actual adherence rate. These factors should be taken into account in future studies.

5 | CONCLUSION AND IMPLICATIONS

In light of its multiple health benefits and excellent safety profile, melatonin treatment should be considered in menopausal women.

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AUTHORS CONTRIBUTION

YTG and RP designed the concept of the study, collected, interpreted, and analyzed the data. YTG drafted the article. RP critically revised the article. YTG and RP approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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