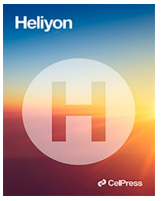
Heliyon 10 (2024) e34604

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Effect of melatonin supplementation on body composition and blood pressure in adults: A systematic review and Dose–Response meta-analysis of randomized controlled trial

Mahdi Vajdi [a], Seyedehelham Moeinolsadat [b], Nooshin Noshadi [c], Fatemeh Pourteymour Fard Tabrizi [d], Mahsa Khajeh [a], Mahdieh Abbasalizad-Farhangi [e,*], Beitullah Alipour [d,**]

[a] Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Department of Biology, Mashhad Branch, Islamic Azad University, Mashhad, Iran
[c] Department of Clinical Nutrition, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Department of Community Nutrition, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran
[e] Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Keywords:
Melatonin
Body composition
Blood pressure
Obesity
Meta-analysis

ABSTRACT

Background: Several randomized controlled trials (RCTs) have explored the impact of melatonin on body composition and blood pressure (BP). However, the findings from these studies remain a topic of debate. This systematic review and meta-analysis of RCTs sought to evaluate the effects of melatonin consumption on body composition (body weight (BW), body mass index (BMI), waist circumference (WC), hip circumference (HC)) and asleep/daytime BP (systolic blood pressure (SBP) and diastolic blood pressure (DBP)) in adults.

Methods: In order to identify eligible RCTs, a systematic literature search was carried out up to June 2024 in PubMed, Embase, Scopus, and Web of Science without any language restrictions. The I^2 statistic was used to perform heterogeneity tests on the selected studies. After evaluating random effects models based on heterogeneity tests, the weighted mean differences (WMD) with a 95 % confidence interval (CI) were calculated using pooled data.

Results: Overall, 28 studies (n = 1,543 participants) met our inclusion criteria. A pooled analysis of studies demonstrated that melatonin consumption led to a significant reduction in HC (WMD: 1.21 cm; 95 % CI: 1.94 to −0.49; P = 0.001), and daytime DBP (WMD: 1.40 mmHg; 95 % CI: 2.46 to −0.34; P = 0.009) in comparison with the control group. However, no substantial effects were observed on BW, BMI, WC, and SBP compared to the control group. ***Conclusion*:** The current meta-analysis of RCTs shows that treatment with melatonin reduces HC and daytime DBP levels in adults. However, further well-designed RCTs with large sample sizes and long durations are necessary to determine the effect of this supplement on body composition and BP.

* Corresponding author. Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
** Corresponding author. Department of Community Nutrition, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz,Iran.
E-mail addresses: abbasalizad_m@yahoo.com (M. Abbasalizad-Farhangi), alipourb@tbzmed.ac.ir (B. Alipour).

https://doi.org/10.1016/j.heliyon.2024.e34604
Received 4 March 2024; Received in revised form 12 July 2024; Accepted 12 July 2024
Available online 14 July 2024

1. Introduction

Obesity is a chronic condition affecting individuals of all age groups and socioeconomic backgrounds, regardless of the country's income level [1–3]. It is estimated that around 30 % of adults worldwide are affected by obesity, and this number is expected to rise to 33 % by 2030 [4,5]. Several factors can contribute to obesity, including genetic predisposition, low physical activity, consuming more energy than required, and sedentariness [6]. Several serious health issues that are potentially life-threatening can result from obesity, such as type 2 diabetes mellitus (T2DM), renal failure, hypertension (HTN), hyperlipidemia, and cardiovascular diseases (CVDs) [7,8]. Through clinical and animal studies, it has been established that there is a strong correlation between obesity and HTN [8]. According to evidence, visceral obesity is the most significant risk factor for HTN and CVD [9]. studies have shown that obese subjects are 3.5 times more likely to develop HTN, and 60 % of HTN cases are attributed to an increase in adipose stores [10].

To reduce the incidence of obesity, several interventions have been implemented to date, including dietary management, medication therapy, and physical activity promotion [11,12]. Moreover, over the past few decades, researchers have concentrated on low-salt diets as the most effective lifestyle change for reducing blood pressure (BP), and current global guidelines emphasize the significance of adopting the dietary approach to stop hypertension (DASH) diet and a low-salt mediterranean diet for optimal BP reduction [13]. Despite the current strategies, obesity is spreading rapidly worldwide, and the desired outcomes are not being achieved [14]. New data suggests that melatonin, when used as a nutritional supplement, has beneficial effects on weight regulation [15,16]. Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine endogenous hormone that plays a role in various physiological processes and is present in nearly all organisms, ranging from primitive photosynthetic bacteria to humans [17]. The pineal gland rhythmically synthesizes melatonin, which acts on the suprachiasmatic nucleus, other parts of the brain, and all peripheral organs [18]. Furthermore, melatonin has been demonstrated to play a role in regulating energy balance, BW, BP, dyslipidemia, and hyperglycemia [19–21].

The impact of melatonin supplementation on obesity and BP has been inconsistent across various studies. Nevertheless, the reasons or mechanisms for improvements in these conditions have not been thoroughly investigated. According to published clinical trials, melatonin supplementation was observed to have a positive impact on anthropometric indices [22–26]. While no substantial changes in anthropometric variables were reported in other studies [27–30]. According to a systematic review and meta-analysis, melatonin supplementation led to a significant reduction in body weight (BW), however, it did not affect waist circumference (WC) or body mass index (BMI) [31]. Another systematic review and meta-analysis of randomized controlled trials (RCTs) performed in 2018 by Akbari et al. demonstrated that supplementation of melatonin substantially decreased systolic blood pressure (SBP) and diastolic blood pressure (DBP) in metabolic disorders patients [32]. In contrast, Hoseini et al. have shown no significant difference in SBP and DBP after melatonin supplementation [33]. Furthermore, Lee et al. [21] conducted a meta-analysis of four RCTs and found that the overall analysis did not show significant effects of melatonin compared to placebo on nocturnal BP. However, their study revealed that controlled-release melatonin significantly reduced nocturnal BP, while fast-release melatonin had no impact on BP. In contrast to our study, this study specifically investigated the impact of melatonin on improving nocturnal HTN but did not explore the effects of melatonin on obesity-related indices. These results indicate that the effect of melatonin on obesity indices and BP variables has been a subject of controversy in previous meta-analyses. Thus, we conducted this systematic review and meta-analyses of published RCTs to assessment the impact of melatonin supplementation on body composition (BW, BMI, hip circumference (HC), WC) and asleep/-daytime BP (SBP and DBP) in adults.

2. Methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34] (Supplementary Table 1), this meta-analysis was registered in the PROSPERO with the code CRD42023470934. The study protocol received approval from the ethics committee of Tabriz University of Medical Sciences (grant number: 73403).

2.1. Search strategy

The PICO model was used in the current systematic review and meta-analysis of RCTs. The model includes population (adult subjects), intervention (melatonin intake), comparison (control/placebo group), and outcomes (BMI, BW, WC, HC, SBP, and DBP). A systematic search of electronic databases such as Web of Science, PubMed, Scopus, and Embase was conducted to identify RCTs that evaluated the impact of melatonin on body composition and BP indices in adults. The search was conducted until June 2024, with no restrictions on language or date. The merger of MeSH and non-MeSH terms were as follows: (melatonin or N-acetyl-5-methoxy tryptamine) AND (blood pressure OR hypertension OR SBP OR DBP OR diastolic OR systolic) AND (weight reduction OR fat mass OR body weight OR body composition OR body compositions OR weight losses OR weight loss OR waist circumference OR BMI OR obesity) AND (intervention OR intervention study OR intervention* OR controlled trial OR random OR clinical trial OR randomized controlled trial OR randomized clinical trial OR RCT OR clinical trials OR trials). We utilized the Boolean operators "AND" and "OR" between or within groups, respectively. To ensure that no eligible studies were overlooked, we manually searched Google Scholar and reference lists of related publications.

2.2. Study selection

Trials were selected for inclusion based on the following criteria [1]: parallel design or cross-over RCTs [2], RCTs with participants

aged 18 years and above [3], At least one of the following measures was reported: BMI, BW, WC, HC, DBP, and SBP before and after the intervention in both treatment and placebo groups [4], reported mean and standard deviation (SD) values of variables. When dealing with datasets that had multiple publications, only the complete study was taken into consideration. However, the exclusion of studies was according to the following criteria [1]: trials that combined melatonin with other ingredients when the single effect of melatonin was not possible [2], trials without a placebo or control group [3], involved pregnant women, children, or animals [4], absence of sufficient data in either control or intervention groups, and [5] *in vitro* and *in vivo* studies, letters, conference abstracts, case reports, or books.

2.3. Data Extraction

The data from each of the eligible articles was extracted separately by two different authors. To achieve a consensus, any inconsistencies were evaluated by a chief investigator. Data on authors' first names, location of the study, study design, publication year, study duration, sample size, melatonin dosage, mean age, sex, and health conditions of participants were collected for each eligible study.

2.4. Quality assessment

The methodological quality and bias risk of the included trials were evaluated independently by two authors (MV, NN), following the Cochrane risk-of-bias tool for randomized trials (RoB 2). The RoB2 assessment evaluates several factors, such as randomization, outcome measurement, missing data, deviations from intended interventions, and selection of reported results. Domains receive a 'high risk' score if methodological errors are present, a 'low risk' score if no errors are detected, and an 'unclear risk' score if data are insufficient [35].

2.5. Statistical analysis

Stata version 14 (StataCorp, College Station, TX, USA) was used to perform all analyses. Using the mean (SD) of BMI, BW, WC, HC, SBP, and DBP, the overall estimates for both the control and intervention groups were calculated. The calculation of effect sizes for all variables involved the use of weighted mean differences (WMDs) and 95 % confidence intervals (CIs) [36]. The inconsistency index (I-squared) was used to quantify Cochran's Q test for assessing heterogeneity between studies [37]. To identify studies with high heterogeneity, a P-value of Q statistic <0.1 and $I^2 \geq 50$ % were employed [38]. Based on age, sex, sample size, dose of supplementation, intervention duration of trial, BMI status, and health status, a subgroup analysis was carried out to identify heterogeneity. To determine if a single study or group of studies influenced the conclusions, a sensitivity analysis was performed. Funnel plots and Begg's and Egger's tests were employed to assess the presence of publication bias [39,40]. Moreover, using a fractional polynomial model, the non-linear impacts of melatonin dosage and treatment duration on body composition and BP indices were determined.

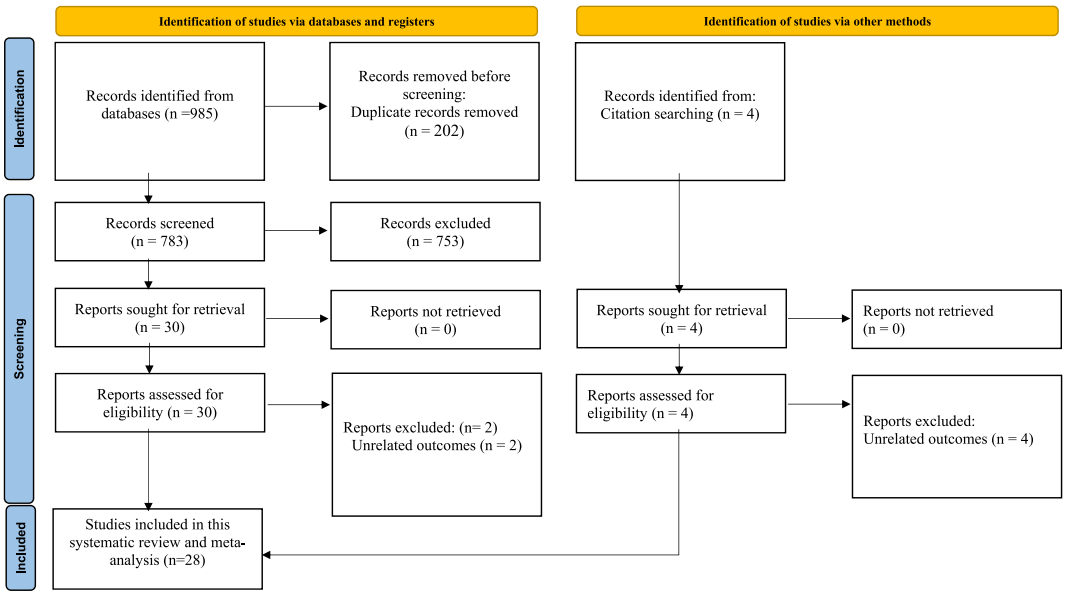


Fig. 1. Flow chart of the number of studies identified and selected into the meta-analysis.

Table 1
Summary of characteristics of included studies.

First Author name	Year/ Country	Study design	Subject	Participants (intervention/ control)	Age (Intervention/ Control)	Baseline BMI (Intervention/ Control)	Duration (wk)	Dose (mg)	Type of administration		Outcomes
									Intervention	Placebo	
Abood Sattar J et al.	2020/Iraq	RCT parallel	MetS	35 (20/15)	45.8/48.07	40.24/41.81	12	10	Metformin + Melatonin	Metformin + Placebo	BMI, WC
Agahi M et al.	2018/Iran	RCT parallel	Treated antipsychotics	100 (50/50)	37.4/37.46		8	3	Melatonin	Placebo	WC, BW, BMI, SBP, DBP
Bazyar H et al.	2021/Iran	RCT parallel	T2DM	50 (25/25)	53.64/51.52	27.38/27.42	8	3	Melatonin supplement	Placebo tablets	SBP, BW, BMI, WC, HC, WHR
Chojnacki C et al.	2018/ Poland	RCT parallel	Psychosomatic disorders	60 (30/30)	57.3/56.2	30.9/30.7	48	8	Melatonin	Placebo	BMI
Chojnacki C et al.	2015/ Poland	RCT parallel	Psychosomatic disorders	60 (30/30)	57.3/56.2	30.9/30.7	24	5	Fluoxetine + Melatonin	Fluoxetine + placebo	BMI
D'Anna R et al.	2017/Italy	Randomised, open trial	Menopausal women	40 (20/20)	49.1/48.7	26.7/25.3	24	3	Myoinositol + Melatonin	Myoinositol	BMI, WC, SBP, DBP
Daneshvar Kakhaki, R et al.	2020/Iran	RCT parallel	Parkinson	51 (25/26)	64.6/66.3	25.1/25.1	12	10	Melatonin	Placebo	BMI, BW
Goyal A et al.	2014/USA	RCT crossover	MetS			34.6/33.8	10	8	Melatonin	Placebo	SBP, DBP
Grossman, E et al.	2006/Israeil	RCT parallel	HTN	38 (19/19)	62/66	27.4/27.3	4	2	CR- melatonin	Placebo	SBP, DBP
Hoseini Ghaffari S. et al.	2021/Iran	RCT parallel	Heart failure	92 (46/46)	62.7/59.1	26.7/27.2	24	10	Melatonin	Placebo	SBP, DBP
Jamilian, M et al.	2019/Iran	RCT parallel	PCOS	56 (28/28)	28.7/28.3	29.1/29.2	12	10	Melatonin	Placebo	BW, BMI
Kim, Y et al.	2021/Korea	RCT parallel	Insomnia	38 (19/19)	61/61	24.9/23.6	6	2	Melatonin	Placebo	SBP, BMI
Kotlarczyk, M. P et al.	2012/USA	RCT parallel	Perimenopausal women	18 (13/5)	50.3/47.5	25.7/21.7	24	3	Melatonin	Placebo	SBP, DBP
Mesri Alamdari N et al.	2015/Iran	RCT parallel	Obesity	44 (22/22)	33.84/34.86	34.1/35.7	40 days	6	Melatonin	Placebo	BW, BMI, WC, HC
Modabbernia, A. et al.	2014/Iran	RCT parallel	schizophrenia	36 (18/18)	32.7/32.8	23.9/23.2	8	3	Melatonin	Placebo	SBP, DBP, HC, WHR BW, BMI,WC
Mohammadi, S et al.	2021/Iran	RCT parallel	Overweight or obesity	38 (19/19)	38.95/37.84	31.01/30.14	12	3	Melatonin	Placebo	BW, WC,BMI
Mousavi, R et al.	2022/Iran	RCT parallel	PCOS	41 (21/20)	25.57/26.2	28.4/26.94	8	6	Melatonin	Placebo	BW, BMI,WC
Nunes, DM et al.	2008/Brazil	RCT parallel	COPD	25 (12/13)	64.17/67.38	23.87/24.1	3	3	melatonin	placebo	BMI
Ostadmohammadi, V et al.	2020/Iran	RCT parallel	Diabetic HD	53 (26/27)	65.6/64.1	26.4/26.4	12	10	melatonin	placebo	BW, BMI, SBP, DBP
Pakravan, H et al.	2017/Iran	RCT parallel	NAFLD	97 (49/48)	42.5/40.6	–	12		melatonin	placebo	BW, WC, SBP, DBP
Rahbari-Oskoui FF et al.	2019/USA	RCT crossover	HTN	–	–	–	4	24	Melatonin	Placebo	SBP, DBP
Raygan, F et al.	2019/Iran	RCT parallel	T2DM	60 (30/30)	67.7/65.3	30.4/29.7	12	10	Melatonin	Placebo	DBP, SBP, BW, BMI
Rezvanfar M R et al.	2017/Iran	RCT parallel	T2DM	64 (64/64)	52/52	–	24	6	Melatonin	Placebo	BW
Rechciński, T et al.	2010/ Poland	RCT parallel	CAD	60 (40/20)	61.15/53.61	–	12	5	Melatonin	Placebo	SBP, DBP
Romo-Nava, F et al.	2014/ Mexico	RCT parallel	Bipolar and schizophrenia	44 (20/24)	30.6/28.6	26.1/26.7	8	5	Melatonin	Placebo	DBP, SBP, BW,BMI,HC, WC
Shabani A et al.	2019/Iran	RCT parallel	PCOS	58 (29/29)	26.5/26	27.1/27.8	12	10	Melatonin	Placebo	BW, BMI
Lusardi et al.	2000/Italy	RCT crossover	HTN	47	38–65	–	4	5	Melatonin	Placebo	SBP, DBP
Scheer et al.	2004/ Netherlands	RCT crossover	HTN	16	55 ± 8	26.8 ± 1.7	3	2.5	Melatonin	Placebo	SBP, DBP

Abbreviation: RCT: Randomised Clinical Trial, T2DM: Type 2 Diabetes Mellitus, NAFLD: Non-Alcoholic Fatty Liver Disease, MetS: metabolic syndrome, PCOS: Poly Cystic Ovary Syndrome, HD: Hemodialysis, COPD: Chronic Obstructive Pulmonary Disease, HTN: Hypertension, CAD: Coronary Artery Disease, BW: Body Weight, BMI: Body Mass Index, WHR: Waist to Hip Ratio, HC: Hip Circumstance, WC: Waist Circumstance, DBP: Diastolic Blood Pressure, SBP: systolic Blood Pressure.

3. Results

3.1. Search results and trial flow

In Fig. 1, the flowchart of the literature search is depicted. Electronic database searches yielded 985 studies in total. Following the removal of 202 duplicate studies, 783 articles underwent assessment via screening of their titles and abstracts. Following a meticulous evaluation of the full text of 30 studies, 28 were deemed eligible for inclusion according to pre-specified criteria. 18 trials were on BMI, 15 were on BW, 11 were on WC, four were on HC, 17 were on daytime SBP, five were on asleep SBP, 15 were on daytime DBP and five were on asleep DBP.

3.2. Study characteristics

The general features of eligible studies are depicted in Table 1. Data were collected from 28 eligible studies including 33 arms, comprising a total of 1,543 subjects, with 820 participants in the intervention and 723 in the control group. The publication dates of the trials spanned from 2000 to 2022. Participants in these studies were between 25 and 67 years old. The sample size of participants in these trials varied from 16 to 100. Studies were carried out in Iran [22,23,26–30,33,41–46], the United States [47–50], Poland [24,51,52], Iraq [25], Israel [53], Italy [54,55], Brazil [56], Korea [57], and Mexico [58]. In various RCTs, in various RCTs, the melatonin dosage ranged from 1 to 24 mg, and the intervention duration of studies varied between three and 48 weeks. While most trials included both sexes, one study was conducted on male participants, and nine trials were conducted on female participants. These studies were conducted in T2DM, metabolic syndrome (MetS), patients treated with the second-generation antipsychotics, psychosomatic disorders, menopausal women, parkinson, HTN, heart failure, polycystic ovary syndrome (PCOS), diabetic hemodialysis patients, woman with insomnia, perimenopausal women, schizophrenia, chronic obstructive pulmonary disease, coronary artery disease, schizophrenia, bipolar disorder, nonalcoholic fatty liver disease (NAFLD), and patients with overweight, and obesity. The quality assessment of the included RCTs for risk of bias is depicted in Fig. 2. Most trials were deemed to have low bias risk according to the RoB2 assessment.

3.3. BMI

The impact of melatonin supplementation on BMI was investigated in 18 trials with 20 treatment arms. The results of the random-effects model's pooled estimate suggests that there were no significant effects on BMI after melatonin supplementation when compared to the control group (WMD: 0.47 kg/m^2; 95 % CI: 0.96 to 0.02; P = 0.059; I^2 = 96.9 %; P < 0.001) (Fig. 3a). Health status and BMI status were identified as the sources of between-study heterogeneity. Moreover, a substantial decrease in BMI was observed in studies with a sample size of ≥50 participants, individuals aged <45 years, those prescribed melatonin doses of ≤5 mg/d, participants with obesity, and across both short-term (≤8 weeks) and longer-term (>8 weeks) interventions. (Supplementary Table 2).

3.4. BW

The combination of 17 estimates from 15 studies demonstrated that melatonin supplementation did not have a substantial impact on BW in comparison to the control group (WMD: 0.38 kg; 95 % CI: 0.92 to 0.15; P = 0.159; I^2 = 83.7 %; P < 0.001) (Fig. 3b). Subgroup

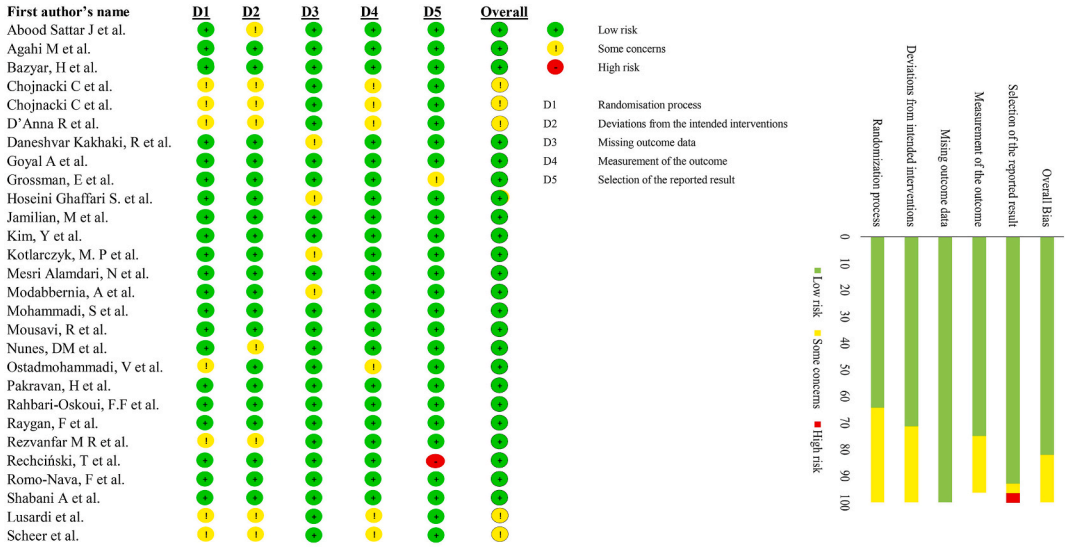


Fig. 2. The methodological quality of the included studies (risk of bias).

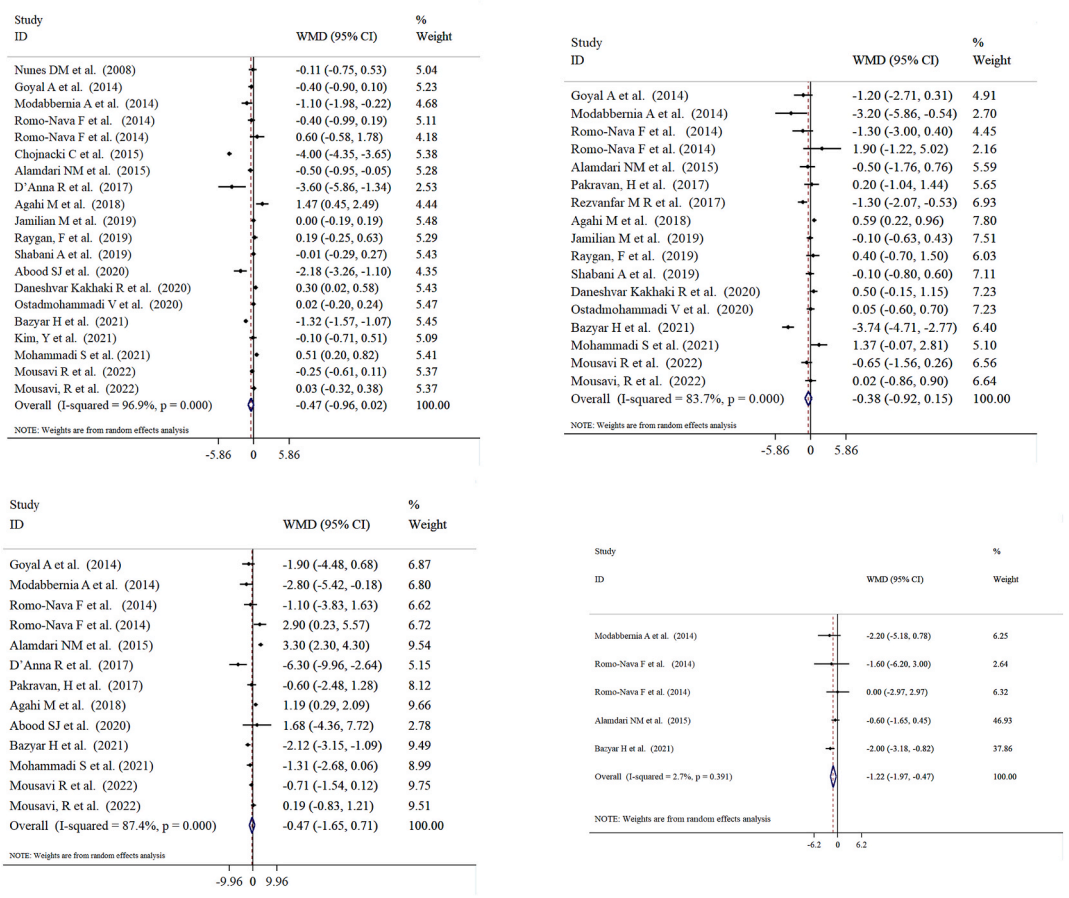


Fig. 3. Forest plot showing the effects of melatonin supplementation on BMI (a), BW (b), WC (c), and HC (d) (WMDs and 95 % CIs) in adults using the random effects model, CI, confidence interval; WMD, weighted mean difference.

analysis has indicated that sex, supplement dose, and health status may contribute to heterogeneity.

In subgroup analyses, melatonin supplementation resulted in a significant reduction in BW in trials involving subjects with normal BMI, individuals <45 years of age, and patients with diabetes (Supplementary Table 2).

3.5. WC

The impact of melatonin supplementation on WC was studied in 11 trials consisting of 13 treatment arms. According to the quantitative meta-analysis, there was no significant difference in WC between the group that received melatonin supplementation and the control group (WMD: 0.47 cm; 95 % CI: 1.65 to 0.71; P = 0.439; I^2 = 87.4 %; P < 0.001) (Fig. 3c). The sources of between-study heterogeneity were identified as age, duration of intervention, and health status through subgroup analysis. The subgroup analysis indicated that melatonin intake significantly reduced WC in subjects with ages ≥45 years old, duration of intervention >8 week, individuals with normal BMI and overweight, healthy and diabetic subjects, and both melatonin dosages (≤5 and > 5 mg/d) (Supplementary Table 2).

3.6. HC

In four studies with five treatment arms, melatonin supplementation was investigated for its effect on HC and indicated a substantial effect on decreasing HC (WMD: 1.22 cm; 95 % CI: 1.97 to −0.47; P = 0.001; I^2 = 2.7 %; P = 0.391) (Fig. 3d). Subgroup analyses revealed that melatonin supplementation led to a substantial decrease in HC in studies conducted on patients with diabetes, studies with both sexes, with a sample size ≥50 participants, individuals aged ≥45 years, RCTs that administered ≤5 mg/d melatonin, and overweight subjects (Supplementary Table 2).

3.7. SBP

The pooled results of the random-effect model on 17 trials with 18 arms demonstrated that there was no substantial impact of melatonin intake on daytime SBP (WMD: 0.78 mmHg; 95 % CI: 2.16 to 0.61; P = 0.271; I^2 = 75.6 %; P < 0.001) (Fig. 4a). The sources of heterogeneity were determined to be sex, BMI status, and health status through subgroup analysis.

In subgroup analyses, melatonin supplementation resulted in a significant reduction in daytime SBP in subjects with obesity and MetS (Supplementary Table 3). Moreover, the pooled results of the random-effect model on five trials demonstrated that there was no substantial impact of melatonin intake on asleep SBP (WMD: 2.02 mmHg; 95 % CI: 7.91 to 3.87; P = 0.502; I^2 = 89.2 %; P < 0.001) (Fig. 4b).

3.8. DBP

The results of 15 RCTs, which included 16 effect sizes, showed that melatonin supplementation substantially reduced daytime DBP when compared to the control group (WMD: 1.40 mmHg; 95 % CI: 2.46 to −0.34; P = 0.009; I^2 = 78 %; P < 0.001) (Fig. 5a). The sources of heterogeneity were determined to be sex, age, BMI status, and health status through subgroup analysis. A more substantial decrease in DBP was observed with melatonin supplementation in studies involving a sample size <50, trials with female subjects, individuals with <45 years, studies that prescribed ≤5 mg/d melatonin, and trials with intervention duration of fewer than eight weeks (Supplementary Table 3). Moreover, the pooled results of the random-effect model on five trials demonstrated that there was no substantial impact of melatonin intake on asleep DBP (WMD: 0.57 mmHg; 95 % CI: 3.62 to 2.47; P = 0.712; I^2 = 84 %; P < 0.001) (Fig. 5b).

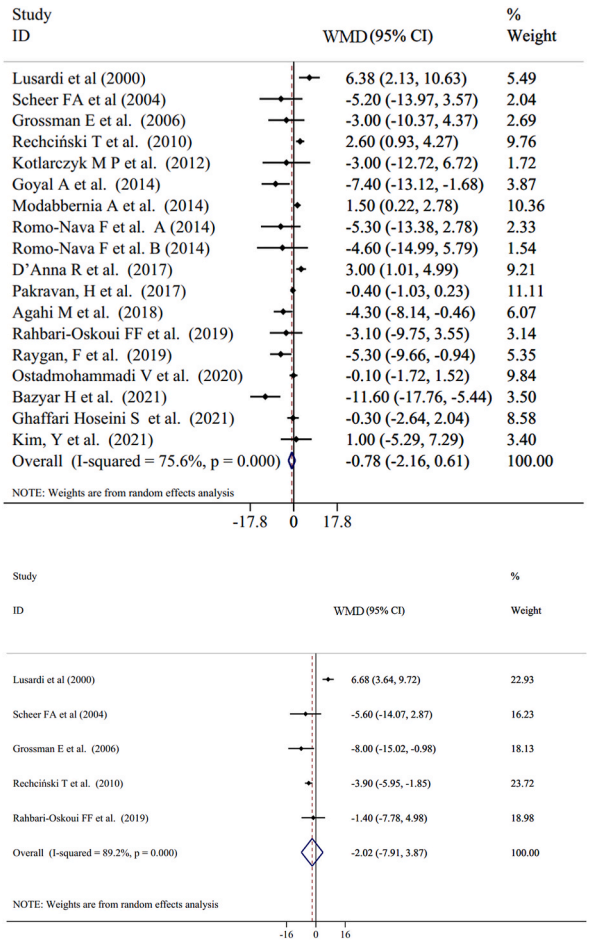


Fig. 4. Forest plot showing the effects of melatonin supplementation on daytime (a)/asleep (b) SBP (WMDs and 95 % CIs) in adults using the random effects model. CI, confidence interval; WMD, weighted mean difference.

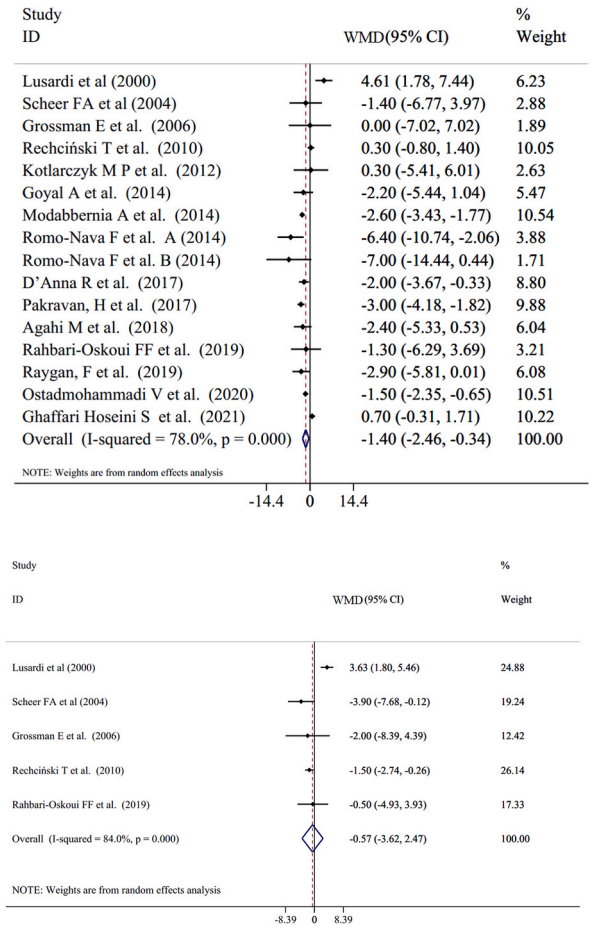


Fig. 5. Forest plot showing the effects of melatonin supplementation on daytime (a)/asleep (b) DBP (WMDs and 95 % CIs) in adults using the random effects model. CI, confidence interval; WMD, weighted mean difference.

3.9. Non-linear analysis

A one-stage non-linear dose-response analysis was carried out to examine the association between melatonin supplementation and BW, BMI, WC, HC. The results indicated that there was a significant non-linear association between the intervention dose and changes in WC (P = 0.031). However, no such relationship was observed for BW (P = 0.639), BMI (P = 0.301), and HC (P = 0.291). Furthermore, the duration of the intervention was substantially associated with changes in WC (P = 0.030), whereas no such relationship was detected for HC (P = 0.313), BW (P = 0.096), and BMI (P = 0.247) (Supplementary Fig. 1 a-h).

3.10. Sensitivity analysis

We conducted a sensitivity analysis to assess the influence of each trial on the overall effect size. We did not observe any substantial impact of any individual trial on the overall effect size of BW, WC, HC, SBP, and DBP. However, the sensitivity analysis for BMI was affected by the exclusion of studies conducted by Agahi et al. [41] (WMD: 0.55 kg/m^2; 95 % CI: 1.05 to −0.06), Mohammadi et al. [44] (WMD: 0.52 kg/m^2; 95 % CI: 1.03 to −0.01), and Romo-Nava et al. [58] (WMD: 0.51 kg/m^2; 95 % CI: 1.01 to −0.01).

3.11. Publication bias

To examine publication bias, we carried out the funnel plot, as well as Begg's and Egger's tests. Asymmetry was observed in the funnel plots upon visual examination. However, according to the results of Begg's and Egger's tests, there was no indication of publication bias for BMI, BW, WC, HC, SBP, and DBP (Supplementary Fig. 2 a-f).

4. Discussion

Through this study, the effects of melatonin supplementation on anthropometric and BP indices in adults were assessed. According

to the results, melatonin supplementation was found to have a significant impact on reducing daytime DBP and HC. However, no significant impact of melatonin on the SBP, BMI, BW, and WC was observed.

Melatonin has emerged as a potential regulatory agent of energy metabolism due to its anti-obesity properties. It has been found to operate by modulating the various phases of energy balance, encompassing intake, storage, and expenditure of energy. Notably, melatonin has been demonstrated to exert its impacts on energy metabolism both centrally and peripherally. In particular, melatonin appears to regulate adipose tissue metabolism, which is critical for the maintenance of energy balance and BW homeostasis. Experimental studies have shown that melatonin supplementation can reduce BW, enhance metabolic profile, and improve glucose homeostasis. Interestingly, these effects appear to be independent of food intake. Moreover, melatonin's anti-obesity effects are attributed to energy expenditure mechanisms, rather than central feeding behavior mechanisms, according to observations [59,60].

This systematic review and meta-analysis revealed nuanced impacts of melatonin supplementation on various anthropometric indices. While the overall impact on BMI, BW, and WC did not exhibit statistically significant changes, subgroup analyses unraveled intricate patterns. Melatonin showcased notable reductions in BMI among studies involving specific demographics: those with larger sample sizes (a sample size $\geq$50), younger individuals ($<$45 years old), females, and subjects with overweight or obesity or diabetes or psychopathy. Additionally, a substantial reduction in BW was observed predominantly in studies involving younger individuals ($<$45 years old) and diabetic patients. These subgroup-specific effects imply the potential for tailored interventions in specific populations. While some investigations demonstrated significant reductions in BW or BMI with melatonin supplementation [22,23,26,31], others echoed our findings, highlighting the absence of substantial alterations in these indices [27,28,30]. These discrepancies underscore the complexity and variability of melatonin's effects, which might be contingent upon diverse factors, including participant demographics and intervention specifics. Factors such as melatonin dosage, duration of intervention, and participant demographics played pivotal roles in influencing the impact of melatonin supplementation. This study revealed that melatonin intake significantly reduced WC in subjects ages $\geq$45 years old, with the duration of intervention $>$8 weeks, individuals with normal BMI and overweight, females, healthy and diabetic subjects, and both dosages of melatonin ($\leq$5 and $>$ 5 mg/d). The observed heterogeneity in outcomes emphasizes the significance of individual characteristics and intervention specifics in determining the efficacy of melatonin. Notably, the influence of sex, age, BMI status, and health conditions became evident in dissecting the varied effects on body composition. These findings emphasize the necessity of considering these factors in future intervention designs for optimized outcomes.

In 2022, Lee et al. [21] conducted a meta-analysis to investigate the efficacy and safety of oral melatonin supplementation for treating HTN in hypertensive patients (receiving or not receiving anti-HTN drug treatment), compared to placebo or no treatment. They found that controlled-release melatonin, used in three RCTs, reduced asleep SBP by $-$4.67 mm Hg and asleep DBP by $-$2.39 mm Hg. They also found reductions in daytime SBP by $-$3.57 mm Hg and daytime DBP by $-$1.06 mm Hg; however, these reductions were not statistically significant. The meta-analysis revealed that despite using a wide range of melatonin doses (2–24 mg), the BP reduction from different doses of melatonin was similar. In contrast to our study, this research specifically investigated the impact of controlled-release melatonin on improving nocturnal HTN but did not explore the effects of melatonin on obesity-related indices.

Our results showed that the melatonin supplementation significantly decreased HC and DBP levels. Lee et al. [21] limited their study to the studies investigating on nocturnal HTN, while we conducted this meta-analysis among all target populations. Furthermore, the number of included trials in our study was more than other studies (17 vs. four [21] and five [61] studies).

The present up-to-date meta-analysis validated the results of the previous meta-analysis study, which demonstrated the significant effects of melatonin supplementation on reducing DBP [32]. Based on the subgroup analysis, a more substantial decrease in DBP was observed with melatonin supplementation in studies involving a sample size $<$50, trials with female subjects, individuals with $<$45 years, studies that prescribed $\leq$5 mg/d melatonin, subjects with normal BMI, NAFLD patients, and trials with intervention duration of fewer than eight weeks. This discrepancy underscores the complexity of melatonin's action on distinct BP parameters, suggesting potential variability based on participant profiles and intervention specifics.

While melatonin supplementation displayed a noteworthy reduction in DBP, its effect on SBP did not exhibit a significant overall change in our analysis. However, the absence of substantial effects of melatonin supplementation on SBP aligns with inconclusive outcomes reported in an earlier study by Hosseini et al. [33]. Although our meta-analysis did not demonstrate a substantial impact of melatonin on SBP overall, subgroup analyses highlighted the influence of intervention specifics and participant characteristics. Notably, studies administering higher doses of melatonin ($>$5 mg/d), individuals with higher BMI ($\geq$30, obese), or those with MetS showcased a significant reduction in SBP, implying a potential beneficial effect in specific health conditions. This variability underscores the complexity and potential specificity of melatonin's effects on BP regulation. Former research has suggested that melatonin, an indole hormone primarily synthesized by the pineal gland, can regulate BP through multiple pathways. Melatonin can act as a potent scavenger of free radicals, which can indirectly improve endothelial function and decrease adrenergic system activity by providing suitable concentrations of nitrogen oxide (NO). Preventing endothelial damage and vascular stiffness, both of which are significant factors in the development of HTN, requires the reduction of chronic inflammation and oxidative stress. According to studies, administering melatonin to hypertensive patients can increase their total antioxidant capacity, associated with the improvement of arterial stiffness and endothelial function [62,63]. Furthermore, it is proposed that melatonin's hypotensive effects are due to its ability to stimulate melatonin receptors in the central nervous system and peripheral vessels [64]. Additionally, Melatonin monotherapy has been found to have antihypertensive effects and antihypertensive action in arterial HTN and coronary heart disease [63]. Melatonin supplementation has also been shown to be effective in controlling anthropometric measurements, like BW, BMI, and WC, and arterial pressure, including SBP, mean arterial pressure, and pulse pressure, in patients with T2DM [26]. Despite these promising findings, the limited number of available trials on the impacts of melatonin supplementation on BP necessitates further research. In order to provide more conclusive evidence in this area, it is necessary to conduct more extensive clinical trials with larger sample sizes. As well, the potential long-term effects of melatonin supplementation on BP require elucidation. Moreover, our results

indicated a significant non-linear association between the dose of intervention and changes in WC. Moreover, there was a substantial non-linear association between the duration of melatonin supplementation and changes in WC. In such a way that melatonin intake (both dosages of melatonin; ≤ 5 or > 5 mg/d) and the intervention duration > 8 weeks significantly reduced WC.

4.1. Strengths and limitations

This study presents a comprehensive systematic review and dose-response meta-analysis of the effect of melatonin supplementation on anthropometric measures, such as BMI, BW, WC, and HC, as well as BP. The study included all RCTs without any restrictions on language or date, and subgroup analyses were carried out according to the inclusion criteria. The study's strengths include the inclusion of a large number of eligible studies and the use of dose-response and subgroup analyses to investigate the sources of between-study heterogeneity. However, there are certain limitations of this study that must be taken into account. The analyses were not restricted to solitarily include patients of one type or age. Furthermore, we could not find the source of heterogeneity between some results. Significant heterogeneity was encountered perhaps due to various regimens, doses, durations, center settings, enrolled populations, etc. Different doses of melatonin were used across the included studies, which had varying intervention periods and participants with different health statuses, with some confounding variables left uncontrolled. Besides, many of the studies suffer from significant sources of bias, and the effect in many occasions was assessed by very few studies; thus, the evidence to support it is low. Additionally, it's important to acknowledge that the majority of studies included in the meta-analysis were conducted exclusively within Eastern countries. This geographical limitation may constrain the broader applicability and relevance of our results. Consequently, there is a pressing need for more diverse, globally representative RCTs to enhance our comprehensive understanding of the topic. Despite the limitations, this meta-analysis provides detailed insights into the potential therapeutic effects of melatonin on obesity and related metabolic disorders. The study's standardized methodology and the randomized placebo-controlled design of the eligible trials are strengths. Nonetheless, to determine the effect of melatonin on these parameters and its use as a supplement for certain health conditions, further well-designed RCTs and mechanistic studies with high quality are required.

5. Conclusion

The meta-analysis demonstratedthat melatonin supplementation had a substantiallowering impacton the HC and DBP level, but no significant effect on other anthropometric measures or SBP level was observed. The available evidence indicates that melatonin could be a beneficial therapeutic agent for treating obesity and related metabolic disorders.However, more research is required to determine the optimal dosing and timing of melatonin supplementation, as well as to clarify the precise mechanisms underlying its effects on energy metabolism.

Funding

The present study has been performed by a grant from Tabriz University of Medical Sciences, Tabriz, Iran, (grant number: 73403).

CRediT authorship contribution statement

Mahdi Vajdi: Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Seyedehelham Moeinolsadat:** Writing – original draft, Methodology, Investigation, Formal analysis. **Nooshin Noshadi:** Writing – original draft, Methodology. **Fatemeh Pourteymour Fard Tabrizi:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation. **Mahsa Khajeh:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization, Writing – original draft, Methodology. **Beitullah Alipour:** Writing – review & editing, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data included in article/supplementary material/referenced in article.

Acknowledgments

We acknowledge the contributions of Tabriz University of Medical Sciences, Tabriz, Iran, for providing facilities in support of the study (grant number: 73403).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34604.

References

[1] K.B. Smith, M.S. Smith, Obesity statistics. Primary care: clinics in office practice 43 (1) (2016) 121–135.
[2] B.M. Popkin, L.S. Adair, S.W. Ng, Global nutrition transition and the pandemic of obesity in developing countries, Nutr. Rev. 70 (1) (2012) 3–21.
[3] D. Jacobi, R. Buzele, C. Couet, Are we facing an obesity pandemic? Presse Med. 39 (9) (2010) 902–906.
[4] T. Fleming, M. Robinson, B. Thomson, N. Graetz, C. Margono, E. Mullany, et al., Global regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013, Lancet. 384 (9945) (2014) 766–781.
[5] E.A. Finkelstein, O.A. Khavjou, H. Thompson, J.G. Trogdon, L. Pan, B. Sherry, et al., Obesity and severe obesity forecasts through 2030, Am. J. Prev. Med. 42 (6) (2012) 563–570.
[6] A. Hruby, F.B. Hu, The epidemiology of obesity: a big picture, Pharmacoeconomics 33 (2015) 673–689.
[7] S.Z. Jiang, W. Lu, X.F. Zong, H.Y. Ruan, Y. Liu, Obesity and hypertension, Exp. Ther. Med. 12 (4) (2016) 2395–2399.
[8] J.E. Hall, The kidney, hypertension, and obesity, Hypertension 41 (3) (2003) 625–633.
[9] A.M. Sironi, A. Gastaldelli, A. Mari, D. Ciociaro, V. Postano, E. Buzzigoli, et al., Visceral fat in hypertension: influence on insulin resistance and β-cell function, Hypertension 44 (2) (2004) 127–133.
[10] G. Seravalle, G. Grassi, Obesity and hypertension, Pharmacol. Res. 122 (2017) 1–7.
[11] H. Khalil, L. Ellwood, H. Lord, R. Fernandez, Pharmacological treatment for obesity in adults: an umbrella review, Ann. Pharmacother. 54 (7) (2020) 691–705.
[12] S.H. Chin, C. Kahathuduwa, M. Binks, Physical activity and obesity: what we know and what we need to know, Obes. Rev. 17 (12) (2016) 1226–1244.
[13] A.F. Cicero, M. Veronesi, F. Fogacci, Dietary intervention to improve blood pressure control: beyond salt restriction, High Blood Pres. Cardiovasc. Prev. 28 (6) (2021) 547–553.
[14] R. Kelishadi, F. Azizi-Soleiman, Controlling childhood obesity: a systematic review on strategies and challenges, J. Res. Med. Sci.: the official journal of Isfahan University of Medical Sciences 19 (10) (2014) 993.
[15] D.X. Tan, L. Manchester, L. Fuentes-Broto, S. Paredes, R. Reiter, Significance and application of melatonin in the regulation of brown adipose tissue metabolism: relation to human obesity, Obes. Rev. 12 (3) (2011) 167–188.
[16] A. Jiménez Aranda, G. Fernández Vázquez, D. Campos, M. Tassi, L. Velasco Perez, D.X. Tan, et al., Melatonin induces browning of inguinal white adipose tissue in Zucker diabetic fatty rats, J. Pineal Res. 55 (4) (2013) 416–423.
[17] D.X. Tan, R. Hardeland, K. Back, L.C. Manchester, M.A. Alatorre-Jimenez, R.J. Reiter, On the significance of an alternate pathway of melatonin synthesis via 5-methoxytryptamine: comparisons across species, J. Pineal Res. 61 (1) (2016) 27–40.
[18] R.J. Reiter, D.X. Tan, A. Galano, Melatonin: exceeding expectations, Physiology. 29 (5) (2014) 325–333.
[19] S. Loloei, M. Sepidarkish, A. Heydarian, N. Tahvilian, M. Khazdouz, J. Heshmati, et al., The effect of melatonin supplementation on lipid profile and anthropometric indices: a systematic review and meta-analysis of clinical trials, Diabetes Metabol. Syndr.: Clin. Res. Rev. 13 (3) (2019) 1901–1910.
[20] F.M. Delpino, L.M. Figueiredo, B.P. Nunes, Effects of melatonin supplementation on diabetes: a systematic review and meta-analysis of randomized clinical trials, Clinical Nutrition 40 (7) (2021) 4595–4605.
[21] E.K.P. Lee, P. Poon, C.P. Yu, V.W.Y. Lee, V.C.H. Chung, S.Y.S. Wong, Controlled-release oral melatonin supplementation for hypertension and nocturnal hypertension: a systematic review and meta-analysis, J. Clin. Hypertens. 24 (5) (2022) 529–535.
[22] N. Mesri Alamdari, R. Mahdavi, N. Roshanravan, N. Lotfi Yaghin, A.R. Ostadrahimi, E. Faramarzi, A double-blind, placebo-controlled trial related to the effects of melatonin on oxidative stress and inflammatory parameters of obese women, Horm. Metab. Res. 47 (7) (2015) 504–508.
[23] H. Pakravan, M. Ahmadian, A. Fani, D. Aghaee, S. Brumanad, B. Pakzad, The effects of melatonin in patients with nonalcoholic fatty liver disease: a randomized controlled trial, Adv. Biomed. Res. 6 (2017).
[24] C. Chojnacki, A. Kaczka, A. Gasiorowska, J. Fichna, J. Chojnacki, T. Brzozowski, The effect of long-term melatonin supplementation on psychosomatic disorders in postmenopausal women, J. Physiol. Pharmacol. 69 (2) (2018).
[25] S.J. Abood, W.K. Abdulsahib, S.A. Hussain, S.H. Ismail, Melatonin potentiates the therapeutic effects of metformin in women with metabolic syndrome, Sci. Pharm. 88 (2) (2020) 28.
[26] H. Bazyar, A. Zare Javid, H. Bavi Behbahani, F. Moradi, B. Moradi Poode, P. Amiri, Consumption of melatonin supplement improves cardiovascular disease risk factors and anthropometric indices in type 2 diabetes mellitus patients: a double-blind, randomized, placebo-controlled trial, Trials 22 (1) (2021) 231.
[27] M.R. Rezvanfar, G. Heshmati, A. Chehrei, F. Haghverdi, F. Rafiee, F. Rezvanfar, Effect of bedtime melatonin consumption on diabetes control and lipid profile, Int. J. Diabetes Dev. Ctries. 37 (2017) 74–77.
[28] A. Shabani, F. Foroozanfard, E. Kavossian, E. Aghadavod, V. Ostadmohammadi, R.J. Reiter, et al., Effects of melatonin administration on mental health parameters, metabolic and genetic profiles in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial, J. Affect. Disord. 250 (2019) 51–56.
[29] Kakhaki R. Daneshvar, V. Ostadmohammadi, E. Kouchaki, E. Aghadavod, F. Bahmani, O.R. Tamtaji, et al., Melatonin supplementation and the effects on clinical and metabolic status in Parkinson's disease: a randomized, double-blind, placebo-controlled trial, Clin. Neurol. Neurosurg. 195 (2020) 105878.
[30] V. Ostadmohammadi, A. Soleimani, F. Bahmani, E. Aghadavod, R. Ramezani, R.J. Reiter, et al., The effects of melatonin supplementation on parameters of mental health, glycemic control, markers of cardiometabolic risk, and oxidative stress in diabetic hemodialysis patients: a randomized, double-blind, placebo-controlled trial, J. Ren. Nutr. 30 (3) (2020) 242–250.
[31] F.M. Delpino, L.M. Figueiredo, Melatonin supplementation and anthropometric indicators of obesity: a systematic review and meta-analysis, Nutrition 91 (2021) 111399.
[32] M. Akbari, V. Ostadmohammadi, N. Mirhosseini, K.B. Lankarani, R. Tabrizi, Z. Keshtkaran, et al., The effects of melatonin supplementation on blood pressure in patients with metabolic disorders: a systematic review and meta-analysis of randomized controlled trials, J. Hum. Hypertens. 33 (3) (2019) 202–209.
[33] S.G. Hoseini, K. Heshmat-Ghahdarijani, S. Khosrawi, M. Garakyaraghi, D. Shafie, H. Roohafza, et al., Effect of melatonin supplementation on endothelial function in heart failure with reduced ejection fraction: a randomized, double-blinded clinical trial, Clin. Cardiol. 44 (9) (2021) 1263–1271.
[34] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Bmj 372 (2021).
[35] J.A.C. Sterne, J. Savović, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, et al., RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ (Clinical research ed) 366 (2019) l4898.
[36] R. DerSimonian, R. Kacker, Random-effects model for meta-analysis of clinical trials: an update, Contemp. Clin. Trials 28 (2) (2007) 105–114.
[37] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, P. Jüni, D. Moher, A.D. Oxman, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, Bmj 343 (2011).
[38] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, Bmj 327 (7414) (2003) 557–560.
[39] M. Egger, G.D. Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, Bmj 315 (7109) (1997) 629–634.
[40] C.B. Begg, M. Mazumdar, Operating characteristics of a rank correlation test for publication bias, Biometrics (1994) 1088–1101.

[41] M. Agahi, N. Akasheh, A. Ahmadvand, H. Akbari, F. Izadpanah, Effect of melatonin in reducing second-generation antipsychotic metabolic effects: a double blind controlled clinical trial, Diabetes Metabol. Syndr.: Clin. Res. Rev. 12 (1) (2018) 9–15.
[42] M. Jamilian, F. Foroozanfard, N. Mirhosseini, E. Kavossian, E. Aghadavod, F. Bahmani, et al., Effects of melatonin supplementation on hormonal, inflammatory, genetic, and oxidative stress parameters in women with polycystic ovary syndrome, Front. Endocrinol. 10 (2019) 273.
[43] A. Modabbernia, P. Heidari, R. Soleimani, A. Sobhani, Z.A. Roshan, S. Taslimi, et al., Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study, J. Psychiatr. Res. 53 (2014) 133–140.
[44] S. Mohammadi, R. Rastmanesh, F. Jahangir, Z. Amiri, K. Djafarian, M.A. Mohsenpour, et al., Melatonin supplementation and anthropometric indices: a randomized double-blind controlled clinical trial, BioMed Res. Int. 2021 (2021) 3502325.
[45] R. Mousavi, M. Alizadeh, M. Asghari Jafarabadi, L. Heidari, R. Nikbakht, H. Babaahmadi Rezaei, et al., Effects of melatonin and/or Magnesium supplementation on biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial, Biol. Trace Elem. Res. 200 (3) (2022) 1010–1019.
[46] F. Raygan, V. Ostadmohammadi, F. Bahmani, R.J. Reiter, Z. Asemi, Melatonin administration lowers biomarkers of oxidative stress and cardio-metabolic risk in type 2 diabetic patients with coronary heart disease: a randomized, double-blind, placebo-controlled trial, Clinical Nutrition 38 (1) (2019) 191–196.
[47] M.P. Kotlarczyk, H.C. Lassila, C.K. O'Neil, F. D'Amico, L.T. Enderby, P.A. Witt-Enderby, 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, J. Pineal Res. 52 (4) (2012) 414–426.
[48] A. Goyal, P.D. Terry, H.M. Superak, C.L. Nell-Dybdahl, R. Chowdhury, L.S. Phillips, et al., Melatonin supplementation to treat the metabolic syndrome: a randomized controlled trial, Diabetol. Metab. Syndrome 6 (1) (2014) 1–11.
[49] F.F. Rahbari-Oskoui, J.L. Abramson, A.M. Bruckman, A.B. Chapman, G.A. Cotsonis, S.A. Johnson, et al., Nighttime administration of high-dose, sustained-release melatonin does not decrease nocturnal blood pressure in African-American patients: results from a preliminary randomized, crossover trial, Complement Ther Med 43 (2019) 157–164.
[50] F.A. Scheer, G.A. Van Montfrans, E.J. van Someren, G. Mairuhu, R.M. Buijs, Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension, Hypertension 43 (2) (2004) 192–197.
[51] T. Rechciński, E. Trzos, K. Wierzbowska-Drabik, M. Krzemińska-Pakuła, M. Kurpesa, Melatonin for nondippers with coronary artery disease: assessment of blood pressure profile and heart rate variability, Hypertens. Res. 33 (1) (2010) 56–61.
[52] C. Chojnacki, E. Walecka-Kapica, G. Klupinska, M. Pawlowicz, A. Blonska, J. Chojnacki, Effects of fluoxetine and melatonin on mood, sleep quality and body mass index in postmenopausal women, J. Physiol. Pharmacol. 66 (5) (2015) 665–671.
[53] E. Grossman, M. Laudon, R. Yalcin, H. Zengil, E. Peleg, Y. Sharabi, et al., Melatonin reduces night blood pressure in patients with nocturnal hypertension, Am. J. Med. 119 (10) (2006) 898–902.
[54] R. D'Anna, A. Santamaria, G. Giorgianni, A. Vaiarelli, G. Gullo, F. Di Bari, et al., Myo-inositol and melatonin in the menopausal transition, Gynecol. Endocrinol. 33 (4) (2017) 279–282.
[55] P. Lusardi, E. Piazza, R. Fogari, Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study, Br. J. Clin. Pharmacol. 49 (5) (2000) 423–427.
[56] D. Nunes, R. Mota, M. Machado, E. Pereira, V. De Bruin, P. De Bruin, Effect of melatonin administration on subjective sleep quality in chronic obstructive pulmonary disease, Braz. J. Med. Biol. Res. 41 (2008) 926–931.
[57] Y. Kim, H.T. Kang, D.C. Lee, Melatonin supplementation for six weeks had No effect on arterial stiffness and mitochondrial dna in women aged 55 Years and older with insomnia: a double-blind randomized controlled study, Int J Environ Res Public Health 18 (5) (2021).
[58] F. Romo-Nava, D. Alvarez-Icaza González, A. Fresán-Orellana, R. Saracco Alvarez, C. Becerra-Palars, J. Moreno, et al., Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial, Bipolar Disord. 16 (4) (2014) 410–421.
[59] TdSMd Farias, M.M. Cruz, RCdCd Sa, I. Severi, J. Perugini, M. Senzacqua, et al., Melatonin supplementation decreases hypertrophic obesity and inflammation induced by high-fat diet in mice, Front. Endocrinol. 10 (2019) 750.
[60] Y.-T. Tung, P.-C. Chiang, Y.-L. Chen, Y.-W. Chien, Effects of melatonin on lipid metabolism and circulating irisin in sprague-dawley rats with diet-induced obesity, Molecules 25 (15) (2020) 3329.
[61] A. Hadi, E. Ghaedi, S. Moradi, M. Pourmasoumi, A. Ghavami, M. Kafeshani, Effects of melatonin supplementation on blood pressure: a systematic review and meta-analysis of randomized controlled trials, Horm. Metab. Res. 51 (3) (2019) 157–164.
[62] C. Franco, E. Sciatti, G. Favero, F. Bonomini, E. Vizzardi, R. Rezzani, Essential hypertension and oxidative stress: novel future perspectives, Int. J. Mol. Sci. 23 (22) (2022) 14489.
[63] X. Zhang, Y. Zheng, Z. Wang, J. Gan, B. Yu, B. Lu, et al., Melatonin as a therapeutic agent for alleviating endothelial dysfunction in cardiovascular diseases: emphasis on oxidative stress, Biomed. Pharmacother. 167 (2023) 115475.
[64] L. Paulis, F. Šimko, Blood pressure modulation and cardiovascular protection by melatonin: potential mechanisms behind, Physiol. Res. 56 (6) (2007).