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Effects of Melatonin Supplementation On Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Melatonin is a physiological indoleamine secreted from the pineal gland into the bloodstream. This hormone has antioxidant effects in cardiovascular disease, but the evidence regarding its effects on blood pressure (BP) has not been conclusive. Therefore, we assessed the impact of melatonin supplementation on systolic BP (SBP) and diastolic BP (DBP) through a systematic review and meta—analysis of available randomized controlled trials (RCTs). Medline, Scopus, Web of Science, Cochrane library, and Google scholar (until May 2018) were searched to identify potential RCTs with information on melatonin supplementation and BP. Mean Differences (MD) were pooled using a random-effects model. Standard methods were used for assessment of heterogeneity, sensitivity analysis, and publication bias. Pooling 5 RCTs (6 treatment arms) together identified significant reduction for SBP (MD: − 3.43 mmHg, 95 % confidence interval (CI): − 5.76 to − 1.09, p = 0.004) and DBP (MD: − 3.33 mmHg, 95 % CI: − 4.57 to − 2.08, p < 0.001) after supplementation with melatonin compared with control treatment. The sensitivity analysis indicated that the results were robust. We did not observe any evidence regarding publication bias. The findings of this meta-analysis support the overall favorable effect of melatonin supplementation on BP regulation.

Introduction

High blood pressure (BP) is known as one of the most common public health challenges to all nations [1]. The prevalence of this problem has been increasing throughout the world and unfortunately, the actual number of people with high BP is estimated to reach over 1.5 billion by the year 2050 [2, 3]. Accumulating evidence has shown that high BP is closely related to a rise in the risk of some chronic diseases namely coronary heart disease, stroke, and renal failures [4, 5]. Thus, if left unchecked, it will have huge implications for population health and for health services expenditure. As a re-

sult, the adoption of appropriate strategies for dealing with high BP is important for any society.

Although pharmacological interventions and lifestyle modifications, in particular, dietary management, are the general approaches for control and treatment of high BP, long-term consumption of synthetic agents exert different adverse side effects, and also compliance to lifestyle changes is difficult to be achieved [6–8]. Considering the aforementioned drawbacks, at present, identifying the new strategies like complementary agents with antihypertensive properties has attracted a lot of interest.

Melatonin (N-acetyl-5-methoxytryptamine), discovered by Aaron Lerner, is a multifunctional hormone, which is mostly known for its involvement in the regulation of circadian rhythm of sleep and wakefulness [9, 10]. This hormone is produced both by plants and animals. In humans, melatonin is synthesized in multiple cells and organs. Nevertheless, the circulating melatonin level is predominantly provided by the pineal gland [10, 11]. Pineal melatonin synthesis/secretion is stimulated by darkness and inhibited by exposure to light [12]. Intervention studies reported that melatonin can improve lipid profile [13], glycemic status [14], immune system function [15], anti-oxidative status [16], and inflammatory parameters [17]. In addition, some studies introduced melatonin as a potential BP regulator [18–20]. Randomized controlled trials (RCTs), which investigated the effects of melatonin supplementation on BP led to inconsistent results. Some investigations have shown the beneficial effects of melatonin supplementation on BP [18, 20], but others failed to find any considerable effects [19, 21]. Therefore, recommending melatonin as a complementary therapy for BP management remained unclear.

According to our search in databases, no study has been published trying to summarize the BP-lowering effects of melatonin supplementation. So, the ultimate goal of this meta-analysis was to determine whether melatonin supplementation could be recommended as a public health policy to improve BP.

Materials and Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [22] in the setting up and report of present meta-analysis, as much as possible (available as checklist in Supporting Information). The protocol was also submitted and approved in the international prospective register of systematic reviews database (PROSPERO) under registration number (CRD42018097196).

Search strategy

A systematic and comprehensive search of the Medline (http://www.ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), ISI Web of Science (http://www.webofscience.com), Google Scholar (http://scholar.google.com), and the Cochrane library (http://www.cochranelibrary.com) was conducted using the following search terms: ("Melatonin" OR "N-acetyl-5-methoxytryptamine") AND ("blood pressure" OR "systolic blood pressure" OR "SBP" OR "diastolic blood pressure" OR "DBP" OR "hypertension") AND ("Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomized" OR "random" OR "randomly" OR "placebo" OR "assignment"). Whenever possible, Medical Subject Headings (MESH) terms were used. This search was restricted to studies published in the English language from inception to May 15, 2018. Electronic database searches were completed along with reference list and citation hand searches. The research work was done by 2 authors (AH and MK) independently and in duplicate. Any disagreement in this regard was resolved by face to face discussion.

Study selection

First, electronic and manual search results were exported to EndNote software, version X6 (Thomson Reuters) and duplicate publications were removed. Then, 2 investigators selected eligible articles separately by reading title, abstract, and where required the full-text version of remaining publications. Finally, all human RCTs (either parallel or cross-over designs) that examined the effects of melatonin supplementation on blood pressure in adults (age ≥ 18-year old) were included. Studies were excluded if they were: (1) RCTs with treatment duration less than 2 weeks and (2) studies without an appropriate control group. To keep away from overlapping, we included studies with larger participants. Disagreements regarding the study selection process were resolved by discussion with the third researcher (SM).

Data extraction

The following data were extracted from the full-text of included studies using a pre-designed abstraction form: first author's specification, publication year, location of the study, study design and blinding, total sample size, dose of melatonin and placebo, study duration, patient characteristics [age, gender, body mass index (BMI) and diseases] and the final result of systolic BP (SBP)/diastolic BP (DBP) comparisons. When the data were reported at multiple measurements, only the outcomes at the end of the intervention were included in the analysis. In cases of lack of relevant data, we contacted the corresponding authors via e-mail to get their help. The whole process of data extraction was undertaken independently by 2 investigators (AH and MK) to minimize potential error. If there was a disagreement, it was resolved by consensus.

Quality assessment of studies

The methodological quality of the eligible studies was assessed using the Cochrane Collaboration's tool based on the following criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), separated for blinding of participants and personnel and blinding of outcome assessment, incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Each domain was classified in 3 categories: low risk of bias, high risk of bias, and unclear risk of bias. According to the mentioned domains, the overall quality of individual study was considered as good (low risk for more than 2 item), fair (low risk for 2 item), and weak (low risk for less than 2 item) [23]. This section was also independently accomplished by 2 researchers (AH and MK). Final scores were discussed by the investigators to make a consensus.

Statistical analysis

All analyses were performed using STATA software version 12 (STATA corp, College Station, TX, USA). The mean difference (MD)

and the standard deviation (SD) of the SBP and DBP (in mmHg) between the intervention and control groups were applied to calculate overall effect size. In studies in which mean change was not directly reported in intervention and control groups, it was calculated by the minus of the post-intervention data from the baseline value. Besides, if only SD for the baseline and final values were provided, the SD for the net changes were imputed according to the method of Follmann et al. using a correlation coefficient of 0.5 [24]. Due to the fact that included RCTs were carried out in different settings, random-effect models were used to conduct all meta-analyses. The heterogeneity between studies was examined by the I-squared (I^2) index. The level of heterogeneity across studies was rated as low, moderate or high corresponding to I^2 value of 0–30 %, more than 30–60 %, and more than 60 %, respectively [25]. We conducted subgroup analysis according to the type of disease (psychotic or metabolic disorders) to assess the impact of this variable on outcomes. Rather, sensitivity analyses were performed, to explore the extent to which inferences might depend on a particular study or group of studies. We also assessed publication bias by 2 formal tests, the Begg—adjusted rank correlation test and the Egger's regression asymmetry test [26, 27]. A p-value <0.05 was accepted as statistically significant, unless otherwise specified.

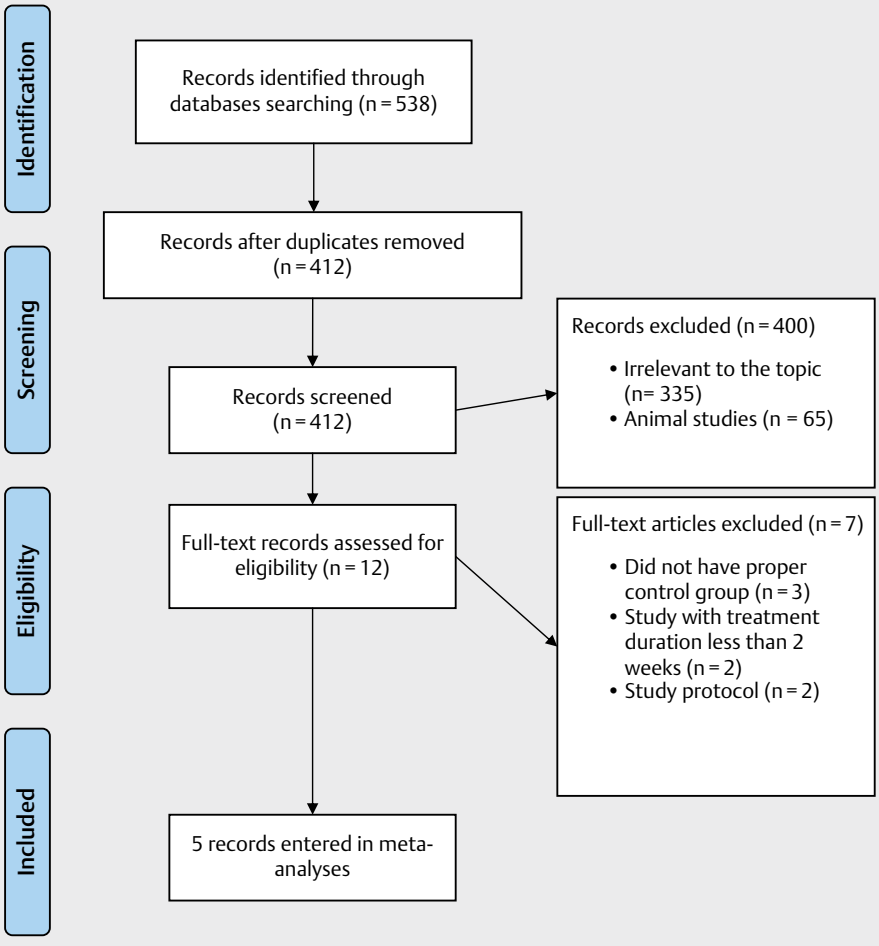
Results

Selection and identification of studies

Among the initial 538 publications that were obtained by electronic and manual search (126 duplicates), 400 were excluded because they were unrelated to present meta-analysis according to our inclusion criteria. After reading the full text of the remaining 12 papers, 7 studies were further excluded for the following reasons: the studies with lack of a true control group (n = 3), melatonin supplement was administrated less than 2 weeks (n = 2) and they were studying protocol (n = 2). In total, 5 eligible RCTs [18–20, 28, 29] with 6 treatment arms were included in our final analysis. A flow chart of the systematic search and study selection process is presented in ▶ **Fig. 1**.

Characteristics of studies

▶ **Table 1** describes the main characteristics of studies included in the present meta-analysis. Overall, 6 effect sizes were extracted from 5 RCTs including 340 participants, 168 subjects in the melatonin group, and 172 in the control group. The mean age of participants in these studies ranged from 29 to 66 years old. Most of the RCTs adopted a parallel study design, whereas only one RCT [18] used a crossover design. These studies were published between



▶ **Fig. 1** PRISMA flow diagram of study selection process.

▲ **Table 1** Characteristics of included trials.

First author (publication year)	Country	Sample size (M/F)	Target population	Mean age (years)	Mean BMI (kg/m²)	RCT design (Blinding)	Duration (weeks)	Intervention	Comparison	Main results
Romo-Nava et al. a (2014)	Mexico	28 (14/14)	Schizophrenia or bipolar disorder (medium risk)	29	26	Parallel (Double)	8	Melatonin (5 mg/d)	Placebo (NR)	Significant reduction was observed in the level of DBP
Romo-Nava et al. b (2014)	Mexico	16 (8/8)	Schizophrenia or bipolar disorder (high risk)	28	27	Parallel (Double)	8	Melatonin (5 mg/d)	Placebo (NR)	Significant reduction was observed in the level of DBP
Goyal et al. (2014)	USA	39 (17/22)	Metabolic syndrome	60	35	Crossover, (Double)	10	Melatonin (8 mg/d)	Placebo (NR)	Significant reduction was observed in the level of SBP
Pakravan et al. (2017)	Iran	97 (60/37)	NAFLD	42	30	Parallel (Double)	6	Melatonin (6 mg/d)	Placebo (NR)	Significant reduction was observed in the level of DBP
Agahi et al. (2017)	Iran	100 (51/49)	patients taking atypical antipsychotics	37	28	Parallel (Double)	8	Melatonin (3 mg/d)	Placebo (NR)	Significant reduction was observed in the level of SBP
Raygan et al. (2017)	Iran	60 (27/33)	T2DM patients with coronary heart disease	66	30	Parallel (Double)	12	Melatonin (10 mg/d)	Placebo (paraffin)	Significant reduction was observed in the levels of SBP and DBP

RCT: Randomized controlled trial; NAFLD: Nonalcoholic fatty liver disease; T2DM: Type 2 diabetes mellitus; NR: Not reported; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

2014 and 2017 and were conducted in Iran [19, 20, 28], Mexico [29], and USA [18]. Melatonin dosing ranged from 3 to 10 mg/day. The duration of intervention also varied from 6 to 12 weeks. Three studies enrolled participants with metabolic impairment including nonalcoholic fatty liver disease (NAFLD) [19], metabolic syndrome [18], and type 2 diabetes mellitus (T2DM) patients with coronary heart disease [20], while, the other studies enrolled participants with neurological impairment including schizophrenia or bipolar disorder [29] and patients taking second-generation antipsychotics (SGA) [28]. The baseline BMI of the participants indicated that all the trials examined overweight and obese participants (BMI > 25 kg/m²).

▶ **Table 2** describes risk of bias assessment based on different quality domains using Cochrane collaboration tool. After evaluating the quality of included studies all of them were classified as good quality. All trials present enough information of sequence generation and allocation concealment. Furthermore, the blinding of participants and staff personnel was adequate in all studies. Of 5 trials, 4 studies [18–20, 29] showed low/unclear risk of bias based on incomplete outcome data, selective outcome reporting and other biases.

Effect of melatonin supplementation on blood pressure

Forest plots summarizing the efficacy of melatonin supplementation on SBP and DBP are shown in ▶ **Fig. 2** and **3**, respectively. Pooling 5 RCTs (6 treatment arms) together identified significant reduction for SBP [MD: −3.43 mmHg, 95 % confidence interval (CI): −5.76 to −1.09, p = 0.004] after melatonin supplementation than placebo consumption. A significant reduction of DBP (MD: −3.33 mmHg, 95 % CI: −4.57 to −2.08, p < 0.001) was also observed after melatonin supplement treatment relative to the placebo. The inter-study heterogeneity was low for SBP (I^2 = 22.3 %) and DBP (I^2 = 0.0 %).

Subgroup analysis

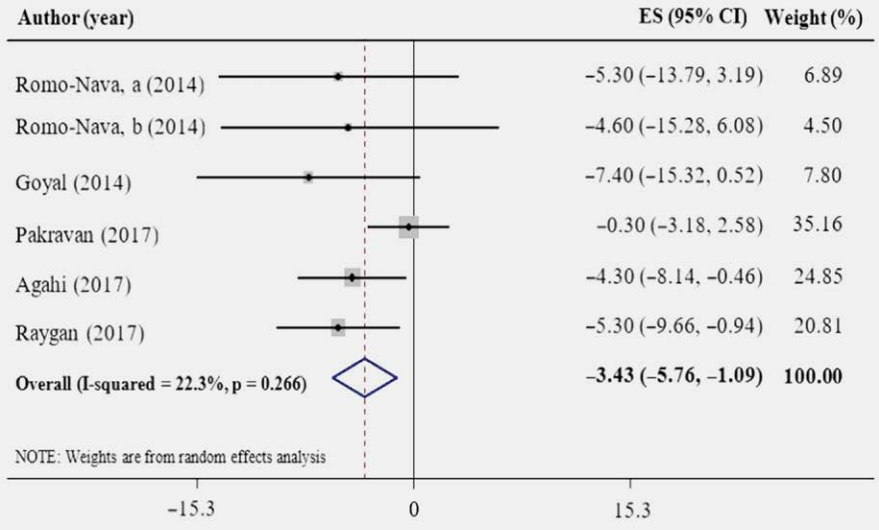
To better explain the BP-lowering effects of melatonin, we performed subgroup analysis. Despite the current reports in the literature that BP is higher in men than in women at similar ages [30, 31], the subgroup analysis by gender of patients cannot be conducted since all of the included RCTs have enrolled both genders of participants concomitantly. In addition, due to the small number of eligible RCTs, subgroup analysis was carried out only based on the type of disease (psychotic vs. metabolic disorders). Totally, the subgroup analysis results revealed that SBP levels reduced in patients with psychotic disorders (MD: −4.48 mmHg, 95 % CI: −7.81 to −1.16), whereas this reduction was not significant in RCTs including patients with metabolic disorders (MD: −3.47 mmHg, 95 % CI: −7.82 to 0.87) (▶ **Fig. 4**). Besides, our finding indicated that DBP reduction in patients with psychotic disorders (MD: −4.29 mmHg, 95 % CI: −7.35 to −1.24) was more than patients with metabolic disorders (MD: −3.10 mmHg, 95 % CI: −4.57 to −1.63) (▶ **Fig. 5**).

Sensitivity analysis

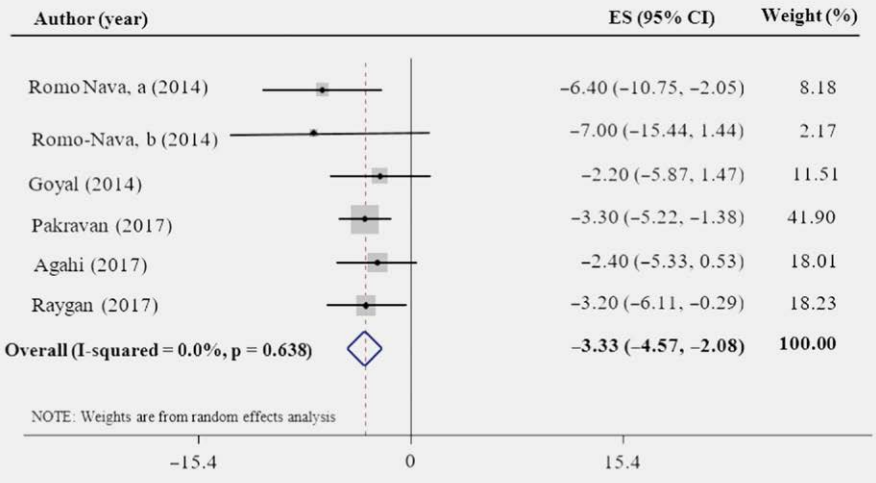
Effect sizes for the influence of melatonin supplement on SBP and DBP were robust in the sensitivity analysis, suggesting that omission of each RCT did not have a significant effect on the results. Pooled estimates ranged from −2.96 to −5.04 mmHg and −3.05 to −3.53 mmHg for SBP and DBP, respectively, and remained statistically significant in all cases.

▶ **Table 2** Quality assessment of included studies based on Cochrane guidelines.

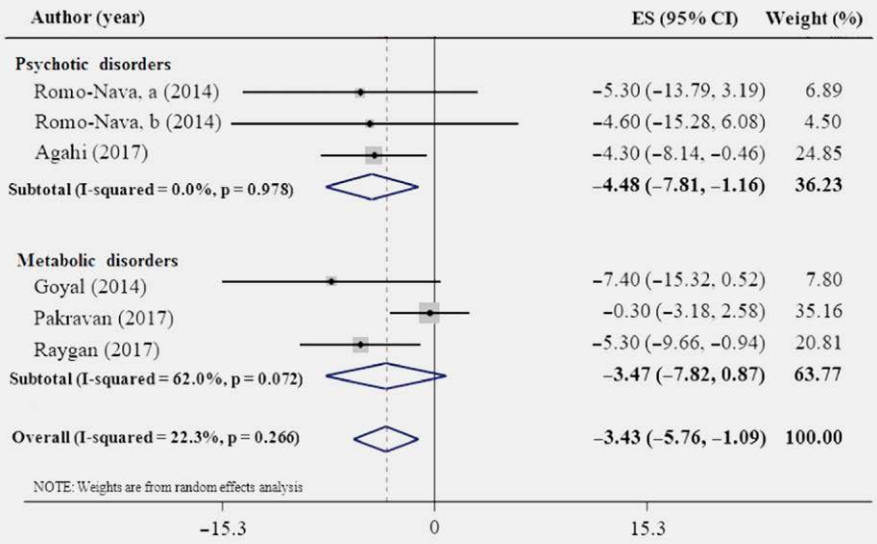
Study	Random sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Score	Overall quality
Romo-Nava (2014)	+	+	+	+	?	+	5	Good
Goyal (2017)	+	+	+	+	?	+	5	Good
Pakravan (2017)	+	+	+	+	?	+	5	Good
Agahi (2017)	+	+	+	-	?	+	4	Good
Raygan (2017)	+	+	+	+	?	+	5	Good



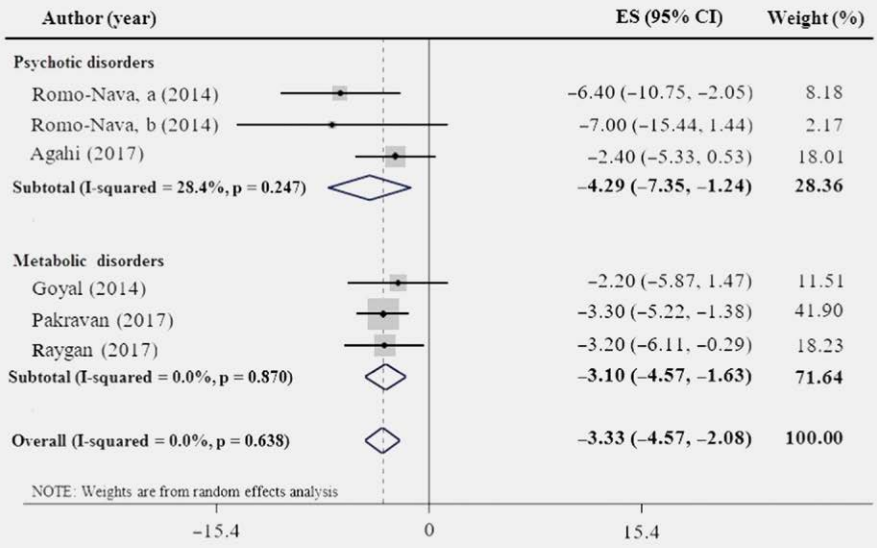
▶ **Fig. 2** Forest plot of the effect of melatonin supplementation on SBP.



▶ **Fig. 3** Forest plot of the effect of melatonin supplementation on DBP.



▶ **Fig. 4** Forest plot of the effect of melatonin supplementation on SBP in the subsets of trials with psychotic and metabolic disorders.



▶ **Fig. 5** Forest plot of the effect of melatonin supplementation on DBP in the subsets of trials with psychotic and metabolic disorders.

Publication bias

Begg's rank correlation and Egger's weighted regression tests were performed to explore the publication bias. The results of Begg's test indicated no publication bias for SBP (p = 0.851) and DBP (p = 0.573). Moreover, the results of Egger's test showed no publication bias for SBP (p = 0.139) and DBP (p = 0.276).

Discussion

Analysis of data from 5 eligible studies (6 treatment arms) showed significant reductions in both SBP (− 3.43 mm Hg) and DBP (− 3.33 mm Hg) after supplementation with melatonin. Our results are inconsistent with the findings of the previous analysis, which reported that exogenous melatonin prescription has no significant effect on nocturnal BP [32]. Although the observed reduction in BP following supplementation with melatonin is small, even a slight reduction of BP at population level can have important clinical health-related outcomes [33].

When the studies were stratified according to their type of patients, SBP-lowering effects of melatonin only in the subset of trials, which enroll patients with psychotic disorders were significant. Moreover, DBP reduction in the subset of psychotic disorders was greater than a subset of metabolic disorders. Overall, the subgroup analysis revealed that patients with psychotic disorders were more susceptible to the antihypertensive effect of melatonin; a result which is not only interesting but also important to emphasize. As

we know, these patients usually take atypical antipsychotic drugs [28, 29]. Preclinical studies reported that this type of antipsychotics drugs may reduce the levels of circulating melatonin [34, 35]. So, it makes sense to record bigger changes in SBP/DBP levels than in a metabolic disorders group.

There are some proposed mechanisms of action of melatonin, which could help explain our findings. Generally, melatonin secretion from the pineal gland is controlled by the suprachiasmatic nucleus (SCN) [36]. There are high-affinity receptors for melatonin in the SCN so it gives feedback via these receptors and influences the rhythm of its own construction and other circadian rhythms. Melatonin increases circadian rhythms via the central pacemaker directly in the night [37]. Recent investigations have shown troubled circadian pacemaker function and day-night rhythms in essential hypertension. Also, it was found in one study that the amounts of 3 chief SCN-neurotransmitters are lessened by more than 50 % in these patients [38]. The SCN affects the autonomic output to the heart system, thus changing the function of the SCN by melatonin is one of the possible mechanism that it can influence on regulation of BP [39]. Another possible explanation for this is that melatonin suppresses sympathetic nervous system and decreases plasma levels of norepinephrine and dopamine so the effect of melatonin on BP may be intermediated by the autonomic nervous system [40]. Experimental studies also provide evidence for an anti-inflammatory action via inhibition of cyclooxygenase-2 (COX-2) enzyme, scavenging of free radicals and activation of antioxidant defense enzymes, an increase in nitric oxide (NO) production and reduce great artery resistance to blood flow, thereby contributing to protection against vascular endothelial damage and vasoconstriction [41–43].

Melatonin has been supplemented in a wide range of doses in human and animal investigations, and there is an extensive agreement regarding its non-toxicity [44]. A major concern in using a high dose of melatonin is related to its adverse effects on skin color. However, Raygan et al. [20] reported that a maximum dose of 10 g/day of melatonin is well tolerated and shows no adverse effects.

Some issues in the current meta-analysis diminish the generalizability of our findings. First and most notable, collective sample size of the analysis was relatively small, albeit enough for detecting significant results. Thus, further studies with broader sample sizes are highly recommended. Second, in all studies included, no information was reported regarding the statistical adjustments for confounding factors such as serum and/or urinary melatonin levels, dietary melatonin intake and seasonal information. Third, RCTs included in our meta-analysis were represented with different chronic conditions, intervention doses and study durations, which might potentially skew the data. Fourth, we were unable to evaluate the dose-response relation between supplementation and BP parameters due to the low number of studies included. Lastly, most studies were not primarily designed to assess the effects of melatonin on BP level. The strength of the current study was the existence of low heterogeneity for both SBP and DBP indices as shown by the I^2 index. Besides, the quality of all studies was high and all of them adequately explained the randomization and blinding procedures. In addition, we tried to minimize any biases in the review process by performing a comprehensive search of the literature and also by conducting and reporting the review by adhering to the PRISMA guidelines.

Conclusions

In summary, an implication of this meta-analysis is the possibility that melatonin therapy may be a new strategy in the treatment of essential hypertension. However, more precise clinical trial investigation on this topic will need to be undertaken.

Authors Contribution

AH and MK carried out the concept, design, and drafting of this study. AH, MK, and SM searched databases, screened articles and extracted data. AH and AGH performed the acquisition, analysis, and interpretation of data. AH and MK critically revised the manuscript. All authors approved the final version of the manuscript. AH and MK are the guarantors of this study.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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