Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1901–1910

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

The effect of melatonin supplementation on lipid profile and anthropometric indices: A systematic review and meta-analysis of clinical trials

Saba Loloei [a], Mahdi Sepidarkish [b], Azadeh Heydarian [c], Negin Tahvilian [c], Maryam Khazdouz [c], Javad Heshmati [d], Hamed Pouraram [a,*]

[a] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Biostatistics and Epidemiology, Babol University of Medical Sciences, Babol, Iran
[c] Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Iran
[d] Department of Nutritional Science, School of Nutritional Science and Food Technology, Kermanshah University of Medical Sciences, Kermanshah, Iran

ARTICLE INFO

Article history:
Received 12 April 2019
Accepted 22 April 2019

Keywords:
Melatonin
Cholesterol
LDL
Cholesterol
HDL
Cholesterol
Body mass index
Body weight

ABSTRACT

Background: Epidemiological evidence suggests that melatonin has some effects on the serum lipid. However, these results are controversial. The aim of this systematic review and meta-analysis is to examine the effect of melatonin supplement on dyslipidemia and anthropometric indices.
Methods: We searched electronic databases including Medline, Embase, Scopus, Web of Science and Cochrane Library up to Des 2018 without any language restriction. To compare the effects of melatonin with placebo, differences in standardized means difference (SMD) with 95% confidence intervals (95% CI) were pooled using random effects model.
Results: Twelve trials including 641 participants included in meta-analysis finally. The dose of melatonin was reported at 0.8–30 mg. Comparing with the control group, melatonin may improve low density lipoprotein cholesterol (LDL-C) (−0.31 mmol/L, 95% CI (−0.61, 0.01), P = 0.049, I2 = 42%) and triglyceride (TG) level (SMD = −0.45 mmol/L; 95% CI, −0.77, −0.13, P = 0.006, I2 = 47%). No significant effect of melatonin on high density lipoprotein cholesterol (HDL-C) and anthropometric indices was found.
Conclusions: The results of our systematic review and Meta-analyzes showed that supplementation of melatonin could be effective in improving lipid parameters and should be considered in the prevention of cardiovascular disease, although the effect of this supplement on anthropometric indices needs further investigation.

1. Introduction

The prevalence of obesity, diabetes and dyslipidemia is rising dramatically in worldwide with lifestyle changes over the past decade [1]. Dyslipidemia plays an important role in the development of http://www.scialert.net/asci/result.php?searchin=Keywords&cat=&ascicat=ALL&Submit=Search&keyword=cardiovascular+disease (cardiovascular disease)">cardiovascular diseases via alteration of the structure of membranes and exacerbation of atherosclerosis [2]. Both obesity and dyslipidemia have an important role in development and aggravation of inflammatory state and subsequently lead to other health problems like; fatty liver disease, cardiovascular disease, hypertension and cancer ([3–5]). Altered lipid homeostasis, generation of lipid metabolites, pro-inflammatory cytokines secretion and imbalance between anti-inflammatory and inflammatory factors are the possible mechanisms involved in relation to raised adipose tissue, obesity and obesity associated metabolic dysfunctions [6]. Yet, previous strategies to treatment or decrease of obesity and associated problems such as dyslipidemia have not been effective [7], therefore, antioxidant supplementation together with other interventions such as calorie restriction, modification of lifestyle and drug therapy may be beneficial in management of obesity, dyslipidemia and related inflammation state [8,9].

Melatonin (*N*-acetyl-5-methoxytryptamine) is an endogenous hormone that is primarily produced and secreted by the pineal

* Corresponding authorDepartment of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, No: 44 Hojjatdost Alley, Naderi St., Keshavarz Blvd, Tehran, Iran.
E-mail address: h-pouraram@tums.ac.ir (H. Pouraram).

https://doi.org/10.1016/j.dsx.2019.04.043
1871-4021/

gland in human and animals [10]. Melatonin as endogenous synchronizer participates in the regulation of seasonal, the light-dark cycle as well as circadian rhythm [11]. Melatonin is also involved in many other biological functions [12]. Some of them are related in the receptors activation while others are produced due to antioxidant effects of melatonin [13]. Various studies have demonstrated that melatonin is an important antioxidant hormone that has got the roles in increasing of antioxidant enzymes activity like superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (3). Also, it is effective in reduction of oxidative stress injuries [14]. In an additional melatonin has been shown to play role in energy balance [15] and blood pressure control [16], hyperglycemia, body weight [13] and regulation of dyslipidemia [15,17]. Previous studies have shown that treatment with melatonin reduced TG and LDL-C levels and elevated HDL-C levels in human [18,19] and animals [15,20]. Melatonin has been involved in metabolism of cholesterol, inhibition of cholesterol absorption, biosynthesis [17] and increase of cholesterol catabolism [21]. Therefore melatonin has been suggested for regulation of dyslipidemia [19]. Moreover, melatonin administration reduces visceral obesity and limits weight gain [22]. Also, reduced circulating levels of melatonin were observed in patients with dyslipidemia [23,24] and obesity [25]. It has been demonstrated that melatonin plays role in etiology of dyslipidemia and obesity; however, as yet, no systematic review and meta-analysis has been published in considering of melatonin beneficial effects in anthropometric indices and lipid profile, so we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) involve the using melatonin in the regulation of dyslipidemia and anthropometric indices.

2. Methods

The design of this systematic review and meta-analysis has been prepared according to the guidelines of the 2015 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2015) statement [26]. Furthermore, reports of the number of included and excluded primary studies in the different stages of current systematic review have been presented using PRISMA flow chart.

2.1. Search strategy

Online databases Medline, Embase, Scopus, Web of Science and Cochrane Library were systematically searched for identification all the relevant RCTs of melatonin supplementation in anthropometric and lipid profile indices using the following key search terms: intervention (“Melatonin” OR “Pineal hormone”) and outcomes [“Waist circumference” OR “High density lipoproteins (HDL)” OR “Triglycerides (TG)”] AND (“Randomized controlled trial”). The reference list of all the included relevant articles manually investigated to find additional eligible studies. Searching electronic bibliographic databases for this systematic review was carried out by two independent reviewers (MS and JH) from 1990 to 2018. Our complete search strategy detail available in supplementary file s1. Our literature search was conducted without language restriction.

2.2. Eligibility criteria

Potentially relevant studies were selected by two independent researches (S.L. and H.P.) according to the inclusion/exclusion criteria. Primary studies in this systematic review were included based on the following inclusion criteria [1]: being a randomized, placebo-controlled trial at least single blind with either parallel or cross-over design [2], assessing the impact of melatonin supplementation compared to placebo group [3], participants aged 18 years or older [4], reporting sufficient data of outcome measures at baseline and at the end of follow-up in both intervention and control group or providing the net change values. While, original studies were excluded if they were [1]: observational studies (cross-sectional, case–control and cohort) [2], melatonin supplementation in combined with multivitamins, minerals and other substances [3], experimental studies in animals or in vitro [4], trials with no report of the exact amounts of desired variables.

2.3. Data extraction

In order to data extraction from all the eligible studies, a standardized electronic abstraction form was designed by principal investigator. Data extraction process was conducted by independently two authors based on the following characteristics, including: author, year of publication, location, study design, design details, daily dose of supplemental melatonin, duration of intervention, participant's age, participant's gender, and number of participants in the intervention and control groups.

2.4. Quality assessment

Risk of bias tool using criteria as outlined in the Cochrane Handbook for Systematic Reviews of Interventions were applied to assess methodological quality ([27]). The following criteria were investigated by two independent reviewers (M.S. and J.H.) for each included study [1]: Sequence generation [2], Allocation concealment [3], Blinding of participants and personnel [4], Blinding of outcome assessment [5] Incomplete outcome data [6], Selective outcome reporting [7], Other potential sources of biases. Any disagreement in the process of quality assessment was resolved by discussion and/or consultation with a third researcher (S.L.).

2.5. Statistical analysis

The mean change (standard deviation) in body weight, body mass index (BMI), WC, HDL-C, LDL-C and TG from baseline was used to calculate the mean difference between the melatonin and the placebo groups. The effect size was measured as SMD and 95% confidence intervals (CI). A separate random-effects model was constructed for each outcome using the DerSimonian–Laird weighting method, which incorporates between-study variability into the calculations. The results of the included studies were tested for statistical heterogeneity by visual inspection of forest plots, by performing the Chi2 test (assessing the P-value) and by calculating the I2 statistic. Statistical heterogeneity was considered substantial if the P-value was less than 0.10 or I2 value exceeded 50%. The statistical analyses were performed using RevMan 5.3 (2008).

3. Results

3.1. Study selection

After removal of duplicates, the initial literature search identified 1339 unique relevant articles (167 from Medline, 1007 from Embase, 426 from Scopus, 7 from Cochrane and 120 from Web of Science). Following screening of titles and abstracts, we reviewed the full text of 114 articles and 12 trials included in meta-analysis finally (Fig. 1).

3.2. Study characteristics

The characteristics of included trials are shown in Table 1. Trials conducted between 2000 and 2018. One was undertaken in United States, three in Poland, four in Iran, one in Italy, one in Iraq, one in

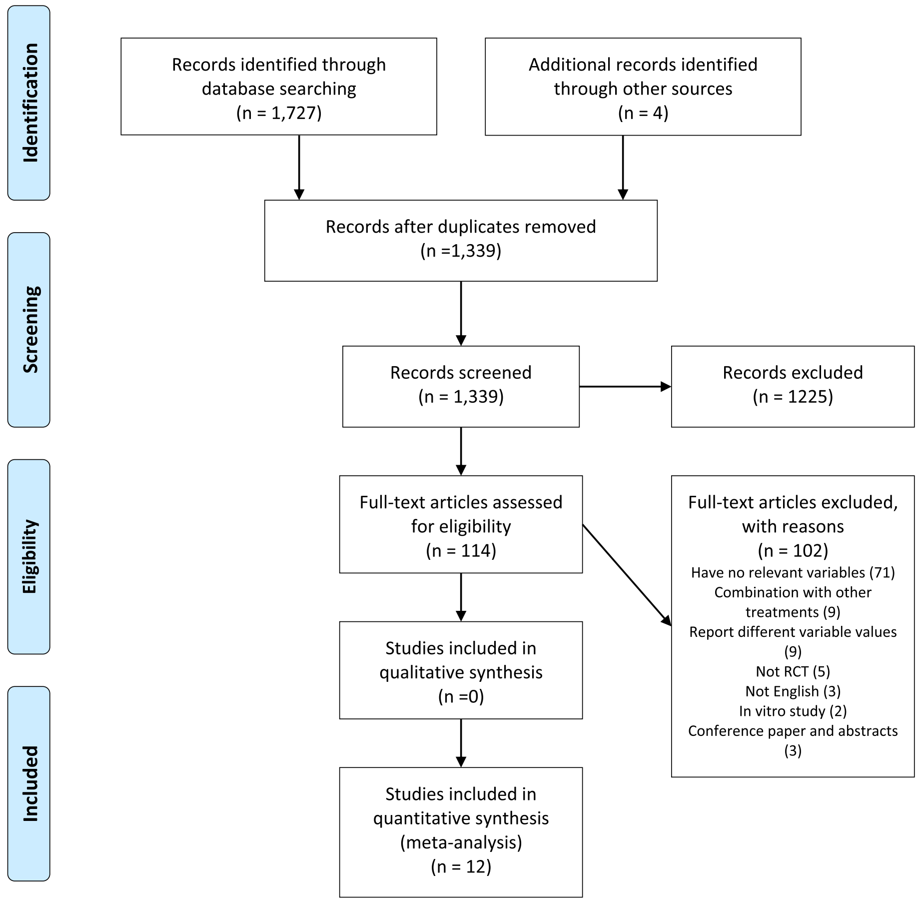

Fig. 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram of study selection.

Table 1
Study characteristic of included articles.

Study	Country	Subjects	Sample size	Melatonin Dosage	Duration(w)	Gender	Age			
							Placebo		Intervention	
							Mean	SD	Mean	SD
Goyal, 2014	USA	Metabolic syndrome	39	0.8 mg	10	Male Female	57.6	10.1	62.7	9.6
Mesri Alamdari, 2014	Iran	Healthy obese women	46	6 mg	6	Female	34.86	7.29	33.86	6.94
Chojnacki, 2015	Poland	Postmenopausal women	64	5 mg	24	Female	56.10	5.8	57.9	5.50
D'Anna, 2016	Italy	Menopause	40	3gr	24	Female	48.7	1.5	49.1	1.7
Al Lami, 2018	Iraq	Chronic Kidney Disease	41	5 mg	12	Male Female	56.1	10.73	58.2	15.2
Modabbernia, 2014	Iran	Schizophrenia	48	3 mg	8	Male Female	32.8	8.2	32.7	7.3
Raygan, 2017	Iran	Type 2 diabetic patients	60	10 mg	12	Male Female	65.3	10.1	67.7	11.4
Cichoz-lach, 2010	Poland	Nonalcoholic steatohepatitis	45	10 mg	4	Male Female	35.4	6.12	33.8	5.78
Celinski, 2014	Poland	Non-alcoholic fatty liver disease	74	10 mg	56	Male Female	36.16	5.77	29.33	9.58
Pakravan, 2017	Iran	Non-alcoholic fatty liver disease	100	10 mg	12	Male Female	40.6	9.8	42.5	10.1
Seabra, 2000	Brazil	Healthy	40	10 mg	4	Male	29	1	29	1
Romo-Nava, 2014	Mexico	schizophrenia or bipolar disorder type I	44	5 mg	8	Male Female	29.5	8.3	29.5	8.3

Mexico and one in Brazil. The sample sizes varied from 39 to 100 participants. The duration of the intervention varied from 4 to 56 weeks. Most trials were of low quality. Six trials used an unclear method of randomization. Only two trials had adequate concealment of allocation. Intention to treat approach was observed only in two trials. Only five trials used appropriate method of blinding. Since the primary and secondary outcomes were objective, all studies were judged as being at low risk for detection bias. The quality of the five trials included in this review are presented in supplementary file s2.

3.3. BMI

Effect of melatonin supplementation on BMI was studied in six trials (151 experimental and 147 placebo). There was no significant reduction in BMI in the melatonin supplemented group. The SMD for BMI between melatonin supplemented and placebo groups from random effects analysis was −0.33 kg/m2 (95% CI: -0.72, 0.06; P = 0.01, Fig. 2). There was noticeable heterogeneity among the trials (P = 0.02, I2 = 64%). In the subgroup analysis, no significant effect was observed in the subset of trials administrating melatonin supplementation for ≤10 weeks (SMD: -0.18 kg/m2, 95% CI: −0.52, 0.16, P = 0.29, I2 = 0%, Fig. 2), and those administrating supplement more than 10 weeks (SMD: -0.47 kg/m2, 95% CI: -1.25, 0.31, P = 0.24, I2 = 83%, Fig. 2). The group of trials (2 trials, n = 94) employing melatonin supplementation at doses lower than 6 mg did not demonstrate a statistically significant increase in BMI levels (SMD: -0.19 kg/m2, 95% CI: -0.59, 0.22, P = 0.36, I2 = 0%, Fig. 3). Also the group of trials (6 trials, n = 204) administering melatonin supplementation at doses higher than 6 mg did not demonstrate a statistically significant increase in BMI levels (SMD: -0.40 kg/m2, 95% CI: -0.98, 0.18, P = 0.18, I2 = 76%, Fig. 3).

3.4. Weight

There were six trials (167 experimental and 171 placebo) in which the effect of melatonin supplementation on weight was studied. Forest plot shows there is no statistically significant reduction in melatonin supplemented group. The pooled SMD for weight between melatonin supplemented and placebo group from random effect analysis was −0.49 kg (95% CI: -1.24, 0.25; P = 0.19) and there was considerable heterogeneity between trials as indicated by I2 = 90% (P < 0.001). Forest plot for subgroup analysis of weight based on intervention duration shows non-significant difference between melatonin alone supplemented and placebo groups (I2 = 53.2% (P = 0.14). The group of trials (4 trials, n = 178) employing melatonin supplementation for ≤ 10 weeks did not demonstrate a statistically significant increase in weight reduction (SMD: -0.86 kg, 95% CI: -2.12, 0.40, P = 0.18, I2 = 93%, Fig. 4). Also the group of trials (2 trials, n = 160) administering melatonin supplementation for >10 weeks did not demonstrate a statistically significant decrease in weight (SMD: 0.11 kg, 95% CI: -0.20, 0.42, P = 0.50, I2 = 0%, Fig. 4). There was no difference between experimental and placebo groups in the subset of trials that administered melatonin in less than 6 mg (SMD: -1.03 kg, 95% CI: -2.85, 0.79, P = 0.27, I2 = 95%) or higher than 6 mg daily (SMD: 0.01 kg, 95% CI: -0.29, 0.30, P = 0.98, I2 = 8%) (Fig. 5).

3.5. Waist circumference (WC)

Fig. 6 shows a forest plot of the pooled effect of melatonin on WC. There were 5 RCT with 274 subjects (137 cases and 137 controls) that compared WC between melatonin and placebo group. The overall SMD was −0.15 cm (95% CI: -0.50, 0.21, I2 = 52%, P = 0.41). It shows no significant difference between melatonin supplementation and placebo. In a subgroup analysis, no significant effect was observed in the subset of trials administering melatonin for ≤10 weeks (SMD: -0.01 cm, 95% CI: -0.54, 0.51, P = 0.96, I2 = 58%), and trials with supplementation durations >10 weeks (SMD: -0.33 cm, 95% CI: -0.93, 0.26, P = 0.41, I2 = 52%) (Fig. 6). In addition, no significant effect was observed in the subset of trials administering melatonin at doses higher than 6 mg (SMD: -0.01 cm, 95% CI: -0.54, 0.51, P = 0.96, I2 = 58%) or doses lower than 6 mg (SMD: -0.33 cm, 95% CI: -0.93, 0.26, P = 0.41, I2 = 52%) (Fig. 7).

3.6. LDL-C

Analysis of change in LDL-C showed significant improvement in melatonin versus placebo groups; the SMD was −0.31 mmol/L (95% CI [-0.61, 0.01], P = 0.049, I2 = 42%, Fig. 8). When trials were restricted to those that administering melatonin more than eight weeks, SMD was −0.48 mmol/L (95% CI [-0.90, −0.07], P = 0.02, I2 = 49%). But no significant effect was observed in the subset of trials administering melatonin lower than 8 weeks (SMD: -0.06 mmol/L, 95% CI: -0.44, 0.32, P = 0.77, I2 = 0%) (Fig. 8). No significant effect was observed in the subset of trials administering melatonin at doses higher than 8 mg (SMD: -0.25 mmol/L, 95% CI: -0.82, 0.31, P = 0.96, I2 = 38%). But a significant effect was observed in the subset of trials administering melatonin at doses lower than 8 mg (SMD: -0.35 mmol/L, 95% CI: -0.70, −0.01, P = 0.05, I2 = 0%) (Fig. 9).

3.7. HDL-C

Seven trials reported effects of melatonin on HDL-C. Use of melatonin was not associated with significant changes in HDL-C levels. There was no difference between the subset of trials administering melatonin lower than 8 weeks (SMD: 0.07 mmol/L, 95% CI: -0.31, 0.45, P = 0.72, I2 = 0%) or those administering

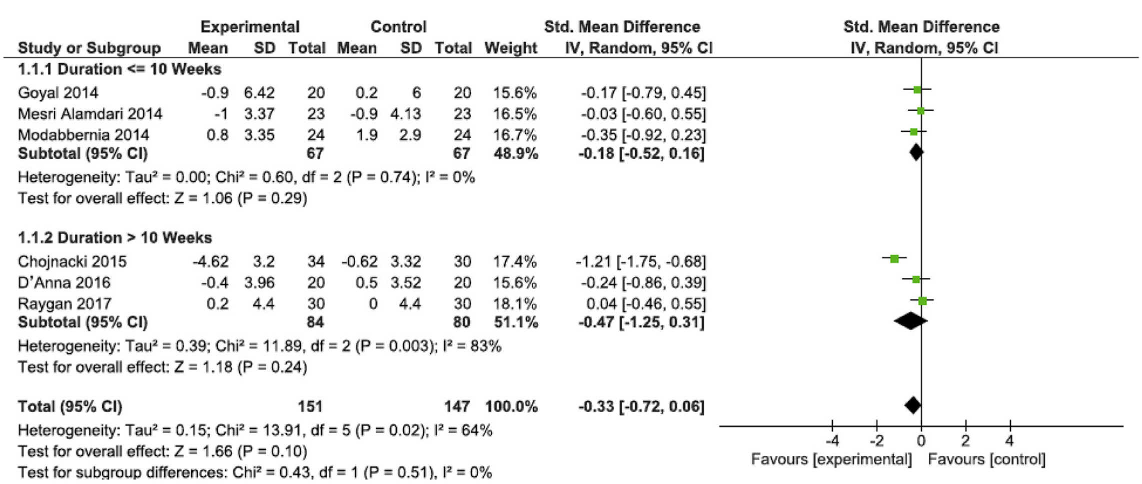

Fig. 2. Forest plot showing the results of subgroup meta-analysis duration of intervention used in studies comparing the effect of melatonin on body mass index.

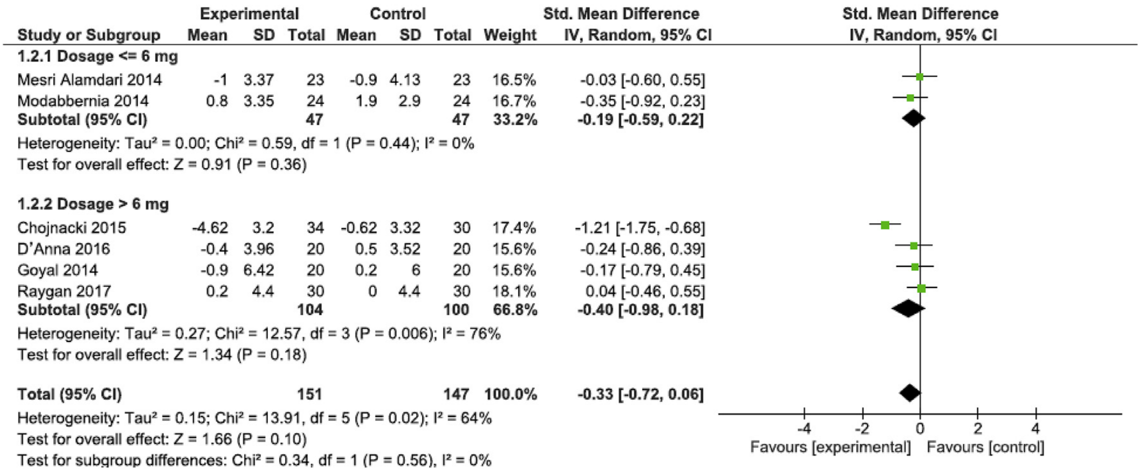

Fig. 3. Forest plot showing the results of subgroup meta-analysis dosage of intervention used in studies comparing the effect of melatonin on body mass index.

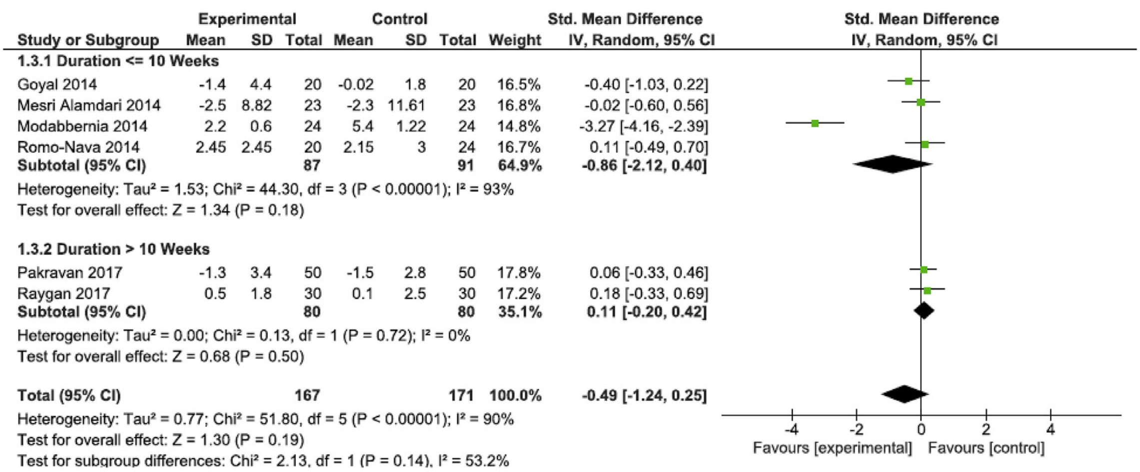

Fig. 4. Forest plot showing the results of subgroup meta-analysis duration of intervention used in studies comparing the effect of melatonin on body weight.

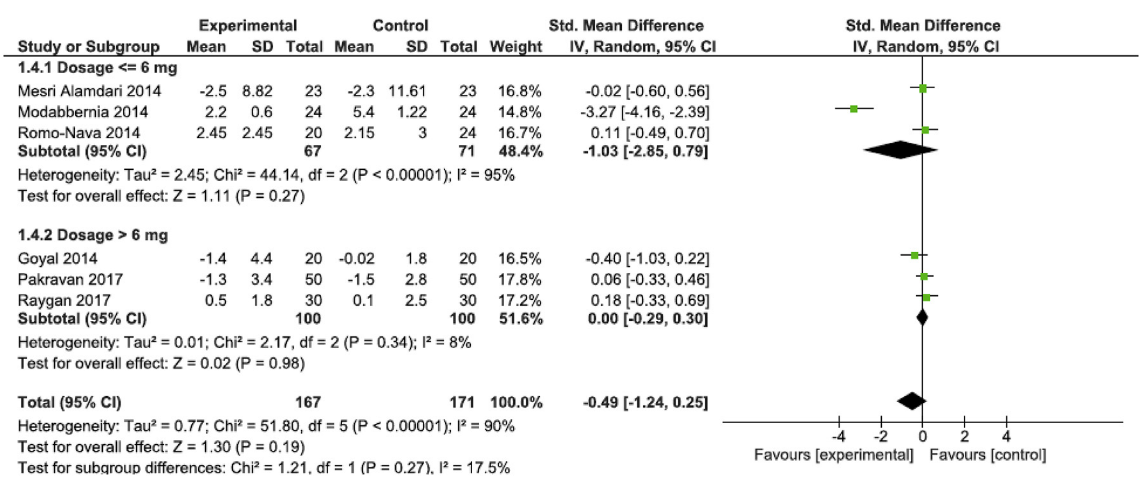

Fig. 5. Forest plot showing the results of subgroup meta-analysis dosage of intervention used in studies comparing the effect of melatonin on body weight.

melatonin higher than 8 weeks (SMD: 0.22 cm, 95% CI: -0.39, 0.83, P = 0.48, I2 = 77%, Fig. 10). Also, There was no difference between the subset of trials administering melatonin at doses higher than 8 mg (SMD: -0.03 mmol/L, 95% CI: -0.33, 0.28, P = 0.86, I2 = 0%) or those administering melatonin at doses lower than 8 mg (SMD: 0.40 mmol/L, 95% CI: -0.33, 1.13, P = 0.28, I2 = 76%, Fig. 11).

3.8. TG

We retrieved seven trials, in which TG levels was compared

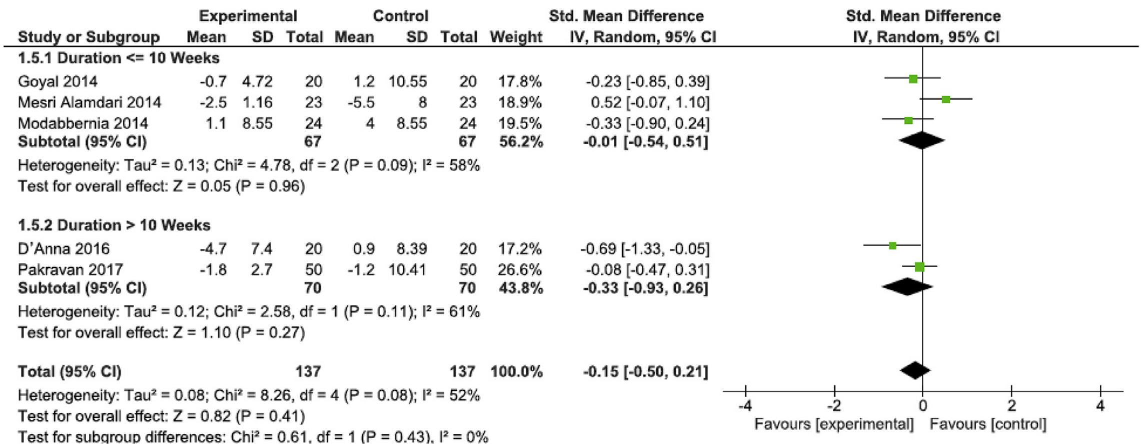

Fig. 6. Forest plot showing the results of subgroup meta-analysis duration of intervention used in studies comparing the effect of melatonin on waist circumference.

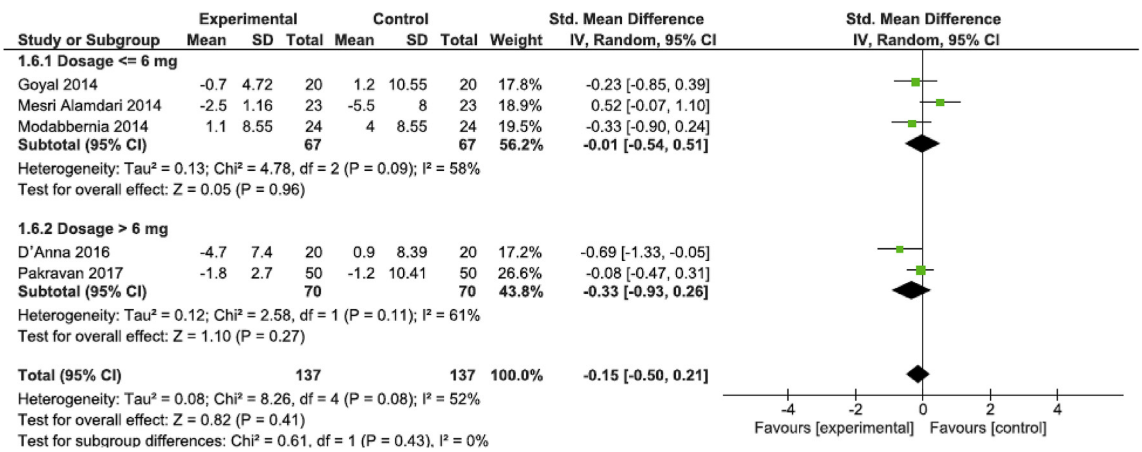

Fig. 7. Forest plot showing the results of subgroup meta-analysis dosage of intervention used in studies comparing the effect of melatonin on waist circumference.

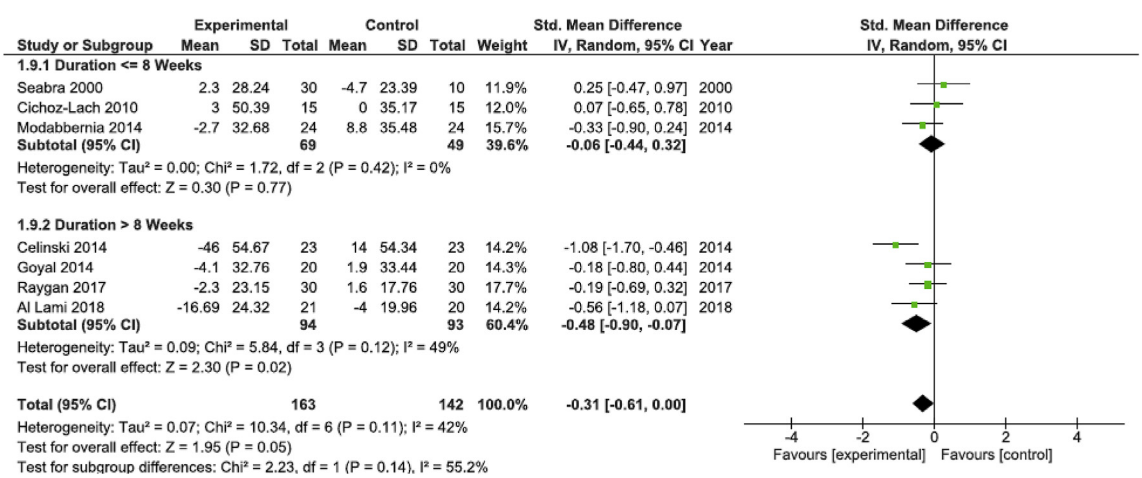

Fig. 8. Forest plot showing the results of subgroup meta-analysis duration of intervention used in studies comparing the effect of melatonin on low density lipoprotein.

between melatonin and placebo (163 experimental and 142 placebo). When the data from seven trials were combined, it was shown that melatonin supplementation can significantly decrease the level of TG ($SMD = -0.45$ mmol/L; 95% CI, -0.77, -0.13, $P = 0.006$) in patients treated with melatonin compared with placebo, although moderate heterogeneity existed among the trials ($P = 0.08$, $I2 = 47\%$). Short term (lower than 8 weeks) use of melatonin significantly decreased TG levels (SMD: -0.69 mmol/L, 95% CI: -1.08, -0.29, $P < 0.001$, $I2 = 3\%$), while use of melatonin higher than 8 weeks had no significant effect on TG levels (SMD: -0.31 mmol/L, 95% CI: -0.75, 0.12, $P = 0.16$, $I2 = 55\%$) (Fig. 12). Use of melatonin supplementation at doses lower than 8 mg was not associated with

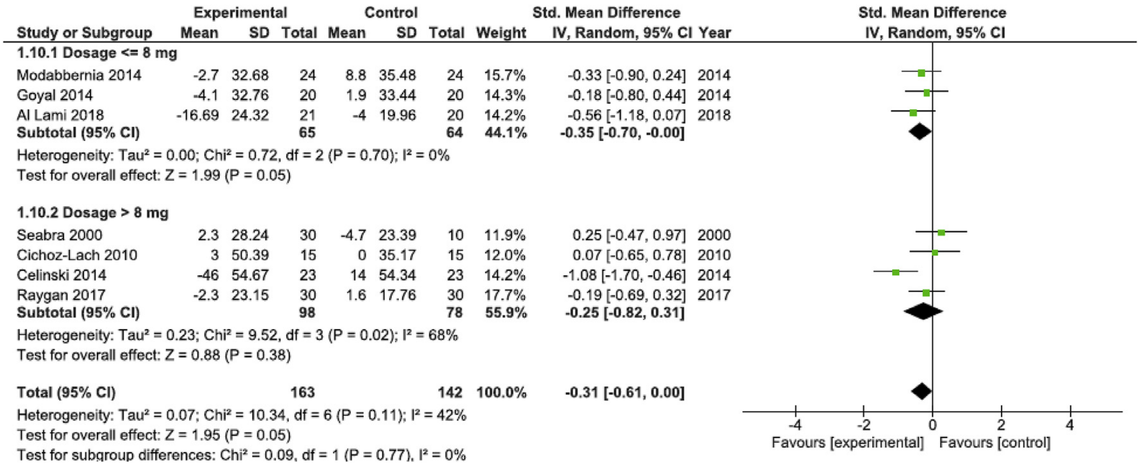

Fig. 9. Forest plot showing the results of subgroup meta-analysis dosage of intervention used in studies comparing the effect of melatonin on low density lipoprotein.

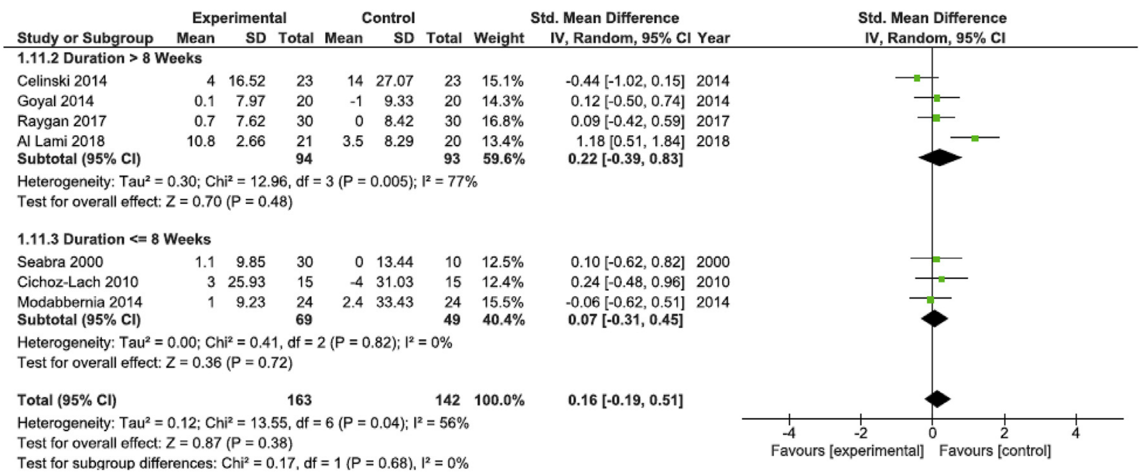

Fig. 10. Forest plot showing the results of subgroup meta-analysis duration of intervention used in studies comparing the effect of melatonin on high density lipoprotein.

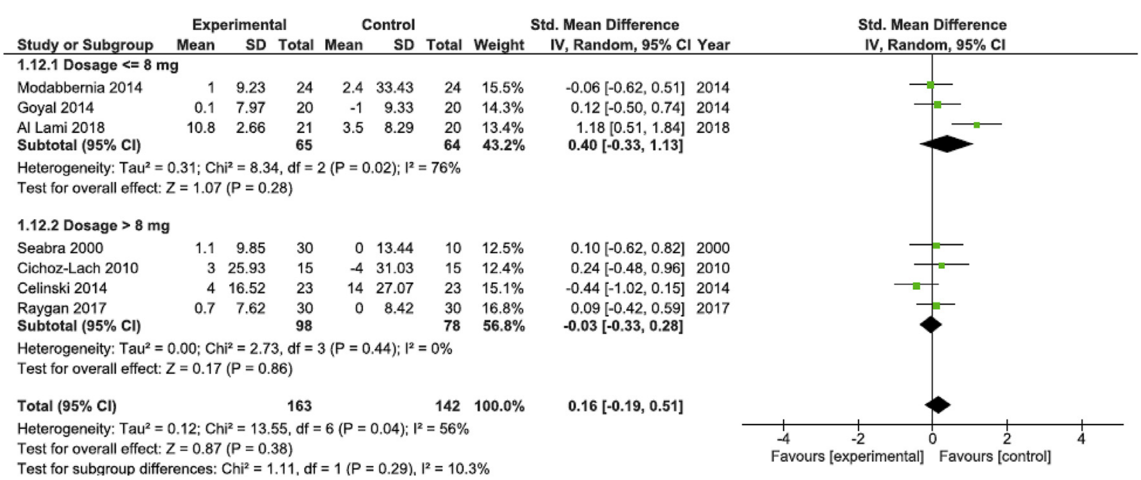

Fig. 11. Forest plot showing the results of subgroup meta-analysis dosage of intervention used in studies comparing the effect of melatonin on high density lipoprotein.

significant changes in TG levels (SMD: -0.46, 95% CI: -1.04, 0.12, $P = 0.12$, $I2 = 63\%$, Fig. 13). However, with higher doses (higher than 8 mg), melatonin supplementation significantly decreased TG levels (SMD: -0.45, 95% CI: -0.89, −0.01, $P = 0.049$, $I2 = 49\%$, Fig. 13).

4. Discussion

The present systematic review and meta-analysis of RCTs, revealed that melatonin supplementation can significantly

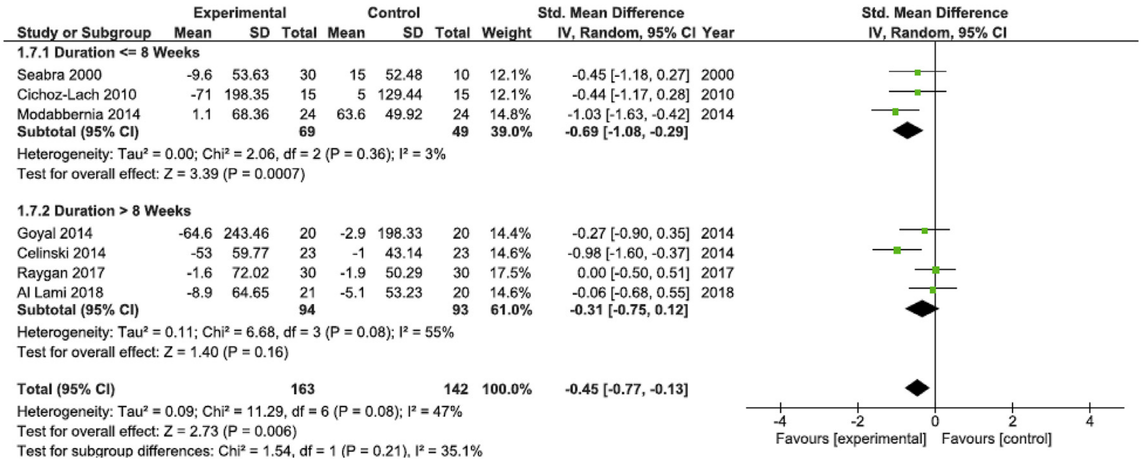

Fig. 12. Forest plot showing the results of subgroup meta-analysis duration of intervention used in studies comparing the effect of melatonin on triglyceride.

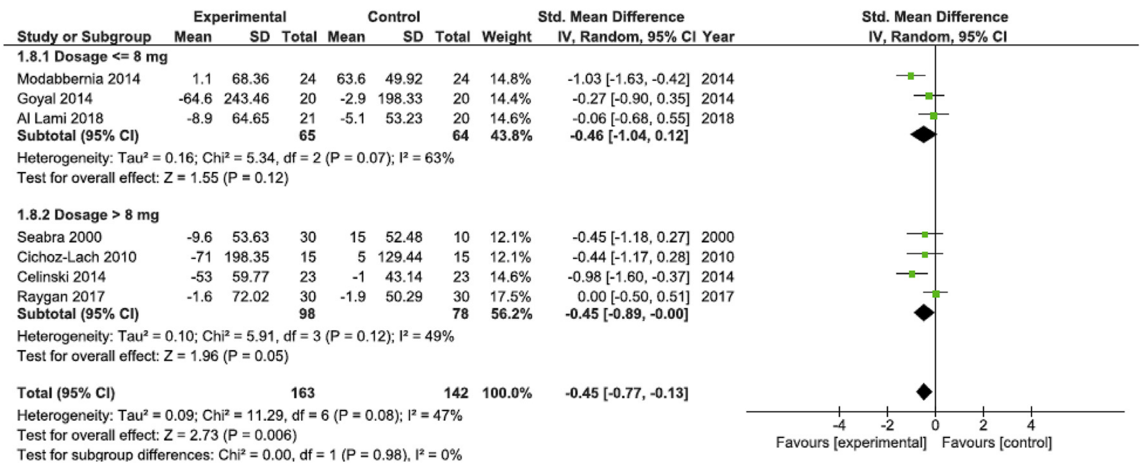

Fig. 13. Forest plot showing the results of subgroup meta-analysis dosage of intervention used in studies comparing the effect of melatonin on triglyceride.

decrease the level of TG and LDL-C. A further novel finding of our study is that the melatonin supplementation could not significantly affect BMI, weight, WC, HDL-C. Present up-date meta-analysis confirmed the results of previous meta-analysis study concerning the significant effects of melatonin supplementation on TG [28]. However, melatonin supplementation effect on LDL-C is opposed to findings of previous meta-analysis. Our data reported reduced levels of LDL-C whereas the results published meta-analysis by Mohammadi-Sartang et al. [28] showed no changes in LDL-C levels. Furthermore in our study effective period time of melatonin use for decrease of TG was shorter than 8 weeks which was in contradiction with the previous meta-analysis study. Both, our results and those reported by Mohammadi-Sartang et al. [28] showed no significant effect on HDL-C. Regarding the anthropometric indicators, a study was conducted in 2017 on the effect of supplementation of melatonin on weight [29], which its results consistent with the results of our study, however only melatonin effects on weight were evaluated in that study, and other anthropometric indices were not assessed. There was heterogeneity between the trials so it is hard to conclude on these outcomes, however, subgroup analyzes were performed to further analyze the results based on the dose of melatonin and the duration of supplementation. The current meta-analysis found that supplementation of melatonin significantly decreased LDL-C. The subgroup analysis based on the dose indicated that the supplementation of melatonin at a dose of less or equal than 8 mg per day reduced LDL-C, and did not have a significant effect in the dose of more than 8 mg per day. One of the possible reasons that more than 8 mg/d of melatonin supplementation have not significant decrease on LDL-C may be the high heterogeneity for studies that use more than 8 mg/d dose. However dose−response studies that have evaluated the capacity of melatonin to reduce LDL-C is limited. The subgroup analysis based on the duration of melatonin supplementation, showed that in studies that had more than 8 weeks of supplementation, the level of LDL-C was significantly decreased, while in studies with a duration of less than 8 weeks this effect was not significant. This results confirm previous reviews results about duration of supplementation of melatonin [9,30]. Previous studies evaluating long term melatonin supplementation on LDL-C observed consistent results [30–32]. Several mechanisms have been proposed for the effect of melatonin on LDL-C, one of the main possible mechanism is the interaction of melatonin with LDL-C receptors. The function of melatonin on LDL-C receptor activity seems to be conducted by a decrease in the number of LDL-C receptors [33]. Another possible mechanisms include; the reduction of free fatty acids [34], as well as the reduction of LDL-C oxidation by increasing the antioxidant factors such as serum glutathione peroxidase, (GSH-PX) [35], has been reported in previous studies.

Consistent with the literature [36], current systematic review found that participants who receive melatonin supplementation show reduction in TG levels. The subgroup analysis showed that the supplementation of melatonin at doses greater than 8 mg/day has significant effect on TG levels, but dosage of less or equal than to 8 mg/day has no significant effect on TG levels, this indicates the dose dependent effect of a melatonin supplement on TG. The subgroup analysis based on supplemental duration also showed that during a period of less than 8 weeks, the supplementation of melatonin resulted in a significant decrease in TG, but did not have a significant effect in duration of more than 8 weeks. Regarding the antioxidant properties of melatonin, it seems that adaptation of the body with the melatonin supplementation may explain the lack of effects in longer durations, however great heterogeneity of more than 8 week duration studies ($I2 = 55\%$) compare to equal or less than 8 week studies ($I2 = 3\%$) may dilute this conclusion about adaptation.

Previous studies confirm melatonin effect on reducing TG (15), possible mechanism of this effect of melatonin can likely be illustrated by its inhibition of visceral fat without affecting subcutaneous deposits, and so ameliorate insulin sensitivity and cause to increased lipoprotein lipase (LPL) activity and decreased lipolytic activity in visceral adipose tissue ([22,37]). The results of current meta-analysis showed that supplementation with melatonin has no effect on serum HDL levels. That confirm previous systematic reviews [28] results in this regard. Our present study confirms the previous studies [38] which demonstrated that the melatonin supplementation could not significantly affect BMI, weight, WC. However several other studies, find beneficial effects of melatonin supplementation on BMI, WC and weight [39,40]. Also the results of the study by chojnacki et al. [41] indicated that daily melatonin supplementation (5 mg-for 24 weeks) in postmenopausal women significantly reduced BMI levels. Similar effects on BMI, WC and body weight were observed in other study by modabbernia et al. [42] following melatonin supplementation (3 mg for 8 weeks). This discrepancy is likely to result from the diversity in dose and duration of melatonin supplementation and study population. Thereby it seems that the effect of melatonin supplementation on anthropometric indices needs further investigation in larger studies.

This systematic review and meta-analysis has several limitations that need to be addressed. The majority of studies did not report the process of blinding and had a selection bias, six studies also did not report blinding of participants process and have performance bias. Six trials did not report blinding process of outcome assessment so they have detection bias. Eight trials have attrition bias because they report incomplete data. Most of the studies were of small size, and as only four trials had a sample size more than 70 participants. Another limitation of this study was the difference in the participant's disease in the primary studies, in a way that increased the heterogeneity and the differences in the type of disease of the participants may affect the results, however, due to limited number of studies, there was not the possibility of subgroup analysis based on the type of disease.

5. Conclusion

The results of our systematic review and Meta-analyzes showed that supplementation of melatonin could be effective in improving lipid parameters and should be considered in the prevention of cardiovascular disease, although the effect of this supplement on anthropometric indices needs further investigation.

Conflicts of interest

None declared.

Financial support

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.04.043.

References

[1] Ranjbar SH, Larijani B, Abdollahi M. Recent update on animal and human evidences of promising anti-diabetic medicinal plants: a mini-review of targeting new drugs. Asian J Anim Vet Adv 2011;6(12):1271–5.
[2] Patel V, Upaganlawar A, Zalawadia R, Balaraman R. Cardioprotective effect of melatonin against isoproterenol induced myocardial infarction in rats: a biochemical, electrocardiographic and histoarchitectural evaluation. Eur J Pharmacol 2010;644(1–3):160–8.
[3] Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014;2014.
[4] Felizola SJ. Ursolic acid in experimental models and human subjects: potential as an anti-obesity/overweight treatment? Cancer 2015;1:2.
[5] Pothiwala P, Jain SK, Yaturu S. Metabolic syndrome and cancer. Metab Syndrome Relat Disord 2009;7(4):279–88.
[6] Jung UJ, Choi M-S. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci 2014;15(4):6184–223.
[7] Kelly T, Yang W, Chen C-S, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes 2008;32(9):1431.
[8] Nduhirabandi F, du Toit EF, Lochner A. Melatonin and the metabolic syndrome: a tool for effective therapy in obesity-associated abnormalities? Acta Physiol 2012;205(2):209–23.
[9] Mozaffari S, Hasani-Ranjbar S, Abdollahi M. The mechanisms of positive effects of melatonin in dyslipidemia: a systematic review of animal and human studies. Int J Pharmacol 2012;8:496–509.
[10] Srinivasan V, Ohta Y, Espino J, Pariente J A, Rodriguez A B, Mohamed M, et al. Metabolic syndrome, its pathophysiology and the role of melatonin. Recent patents on endocrine. Metab Immune Drug Discov 2013;7(1):11–25.
[11] Zawilska JB, Skene DJ, Arendt J. Physiology and pharmacology of melatonin in relation to biological rhythms. Pharmacol Rep 2009;61(3):383–410.
[12] Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res 2016;61(3): 253–78.
[13] Navarro-Alarcón M, Ruiz-Ojeda FJ, Blanca-Herrera RM, A-Serrano MM, Acuña-Castroviejo D, Fernández-Vázquez G, et al. Melatonin and metabolic regulation: a review. Food Funct 2014;5(11):2806–32.
[14] De Filippis D, Iuvone T, Esposito G, Steardo L, Herman Arnold G, Pelckmans Paul A, et al. Melatonin reverses lipopolysaccharide-induced gastro-intestinal motility disturbances through the inhibition of oxidative stress. J Pineal Res 2008;44(1):45–51.
[15] Agil A, Navarro-Alarcón M, Ruiz R, Abuhamadah S, El-Mir MY, Vázquez GF. Beneficial effects of melatonin on obesity and lipid profile in young Zucker diabetic fatty rats. J Pineal Res 2011;50(2):207–12.
[16] Huang L, Zhang C, Hou Y, Laudon M, She M, Yang S, et al. Blood pressure reducing effects of piromelatine and melatonin in spontaneously hypertensive rats. Eur Rev Med Pharmacol Sci 2013;17(18):2449–56.
[17] Hussain SAR. Effect of melatonin on cholesterol absorption in rats. J Pineal Res 2007;42(3):267–71.
[18] Tamura H, Nakamura Y, Narimatsu A, Yamagata Y, Takasaki A, Reiter RJ, et al. Melatonin treatment in peri-and postmenopausal women elevates serum high-density lipoprotein cholesterol levels without influencing total cholesterol levels. J Pineal Res 2008;45(1):101–5.
[19] Koziróg M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res 2011;50(3):261–6.
[20] Hoyos M, Guerrero JM, Perez-Cano R, Olivan J, Fabiani F, Garcia-Pergañeda A, et al. Serum cholesterol and lipid peroxidation are decreased by melatonin in diet-induced hypercholesterolemic rats. J Pineal Res 2000;28(3):150–5.
[21] Pita ML, Hoyos M, Martin-Lacave I, Osuna C, Fernández-Santos JM, Guerrero JM. Long-term melatonin administration increases polyunsaturated fatty acid percentage in plasma lipids of hypercholesterolemic rats. J Pineal Res 2002;32(3):179–86.
[22] Rasmussen DD, Boldt BM, Wilkinson C, Yellon SM, Matsumoto AM. Daily melatonin administration at middle age suppresses male rate visceral fat, plasma leptin, and plasma insulin to youthful levels. Endocrinology 1999;140(2):1009–12.
[23] Tutuncu NB, Batur MK, Yildirir A, Tutuncu T, Deger A, Koray Z, et al. Melatonin levels decrease in type 2 diabetic patients with cardiac autonomic neuropathy. J Pineal Res 2005;39(1):43–9.

[24] Yaprak M, Altun A, Vardar A, Aktoz M, Ciftci S, Ozbay G. Decreased nocturnal synthesis of melatonin in patients with coronary artery disease. Int J Cardiol 2003;89(1):103–7.
[25] Hardeland R. Melatonin in aging and disease—multiple consequences of reduced secretion, options and limits of treatment. Aging Dis. 2012;3(2):194.
[26] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1.
[27] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[28] Mohammadi-Sartang M, Ghorbani M, Mazloom Z. Effects of melatonin supplementation on blood lipid concentrations: a systematic review and meta-analysis of randomized controlled trials. Edinburgh, Scotland): Clinical nutrition; 2017.
[29] Mostafavi S-A, Akhondzadeh S, Reza Mohammadi M, Keshtkar A-A, Hosseini S, Reza Eshraghian M, et al. Role of melatonin in body weight: a systematic review and meta-analysis. Curr Pharmaceut Des 2017;23(23):3445–52.
[30] Sun H, Huang F-f, Qu S. Melatonin: a potential intervention for hepatic steatosis. Lipids Health Dis 2015;14(1):75.
[31] Nishida S, Segawa T, Murai I, Nakagawa S. Long-term melatonin administration reduces hyperinsulinemia and improves the altered fatty-acid compositions in type 2 diabetic rats via the restoration of Δ-5 desaturase activity. J Pineal Res 2002;32(1):26–33.
[32] Kadhim HM, Ismail SH, Hussein KI, Bakir IH, Sahib AS, Khalaf BH, et al. Effects of melatonin and zinc on lipid profile and renal function in type 2 diabetic patients poorly controlled with metformin. J Pineal Res 2006;41(2):189–93.
[33] Mullerwieland D, Behnke B, Koopmann K, Krone W. Melatonin inhibits LDL receptor activity and cholesterol-synthesis in freshly isolated human mononuclear leukocytes. Biochem Biophys Res Commun 1994;203(1):416–21.
[34] Wang Z, Ni L, Wang J, Lu C, Ren M, Han W, et al. The protective effect of melatonin on smoke-induced vascular injury in rats and humans: a randomized controlled trial. J Pineal Res 2016;60(2):217–27.
[35] Hussein MR, Ahmed OG, Hassan AF, Ahmed MA. Intake of melatonin is associated with amelioration of physiological changes, both metabolic and morphological pathologies associated with obesity: an animal model. Int J Exp Pathol 2007;88(1):19–29.
[36] Mohammadi-Sartang M, Ghorbani M, Mazloom Z. Effects of melatonin supplementation on blood lipid concentrations: a systematic review and meta-analysis of randomized controlled trials. Clin Nutr 2018;37(6):1943–54.
[37] Wolden-Hanson T, Mitton D, McCants R, Yellon S, Wilkinson C, Matsumoto A, et al. Daily melatonin administration to middle-aged male rats suppresses body weight, intraabdominal adiposity, and plasma leptin and insulin independent of food intake and total body fat. Endocrinology 2000;141(2):487–97.
[38] Goyal A, Terry PD, Superak HM, Nell-Dybdahl CL, Chowdhury R, Phillips LS, et al. Melatonin supplementation to treat the metabolic syndrome: a randomized controlled trial. Diabetol Metab Syndrome 2014;6(1):124.
[39] Alamdari NM, Mahdavi R, Roshanravan N, Yaghin NL, Ostadrahimi A, Faramarzi E. A double-blind, placebo-controlled trial related to the effects of melatonin on oxidative stress and inflammatory parameters of obese women. Horm Metab Res 2015;47(07):504–8.
[40] Raygan F, Ostadmohammadi V, Bahmani F, Reiter RJ, Asemi Z. 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. Edinburgh, Scotland): Clinical nutrition; 2017.
[41] Chojnacki C, Walecka-Kapica E, Klupinska G, Pawlowicz M, Blonska A, Chojnacki J. Effects of fluoxetine and melatonin on mood, sleep quality and body mass index in postmenopausal women. J Physiol Pharmacol 2015;66(5):665–71.
[42] Modabbernia A, Heidari P, Soleimani R, Sobhani A, Roshan ZA, Taslimi S, 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 2014;53:133–40.