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Meta-analyses

Effects of melatonin supplementation on blood lipid concentrations: A systematic review and meta-analysis of randomized controlled trials

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SUMMARY

Background & aims: Melatonin supplementation may be associated with blood lipids improvement; however, the current evidence from randomized controlled trials (RCTs) is inconsistent. The present study aimed to systematically review and analyze RCTs assessing the effects of melatonin supplementation on blood lipids.

Methods: A comprehensive literature search in several database was performed up to January 2017. Quantitative data synthesis was performed using a fixed or random-effects model, with weight mean difference (WMD) and 95% confidence intervals (CI). Standard methods were used for assessment of heterogeneity, meta-regression, sensitivity analysis and publication bias.

Results: A total of 8 RCTs were eligible. Meta-analysis suggested a significant association between melatonin supplementation and a reduction in triglycerides (WMD: −31.54 mg/dL, 95% CI: −50.71, −12.38, p = 0.001), and total cholesterol levels (WMD: −18.48 mg/dL, 95% CI: −35.33, −1.63, p = 0.032), while no significant effect on LDL-C (WMD: −2.37 mg/dL, 95% CI: −11.61, −6.86, p = 0.615) and HDL-C (WMD: 1.28 mg/dL, 95% CI: −0.66, 3.23, p = 0.197) was found. In sub-group analysis, a significant decrease in triglycerides was found at doses ≥8 mg/d and when trials last ≥8 weeks. In addition, a significant decrease of total cholesterol was found at doses ≥8 mg/d and when total cholesterol baseline levels were ≥200 mg/dL.

Conclusions: Melatonin supplementation has significant effects on triglycerides and total cholesterol levels, which was more evident in higher dose and longer duration and also in a higher concentration of cholesterol levels. Further studies are required to determine the benefits of melatonin on lipid profile.

1. Introduction

Increasing data have revealed that lipid concentrations are one of the major risk factors in atherosclerosis and cardiovascular disease [1,2]. Dyslipidemia, which is characterized by increased in plasma levels triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C) or reduced levels of high-density lipoprotein cholesterol (HDL-C) is an important but modifiable risk factor for atherosclerosis and cardiovascular disease [3]. Therefore, prevention and treatment of cardiovascular disease and atherosclerosis are important public health concern for many years [4]. Although a number of lipid-altering agents are in existence, their efficacy to achieve normal levels of lipids is limited [3]. Moreover, statins and fibrates, the most common hypolipidemic drugs, have adverse effects including hepatotoxicity and myopathy [5,6]. Considering these drawbacks and adverse effects, at present, identifying the new strategies like complementary agents with lipid-improving properties has attracted a lot of interest which can be used alongside low doses of statins [7–9].

Melatonin (N-acetyl-5-methoxy tryptamine) (chemical structure $C_{13}H_{16}N_2O_2$) is a ubiquitous molecule which is widely distributed in nature including animals, plants, fungi, and unicellular organism as well as humans. In human melatonin is not only produced mainly by the pineal gland which can regulate the sleep cycle and circadian rhythm but also synthesized in other areas of the body which may positively affect diverse physiological

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functions and signaling pathways [10]. The biosynthesis of melatonin in the body, mainly in the pinealocytes, occurs from tryptophan through enzymatic activity [11]. Additional surveys have shown that melatonin also has an anti-inflammatory and antioxidant property with a potent free-radical scavenging and immunomodulatory activities [12]. Importantly, current researches indicate that melatonin has an important function in several cardiovascular events, such as heart failure [13,14], atherosclerosis [15], myocardial ischemia-reperfusion injury [16], and hypertension [17]. Promising experimental studies have shown that melatonin also has a role in the regulation of lipid metabolism [18,19] and can improve dyslipidemia [12] probably via its effect on increasing the activity of lipoprotein lipase (LPL), decreasing lipolysis, increasing the activity of LDL receptor, inhibition of cholesterol absorption from the intestine [12,18] and conversion of cholesterol to bile acids [20].

Various clinical trials have assessed the effects of melatonin supplementation on circulating lipids concentrations in different populations [21–24]. Some have shown the positive effects of melatonin supplementation on circulating lipid levels [22] while others have demonstrated that melatonin supplementation increased or has a little effect on lipid parameters [25]. Although in some studies [26], triglycerides and total cholesterol were significantly reduced, LDL-C was slightly increased. Given that available published RCTs had a substantial amount of uncertainty regarding the net effect of melatonin supplementation on plasma lipid levels and to resolve the current controversy and considering the point that these studies are limited in sample size, a meta-analysis would be appropriate to reach a conclusive result for the effect of melatonin on plasma lipid concentration. To date, the current study is the first meta-analysis to assess this effect.

2. Methods

2.1. Search strategy

Our meta-analysis was designed on the guidelines of the PRISMA statement. PubMed, Medline via Ovid, EMBASE, and ISI Web of Sciences databases were searched for English-language reports of relevant RCTs published until January 2017 that explored the effect of melatonin on blood lipids, using the following the MeSH terms and related keywords: ((“Melatonin” [Mesh Terms]) AND (Cholesterol [MeSH Terms] OR cholesterol, HDL [MeSH Terms] OR cholesterol, LDL [MeSH Terms] OR lipoproteins [MeSH Terms] OR triglycerides [MeSH] OR cholesterol [Text Word] OR total cholesterol [Text Word] OR serum cholesterol [Text Word] OR plasma cholesterol [Text Word] OR lipids [Text Word] OR serum lipid [Text Word] OR plasma lipid [Text Word] OR high-density lipoprotein cholesterol [Text Word] OR high-density lipoprotein [Text Word] OR HDL cholesterol [Text Word] OR HDL-C [Text Word] OR HDLC [Text Word] OR HDL [Text Word] OR low-density lipoprotein cholesterol [Text Word] OR low-density lipoprotein [Text Word] OR LDL cholesterol [Text Word] OR LDL-C [Text Word] OR LDLC [Text Word] OR LDL [Text Word] OR triglycerides [Text Word] OR TG [Text Word])) AND ((“Randomized Controlled Trial” [Publication Type]) OR “Controlled Clinical Trial” [Publication Type]) OR “Clinical Trial” [Publication Type]) OR “Meta-Analysis” [Publication Type]) OR “Review” [Publication Type]) OR “Random Allocation” [Mesh]) OR “Single-Blind Method” [Mesh]) OR “Double-Blind Method” [Mesh]) OR “Cross-Over Studies” [Mesh]) OR “Clinical Trials as Topic” [Mesh]) OR “Comparative Study” [Publication Type]) OR “Follow-Up Studies” [Mesh]) OR “Clinical Trial*” [Title/Abstract]) OR “Controlled Trial*” [Title/Abstract]) OR Intervention* [Title/Abstract]) OR Randomised [Title/Abstract]) OR Randomized [Title/Abstract]) OR “Pilot study” [Title/Abstract]) OR randomly [Title/Abstract]) OR placebo [Title/Abstract]) OR trial [Text Word]) OR assignment [Text Word]) OR RCT [Title/Abstract]) OR “crossover” [Text Word]) OR parallel [Text Word]) OR “single-blind” [Title/Abstract]) OR “double-blind” [Title/Abstract]). The search was limited to the English language as well as to human subjects. Details of our search strategy in EMBASE databases are shown in Appendix S1. Moreover, we hand-searched the reference list of included articles, as well as related reviews and meta-analysis. The PubMed's ‘My NCBI’ (National Centre for Biotechnology Information) email alert service was created for identifying new articles that may be published after our search.

2.2. Study selection

Two investigators (M.MS and M.GH) reviewed titles and abstracts of all identified studies to ascertain whether these studies are eligible for this meta-analysis based on our inclusion criteria. Discrepancies were resolved by discussion. Studies were chosen for analysis according to the following inclusion criteria: 1) the study was a placebo-controlled trials with either a parallel or crossover design; 2) The effects of melatonin on blood lipids could be extracted from the article (adequate information on lipid indices with standard deviations (SDs), standard errors (SEs), or 95% CIs at baseline and at the end of follow-up in intervention and control group); 3) the studies with an appropriate controlled design, i.e., the only difference between the control and intervention groups was melatonin; 4) having an intervention duration at least 2 weeks; 5) conducted in adults (age $\geq$18 years).

Studies were excluded if i) we couldn't extract the net effect of melatonin; ii) melatonin supplementation duration was <2 wk; iii) non-RCTs studies; iv) if we were unable to extract adequate information on baseline or follow-up of lipid parameters.

2.3. Data extraction

Eligible articles were selected using inclusion-exclusion screening forms and the following data were abstracted independently by two authors (M.MS and M.GH): first author's name, study location, year of publication, sample size in each group, type and dose of intervention and placebo, duration of the intervention, study design (crossover or parallel), patient's status and other information including age, gender, and % women. We also extracted the mean values and SDs lipid parameters at the study baseline and end of the study. When the data were reported at multiple measurements, only the values at the end of trials were used. Those studies used several doses of melatonin, each dose was separately included in the analysis.

2.4. Quality assessment

The quality of included studies was assessed using the quantitative 5-point Jadad scale [27]. Articles were assigned 0 or 1 point for each of the following 5 criteria: 1) randomization, 2) suitable method of randomization, 3) double blinding, 4) suitable method of double blinding, and 5) explanation and reason of withdrawals and dropouts [27]. The total scores equal or more than $\geq$3 were considered as high quality [28].

2.5. Quantitative data synthesis and statistical analysis

We assessed the influence of melatonin supplementation on the change of the following outcomes: (i) triglycerides (mg/dL), (ii) total cholesterol (mg/dL), (iii) LDL-C (mg/dL), and (iv) HDL-C (mg/dL). Weighted mean differences (WMD) and 95% confidence intervals (CI) were used for expression of effect sizes. We extracted the mean and SD of the blood lipid levels pre and post-intervention period for

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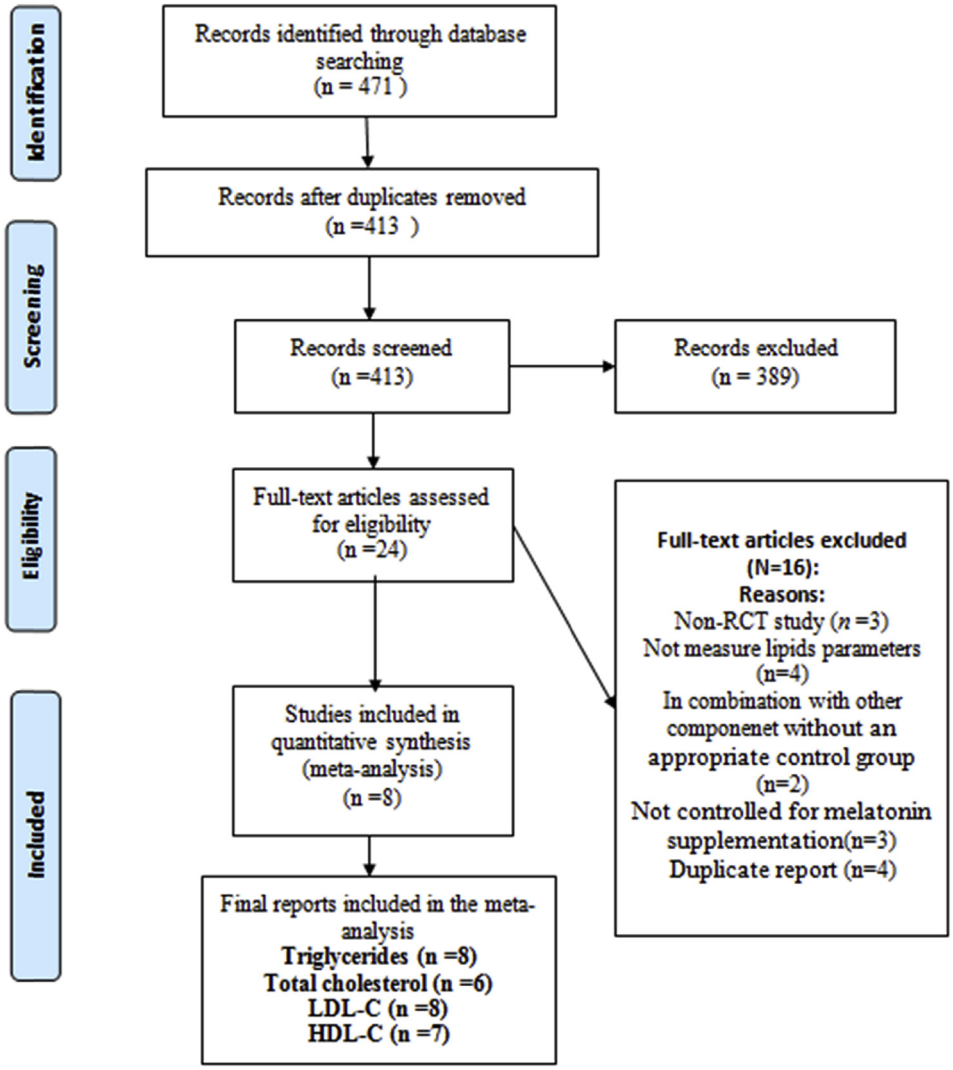

Fig. 1. Flow diagram of the study selection procedure showing the number of eligible randomized controlled trials for the meta-analysis of the effect of melatonin supplementation on blood lipid concentration. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

both melatonin control for calculation of the net changes in each group: value at end of trial − value at baseline of trial. The mean difference was also calculated as follows: (*value at end of follow-up in the treatment group − value at baseline in the treatment group*) − (*value at end of follow-up in the control group − value at baseline in the control group*). In the event of no reported SD of the mean difference, it was calculated as follows: $SD = square\ root\ [(SD\ pre\text{-}treatment)^2 + (SD\ post\text{-}treatment)^2 - (2\ R \times SD$

Table 1
Demographic characteristics of the included studies.

Author	Year	Location	Patient status	Sample size (n)	Mean age (years)	BMI	Women (%)	Design	Duration (weeks)	Melatonin dose (mg/d)	Jadad score
Celinski	2014	Poland	Non-alcoholic steatohepatitis	74	M: 36.16 C: 29.33	29.1	31	PC, R, P	14	10	1
Cichoz-Lach	2010	Poland	Non-alcoholic steatohepatitis	60	47.4	28	31.5	PC, P	4	10	1
Gonciarz	2012	Poland	Non-alcoholic steatohepatitis	42	M: 41.5 C: 40.8	NR	73	PC, R, P	24	10	3
Goyal	2014	USA	Metabolic syndrome	39	M: 62.7 C: 57.6	35.2	53.5	DB, PC, R, Co	10	8	5
Modabbernia	2014	Iran	Patients with first-episode schizophrenia	36	68	23.9	30.5	DB, PC, R, P;	8	3	5
Rindone	1997	USA	Hypercholestrolemia	16	54.9	NR	12	SB, PC, R, CO	6	0.3, 3	1
Romo-Nava,	2014	Mexico	Schizophrenia or bipolar disorder	44	M: 30.6 C: 28.6	26	50	DB, PC, R, P;	8	5	5
Seabra	2010	Brazil	Healthy male	40	29	23.1	0	DB, PC, R, P;	4	10	1

C, control; CO, cross-over; DB, doubl-blind; M, melatonin; NR, not reported; P, parallel; PC, placebo-controlled; R, randomized; SB, single-blind.

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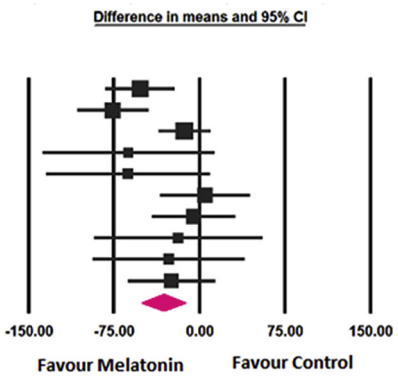
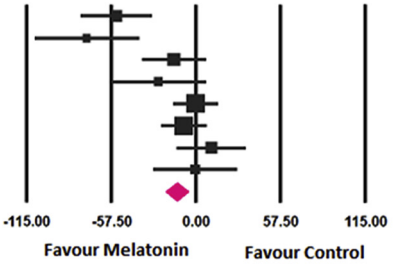
A.Triglycerides

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Celinski, 2014	52.000-	15.369	236.202	82.122-	21.878-	3.383-	0.001
Cichoz-Lach, 2010	76.000-	15.795	249.469	106.957-	45.043-	4.812-	0.000
Gonciarz,2012	13.170-	11.540	133.182	35.789-	9.449	1.141-	0.254
Goyal, 2014	62.100-	38.390	1473.809	137.343-	13.143	1.618-	0.106
Modabbernia, 2014	62.500-	36.538	1335.042	134.114-	9.114	1.711-	0.087
Rindone, 1997, a	5.000	19.870	394.836	33.945-	43.945	0.252	0.801
Rindone, 1997, b	5.000-	18.497	342.136	41.253-	31.253	0.270-	0.787
Romo-Nava, 2014 a	18.600-	37.643	1416.997	92.379-	55.179	0.494-	0.621
Romo-Nava, 2014 b	26.800-	33.818	1143.675	93.083-	39.483	0.792-	0.428
Seabra, 2000	24.600-	19.415	376.962	62.654-	13.454	1.267-	0.205
	31.549-	9.781	95.658	50.719-	12.380-	3.226-	0.001



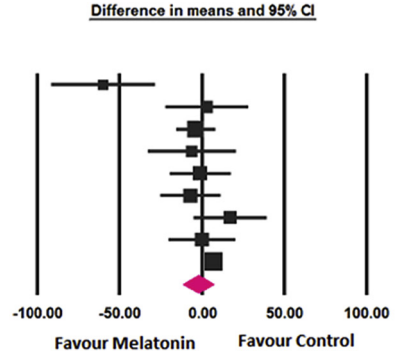
B. Total cholesterol

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Celinski, 2014	54.000-	12.131	147.168	77.777-	30.223-	4.451-	0.000
Cichoz-Lach, 2010	74.000-	18.027	324.970	109.332-	38.668-	4.105-	0.000
Gonciarz,2012	14.780-	11.023	121.503	36.384-	6.824	1.341-	0.180
Modabbernia, 2014	25.400-	16.453	270.711	57.648-	6.848	1.544-	0.123
Rindone, 1997, a	0.000	7.690	59.141	15.073-	15.073	0.000	1.000
Rindone, 1997, b	8.000-	7.690	59.141	23.073-	7.073	1.040-	0.298
Romo-Nava, 2014 a	10.600	11.914	141.934	12.750-	33.950	0.890	0.374
Romo-Nava, 2014 b	0.300-	14.419	207.908	28.561-	27.961	-0.021	0.983
	12.926-	3.850	14.822	20.472-	5.381-	3.358-	0.001



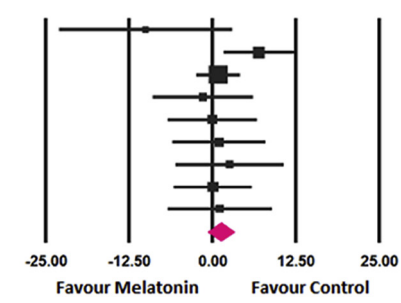
C. LDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Celinski, 2014	60.000-	16.073	258.332	91.502-	28.498-	3.733-	0.000
Cichoz-Lach, 2010	3.000	12.780	163.333	22.049-	28.049	0.235	0.814
Goyal, 2014	3.800-	5.901	34.824	15.366-	7.766	0.644-	0.520
Modabbernia, 2014	6.100-	13.558	183.814	32.673-	20.473	0.450-	0.653
Rindone, 1997, a	1.000-	9.280	86.125	19.189-	17.189	0.108-	0.914
Rindone, 1997, b	7.000-	9.280	86.125	25.189-	11.189	0.754-	0.451
Romo-Nava, 2014 a	17.000	11.259	126.766	5.067-	39.067	1.510	0.131
Romo-Nava, 2014 b	0.000	10.206	104.168	20.004-	20.004	0.000	1.000
Seabra, 2010	7.000	2.104	4.428	2.876	11.124	3.327	0.001
	2.373-	4.714	22.226	11.613-	6.867	0.503-	0.615



D. HDL-C

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Celinski, 2014	10.000-	6.610	43.697	22.956-	2.956	1.513-	0.130
Cichoz-Lach, 2010	7.000	2.688	7.226	1.732	12.268	2.604	0.009
Goyal, 2014	0.900	1.637	2.678	2.308-	4.108	0.550	0.582
Modabbernia, 2014	1.400-	3.817	14.571	8.881-	6.081	0.367-	0.714
Rindone, 1997, a	0.000	3.363	11.313	6.592-	6.592	0.000	1.000
Rindone, 1997, b	1.000	3.536	12.500	5.930-	7.930	0.283	0.777
Romo-Nava, 2014 a	2.590	4.095	16.772	5.437-	10.617	0.632	0.527
Romo-Nava, 2014 b	0.100	2.962	8.774	5.705-	5.905	0.034	0.973
Seabra, 2010	1.100	3.946	15.568	6.633-	8.833	0.279	0.780
	1.284	0.995	0.991	0.667-	3.235	1.290	0.197



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pre-treatment × *SD post-treatment)]*, assuming a correlation coefficient of 0.5, as a conservative estimate for R which ranges between 0 and 1 [29]. When SD was not directly available and a standard error of the mean (SEM) was reported instead of SD, we converted it to SD for analyses using the following formula: $SDs = SEs \times square\ root\ (n)$, where n was the number of participant in each group. In case of medians and ranges or 95% CIs, mean and SD values were estimated using Hozo et al. method [30]. Plot digitizer software was used to extract the data when the outcome variable was presented only in the graphic form. Heterogeneity was evaluated by Cochran's Q-test (with significance set at $p < 0.1$) and the I^2 test for calculating the percentage of heterogeneity (I^2 value $\geq$ 50% indicating significant heterogeneity). In the presence of heterogeneity a random effects model was used; otherwise, the fixed-effects model was applied. Our sensitivity analysis was done using the leave-one-out method (i.e. removing a single trial each time and repeating the analysis) to assess the impact of each study on the overall effect size [31].

A pre-defined subgroup analysis of baseline lipid parameters, dose of supplementation, duration of supplementation and quality assessment using the Jadad scale was conducted to evaluate the impact of this factors on the results. Meta-regression was performed to assess the association between the effect size and potential moderator variables including dose of supplementation and duration of supplementation.

Any potential publication bias was identified using the funnel plot and also with Begg's rank correlation and Egger's weighted regression tests. For adjusting the analysis in the effects of publication bias, we used the Duval & Tweedie "trim and fill" and "fail-safe N" methods [32]. The meta-analysis was performed using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [33]. Probability value (p value) < 0.05 was considered as statistically significant.

3. Results

3.1. Flow and characteristics of included studies

The flowchart of the selection process in meta-analysis is shown in Fig. 1. A total of 471 reports were initially identified; after removing duplicates (n = 58), 413 articles remained. Of the 413 articles, 389 were excluded because they were either not RCTs in humans or unrelated to our present meta-analysis according to inclusion criteria, after a careful review of the titles and abstracts. Therefore, 24 potentially relevant articles were selected for full-text evaluation and detailed examination. An additional 16 articles were excluded for one or more of the following reasons: because the studies were not randomized placebo-controlled studies (n = 3), lipid measurements were not performed (n = 4), used melatonin in combination with other component without an appropriate control group (n = 2), not controlled for melatonin supplementation (n = 3), or were duplicated (n = 4). After final assessment, 8 eligible randomized controlled studies with 10 treatment arms satisfied the inclusion criteria and qualified for the final meta-analysis [21,23–26,34–36].

3.2. Characteristics of included studies

The characteristics of the eligible studies are presented in Table 1. Data were pooled from eight eligible studies comprising 10 treatment arms in which 377 subjects overall were randomly assigned (206 subjects in the melatonin group and 171 in the control group). The number of participants in these trials ranged from 16 [21] to 74 [34]. The included studies were published between 1997 and 2014 and were conducted in Poland (three studies) [24,26,34], USA (two studies) [21,23], Brazil [36], Mexico [25], and Iran [35]. The mean age of the participants ranged from 28.6 to 68.0 years old. Only one trial was conducted exclusively on men [36], and the remaining trials on both sexes. The duration of supplementation varied from 4 [26,36] to 24 [24] weeks. Most of the trials (6 of 8) adopted a parallel study design [24–26,34–36], whereas only two trials used a crossover design [21,23]. Of the eight studies, three included non-alcoholic steatohepatitis participants [24,26,34], eight had participants with type 2 diabetes [37–44], one included participants with metabolic syndrome [23], one included participants with Patients with first-episode schizophrenia [35], one included participants with hypercholesterolaemia [21], one included participants Schizophrenia or bipolar disorder [25], and one included healthy adults [36].

3.3. Data quality

Four trials [23–25,35] were classified as high quality (Jadad score $\geq$ 3), and the remaining five trials [21,26,34,36] were low quality (Jadad score < 3). All studies reported randomization, but one study [26] did not mention whether the trial was randomized. When we included or excluded this study, no difference was found in the meta-analysis results. Furthermore, four studies [5,7,45,46] did not adequately explain the randomization procedure. Of the eight included studies, four trials [4,9,25,47] reported blinding whereas five trials [21,24,26,34,36] did not clearly describe the blinding procedure. Details related to dropouts were reported in four studies [23–25,35]. The last column of Table 1 provides results of quality assessment of the studies.

3.4. Meta-analysis results

Forest plots summarizing the meta-analysis of trials on each lipid parameter are illustrated in Fig. 2 A–D. The results for triglycerides were reported in 10 comparisons from 8 studies representing 377 participants**.** Pooled results from the random-effect model showed that melatonin supplementation significantly reduced triglycerides level (WMD: −31.54 mg/dL, 95% CI: −50.71, −12.38, p = 0.001), with significant heterogeneity (I^2 = 53.25%, p = 0.023) (Fig. 2 panel A). Six trials with 8 treatment arms totaling 260 patients provided data on total cholesterol levels. Figure 2 shows the pooled results from the random-effects model combing the WMD for the effect of melatonin supplementation on total cholesterol levels in the study population, which demonstrates that the levels of total cholesterol were significantly reduced in the melatonin treatment groups compared with the control groups (WMD: −18.48 mg/dL, 95% CI: −35.33, −1.63, p = 0.032), with significant heterogeneity among the studies (I^2 = 77.74%, p < 0.001) (Fig. 2 panel B). The results of LDL-C were shown in 10 comparisons from 8 studies including 321 subjects. Overall, intervention of melatonin did not significantly affect LDL-C (WMD: −2.37 mg/dL, 95% CI: −11.61, −6.86, p = 0.615), with significant heterogeneity among the studies (I^2 = 65.77%, p = 0.003) (Fig. 2 panel C). The impact of melatonin supplementation on HDL-C (7 trials; 9 treatment arms, 336 participants) was also assessed. Pooled results from the fixed-effect model did not support a

Fig. 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the effect of melatonin supplementation on blood lipids. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

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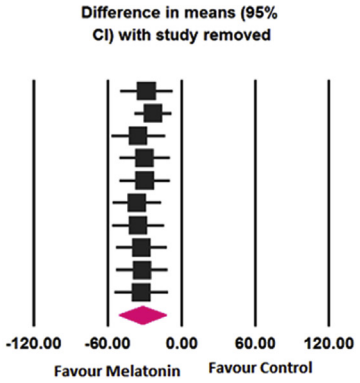
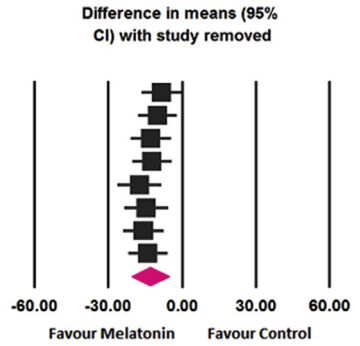
A.Triglycerides

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Celinski, 2014	28.321-	10.731	115.144	49.353-	7.290-	2.639-	0.008
Cichoz-Lach, 2010	23.031-	7.572	57.328	37.871-	8.191-	3.042-	0.002
Gonciarz,2012	35.095-	10.959	120.110	56.575-	13.615-	3.202-	0.001
Goyal, 2014	29.952-	10.217	104.394	49.977-	9.926-	2.931-	0.003
Modabbernia, 2014	29.798-	10.222	104.493	49.833-	9.762-	2.915-	0.004
Rindone, 1997, a	36.099-	9.966	99.330	55.633-	16.565-	3.622-	0.000
Rindone, 1997, b	35.191-	10.519	110.656	55.809-	14.574-	3.345-	0.001
Romo-Nava, 2014 a	32.337-	10.397	108.087	52.714-	11.960-	3.110-	0.002
Romo-Nava, 2014 b	31.935-	10.496	110.173	52.508-	11.363-	3.043-	0.002
Seabra, 2000	32.577-	11.066	122.454	54.266-	10.888-	2.944-	0.003
	31.549-	9.781	95.658	50.719-	12.380-	3.226-	0.001



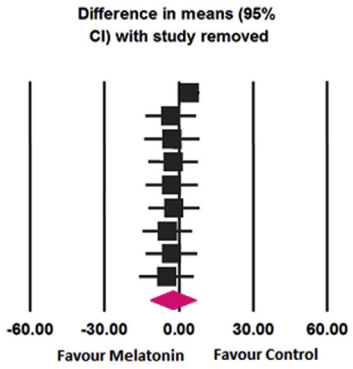
B. Total cholesterol

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Celinski, 2014	8.327-	4.060	16.481	16.284-	0.370-	2.051-	0.040
Cichoz-Lach, 2010	10.008-	3.941	15.530	17.732-	2.284-	2.540-	0.011
Gonciarz,2012	12.669-	4.109	16.881	20.722-	4.616-	3.084-	0.002
Modabbernia, 2014	12.204-	3.960	15.680	19.965-	4.443-	3.082-	0.002
Rindone, 1997, a	17.249-	4.447	19.778	25.966-	8.533-	3.879-	0.000
Rindone, 1997, b	14.574-	4.447	19.778	23.291-	5.858-	3.277-	0.001
Romo-Nava, 2014 a	15.670-	4.068	16.550	23.643-	7.696-	3.852-	0.000
Romo-Nava, 2014 b	13.896-	3.995	15.959	21.726-	6.066-	3.478-	0.001
	12.926-	3.850	14.822	20.472-	5.381-	3.358-	0.001



C. LDL-C

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Celinski, 2014	4.306	2.076	4.310	0.237	8.375	2.074	0.038
Cichoz-Lach, 2010	3.067-	5.130	26.319	13.122-	6.988	0.598-	0.550
Goyal, 2014	2.605-	5.609	31.463	13.599-	8.389	0.464-	0.642
Modabbernia, 2014	2.193-	5.044	25.442	12.079-	7.693	0.435-	0.664
Rindone, 1997, a	2.832-	5.296	28.052	13.213-	7.549	0.535-	0.593
Rindone, 1997, b	1.933-	5.171	26.735	12.067-	8.202	0.374-	0.709
Romo-Nava, 2014 a	4.522-	5.058	25.585	14.436-	5.392	0.894-	0.371
Romo-Nava, 2014 b	2.909-	5.244	27.503	13.188-	7.370	0.555-	0.579
Seabra, 2010	4.853-	5.586	31.207	15.802-	6.096	0.869-	0.385
	2.373-	4.714	22.226	11.613-	6.867	0.503-	0.615



D. HDL-C

Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Celinski, 2014	1.546	1.007	1.014	0.427-	3.519	1.536	0.125
Cichoz-Lach, 2010	0.376	1.071	1.148	1.724-	2.476	0.351	0.726
Goyal, 2014	1.510	1.254	1.572	0.948-	3.967	1.204	0.229
Modabbernia, 2014	1.480	1.031	1.063	0.541-	3.501	1.436	0.151
Rindone, 1997, a	1.407	1.042	1.086	0.635-	3.450	1.351	0.177
Rindone, 1997, b	1.309	1.037	1.076	0.724-	3.342	1.262	0.207
Romo-Nava, 2014 a	1.202	1.026	1.053	0.809-	3.213	1.172	0.241
Romo-Nava, 2014 b	1.435	1.057	1.117	0.636-	3.506	1.358	0.175
Seabra, 2010	1.297	1.029	1.058	0.719-	3.313	1.261	0.207
	1.284	0.995	0.991	0.667-	3.235	1.290	0.197

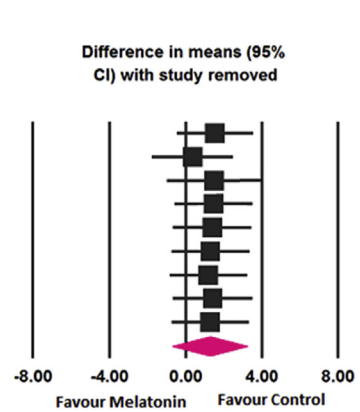


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Table 2
Results of subgroup analysis of included randomized controlled trials in meta-analysis of melatonin and lipid parameters.

Variables	Dose (mg/d)		Duration (weeks)		Baseline (mg/dL)		Study quality (Jadad score)	
Triglycerides (mg/dL)	**≥8**	**<8**	**≥8**	**<8**	**≥200**	**<200**	**High (≥3)**	**Low (<3)**
No. of comparison	5	5	6	4	5	5	5	5
WMD (95% CI)	−42.82 (−69.61, −16.04)	−10.96 (−33.17, 11.25)	−32.25 (−51.21, −13.28)	−26.23 (−64.27, 11.80)	−36.86 (, −70.00, −3.72)	−19.81 (−37.35, −2.28)	−21.33 (−40.45, −2.22)	−32.01 (−61.86, −2.16)
P value	0.002	0.334	0.001	0.176	0.029	0.027	0.029	0.036
I^2 (%)	66.98	0.00	13.29	77.75	73.05	0.00	0.00	73.16
P-heterogenity	0.017	0.558	0.330	0.004	0.005	0.772	0.570	0.005
Total cholesterol (mg/dL)	**≥8**	**<8**	**≥8**	**<8**	**≥200**	**<200**	**High (≥3)**	**Low (<3)**
No. of comparison	3	5	5	3	5	3	4	4
WMD,95% CI	−39.56 (−54.13, −25.00)	−3.15, (−11.97, 5.66)	-16.65 (−27.86, −5.44)	−9.83 (−20.04, 0.36)	−16.40 (−25.00, −7.80)	−1.32 (−17.04, 14.39)	−5.98 (−18.69, 6.72)	−16.70 (−26.08, −7.33)
P value	<0.001	0.483	0.004	0.059	<0.001	0.869	0.356	<0.001
I^2 (%)	80.23	0.00	75.47	86.07	84.36	36.46	27.22	88.26
P-heterogenity	0.006	0.439	0.003	0.001	<0.001	0.207	0.249	<0.001
LDL-C (mg/dL)	**≥8**	**<8**	**≥8**	**<8**	**≥130**	**<130**	**High (≥3)**	**Low (<3)**
No. of comparison	4	5	5	4	4	5	4	5
WMD , 95% CI)	−8.04 (−25.80, - 9.71)	0.17 (−8.94, 9.29)	-7.94 (−0.26, 0.009)	2.90 (2.02, 0.78)	−13.68 (−35.84, 8.46)	4.25 (−1.80, 10.31)	−0.15 (−8.78, 8.46)	−7.52 (−23.99, 8.93)
P value	0.374	0.970	0.401	0.30	0.226	0.169	0.255	0.370
I^2 (%)	84.60	0.00	74.66	0.00	74.44	20.78	0.00	79.35
P-heterogenity	0.001>	0.548	0.003	0.422	0.008	0.282	0.408	0.001
HDL-C (mg/dL)	**≥8**	**<8**	**≥8**	**<8**	**≥40**	**<40**	**High (≥3)**	**Low (<3)**
No. of comparison	4	5	5	4	6	3	4	5
WMD, 95% CI	1.91 (−0.61, 4.44)	0.36 (−2.69, 3.42)	0.27 (−2.17, 2.73)	3.01 (−0.20, 6.23)	0.36 (−1.91, 2.63)	3.85 (−0.05, 7.64)	0.65 (−1.83, 3.15)	2.26 (−0.86, 5.38)
P value	0.138	0.815	0.825	0.066	0.755	0.057	0.605	0.156
I^2 (%)	58.64	0.00	0.00	15.77	0.00	40.46	0.00	44.55
P-heterogenity	0.064	0.967	0.545	0.313	0.753	0.186	0.903	0.125

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; WMD, weight mean difference

significant effect of melatonin supplementation in altering HDL-C concentrations (WMD: 1.28 mg/dL, 95% CI: −0.66, 3.23, p = 0.197), with no significant heterogeneity (I^2 = 4.77%, p = 0.395) (Fig. 2 panel D).

Because the test for heterogeneity was statistically significant for triglycerides, total cholesterol and LDL-C, we reported the results from random-effects, but as no significant heterogeneity was found for HDL-C, the results were reported based on fixed-effect models.

3.5. Sensitivity analysis

The effect sizes for the influence of melatonin on triglycerides, total cholesterol and HDL-C were robust in the leave-one-out sensitivity analysis, suggesting the omission of each single trial did not have a significant effect on the results of meta-analysis, but the effect of melatonin on LDL-C was sensitive to the study performed by Celinski et al., [33]. Removing this study from the analysis renders the effect of melatonin on LDL-C, significant (Fig. 3 panel A–D).

3.6. Sub-group analysis

The subgroup analyses were done based on the following variables: dose of supplementation, intervention duration and baseline lipid profile. The results are summarized in Table 2. When the meta-analysis was stratified according to dose of supplementation, a significant reduction in triglycerides was found in studies using ≥8 mg/d (WMD: −42.82 mg/dL, 95% CI: −69.61, −16.04, p = 0.002), but not lower doses (WMD: −10.96 mg/dL, 95% CI: −33.17, 11.25, p = 0.334). Total cholesterol concentrations also decreased significantly in the interventions using melatonin doses ≥8 mg/d (WMD: −39.56 mg/dL, 95% CI: −54.13, −25.00, p < 0.001), versus lower doses (WMD: −3.15 mg/dL, 95% CI: −11.97, 5.66, p = 0.483). When the studies were stratified according to their duration, there was a significantly greater effect on triglycerides levels in the subset of trials with ≥8 weeks of duration (WMD: −32.25 mg/dL, 95% CI: −51.21, −13.28, p = 0.001) versus the subset lasting < 8 weeks (WMD: −26.23, 95% CI: −64.27, 11.80, p = 0.176). Similarly, the effect of melatonin on total cholesterol levels were significantly lower in the subgroup with duration of intervention ≥8 weeks (WMD: −16.65 mg/dL, 95% CI: −27.86, −5.44, p = 0.004) compared with studies with shorter duration (WMD: −9.83 mg/dL, 95% CI: −20.04, 0.36, p = 0.059) (Table 2). We also stratified the included studies according to the baseline lipid status. Significant reductions were found in those studies with baseline total cholesterol ≥200 mg/dl (WMD: −16.40 mg/dL, 95% CI: −25.00, −7.80, p < 0.001) but not with lower initial concentrations (WMD: −1.32 mg/dL, 95% CI: −17.04, 14.39, p = 0.869). The results of subgroup analysis of this study also suggested more pronounced but not significant reduction of LDL-C levels in subset of trials with higher (≥100 mg/dL) baseline levels (WMD: −13.68, 95% CI: −35.84, 8.46, p = 0.226) versus those with lower baseline levels (WMD: 4.25, 95% CI, −1.80. 10.31, p = 0.169).

3.7. Meta-regression

Significant association was found between change in triglycerides and total cholesterol concentrations with dose of supplementation but not with LDL-C and HDL-C (Fig. 4 panel A–D and

Fig. 3. Leave-one-out sensitivity analysis of the impact of melatonin supplementation on blood lipids. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

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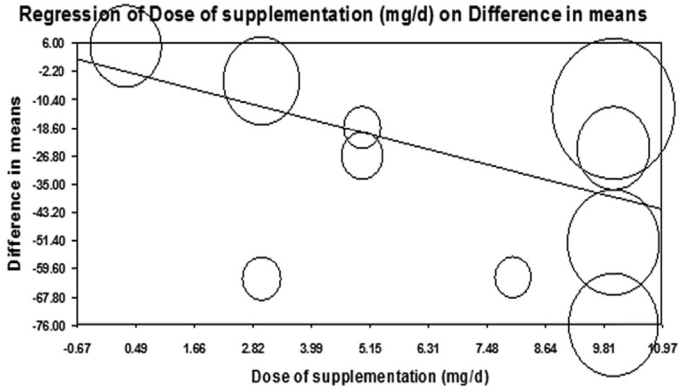
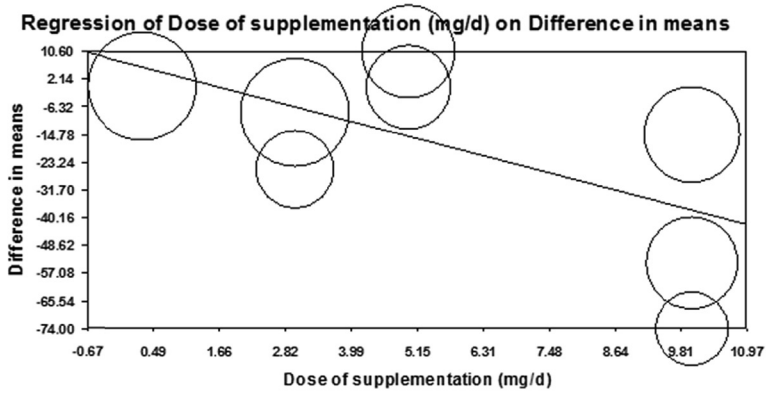
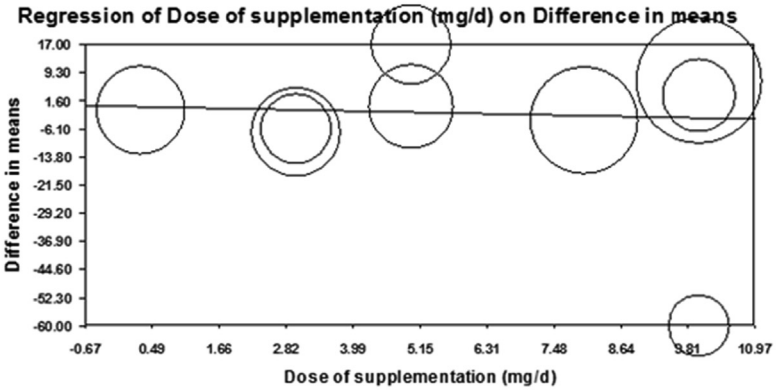
A.Triglycerides



B. Total cholesterol



C. LDL-C



D. HDL-C

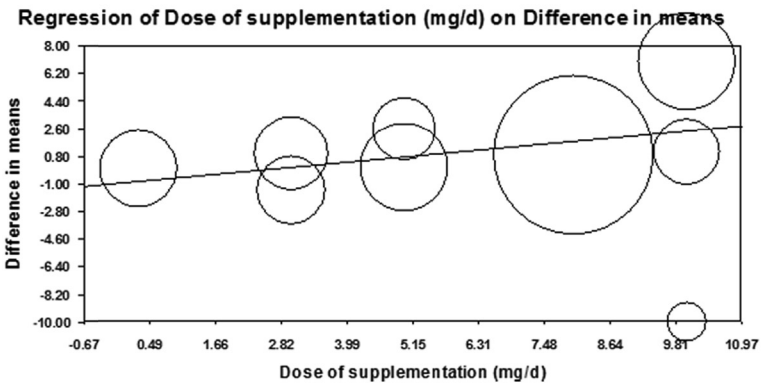


Table 3
Meta-regression between changes in body lipid profiles and administered doses and intervention duration of melatonin.

Model	Fixed effect			Random effect		
	Slope	95% CI	P value	Slope	95% CI	P value
Triglycerides						
Dose of supplementation	−3.75	−7.17 to −0.33	0.031	−4.50	−7.87 to −1.14	0.008
Intervention duration	1.03	−0.44 to 2.50	0.170	0.75	−1.77 to 3.28	0.559
Total cholesterol						
Dose of supplementation	−4.50	−7.87 to −1.14	0.008	−3.92	−5.99 to −1.85	0.0002
Intervention duration	−0.15	−2.98 to 2.68	0.917	−0.73	−1.99 to 0.52	0.253
LDL-C						
Dose of supplementation	0.98	−0.39 to 2.36	0.168	−0.31	−2.77 to 2.13	0.079
Intervention duration	−2.81	−4.41 to −1.20	0.0006	−2.81	−4.41 to −1.20	0.0006
HDL-C						
Dose of supplementation	0.31	−0.30 to 0.98	0.303	0.31	−0.30 to 0.98	0.303
Intervention duration	−0.75	−1.54 to 0.03	0.059	−0.75	−1.54 to 0.03	0.059

Table 3). Considering the duration of supplementation with melatonin, significant associations were found with changes in LDL-C but not with triglycerides, total cholesterol and HDL-C levels (Fig. 5 panel A–D and Table 3).

3.8. Publication bias

The funnel plots indicated an asymmetry in the meta-analyses of melatonin effects on lipids parameters. Using “trim and fill” method, 2, 0, 3, 1 and 3 potentially missing studies were imputed for triglycerides, Total cholesterol, LDL-C, and HDL-C respectively (Supplementary Fig. 1 A–D). Corrected effect sizes and the results of Egger's linear regression, Begg's rank correlation, and “fail safe N” tests are summarized in Supplementary Table 1.

4. Discussion

In our present study, we comprehensively and systematically reviewed the currently available literature that investigates the effects of melatonin supplementation on blood lipid parameters in adults. The findings from the current study revealed that participants receiving melatonin supplementation significantly had improvements in triglycerides, and total cholesterol while no significant effect on LDL-C and HDL-C was observed. Nevertheless, triglycerides levels were significantly reduced only at doses ≥8 mg/day and when the trials lasted for 8 or more weeks. Total cholesterol levels were also significantly reduced only at doses ≥8 mg/day and when total cholesterol baseline levels were equal or higher than 200 mg/dL.

In the present review, we confirmed the results of other animal and human studies concerning the significant effects of melatonin supplementation on triglycerides [18,22], and total cholesterol [26]. However, its effect on HDL-C and LDL-C is somewhat unpredicted and opposed to previous findings in experimental studies [18,48]. There have been inconsistent findings regarding the effect of melatonin supplementation on circulating LDL-C and HDL-C; some trials reported significant effects [22] while others reported slight [35] or no reduction [26] as our finding. The beneficial effect of melatonin treatment on dyslipidemia has been demonstrated [12]. In a 14-month follow up when nonalcoholic fatty liver disease patients were treated with 10 mg per day of melatonin, a significant decrease in triglycerides and LDL cholesterol (LDL-C) levels was observed in comparison with control group treated with essential [22].

The lipid-reducing mechanisms of melatonin in experimental studies were attributed to its suppressing effect on visceral fat [45,49], thereby enhancing insulin sensitivity and resulting in increased activity of lipoprotein lipase (LPL) and decreasing lipolysis in adipose tissue [45], prevention of cholesterol absorption [50] and synthesis [20], increasing the conversion of cholesterol to bile acids, enhancing the activity of LDL receptor [20,51], inhibition of metabotropic receptors that play a role in fatty acid transportation [52]. Moreover, a noticeable reduction of VLDL cholesterol was observed after melatonin supplementation [50]. The VLDL is an important transporter in cholesterol and triglyceride metabolism when the palmitic acid is absorbed. The effect of melatonin supplementation on VLDL cholesterol reduction could be caused not only by a decrease in VLDL secretion from the liver, but also a reduction of VLDL secretion in the intestine might contribute; this is in agreement with suppression of intestinal cholesterol absorption [50].

Based on the sub-group results, higher doses (≥8 mg/d) and longer duration (≥8 weeks) are required to see the beneficial effect of melatonin. This finding is in line with the results of a study regarding the effects of 14 weeks of 10 mg per day melatonin supplementation on non-alcoholic fatty liver disease subjects [22]. Moreover, the results of Pan et al. [53] supported the dose-dependency effect of melatonin on triglycerides metabolism in rats. Another point of emphasis is that the effects of melatonin supplementation on plasma total cholesterol were more pronounced in studies with higher baseline cholesterol (>200 mg/dL) [20,21,23,25]. Therefore, the higher plasma total cholesterol made the subjects more likely to be affected by the melatonin supplementation.

On the whole, the triglycerides and total cholesterol-lowering effect of melatonin, along with its minor effect on improving LDL and HDL-C and other finding which showed that melatonin can protect LDL from oxidation [46,48,54] may contribute to its promising beneficial role in atherosclerosis prevention, given that LDL oxidation is an important activating step in the pathogenesis of atherosclerosis [55]. The significant effect of melatonin on reducing plasma triglycerides is an important consequence due to the remnant lipoprotein particles which are triglyceride-rich lipoproteins, have an emerging role in the pathophysiology of atherosclerosis [56]. Moreover, a very large body of evidence showed that melatonin is a strong antioxidant through the scavenging and detoxifying of free radicals at both physiologic and pharmacologic concentrations [47,57,58].

Fig. 4. Meta-regression plots of the association between mean changes in blood lipids and dose of melatonin supplementation. The size of each circle is inversely proportional to the variance of change. The effect of melatonin supplementation on blood lipids. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

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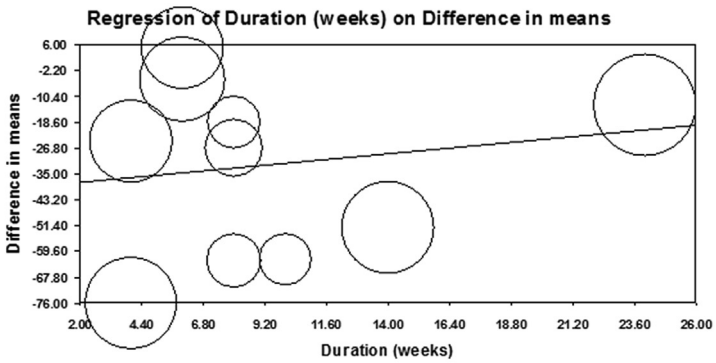
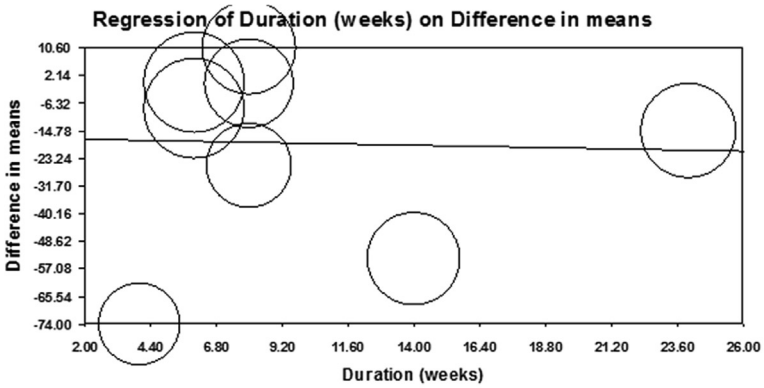
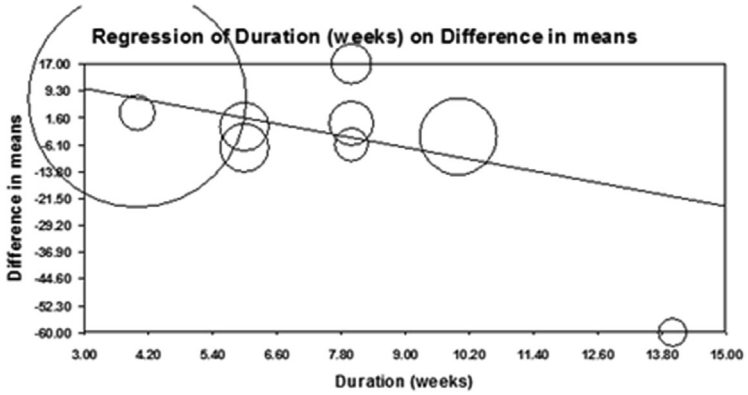
A.Triglycerides



B. Total cholesterol



C. LDL-C



D. HDL-C

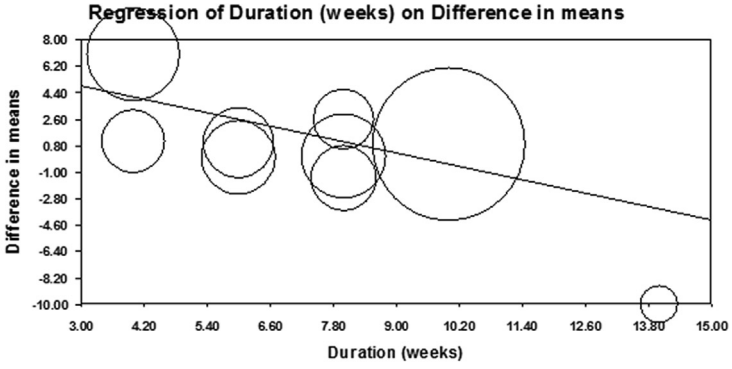


Fig. 5. Meta-regression plots of the association between mean changes in blood lipids and duration of melatonin supplementation. The size of each circle is inversely proportional to the variance of change. Effect of melatonin supplementation on blood lipids. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

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Melatonin has been supplemented to humans and animals in a wide range of doses in both physiological and pharmacological amounts, and there is extensive agreement regarding its non-toxicity [36]. Therefore, given that melatonin is affordable and inexpensive and can be easily produced in a pharmacologically pure form and importantly, due to its beneficial role in protecting against cardiovascular risk factors through its hypolipidemic and anti-oxidative stress properties, it could be considered for the improvement of dyslipidemia [59].

The current meta-analysis has pooled up the results of available RCTs regarding the effect of melatonin on plasma lipid indices, and we believe that our findings are valuable for researchers and clinicians. Nevertheless, this study had several weaknesses, and the findings should be interpreted with caution. Most importantly, there were few eligible studies and most of them included small sample sizes. Furthermore, the significant heterogeneity between studies indicated that the effects of melatonin on lipid indices are not uniform, because the eligible studies have different methodologies and were performed among different populations.

In conclusion, sufficient evidences were found regarding the significant effect of melatonin on triglycerides and cholesterol levels in our meta-analysis, while no significant effect was seen on LDL and HDL-C concentration.

The positive effect of melatonin is more evident in higher doses and longer duration. Additional high-quality well-designed studies should be performed to approve our findings.

Author contributions

The authors' responsibilities were as follows: M.MS conceived the study. M.MS carried out the literature search. M.MS and M.GH carried out data extraction and independent reviewing. M.MS and Z.M conducted the quality of included studies. M.MS conducted data analysis and interpretation. M.MS wrote the manuscript. Z.M conducted critical revision. All authors approved the final manuscript.

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Conflict of Interest

The author declares no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2017.11.003.

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