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Inflammopharmacology

REVIEW

The effects of melatonin supplementation on inflammatory markers among patients with metabolic syndrome or related disorders: a systematic review and meta-analysis of randomized controlled trials

Maryam Akbari[1] · Vahidreza Ostadmohammadi[2] · Reza Tabrizi[1] · Kamran B. Lankarani[3] · Seyed Taghi Heydari[3] · Elaheh Amirani[2] · Russel J. Reiter[4] · Zatollah Asemi[2]

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Abstract

Objective This systematic review and meta-analysis of randomized controlled trials (RCTs) was carried out to determine the effect of melatonin supplementation on the inflammatory markers among individuals with metabolic syndrome (MetS) and related disorders.

Methods We searched the following databases up to March 2018: PubMed, MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. Three reviewers independently assessed study eligibility, extracted data, and evaluated risk of bias of included primary studies. Statistical heterogeneity was assessed using Cochran's Q test and I-square (I^2) statistic. Data were pooled using the random effect model and standardized mean difference (SMD) was considered as the summary effect size.

Results Six trials of 317 potential reports were identified to be suitable for our meta-analysis. The pooled results using random effects model indicated that melatonin supplementation significantly reduced C-reactive protein (CRP) (SMD = − 1.80; 95% CI − 3.27, − 0.32; $P = 0.01$; I^2: 95.2) and interleukin 6 (IL-6) concentrations (SMD = − 2.02; 95% CI − 3.57, − 0.47; $P = 0.01$; I^2: 91.2) among patients with MetS and related disorders; however, it did not affect tumor necrosis factor-α (TNF-α) concentrations (SMD = − 1.87; 95% CI − 3.81, 0.07; $P = 0.05$; I^2: 94.4).

Conclusions In summary, the current meta-analysis showed the promising effect of melatonin administration on reducing CRP and IL-6, but not TNF-α levels among patients with MetS and related disorders. Additional prospective studies are recommended using higher supplementation doses and longer intervention period.

Keyword Melatonin · Inflammatory markers · Meta-analysis

Introduction

Metabolic syndrome (MetS) is associated with increased systemic inflammation (Leisegang et al. 2016). This status is seen more commonly in obese individuals compared with lean people (Usta et al. 2018). Obesity and overweight cause the production and release of a variety of pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which in turn can induce the production of reactive oxygen species (ROS) and free radicals (Fantuzzi 2005). It was previously reported that patients with MetS are susceptible to a two-fold increased risk of cardiovascular disease (CVD) over the subsequent 5–10 years (Alberti et al. 2009). In addition, increased levels of inflammatory cytokines play a key role in the progression of atherosclerotic events

✉ Zatollah Asemi
asemi_r@yahoo.com

1 Health Policy Research Center, Institute of Health, Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

2 Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran

3 Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran

4 Department of Cellular and Structural Biology, University of Texas Health Science, Center, San Antonio, TX, USA

(Ballantyne and Nambi 2005) and type 2 diabetes mellitus (T2DM) (Liu et al. 2016).

Complementary therapies including antioxidant supplementation are recommended in individuals with MetS and related disorders to improve their nutritional status and boost their immune system (Tabrizi et al. 2017). Mechanistic studies have documented the powerful antioxidant and anti-inflammatory actions of melatonin (Maldonado et al. 2016; Mauriz et al. 2013). Melatonin and its metabolites directly scavenge free radicals, and reduce oxidative damage (Galano et al. 2013). Moreover, they stimulate gene expression related to antioxidant enzymes (Rodriguez et al. 2004). In addition, it has been suggested that melatonin decreases the production of pro-inflammatory markers by inhibiting the expression of TNF-α, IL-1β and IL-6 (Cuzzocrea and Reiter 2002; Radogna et al. 2010). In a study conducted by Mesri Alamdari et al.(2015), melatonin supplementation at a dosage of 6 mg/day for 40 days significantly reduced TNF-α and IL-6, but did not affect hs-CRP levels in obese women. In contrast, taking melatonin (10 mg/day) for 1 month by patients with severe and advanced atherosclerosis did not affect hs-CRP levels (Javanmard et al. 2016).

There are no systematic reviews or meta-analyses of randomized controlled trials (RCTs) assessing the effect of melatonin supplementation on inflammatory markers among individuals with MetS or related disorders. Thus, the present meta-analysis was conducted to summarize the available evidence regarding the effect of melatonin supplementation on inflammatory markers among patients with these conditions.

Materials and methods

Search strategy and selection studies

Two independent authors systematically searched the online databases, including Cochrane Library, EMBASE, PubMed, and Web of Science databases for relevant studies published before 30 March 2018. Searches were restricted to human clinical RCTs and those published in English. Two independent authors performed the literature search to retrieve RCTs that have examined the association between melatonin supplementation and the inflammatory markers using the following MeSH and text keywords: patients ["Mets" OR "disorders related to MetS" OR "diabetes" OR "T1DM" OR "T2DM" OR "overweight" OR "obese" OR "chronic kidney disease (CKD)" OR "hypertension" OR "high blood pressure" OR "dyslipidemia" OR "CVD"], intervention ("melatonin" AND "supplementation" OR "intake"), and outcomes ("CRP " OR "IL-6" OR "TNF-α").

Inclusion and exclusion criteria

Two authors (MA and VO) investigated the titles/abstracts to identify related studies and to omit duplicates. Then the full texts of relevant studies were retrieved to ascertain whether these studies were suitable for our meta-analysis. RCTs were selected for analysis based on the following inclusion criteria: the study was a human RCT (either parallel or cross-over design), and contained adequate data extracted from RCTs including the mean changes of CRP, IL-6, and TNF-α with standard deviations (SDs) and related 95% confidence intervals (CIs) for the intervention and placebo groups. Other studies such as animal experiments, in vitro studies, case reports, observational studies, investigations without control, and studies that did not achieve the least quality assessment score were excluded from this meta-analysis.

Data extraction and quality assessment

Two independent authors (VO and MA) extracted the following data from selected studies: first authors' name, year of publication, study location, age, study design, sample size, dose of intervention, duration of study, type of disease, the mean and standard deviation (SD) for CRP, IL-6, and TNF-α. When discrepancies occurred between the authors, it was resolved by discussion with a third author (ZA). The quality of the selected RCTs was assessed by two authors (MA and RT) independently using the Cochrane Collaboration risk of bias tool based on the following criteria: "randomization generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting, and the other sources of bias".

Data synthesis and statistical analysis

The authors determined the effects of melatonin supplementation on the changes of the following outcomes: (1) CRP, (2) IL-6 and (3) TNF-α levels. The standardised mean differences (SMDs) with 95% CI were used to pooled effect sizes using STATA software version 12.0 (Stata Corp., College Station, TX) and RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK). Heterogeneity was assessed using Cochran's Q test (with significance P value lower than 0.1) and I-square test (I^2 more than 50% showing significant heterogeneity). Since the indications influencing pooled SMD were different among included RCTs, we used random effects models to conduct meta-analyses. Sensitivity analyses were done to explore the impact of each included study on the reliability of the pooled mean difference using leave-one-out method. Also

subgroup analyses were conducted to assess the source of heterogeneity based on the potential moderator variables. Publication bias was examined using Egger's regression tests. P values < 0.05 were considered as statistically significant.

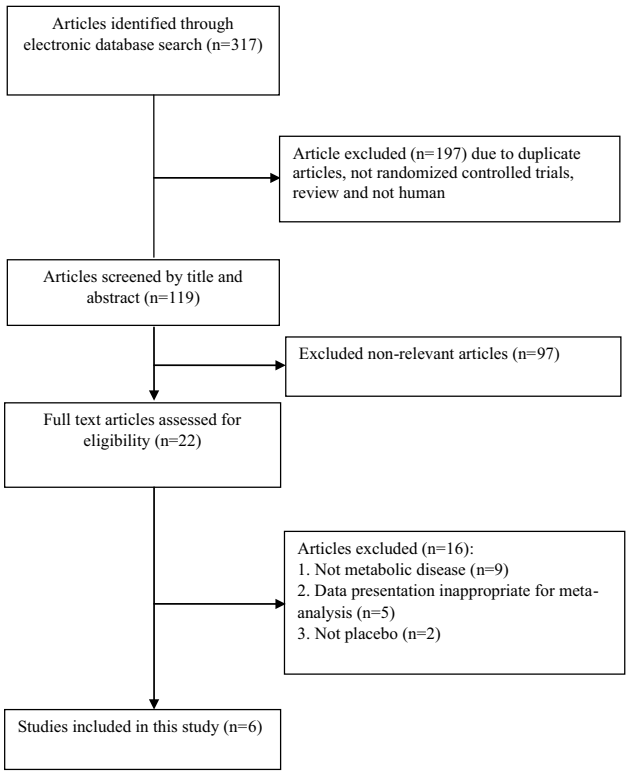

Fig. 1 Literature search and review flowchart for selection of studies

Results

Figure 1 shows the flowchart of step by step study identification and selection. Finally, six RCTs of 317 repots were selected to be included in our meta-analysis. All selected studies were randomized, double-blind, placebo-controlled trial design of which 316 persons were randomly assigned (159 subjects in intervention group and 157 in placebo group). Four trials assessed the effects of melatonin on CRP (Javanmard et al. 2016; Mesri Alamdari et al. 2015; Pakravan et al. 2017; Raygan et al. 2017), three trials on IL-6 (Celinski et al. 2014; Cichoz-Lach et al. 2010; Mesri Alamdari et al. 2015), and three on TNF-α levels (Celinski et al. 2014; Cichoz-Lach et al. 2010; Mesri Alamdari et al. 2015). The sample size of RCTs included in this meta-analysis varied from 30 to 97 participants. Duration of intervention ranged from 4 weeks to 14 months. The selected RCTs were published between 2010 and 2017. Dosage of melatonin supplements ranged from 6 to 10 mg/day. The detailed characteristics of selected RCTs are summarized in Table 1.

The methodological quality assessment of RCTs based on Cochrane Collaboration risk of bias tool is shown in Fig. 2.

Main outcomes

Forest plots reporting the effect sizes of melatonin on inflammatory markers are indicated in Fig. 3. The pooled findings indicated that melatonin supplementation significantly reduced CRP (SMD = − 1.80; 95% CI − 3.27, − 0.32; $P = 0.01$; I^2: 95.2) and IL-6 concentrations levels (SMD = − 2.02; 95% CI − 3.57, − 0.47; $P = 0.01$; I^2: 91.2) in patients with MetS and related disorders. Moreover, pooled findings from the random effects model did support

Table 1 Characteristics of included studies

Authors (Ref)	Publication year	Sample size (control/intervention)	Country/population	Intervention (name and daily dose)	Duration	Presented data	Age (years) (control, intervention)
Raygan et al. (2017)	2017	30/30	Iran/T2DM with CHD	10 mg melatonin	12 weeks	CRP	65.3 ± 10.1, 67.7 ± 11.4
Mesri Alamdari et al. (2015)	2014	22/22	Iran/obese women	6 mg melatonin	40 days	CRP, IL-6, TNF-α	20–50 years
Pakravan et al. (2017)	2015	48/49	Iran/NAFLD	10 mg melatonin	3 months	CRP	22–65 years
Celinski et al. (2014)	2014	23/23	Poland/NAFLD	10 mg melatonin	14 months	IL-6, TNF-α	29.33 ± 9.58, 36.16 ± 5.77
Cichoz-Lach et al. (2010)	2010	15/15	Poland/steatohepatitis	10 mg melatonin	4 weeks	IL-6, TNF-α	22–58 years
Javanmard et al. (2016)	2016	19/20	Iran/CHD	10 mg melatonin	1 month	CRP	58.63 ± 5.8, 60.15 ± 6.3

IL-6 interleukin-6, *CRP* C-reactive protein, *TNF-α* tumor necrosis factor-alpha, *CHD* coronary heart disease, *MetS* metabolic syndrome, *T2DM* type 2 diabetes mellitus, *NAFLD* non-alcoholic fatty liver disease

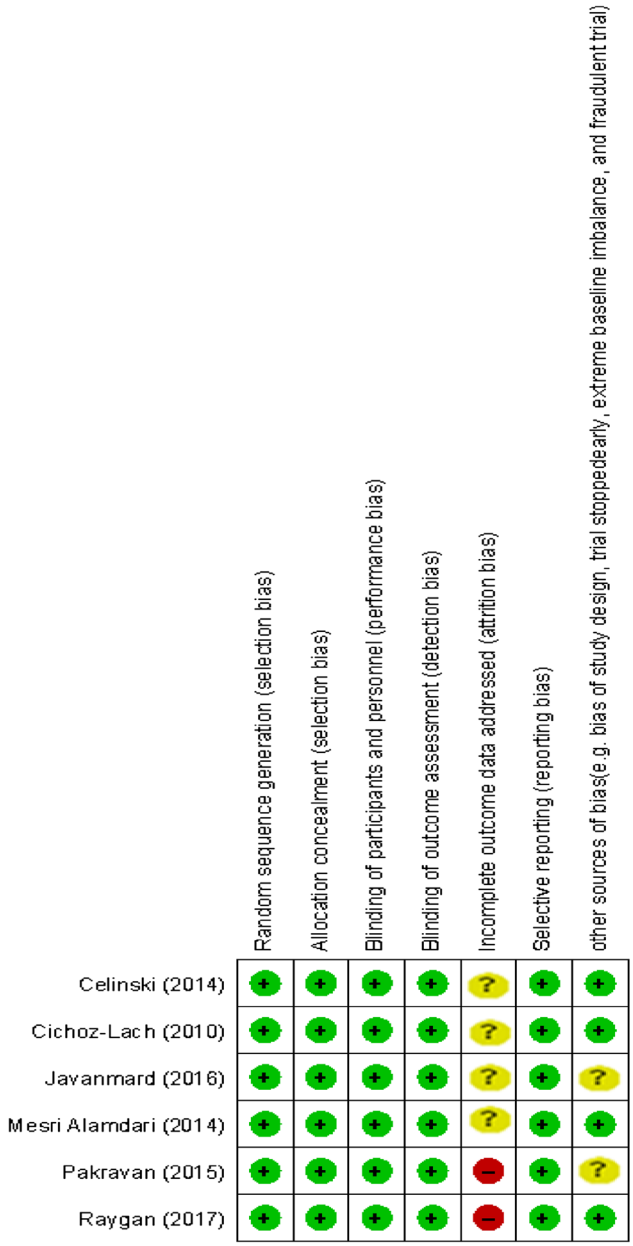

Fig. 2 The methodological quality of included studies (risk of bias)

no significant impact of melatonin supplementation on TNF-α concentration (SMD = − 1.87; 95% CI − 3.81, 0.07; $P = 0.059$; I^2: 94.4).

Pooled estimates of the SMDs based on the information at baseline and at the end of study in intervention and control groups are presented in Table 2.

Sensitivity analyses and subgroup analysis

The results of sensitivity analyses showed that the effect of melatonin on CRP, IL-6, and TNF-α levels was sensitive to the studies conducted by Javanmard et al. (2016), Mesri Alamdari et al. (2015), and Cichoz-Lach et al. (2010), respectively. Excluding these studies from the analyses changed the pooled SMD effect of melatonin on CRP (SMD − 1.79; 95% CI − 3.26, 0.32), IL-6 (SMD − 1.30; 95% CI − 2.65, 0.03), and TNF-α (SMD − 2.77; 95% CI − 4.28, − 1.25). Table 3 reports the lower and higher pooled SMDs in the sensitivity analyses for inflammatory markers. The subgroup analyses were performed based on the following variables: geographic area (Iran vs. Poland), duration of study (≤ 8 weeks vs. > 8 weeks), and dosage of melatonin (6 vs. 10 mg melatonin). According to geographic area, there was a significant reduction in CRP concentrations using RCTs conducted in Iran (SMD − 1.80; 95% CI − 3.27, − 0.32). IL-6 concentrations reduced significantly in Iran studies as well (SMD − 3.54; 95% CI − 4.50, − 2.58), versus Poland studies (SMD − 1.31; 95% CI − 2.65, 0.04). For TNF-α, we observed similar findings including Iran studies (SMD − 2.03; 95% CI − 2.76, − 1.30), versus Poland studies (SMD − 1.80; 95% CI − 5.25, 1.65). The findings of subgroup analysis based on the duration of study revealed greater significant reduction in CRP concentrations in the strata of > 8 weeks intervention (SMD − 2.22; 95% CI, − 3.37, − 1.08) rather than the strata of ≤ 8 weeks (SMD − 1.38; 95% CI − 4.57, 1.38). Similarly, the melatonin supplementation significantly decreased IL-6 levels in the subgroup with duration > 8 weeks (SMD − 2.22; 95% CI − 3.37, − 1.08) compared to ≤ 8 weeks subgroup (SMD − 2.22; 95% CI − 3.37, − 1.08) and for TNF-α levels, we observed similar findings based on the duration of intervention > 8 weeks (SMD − 1.99; 95% CI − 2.70, − 1.28) versus ≤ 8 weeks (SMD − 2.06; 95% CI − 4.92, 0.80). The findings of subgroup analysis based on the quality assessment score indicated that melatonin supplementation significantly decreased CRP levels in RCTs with high risk of bias (SMD − 2.22; 95% CI − 3.37, − 1.08) compared with RCTs having unclear risk (SMD − 1.38; 95% CI − 4.57, 1.38). The detailed findings of subgroups analyses are summarized in Table 4.

Publication bias

Egger's regression test was applied to determine the probability of publication bias among RCTs included in the meta-analysis. This test showed no significant evidence of publication bias for meta-analyses assessing the effect of melatonin on CRP ($B = -6.69$, $P = 0.69$), IL-6 ($B = -16.93$, $P = 0.43$) and TNF-α levels ($B = -24.07$, $P = 0.38$).

Discussion

To our best knowledge, this is the first meta-analysis of RCTs that evaluated the effects of melatonin supplementation on inflammatory markers among individuals with metabolic

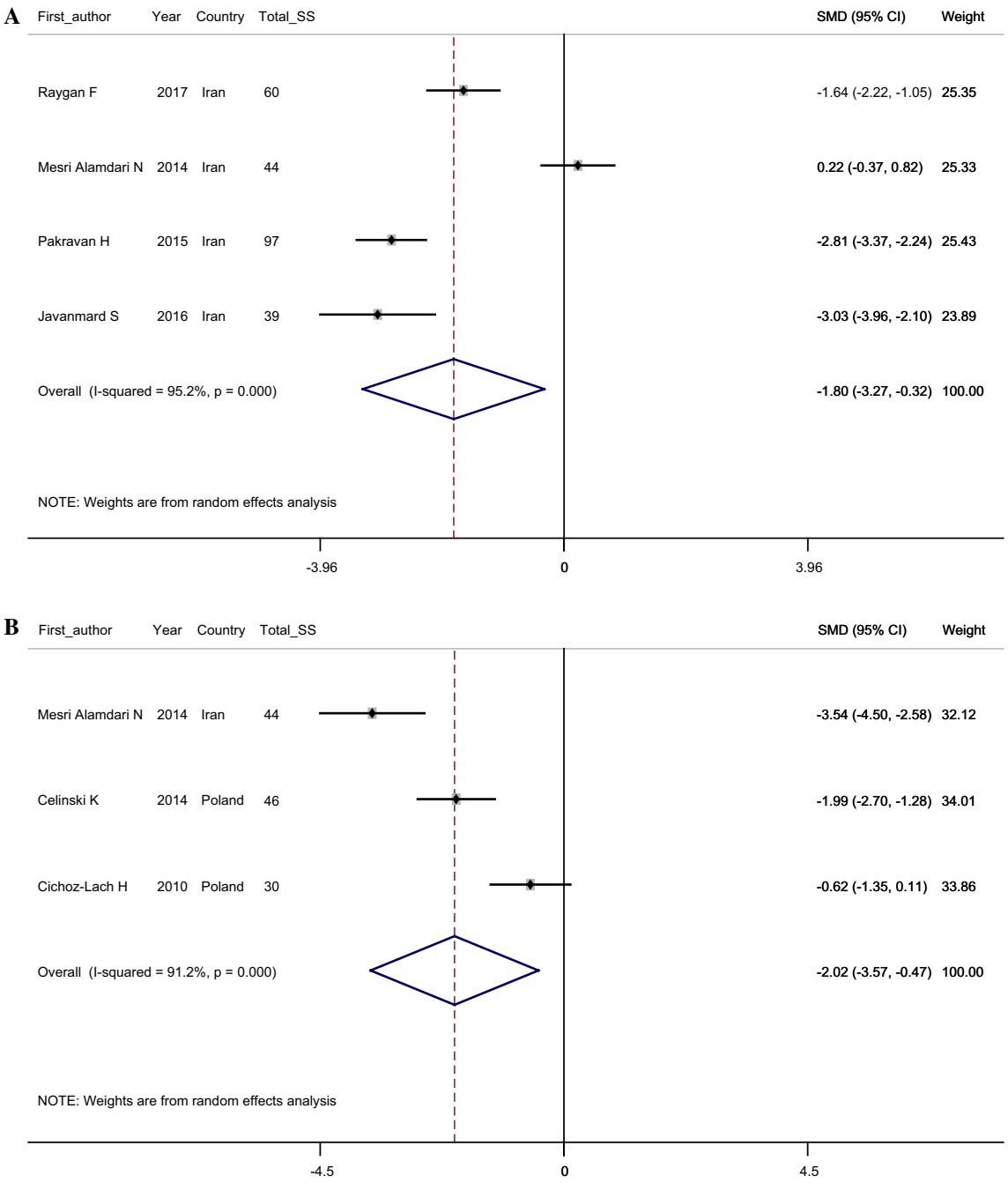

Fig. 3 Meta-analysis glycemic control standardized mean differences estimates for (**a**) high-sensitivity C-reactive protein, (**b**) for interleukin-6, and (**c**) for tumor necrosis factor-alpha in melatonin supplements and placebo groups (CI = 95%)

diseases. In the present meta-analysis, we clarified that melatonin supplementation significantly reduced CRP and IL-6, but did not affect TNF-α levels in patients with MetS or related disorders. Generally, inflammatory markers increase in not only metabolic conditions, but also in multiple non-metabolic disorders including rheumatoid arthritis (Zhang et al. 2014) and cystic fibrosis (Bruscia and Bonfield 2016). Moreover, metabolic abnormalities with the inflammation as one of their main pathophysiological causes are part of different chronic conditions including obesity, T2DM, CVD, stroke, fatty liver, and other metabolic diseases. Therefore, due to similar metabolic status, different metabolic disorders were included in the current meta-analysis.

The published clinical literature about the effects of melatonin supplementation on inflammatory markers is scarce. In a study conducted by Pakravan et al. (2017), melatonin

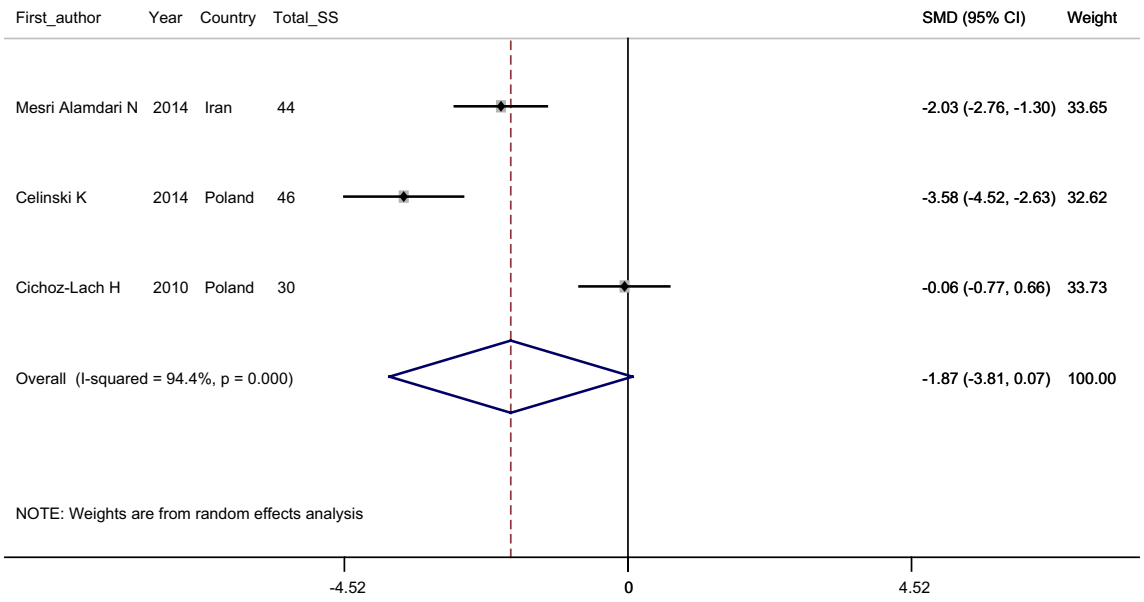

Fig. 3 (continued)

Table 2 The effects of melatonin supplementation on inflammatory markers based on subgroup analysis

Variables		Number of study	Standardized mean difference	CI 95%	*P* value	Heterogeneity		
						I^2 (%)	*Q*	*P* value heterogeneity
CRP	Intervention group (after vs. before)	4	− 1.13	− 1.70, − 0.55	< 0.001	75.5	12.24	0.007
	Placebo group (after vs. before)	4	− 0.47	− 1.48, 0.53	0.356	92.2	38.62	< 0.001
	Change intervention group vs. placebo group	4	− 1.80	− 3.27, − 0.32	0.017	95.2	62.91	< 0.001
IL-6	Intervention group (after vs. before)	3	− 1.03	− 1.73, − 0.32	0.004	69.6	6.57	0.037
	Placebo group (after vs. before)	3	− 0.29	− 0.65, 0.07	0.114	0.0	1.38	0.502
	Change intervention group vs. placebo group	3	− 2.02	− 3.57, -0.47	0.010	91.2	22.83	< 0.001
TNF-α	Intervention group (after vs. before)	3	− 2.40	− 4.44, − 0.37	0.020	94.1	33.91	< 0.001
	Placebo group (after vs. before)	3	− 0.96	− 1.73, − 0.19	0.015	74.8	7.94	0.019
	Change intervention group vs. placebo group	3	− 1.87	− 3.81, 0.07	0.059	94.4	35.99	< 0.001

IL-6 interleukin-6, *CRP* C-reactive protein, *TNF-α* tumor necrosis factor-alpha

Table 3 The assessment of association between melatonin supplementation on inflammatory markers based on subgroup analysis

Variables	Pre-sensitivity analysis			Upper and lower of effect size	Post-sensitivity analysis		
	No. of studies included	Pooled SMD (random effect)	95% CI		Pooled SMD (random effect)	95% CI	Excluded studies
CRP	4	− 1.80	− 3.27, − 0.32	Upper	− 1.79	− 3.26, 0.32	Javanmard
				Lower	− 2.45	− 3.33, − 1.57	Mesri Alamdari
IL-6	3	− 2.02	− 3.57, − 0.47	Upper	− 1.30	− 2.65, 0.03	Mesri Alamdari
				Lower	− 2.73	− 4.24, − 1.21	Cichoz-Lach
TNF-α	3	− 1.87	− 3.81, 0.77	Upper	− 1.04	− 2.97, 0.89	Celinski
				Lower	− 2.77	− 4.28, − 1.25	Cichoz-Lach

IL-6 interleukin-6, *CRP* C-reactive protein, *TNF-α* tumor necrosis factor-alpha

Table 4 The assessment of association between melatonin supplementation on inflammatory markers based on subgroup analysis

Variables		Number of SMD included	Subgroups	Pooled OR (random effect)	95% CI	I^2 (%)	Overall I^2 (%)
CRP	Geographic area	4	Iran	−1.80	−3.27, −0.32	95.2	95.2
		–	Poland	–	–	–	
	Duration of study (week)	2	>8 weeks	−2.22	−3.37, −1.08	87.4	
		2	≤8 weeks	−1.38	−4.57, 1.38	97.0	
	Dosage of melatonin (mg/day)	3	10 mg melatonin	−2.45	−3.34, −1.57	80.4	
		1	6 mg melatonin	0.22	−0.37, 0.82	–	
	Quality assessment score	2	High risk	−2.22	−3.37, −1.08	87.4	
		2	Unclear risk	−1.38	−4.57, 1.38	97.0	
IL-6	Geographic area	1	Iran	−3.54	−4.50, −2.58	–	91.2
		2	Poland	−1.31	−2.65, 0.04	85.5	
	Duration of study (week)	1	>8 weeks	−1.99	−2.70, −1.28	–	
		2	≤8 weeks	−2.06	−4.92, 0.80	95.5	
	Dosage of melatonin (mg/day)	2	10 mg melatonin	−1.31	−2.65, 0.04	85.5	
		1	6 mg melatonin	−3.54	−4.50, −2.58	–	
	Quality assessment score	–	High risk	–	–	–	
		3	Unclear risk	−2.02	−3.57, −0.47	91.2	
TNF-α	Geographic area	1	Iran	−2.03	−2.76, −1.30	–	94.4
		2	Poland	−1.80	−5.25, 1.65	97.0	
	Duration of study (week)	1	>8 weeks	−3.58	−4.52, −2.63	–	
		3	≤8 weeks	−1.04	−2.97, 0.89	93.0	
	Dosage of melatonin (mg/day)	2	10 mg melatonin	−1.80	−5.25, 1.65	97.0	
		1	6 mg melatonin	−2.03	−2.76, −1.30	–	
	Quality assessment score	–	High risk	–	–	–	
		3	Unclear risk	−1.87	−3.81, 0.07	94.4	

IL-6 interleukin-6, *CRP* C-reactive protein, *TNF-α* tumor necrosis factor-alpha

supplementation for 12 weeks to patients with non-alcoholic fatty liver disease significantly reduced hs-CRP concentrations. In addition, Mesri Alamdari et al. (2015) demonstrated that melatonin supplementation (6 mg/day) for 40 days lowered TNF-α and IL-6 levels in obese women, but did not affect hs-CRP levels. Taking 10 mg/day melatonin for 12 weeks by diabetic patients with CVD was associated with a significant reduction in hs-CRP levels (Raygan et al. 2017). Conversely, melatonin administration (10 mg/day) for 1 month to the patients with severe and advanced atherosclerosis did not influence hs-CRP levels (Javanmard et al. 2016). Different study designs, different baseline values of dependent variables, different doses of melatonin used along with characteristics of study participants might explain the discrepancies among included studies. Elevated levels of CRP are associated with insulin resistance, the incidence of T2DM and the increased risk of CVD (Odegaard et al. 2016). A review on micro-inflammation has suggested a possible mechanistic link between a pro-inflammatory diet and MetS (Tang et al. 2015). Moreover, a meta-analysis of 16 studies reported a relation between hs-CRP levels and the incidence of diabetes (Lee et al. 2009) although a nested case–control study in the European Prospective Investigation of Cancer (EPIC)-Norfolk cohort demonstrated that this correlation might be confounded by central adiposity (Lee et al. 2009). With respect to CVD, higher circulating levels of hs-CRP were independently correlated with carotid intima-media thickness (Willeit et al. 2016). In a meta-analysis conducted by Kaptoge et al. (2010), there was a significant association between hs-CRP levels and the risk of coronary heart disease, stroke and both vascular and non-vascular mortality. Melatonin may reduce inflammation through downregulation of the nuclear factor kappa *B* (Veneroso et al. 2009), thereby suppressing the upregulation of a variety of pro-inflammatory markers (Mauriz et al. 2013) as well as reducing tissue/organ damage (Chen et al. 2014; Galano et al. 2013). In addition, melatonin may decrease inflammatory markers through scavenging toxic oxygen derivatives in the inflamed tissues (Radogna et al. 2010).

This meta-analysis has some limitations. The number of eligible RCTs included was low, and most of them included a modest number of participants. Various doses of melatonin were administered for intervention in the included studies. We were unable to evaluate the dose–response relation

between supplementation and inflammatory markers due to the low number of studies included. In addition, RCTs included in our meta-analysis were represented with different chronic conditions and study durations, which might potentially skew the data. However, all selected patients in our meta-analysis had some kind of metabolic disorders and the main outcome of interest was inflammation. Previous studies have documented the increased levels of inflammatory markers in patients with MetS, diabetes (Ben-Shmuel et al. 2016), being overweight, CKD (Zoccali 2009), hypertension and CVD (Mozos et al. 2017). Due to mentioned limitations of this study, in discussion and conclusion, though, we interpreted our results cautiously. Most of the studies included in our analyses had small sample sizes and low duration of intervention. Trial with small sample sizes might be less robust, and more susceptible to report larger effect sizes (Nuesch et al. 2010).

Conclusions

In summary, the current meta-analysis showed a promising action of melatonin administration for reducing CRP and IL-6 levels in patients with MetS and related disorders. Additional prospective studies regarding the effect of melatonin supplementation on inflammatory markers in patients with MetS and related disorders seem necessary.

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Author contributions ZA, MA, VO and RT contributed in conception, design, statistical analysis and drafting of the manuscript. KB-L and TH contributed in conception, data collection and manuscript drafting. Dr. J. Reiter Russel reviewed the manuscript, and offered critical comments.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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