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The Effects of Melatonin Supplementation on Glycemic Control: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

This systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to clarify the effect of melatonin supplementation on glycemic control. Databases including PubMed, MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials were searched until July 30th, 2018. Two reviewers independently assessed study eligibility, extracted data, and evaluated the risk of bias for included trials. Heterogeneity among included studies was assessed using Cochran's Q test and I-square (I^2) statistic. Data were pooled using random-effect models and mean difference (MD) was considered as the overall effect size. Twelve trials out of 292 selected reports were identified eligible to be included in current meta-analysis. The pooled findings indicated that melatonin supplementation significantly reduced fasting glucose (MD = −6.34; 95 % CI, −12.28, −0.40; p = 0.04; I^2: 65.0) and increased the quantitative insulin sensitivity check index (QUICKI) (MD = 0.01; 95 % CI, 0.00, 0.02; p = 0.01; I^2: 0.0). However, melatonin administration did not significantly influence insulin levels (MD = −1.03; 95 % CI, −3.82, 1.77; p = 0.47; I^2: 0.53), homeostasis model assessment of insulin resistance (HOMA-IR) (MD = −0.34; 95 % CI, −1.25, 0.58; p = 0.37; I^2: 0.37) or HbA1c levels (MD = −0.22; 95 % CI, −0.47, 0.03; p = 0.08; I^2: 0.0). In summary, the current meta-analysis showed a promising effect of melatonin supplementation on glycemic control through reducing fasting glucose and increasing QUICKI, yet additional prospective studies are recommended, using higher supplementation doses and longer intervention period, to confirm the impact of melatonin on insulin levels, HOMA-IR and HbA1c.

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Abbreviations

CHD	Coronary heart disease
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
HOMA-IR	Homeostasis model of assessment-estimated insulin resistance
NASH	Nonalcoholic steatohepatitis
QUICKI	Quantitative insulin-sensitivity check index
T2DM	Type 2 diabetes mellitus

Introduction

Diabetes mellitus is a chronic, life-threatening metabolic disorder, which is or will soon became a massive economic burden for many communities [1]. The global prevalence of diabetes among adults (aged 20–79 years) was 6.4% in 2010, affecting 285 million adults. Unfortunately, this will increase to 7.7%, involving 439 million adults, by 2030. Between 2010 and 2030, there will be a 69% increase in the number of adults suffering from diabetes in developing countries and a 20% increase in developed countries [1]. Type 2 diabetes mellitus (T2DM) has been significantly associated with the development of microvascular and macrovascular complications [2–4]. Studies have also shown that T2DM is associated with increased oxidative stress occurring as a consequence of hyperglycemia, hyperinsulinemia, increased insulin resistance, reduced insulin sensitivity, and dyslipidemia [5–8].

Melatonin is an endogenous indole amine, secreted by the pineal gland, which facilitates physiologic timings based on circadian patterns [9]. Previously, the beneficial effects of melatonin on metabolic profiles and inhibitory actions on adrenocorticotropic hormone responses were documented [10–13]. In addition, animal studies and non-randomized human trials have proposed the possible impact of melatonin administration on improving glycemic control, insulin resistance, hypertension, and dyslipidemia [14, 15]. Melatonin intake has been shown to regulate blood glucose levels through its ability to bind directly to melatonin receptors on hepatocytes [16] and regulate the uptake of glucose in adipocytes, by modulating the expression of the glucose uptake transporter [17]. Moreover, melatonin has been reported to stimulate the secretion of glucagon, another hormone that is important in glucose and insulin metabolism [18]. However, few randomized controlled trials (RCTs) have evaluated the effects of melatonin on glycemic control, and the published findings are inconsistent. In a study conducted by Rezvanfar et al. [19], melatonin administration at a dosage of 6 mg for 12 weeks decreased fasting glucose in diabetic patients. The same research group has recently found that melatonin administration at a dosage of 10 mg/day for 12 weeks improved glycemic control in diabetic patients suffering from coronary heart disease (CHD) [20]. Moreover, a 12-week trial using melatonin showed significant improved insulin sensitivity and the inflammatory status in obese patients with Acanthosis Nigricans [21]. There are, however, results as well that, for example, 5 mg/day melatonin supplementation for 2 months did not affect fasting glucose in patients diagnosed with metabolic syndrome (MetS) [15]. Differences in study design, study population characteristics, the dosage of melatonin used, and the duration of intervention might explain the discrepancies among the findings published to date.

To the best of our knowledge, there is no systematic review or meta-analyses of RCTs determining the effect of melatonin supplementation on glycemic control. Thus, the present meta-analysis was summarized available publications demonstrating an effect of melatonin supplementation on glycemic control and examined the impact of melatonin on glycemic control using meta-analysis.

Materials and Methods

Search and studies selection strategies

The scientific international databases, including Cochrane Library, EMBASE, PubMed, and Web of Science were searched for relevant studies published until July 30th, 2018. A search strategy was developed using the following MeSH and text keywords; intervention ("melatonin" AND "supplementation" OR "intake"), and outcomes ["fasting glucose" OR "FPG" OR "insulin" OR "homeostasis model assessment of insulin resistance (HOMA-IR)" OR "HbA1c" OR "quantitative insulin sensitivity check index (QUICKI)].

Inclusion and exclusion criteria

RCTs with the following criteria were included in meta-analysis: human trial with either parallel or cross-over design, data for the effect of melatonin on glycemic control extracted from RCTs (including mean changes of glucose, insulin, HOMA-IR, HbA1c, and QUICKI with standard deviations (SDs) and related 95% confidence intervals (CIs) for the both intervention and placebo groups). Other studies such as animal experiments, in vitro studies, case reports, observational studies, investigations without control group, and studies that did not achieve the least quality score were excluded from this meta-analysis.

Data extraction and quality assessment

Two independent authors (VO and NM) screened the retrieved articles based on the eligibility criteria. In the first step the title and abstract of studies were reviewed. Then, the full-text of relevant studies was retrieved and assessed to ascertain the suitability of a study for the meta-analysis. Any disagreement was resolved through the judgment of the third author (ZA).

The following data were extracted from selected studies: the 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 fasting glucose, insulin, HOMA-IR, HbA1c, and QUICKI in each intervention group. The quality of the selected RCTs was assessed by same independent authors using the Cochrane Collaboration risk of bias tool based on the following criteria: "randomization generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, and selective outcome reporting, and other sources of bias".

Data synthesis and statistical analysis

The effects of melatonin supplementation on the changes of the following outcomes were calculated: 1) fasting glucose, 2) insulin, 3) HOMA-IR, 4) HbA1c, and 5) QUICKI. The mean differences (MDs) with 95% CI were used for pooling data to determine effect sizes. The change score approach was used to calculate the effect size of melatonin supplementation on the identified outcome. The random-effect model was used to report the pooled effect sizes using 95% confidence interval (CI).

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Heterogeneity and publication bias

Heterogeneity across included studies was assessed using Cochran's Q test (with significant p-value lower than 0.1) and I-square test (I^2 greater than 50 percent showing significant heterogeneity). The funnel plot, as well as the Beggs's and Egger's regression tests were used to determine the publication bias. Both STATA 11.0 (Stata Corp., College Station, TX, USA) and Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) were applied for data analysis.
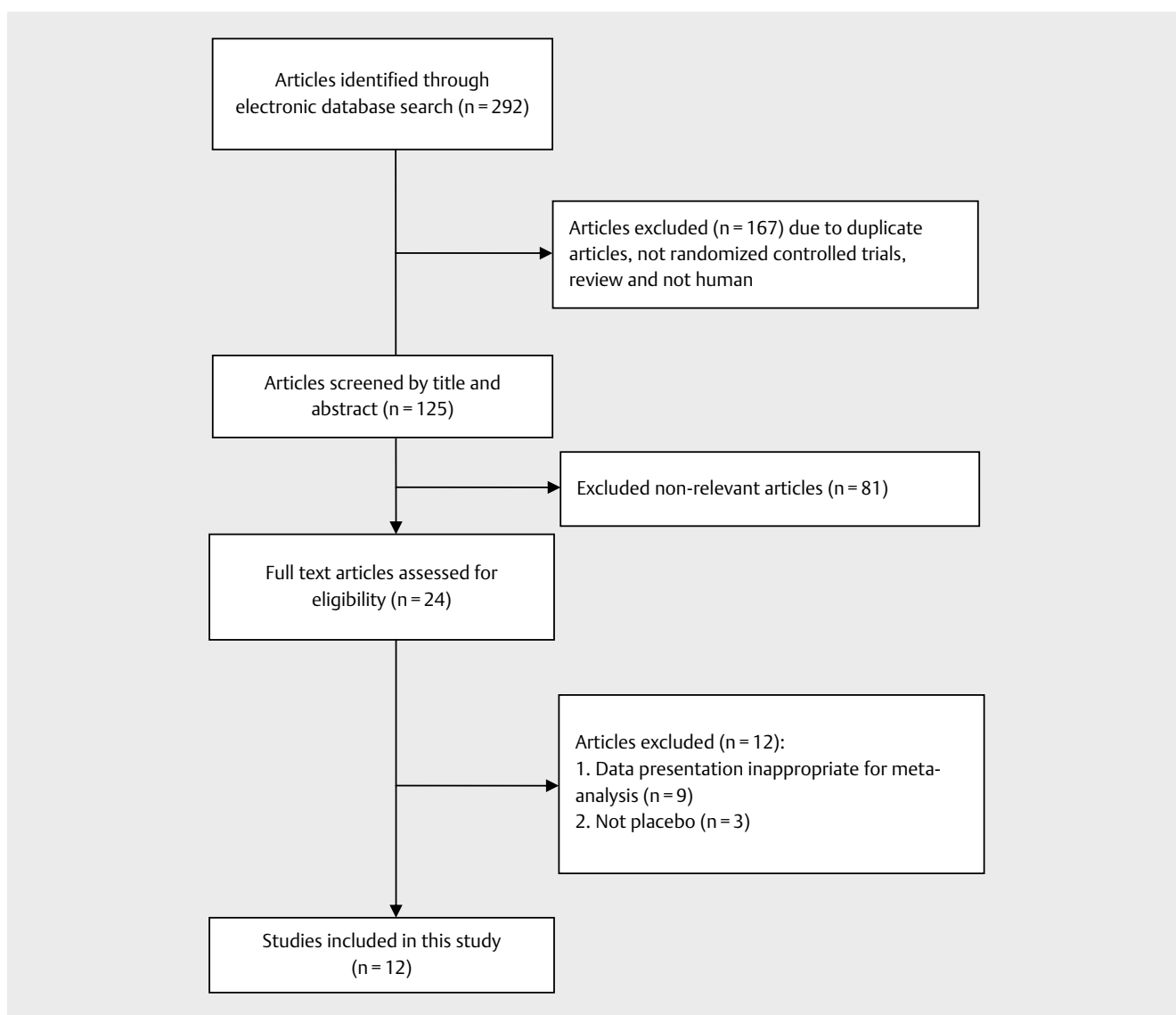
Results

The step by step flowchart for identification and selection is illustrated in ▶ **Fig. 1**. Finally, 12 RCTs out of 292 articles were selected to be included in meta-analysis. Ten trials had measured the effects of melatonin on fasting glucose, 4 on insulin, 3 on HOMA-IR, 3 on HbA1c and 2 on QUICKI. The sample size of included RCTs in this meta-analysis varied from 20 to 128 participants. Duration of intervention ranged from 30 days to 24 weeks. Selected RCTs were published between 2005 and 2018. Dosage of melatonin supplements varied from 3 to 10 mg/day. The detailed characteristics of selected RCTs are summarized in ▶ **Table 1**.

Main outcomes

Forest plots reporting the effect sizes of primary RCTs on glycemic control parameters are indicated in ▶ **Fig. 2 1–5**. The pooled findings using random-effect models indicated that melatonin supplementation significantly reduced fasting glucose (MD = −6.34; 95% CI, −12.28, −0.40; p = 0.04; I^2: 65.0) and increased QUICKI (MD = 0.01; 95% CI, 0.00, 0.02; p = 0.01; I^2: 0.0). However, melatonin administration did not influence insulin levels (MD = −1.03; 95% CI, −3.82, 1.77; p = 0.47; I^2: 0.53), HOMA-IR (MD = −0.34; 95% CI, −1.25, 0.58; p = 0.37; I^2: 0.37) and HbA1c (MD = −0.22; 95% CI, −0.47, 0.03; p = 0.08; I^2: 0.0).
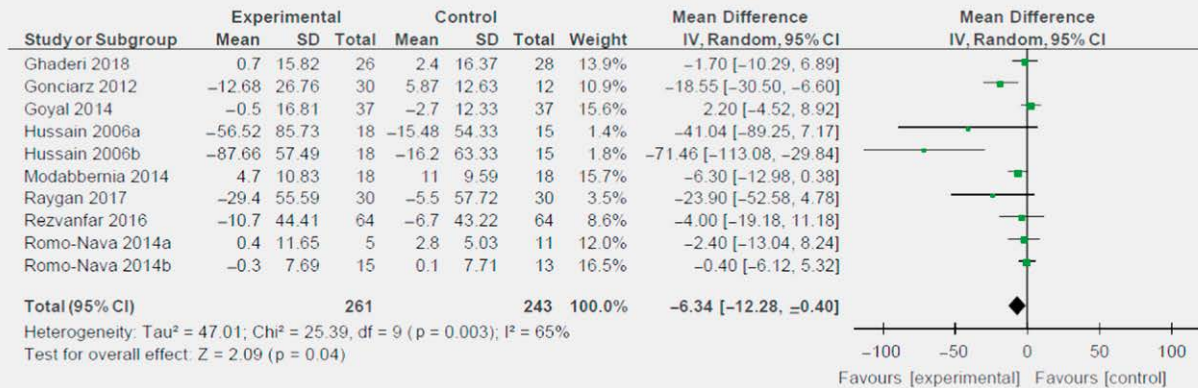

▶ **Fig. 1** Literature search and review flowchart for selection of studies.

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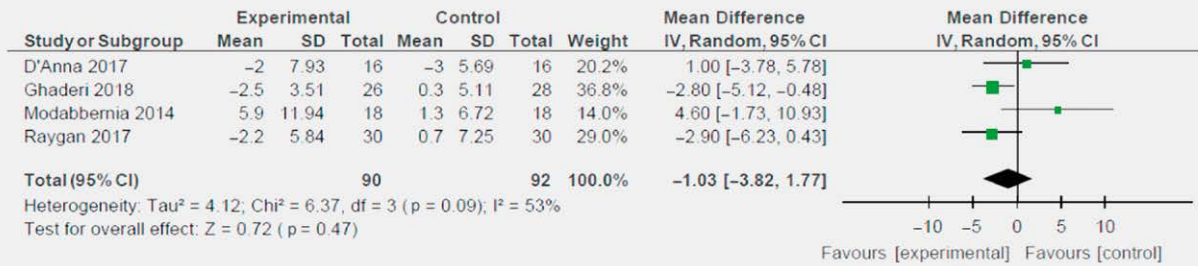▶ **Table 1** Characteristics of included studies.

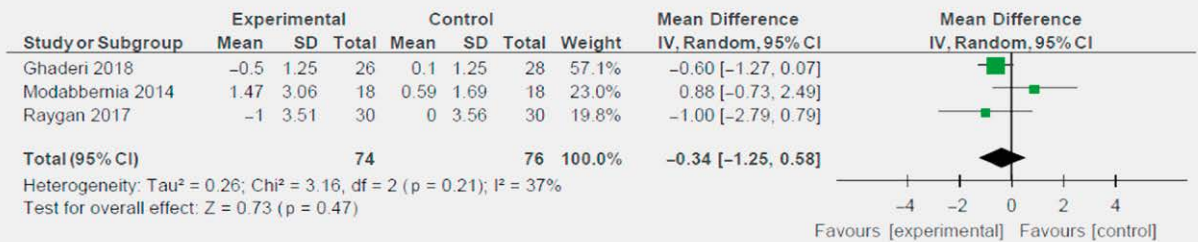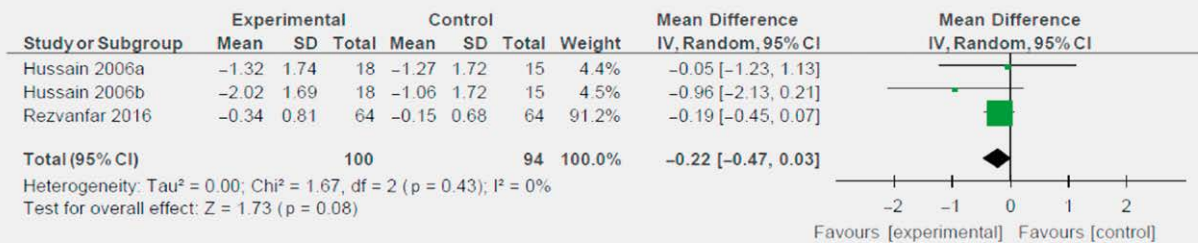| Authors [Ref]	Publication year	Sample size (control/intervention)	Country/population	Intervention (name and daily dose)	Duration	Presented data	Age (years) (control, intervention)	Results
Agahi et al. [38]	2017	50/50	Iran/patients treated with the second-generation antipsychotics	3 mg/d melatonin	8 weeks	FPG	37.46 ± 12.42, 37.4 ± 10.3	Decreased FPG
D'Anna et al. [29]	2016	16/16	Italy/women during menopausal transition	3 mg/d melatonin + 2 g/d myo-inositol	24 weeks	Insulin	48.7 ± 1.5, 49.1 ± 1.7	No effect
Ghaderi et al. [39]	2018	28/26	Iran/patients under methadone maintenance treatment	10 mg/d melatonin	12 weeks	FPG, insulin, HOMA-IR, QUICKI	42.7 ± 9.9, 42.5 ± 8.0	Decreased insulin and HOMA-IR, Increased QUICKI
Goyal et al. [40]	2014	37/37	USA/metabolic syndrome	8 mg/d melatonin	10 weeks	FPG	57.6 ± 10.1, 62.7 ± 9.6	No effect
Gonciarz et al. [41]	2012	12/30	Poland/NASH	10 mg/d melatonin	24 weeks	FPG	40.8 ± 3.6, 41.5 ± 4	Decreased FPG
Hussain et al. [42]	2006	15/18	Iraq/T2DM	10 mg/d melatonin + other nutrients	30 days	FPG, HbA1c	49.1 ± 6	Decreased FPG
Hussain et al. [42]	2005	15/18	Iraq/T2DM	10 mg/d melatonin + other nutrients	90 days	FPG, HbA1c	49.1 ± 6	Decreased FPG
Modabbernia et al. [43]	2014	18/18	Iran/schizophrenia	3 mg/d melatonin	8 weeks	FPG, insulin, HOMA-IR	32.8 ± 8.2, 32.7 ± 7.3	No effect
Rezvanfar et al. [44]	2016	64/64	Iran/T2DM	6 mg/d melatonin	12 weeks	FPG, HbA1c	52 ± 8	No effect
Romo-Nava et al. [45]	2013	11/5	Mexico/bipolar disorder and schizophrenia (high risk)	5 mg/d melatonin	8 weeks	FPG	28.6 ± 9, 30.6 ± 7.5	No effect
Romo-Nava et al. [45]	2013	13/15	Mexico/bipolar disorder and schizophrenia (medium risk)	5 mg/d melatonin	8 weeks	FPG	28.6 ± 9, 30.6 ± 7.5	No effect
Raygan et al. [20]	2017	30/30	Iran/T2DM with CHD	10 mg/d melatonin	12 weeks	FPG, insulin, HOMA-IR, QUICKI	65.3 ± 10.1, 67.7 ± 11.4	Decreased FPG, insulin and HOMA-IR, increased QUICKI

For abbreviations: see text.

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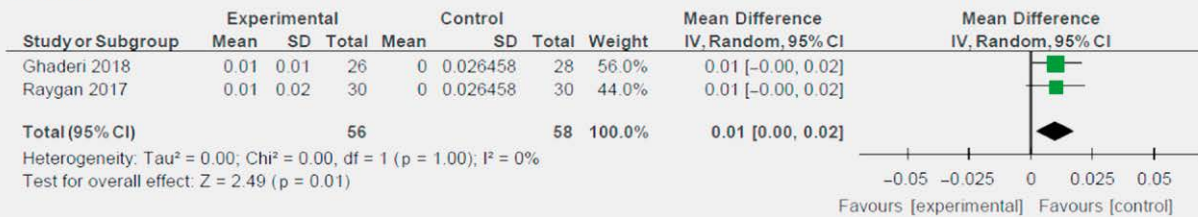Doosti-Irani A et al. Melatonin Supplementation and Glycemic Control … Horm Metab Res 2018; 50: 783–790

2.1 FPG

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ghaderi 2018	0.7	15.82	26	2.4	16.37	28	13.9%	−1.70 [−10.29, 6.89]
Gonciarz 2012	−12.68	26.76	30	5.87	12.63	12	10.9%	−18.55 [−30.50, −6.60]
Goyal 2014	−0.5	16.81	37	−2.7	12.33	37	15.6%	2.20 [−4.52, 8.92]
Hussain 2006a	−56.52	85.73	18	−15.48	54.33	15	1.4%	−41.04 [−89.25, 7.17]
Hussain 2006b	−87.66	57.49	18	−16.2	63.33	15	1.8%	−71.46 [−113.08, −29.84]
Modabbernia 2014	4.7	10.83	18	11	9.59	18	15.7%	−6.30 [−12.98, 0.38]
Raygan 2017	−29.4	55.59	30	−5.5	57.72	30	3.5%	−23.90 [−52.58, 4.78]
Rezvanfar 2016	−10.7	44.41	64	−6.7	43.22	64	8.6%	−4.00 [−19.18, 11.18]
Romo-Nava 2014a	0.4	11.65	5	2.8	5.03	11	12.0%	−2.40 [−13.04, 8.24]
Romo-Nava 2014b	−0.3	7.69	15	0.1	7.71	13	16.5%	−0.40 [−6.12, 5.32]
Total (95% CI)			**261**			**243**	**100.0%**	**−6.34 [−12.28, −0.40]**

Heterogeneity: Tau² = 47.01; Chi² = 25.39, df = 9 (p = 0.003); I² = 65%
Test for overall effect: Z = 2.09 (p = 0.04)

Mean Difference IV, Random, 95% CI
−100 −50 0 50 100
Favours [experimental] Favours [control]

2.2 Insulin

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
D'Anna 2017	−2	7.93	16	−3	5.69	16	20.2%	1.00 [−3.78, 5.78]
Ghaderi 2018	−2.5	3.51	26	0.3	5.11	28	36.8%	−2.80 [−5.12, −0.48]
Modabbernia 2014	5.9	11.94	18	1.3	6.72	18	14.0%	4.60 [−1.73, 10.93]
Raygan 2017	−2.2	5.84	30	0.7	7.25	30	29.0%	−2.90 [−6.23, 0.43]
Total (95% CI)			**90**			**92**	**100.0%**	**−1.03 [−3.82, 1.77]**

Heterogeneity: Tau² = 4.12; Chi² = 6.37, df = 3 (p = 0.09); I² = 53%
Test for overall effect: Z = 0.72 (p = 0.47)

Mean Difference IV, Random, 95% CI
−10 −5 0 5 10
Favours [experimental] Favours [control]

2.3 HOMA-IR

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ghaderi 2018	−0.5	1.25	26	0.1	1.25	28	57.1%	−0.60 [−1.27, 0.07]
Modabbernia 2014	1.47	3.06	18	0.59	1.69	18	23.0%	0.88 [−0.73, 2.49]
Raygan 2017	−1	3.51	30	0	3.56	30	19.8%	−1.00 [−2.79, 0.79]
Total (95% CI)			**74**			**76**	**100.0%**	**−0.34 [−1.25, 0.58]**

Heterogeneity: Tau² = 0.26; Chi² = 3.16, df = 2 (p = 0.21); I² = 37%
Test for overall effect: Z = 0.73 (p = 0.47)

Mean Difference IV, Random, 95% CI
−4 −2 0 2 4
Favours [experimental] Favours [control]

2.4 HbA1c

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hussain 2006a	−1.32	1.74	18	−1.27	1.72	15	4.4%	−0.05 [−1.23, 1.13]
Hussain 2006b	−2.02	1.69	18	−1.06	1.72	15	4.5%	−0.96 [−2.13, 0.21]
Rezvanfar 2016	−0.34	0.81	64	−0.15	0.68	64	91.2%	−0.19 [−0.45, 0.07]
Total (95% CI)			**100**			**94**	**100.0%**	**−0.22 [−0.47, 0.03]**

Heterogeneity: Tau² = 0.00; Chi² = 1.67, df = 2 (p = 0.43); I² = 0%
Test for overall effect: Z = 1.73 (p = 0.08)

Mean Difference IV, Random, 95% CI
−2 −1 0 1 2
Favours [experimental] Favours [control]

2.5 QUICKI

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ghaderi 2018	0.01	0.01	26	0	0.026458	28	56.0%	0.01 [−0.00, 0.02]
Raygan 2017	0.01	0.02	30	0	0.026458	30	44.0%	0.01 [−0.00, 0.02]
Total (95% CI)			**56**			**58**	**100.0%**	**0.01 [0.00, 0.02]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (p = 1.00); I² = 0%
Test for overall effect: Z = 2.49 (p = 0.01)

Mean Difference IV, Random, 95% CI
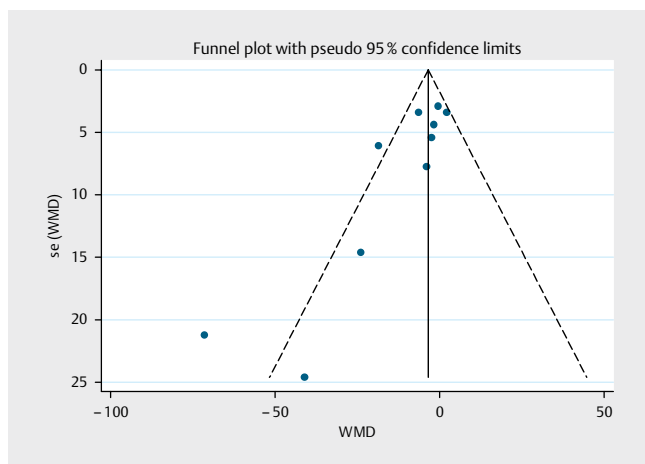−0.05 −0.025 0 0.025 0.05
Favours [experimental] Favours [control]

▶ **Fig 2** **1–5**: Meta-analysis lipid profiles mean differences estimates for **1** fasting glucose, **2** for insulin, **3** for homeostasis model assessment of insulin resistance, **4** for HbA1c, **5** and for quantitative insulin sensitivity check index in melatonin and placebo groups.

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▶ **Fig. 3** Funnel plot for assess the publication bias for the effect of melatonin on fasting glucose.

Publication bias

Funnel plots demonstrating publication bias are illustrated in ▶ **Fig 3**. Results of Begg's (p = 0.02) and Egger's (p = 0.008) tests for the effects of melatonin supplementation on fasting glucose were statistically significant.

Discussion

To our best knowledge, this is the first meta-analysis of RCTs evaluating the effect of melatonin supplementation on glycemic control. The current meta-analysis showed the beneficial impact of melatonin supplementation on glycemic control including a significant reduction in fasting glucose and an increase in QUICKI, though melatonin did not affect insulin levels, HOMA-IR, and HbA1c.

Existing evidence are promising regarding the impact of melatonin on glycemic control. In healthy individuals, glucose homeostasis is tightly controlled via a complex pathway of regulatory mechanisms involving multiple organs and tissues. Normal glucose balance is usually impaired due to a sustained reduction in both pancreatic beta-cell function and insulin secretion [22]. In animal models, melatonin has been shown to regulate circulating serum glucose levels through its ability to bind directly to melatonin receptors on hepatocytes [16] as well as to regulate the uptake of glucose by adipocytes, through modulating the expression of the glucose uptake transporter [17]. Abnormal nocturnal melatonin profiles have been reported in diabetic patients, especially for those suffering from diabetic neuropathy [23]. Low melatonin secretion has also been independently correlated with a higher risk of developing T2DM; an association that further establishes the roles of melatonin in glycemic control and insulin sensitivity [24]. There is a new evidence suggesting a relationship between melatonin production disturbances and impairment of insulin, glucose and lipid metabolism [25]; and antioxidant capacity [26]. Results from both in vivo and in vitro studies have shown that in patients diagnosed with MetS, night-time melatonin level is significantly correlated to nighttime insulin concentrations [27]. Moreover, melatonin stimulates the secretion of glucagon, which is the second hormone important in glucose metabolism [18]. In a meta-analysis, we have

previously reported that melatonin significantly decreased inflammatory markers including CRP and IL-6, but not TNF-α levels in patients with MetS and related disorders [28]. However, some of the RCTs that assessed the effects of melatonin supplementation on glycemic control have yielded inconsistent results. Rezvanfar et al. [19] found that melatonin administration at a dosage of 6 mg to type 2 diabetic patients for 12 weeks decreased fasting glucose levels. In addition, combined myo-inositol and melatonin supplementation for 6 months significantly improved glucose metabolism among women experiencing the menopausal transition [29]. Moreover, a 12-week supplementation of melatonin improved insulin sensitivity and the inflammatory status of obese patients with Acanthosis Nigricans [21]. Controversial findings also exist; as an example, 5 mg/day melatonin supplementation for 2 months did not affect fasting glucose levels in patients with MetS [15]. Differences in study design, study population characteristics, the dosage of melatonin used and the duration of intervention might explain the discrepancies among existing evidence.

Melatonin receptors (MT1 and MT2) are present in both animal [30, 31] and human [32] pancreatic islets. In addition, an increase in the expression of MT1 and MT2 receptors is reported in the pancreas of diabetic rats and in subjects with T2DM [33]. Associations between single nucleotide polymorphisms situated close to (or within) the gene encoding MT2 (MTNR1B), and an increased risk of developing T2DM [34], diminished B-cell function [35] and impaired glycemic control [36] have been reported in different cohorts from a variety of different ethnicities. The inhibitory effects of melatonin intake on elevated fasting glucose may be mediated through the function of 2 G-protein-coupled receptors. These receptors are expressed in both the beta cells of the pancreatic islets and the adipocytes, playing important roles in the regulation of blood glucose [37].

This meta-analysis has some limitations. There were few eligible RCTs including a modest number of participants. Various doses of melatonin were administered for intervention in the included studies. The results of publication bias were statistically significant for the effects of melatonin supplementation on FPG. Thus, additional RCTs are required to obtain the necessary pooled effect size. In addition, due to low number of RCTs included for the effect of melatonin supplementation on insulin, HOMA-IR, HbA1c and QUICKI, we could not assess the publication bias for these outcomes.

Conclusions

In summary, the current meta-analysis showed a potentially beneficial of melatonin supplementation on improving glycemic control through reducing fasting glucose and increasing QUICKI. However, additional prospective studies are recommended using higher supplementation doses and longer intervention period to determine the impact of melatonin on insulin levels, HOMA-IR, and HbA1c.

Author Contributions

ZA, AD-I, VO, NM, M-AM, MK, MR, and MR contributed to the conception, design, statistical analysis, and drafting of the manuscript. RJR reviewed the manuscript and offered critical comments.

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Funding

Conflict of Interest

The authors declare that they have no conflict of interest.

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Notice

Please note: This article was changed according to the Erratum on November 14th 2018.

Erratum

1. In the article, the name of the co-author was given incorrectly. The correct name of the author is Mohammad Ali Mansournia.

2. In the abstract section the correct abbreviation of "mean difference" is MD.

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