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Effect of green tea on glycemic control in patients with type 2 diabetes mellitus: A systematic review and meta-analysis

Omid Asbaghi [a], Faezeh Fouladvand [a], Michael J. Gonzalez [b], Damoon Ashtary-Larky [c], Razieh Choghakhori [d], Amir Abbasnezhad [e, *]

[a] Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran
[b] School of Public Health, Department of Human Development, University of Puerto Rico Medical Sciences Campus, Puerto Rico
[c] Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[d] Razi Herbal Medicines Research Center, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran
[e] Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

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ABSTRACT

Background and aims: Several studies have investigated the potential beneficial effects of green tea in patients with type 2 diabetes mellitus (T2DM). Therefore, we aimed to perform a systematic review and meta-analysis of the randomized controlled trials (RCTs) that assessed the effect of supplementary intake of green tea on fasting plasma glucose (FPG), fasting insulin, hemoglobin A1c (HbA1c) and HOMA-IR in patients with T2DM.

Methods: A systematic search was performed in Web of Science, PubMed and Scopus without any language and time restriction up to June 2019, to retrieve the related RCTs. Meta-analysis was carried out using both the random and fixed effects model where appropriate. I2 index was used to evaluate the heterogeneity.

Results: Initial search yielded 780 publications. Fourteen articles were eligible. Our meta-analysis indicated that the supplementary intake of green tea had no significant effect on FPG, fasting insulin, HbA1c and HOMA-IR in patients with T2DM.

Conclusion: Results of the present systematic review and meta-analysis indicated that the supplementary intake of green tea had no significant effect on FPG, fasting insulin, HbA1c and HOMA-IR in patients with T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major worldwide problem, characterized by the chronic hyperglycemia, impaired insulin secretion and/or insulin function [1]. The prevalence of diabetes in adults was estimated to be 8.4% in 2017, and predicted to rise to 9.9% in 2045 [2]. In 2013, International Diabetes Federation (IDF) reported that the North Africa and Middle East had the highest worldwide prevalence of diabetes at 10.9% [3]. T2DM is mainly the consequence of obesity and physical inactivity [4], and it is associated with macrovascular and microvascular complications, and changes in bone and mineral metabolism [5,6].

The use of alternative medicines in the treatment of the diseases has recently increased and has attracted the attention of many researchers worldwide [6–8]. Several studies have investigated the potential beneficial effects of several medicinal plants in patients with diabetes [9,10]. Camellia sinensis (L.) Kuntze, popularly known as green tea, is one of these plant-based therapies [11]. It contains catechins, such as epigallocatechin-3-gallate (EGCG), as well as quercetin, the arubigins, theaflavins, theanine, caffeine, chlorogenic acid and gallic acid [11,12]. A meta-analysis of 17 randomized controlled trials (RCTs) which included both healthy subjects and patients with chronic disease such as obesity, T2DM or hypertension showed that green tea consumption significantly reduced circulating levels of fasting glucose, HbA1c and fasting insulin [13]. The aim of present systematic review and meta-analysis was to pool data from RCTs that assessed the effect of supplementary intake of green tea on fasting plasma glucose (FPG), fasting insulin,

* Corresponding author. Nutritional Health Research Center, Department of Nutrition, Lorestan University of Medical Sciences, Goledasht Blvd, Khorramabad, PO Box: 6813833946, Iran.
E-mail addresses: abbasnezhad.amir@lums.ac.ir, Abbasnezhad.a@ajums.ac.ir (A. Abbasnezhad).

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hemoglobin A1c (HbA1c) and homeostatic model assessment for insulin resistance (HOMA-IR) in patients with T2DM.

2. Method

This systematic review and meta-analysis adhered to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline [14].

2.1. Search strategy

In the present study, the electronic databases including the Scopus, PubMed, and ISI Web of science was systematically searched to find RCTs which assessed the effect of green tea on glycemic control in patients with T2DM, with no language and date restriction, until June 2019. The merge of MESH and non-MESH terms were used as follows: ("green tea" OR "green tea extract" OR "green tea extract AR25" OR "catechin" OR "catechins" OR "EGCG" OR "Camellia sinensis" OR "tea polyphenols" OR "catechinic acid" OR "acid catechinic" OR "sinensis Camellia" OR "Thea sinensis" OR "sinensis Thea" OR "tea polyphenols") AND ("Type 2 diabetes" OR T2DM OR diabetes). In addition, all the reference list of the included articles and related reviews were manually checked to avoid missing any relevant studies. The complete search strategy is indicated in the supplemental file 1.

2.2. Including and excluding criteria

Inclusion criteria were as follows: 1) RCTs which were conducted on patients with T2DM, 2) RCTs included subjects ≥18 years old), 3) RCTs that provided sufficient data on baseline and final measures of fasting plasma glucose (FPG) levels, insulin levels, hemoglobin A1C and HOMA-IR in both green tea and control groups. Exclusion criteria were as follows: 1) RCTs that were conducted on children, animal and subjects without T2DM, 2) studies that were not RCT, 3) and did not provide sufficient information for the outcomes in the green tea or control groups.

2.3. Data extraction

Two investigators (OA and FF) individually screened the records and two others (DA and RC) extracted the data. Any disagreements were resolved under a chief investigator (AA). The following data were extracted from each study: publication year, first author's name, study design, study duration, region of the study, mean age and sex of the participants, sample size in each group, and the mean and standard deviation (SD) of outcome measures at the baseline and the final stage of the study.

2.4. Quality assessment

We evaluated the quality of eligible studies by using the Cochrane scoring system [15]. This scoring system includes 7

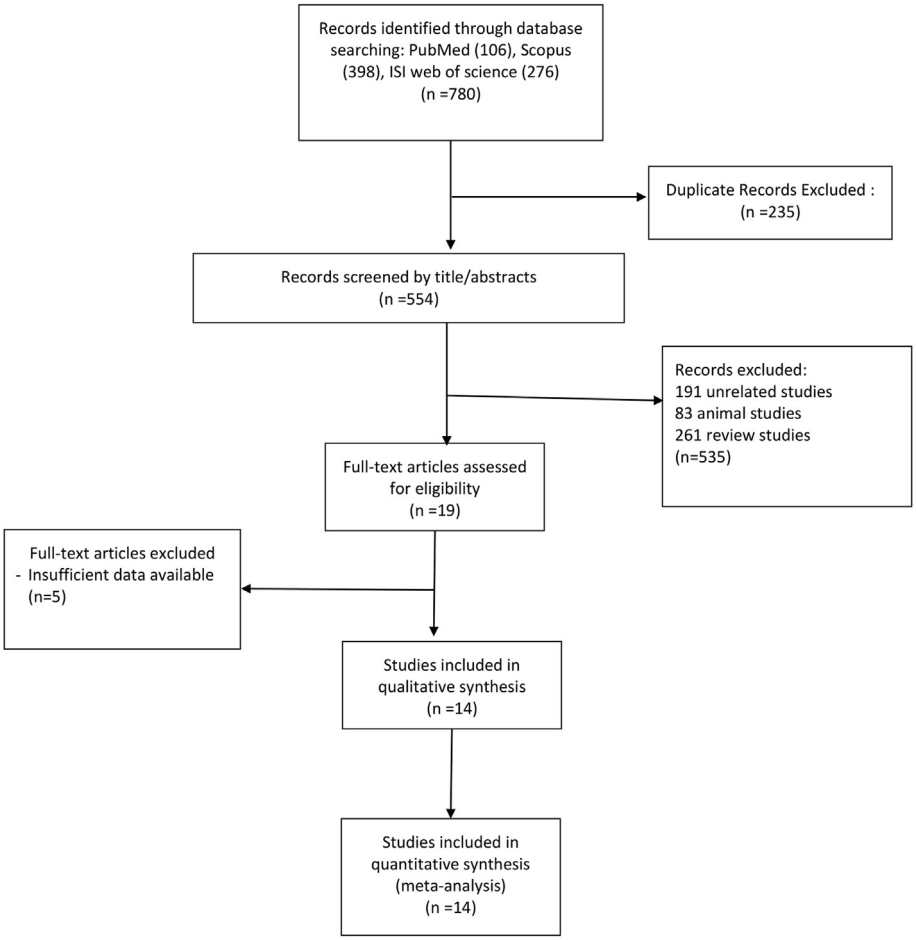

Fig. 1. Flow chart of study selection for inclusion in meta-analysis.

criteria to evaluate the risk of bias: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, and 7) other source of biases. After evaluating the studies based on these items, each item takes one of the following points: (1) high risk, (2) low risk, and (3) unknown risk. All the selected articles were scored by 2 authors (DA and RC). Disagreement between the authors was resolved by a third assessor (AA).

2.5. Data synthesis and statistical analysis

Effect sizes of all intended outcomes were expressed as weighted mean differences (WMDs) and 95% CI. The effect sizes were pooled exerting a random effects model with DerSimonian and Laird method [16]. The mean net changes (mean values ± standard deviation) of all the variables between the baseline and the final stage of the study were calculated. When standard error of the mean (SEM) was reported, SD was estimated by using the following formula: SD = SEM × sqrt (n) (n is the number of subjects) [17]. Heterogeneity between the studies was evaluated by Cochrane's Q test (significance point at $p < 0.05$) and I [2] index. Any potential publication bias was identified using the funnel plot. All statistical analyses were done using STATA software version 14 (STATA Corp, College Station, Texas). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study selection

In the primary search, 780 papers were identified (Fig. 1). Of these, 235 articles identified as duplicates and removed. 554 articles remained for screening based on title and abstract. Of these, 539 articles were excluded due to unrelated issues. In the next step, 19 articles were evaluated based on full-text. Among them, 5 articles were excluded due to insufficient data available. Finally, 14 articles [18–31] included in the present meta-analysis.

3.2. Characteristics of included studies

Characteristics of the eligible articles are presented in Table 1. Sample size of the eligible studies ranged from 20 to 120 patients, with ages between 50.2 and 64.9 years. Two studies conducted on female [29,31] and others on both sexes [18–28,30]. Duration of intervention ranged between 8 and 16 weeks. Supplementation dosage varied between 300 and 10000 mg daily. The type of green tea supplementation were as follows: green tea [24], green tea extract [18–23,25–27,29–31] and epigallocatechin-gallate [28]. These studies were accomplished in Japan [18,19,21], Iran [20,22,24,28,29,31], Taiwan [23,26], Lithuania [25], Brazil [27] and Mexico [30], and were published between 2005 and 2019.

3.3. Quality assessment and publication bias

Eight studies [22,23,26–31] provided comprehensive explanations of random sequence generation. Six studies [23,26–28,30,31] had low-risk of bias regarding allocation concealment. On the other hand, nine articles [21–23,25–28,30,31] had low-risk of bias regarding the blinding of participant's/personnel, and the majority [18–27,30] of studies had low-risk of bias regarding the blinding of outcome assessors. In addition, ten articles [18,19,21,23,24,26–28,30,31] were low-risk of bias in relation to incomplete outcome data. All the studies [18–31] had low risk of bias regarding the selective outcome reporting (Supplemental Table 1). Evaluation of publication bias by funnel plots did not uncover any publication bias within any of the studies (Supplemental Fig. 1-4). Furthermore, results from the Begg's tests did not indicate any publication bias (p

Table 1
Characteristic of the included studies in meta-analyses.

Author	Year	Country	Study design	sex	Mean age (intervention/control)	Trial duration	Daily dose of GT (mg)	Sample size (intervention/control)	BMI (intervention/control)
Fukino et al., 2005	2005	Japan	Parallel	F/M	53.5/53.5	2 months	544	33/33	25.5/25.9
Fukino et al., 2008	2008	Japan	Cross-over	F/M	53.9/53.4	2 months	544	60/60	25.4/26
Mirzaei et al., 2009	2009	Iran	Parallel	F/M	54.56/54.56	8 weeks	1500	26/46	NR
Nagao et al., 2010	2009	Japan	Parallel	F/	64.9/62.8	4 weeks	582.8	23/20	25.6/24
				M	64.9/62.8	8 weeks		23/20	25.6/24
					64.9/62.8	12 weeks		23/20	25.6/24
Mohammadi et al., 2010	2010	Iran	Parallel	F/M	55.14/55.14	8 weeks	1500	29/29	28.64/29.37
Hsu et al., 2011	2011	Taiwan	Parallel	F/M	50.5/52.2	16 weeks	1500	35/33	NR
Mousavi et al., 2013	2013	Iran	Parallel	F/	54.6/52	8 weeks	10000	26/14	27.4/28.1
				M	56.2/52		5000	25/14	28.1/28.1
Lasaite et al., 2014	2014	Taiwan	Parallel	F/M	55.06/53.56	16 weeks	500	46/46	NR
Liu et al., 2014	2014	Lithuania	Parallel	F/	62.18/62.18	2 months	400	20/25	35.23/34.98
				M	62.18/62.18		600	20/25	35.23/34.98
Borges et al., 2016	2016	Brazil	Parallel	F/M	63/59	12 weeks	800	23/24	30.6/32.7
Zandi Dareh Gharibi et al., 2018	2018	Iran	Parallel	F	50.66/55.9	10 weeks	1500	12/10	32.6/34.61
Sobhani et al., 2019	2019	Iran	Parallel	F	62.52/60.82	8 weeks	1500	11/11	26.82/26.88
Quezada-Fernández et al., 2019	2019	Mexico	Parallel	F/M	50.2/56.1	12 weeks	400	10/10	29.8/30.4
Hosseini et al., 2018	2018	Iran	Parallel	F/	52.25/55.25	2 month	300	20/20	29.48/28.35
				M	53.60/55.25	2 month	300	20/20	29.59/28.35

F, female; M, male; NR, not reported; GT, green tea.

value for FBS = 0.685, *p* value for hemoglobin A1c = 0.855, *p* value for HOMA-IR = 0.466, *p* value for Insulin = 0.214).

3.4. Effect of green tea supplementation on glycemic control

Analysis of the effect of green tea on FPG levels, insulin levels, hemoglobin A1C and HOMA-IR are shown in Figs. 2–5. Following green tea supplementation, there were no significant changes in FPG levels (WMD: −1.79, 95% CI [-7.89, 4.31], $p = 0.565$; between-study heterogeneity: I [2] = 67.6%, $p = 0.000$), insulin levels (WMD: 0.27, 95% CI [-0.51, 1.04], $p = 0.500$; between-study heterogeneity: I [2] = 35.3%, $p = 0.116$), hemoglobin A1C (WMD: −0.14, 95% CI [-0.38, 0.10], $p = 0.0.254$); between-study heterogeneity: I [2] = 75.0%, $p = 0.000$) and HOMA-IR (WMD: 0.16, 95% CI [-0.17, 0.49], $p = 0.336$; between-study heterogeneity: I [2] = 9.5%, $p = 0.356$).

3.5. Subgroup analysis

We stratified studies based on duration of intervention (≤8 and > 8 weeks) and intervention dosage (≤800 and > 800 mg/day). Subgroup analysis showed that the green tea supplementation longer than 8 weeks, resulted in a significant decrease in FPG levels (WMD: −8.61, 95% CI [-15.57, −1.66], $p = 0.015$). Furthermore, intervention equal or shorter than 8 weeks resulted in a significant reduction in hemoglobin A1C (WMD: −0.40, 95% CI [-0.72, −0.08], $p = 0.013$) (Table 2).

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to assess the effect of green tea on glycemic control in T2DM patients. Our meta-analysis revealed that the supplementary intake of green tea had no significant effect on FPG, fasting insulin, HbA1c and HOMA-IR in patients with T2DM. However, subgroup analyses based on duration of interventions (≤8 and > 8 weeks) and intervention dosage (≤800 and > 800 mg/day) showed that the green tea consumption longer than 8 weeks resulted in a significant decrease in FPG levels. Moreover, green tea consumption equal or shorter than 8 weeks resulted in a significant reduction in HbA1c.

It has been well known that the green tea increases the glucose uptake by different tissues. Green tea extract can increase adipocytes and skeletal muscle capacity for glucose uptake by increasing the expression of GLUT IV [32]. In addition, according to in vitro studies, EGCG inhibits the proliferation and differentiation of adipocytes and increases glucose reception by the cells through protein kinase by AMP activation [33]. Moreover, green tea extract regulates genes which encode gluconeogenic enzymes and protein-tyrosine phosphorylation by modulating the redox state of the cell [34]. Previous investigations revealed that catechin can suppress the glucose absorption in the small intestine [35]. Furthermore, it has been reported that the water extract of green tea had insulin-like activities and reduced the serum concentrations of glucose

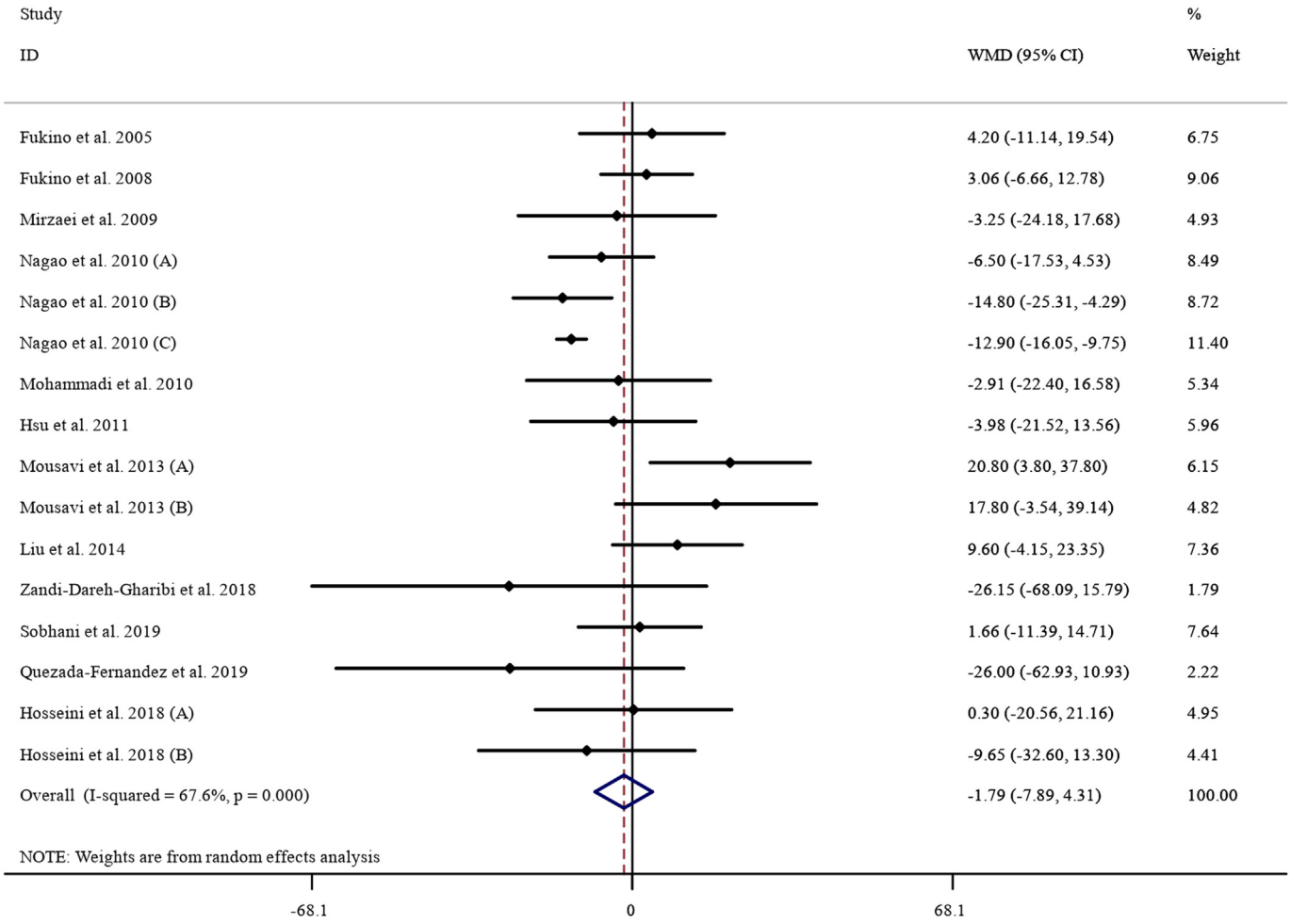

Fig. 2. Forest plot of the random-effects meta-analysis of the effect of the green tea on fasting plasma glucose.

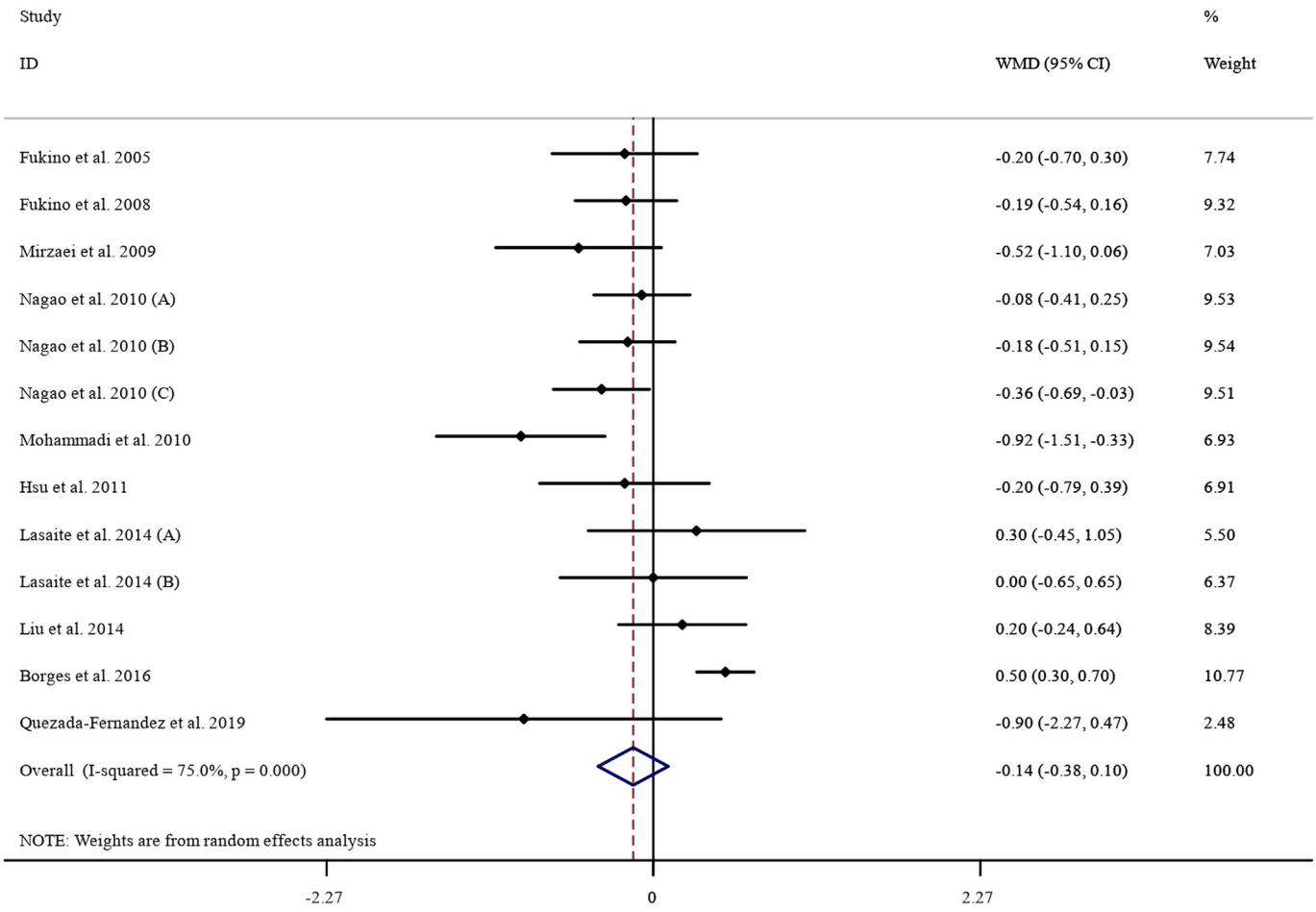

Fig. 3. Forest plot of the random-effects meta-analysis of the effect of the green tea on hemoglobin A1c.

[35]. Although, in vitro and in vivo studies revealed the beneficial effect of green tea on glucose metabolism, results of the RCTs assessed the effect of green tea on serum levels of glucose are controversial. The study by Fukin et al. [18], indicated that the intake of green tea polyphenols did not have clear effects on blood glucose level, HbA1c level and insulin resistance. Whereas, another study indicated that the green tea-extract powder lowered the HbA1c level in individuals with borderline diabetes [35]. Furthermore, another study demonstrated that green tea extract significantly improved insulin resistance [36]. In 2013, a systematic review and meta-analysis, which included both healthy subjects and patients with chronic disease, concluded that green tea consumption significantly reduced the fasting glucose and HbA1c [13]. Our systematic review and meta-analysis indicated that supplementary intake of green tea had no significant effect on glycemic control in T2DM patients. However, further stratified analyses indicated the beneficial effect of green tea extract/powder on FPG in long-term interventions, in such patients.

It should be noted that all the articles included in this meta-analysis and reported a significant improvement in glycemic response, were conducted in Asia [31,35], [-39] and other studies conducted in non-Asian population failed to show a significant improvement in glycemic response [40–43]. It has been shown that Asian populations are more sensitive to supplementary intake of green tea [33,44]. It seems that this is due to the polymorphism of catechol-O-methyltransferase (COMT) the major enzyme, which is responsible for the catabolism of green tea catechin [45,46]. Therefore, Asian population may metabolize tea catechins slower than those with the Caucasian people, allowing the bioactive components to be retained longer and resulting in the greater benefits from green tea intake [47,48]. It shows the importance of the impact of ethnicity on the results of these studies. Furthermore, another reason for the discrepancy between the results of studies evaluating the effects of green tea extract on glycemic control might be the different doses administered in these studies. A meta-analysis which investigated the association between green tea consumption and the risk of T2DM, reported that patients who ingested four or more cups of tea per day had a 20% lower risk of T2DM than participants who ingested less or none [49]. However, in another meta-analysis study, the results of the meta-regression analysis did not show a significant dose-response effect between green tea consumption and FPG or fasting plasma insulin [13]. Moreover, we found that the supplementary intake of green tea at each dose had no significant effect on glycemic control in T2DM patients. Based on these results, it is therefore difficult to determine the optimal dose for a diet program as part of a health plan aimed at improving diabetic health. Therefore, further well-designed clinical trials, considering these confounders, are necessary to clarify more facts regarding the effects of green tea on glycemic control in diabetic patients. Moreover, RCTs comparing short and long-term

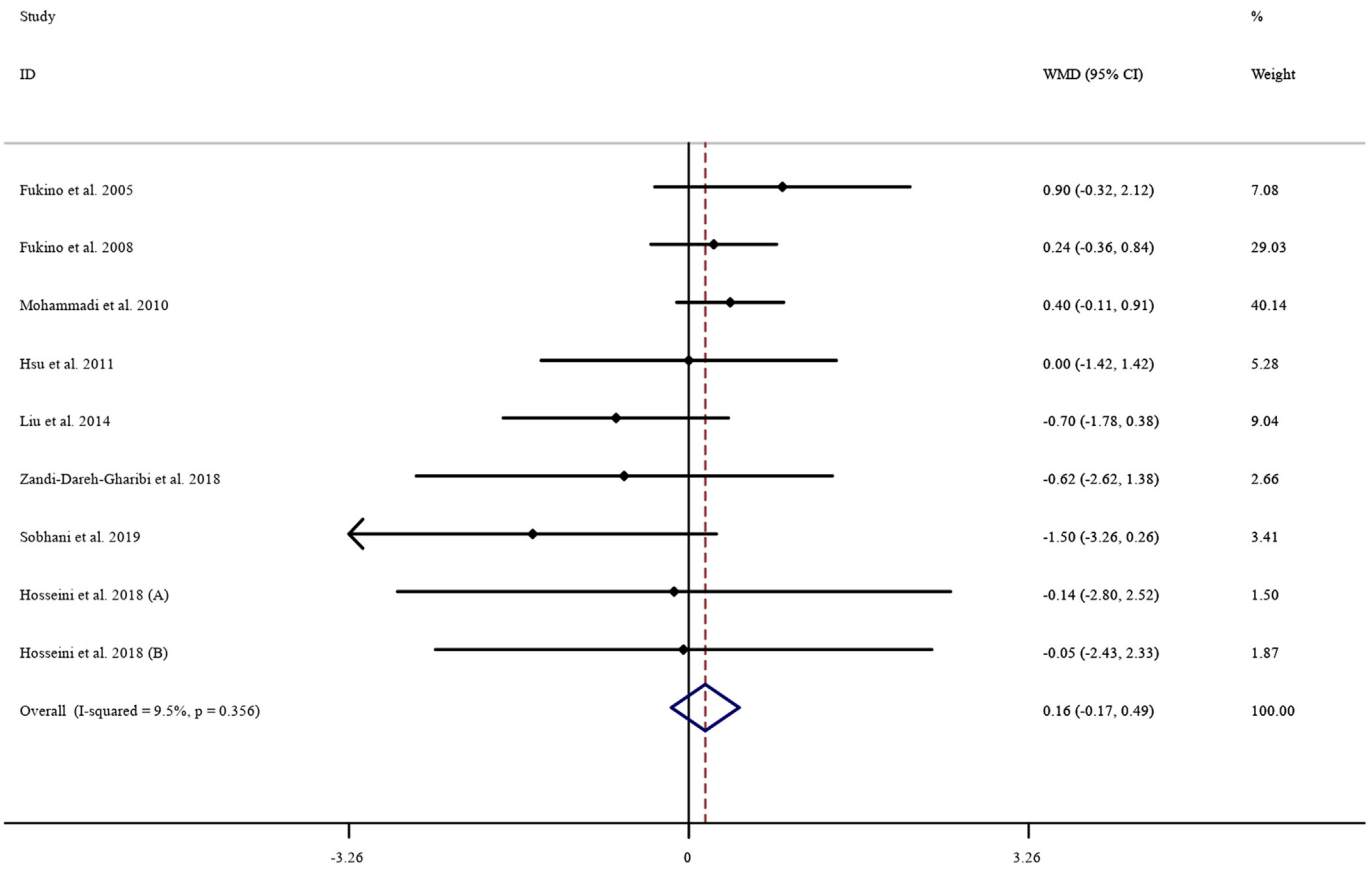

Fig. 4. Forest plot of the fixed-effects meta-analysis of the effect of the green tea on HOMA-IR.

supplementary intake of green tea on glycemic control in diabetic patients, can help determine the optimal timing of green tea effect.

As the subgroup analyses indicated, unlike FPG, a significant reduction in HbA1c was observed in a short-term supplementary intake of green tea. HbA1c is currently the gold standard for glucose monitoring in patients with diabetes and is expression of average fasting as well as postprandial blood glucose in the past 2–3 months [50]. Although, HbA1c test has been used clinically as a test of glycemic control in individuals with diabetes [51], it is subject to certain limitations. The levels of HbA1c is affected by red blood cell turnover (hemolysis, blood loss) and hemoglobin variants, particularly when the HbA1C result does not correlate with the patient's blood glucose levels [52]. In addition, lengthened RBC life span and the low levels of proteins may wrongly alter the result of HbA1c test [53]. More well-designed RCTs are needed to determine the effects of short- and long-term supplementary intake of green tea on HbA1c.

5. Strengths and limitations

Our systematic review and meta-analysis has several strengths. First, this is the first meta-analysis to assess the effect of green tea on glycemic control in patients with T2DM. Second, we included RCTs, which examined complementary endpoints, providing a comprehensive review on this topic. Third, this review is based on an up to date literature search from a large number of databases and included 14 studies. A possible limitation of this meta-analysis is that most of the studies included in this meta-analysis were conducted in Asia. In addition, the lack of PROSEPERO registration and GRADE analysis were other limitations.

In conclusion, our systematic review and meta-analysis indicated that the supplementary intake of green tea had no significant effect on FPG, fasting insulin, HbA1c and HOMA-IR in patients with T2DM. However, further well-designed trials, considering the confounders such as ethnicity, dose of supplementation and the duration of supplementation, are necessary to clarify more facts regarding the effect of green tea on glycemic control in T2DM patients.

Conflict-of-interest statement

The authors declare that no conflict of interest exists.

Financial support

There are no financial or other competing interests for principal investigators, patients included or any member of the trial.

Author contributions

AA and OA designed the study. FF and OA reviewed and selected the articles. RC and DA extracted needed data from articles. AA and OA performed data analysis and interpretation. MJG revised the article for important intellectual content. AA drafted the manuscript.

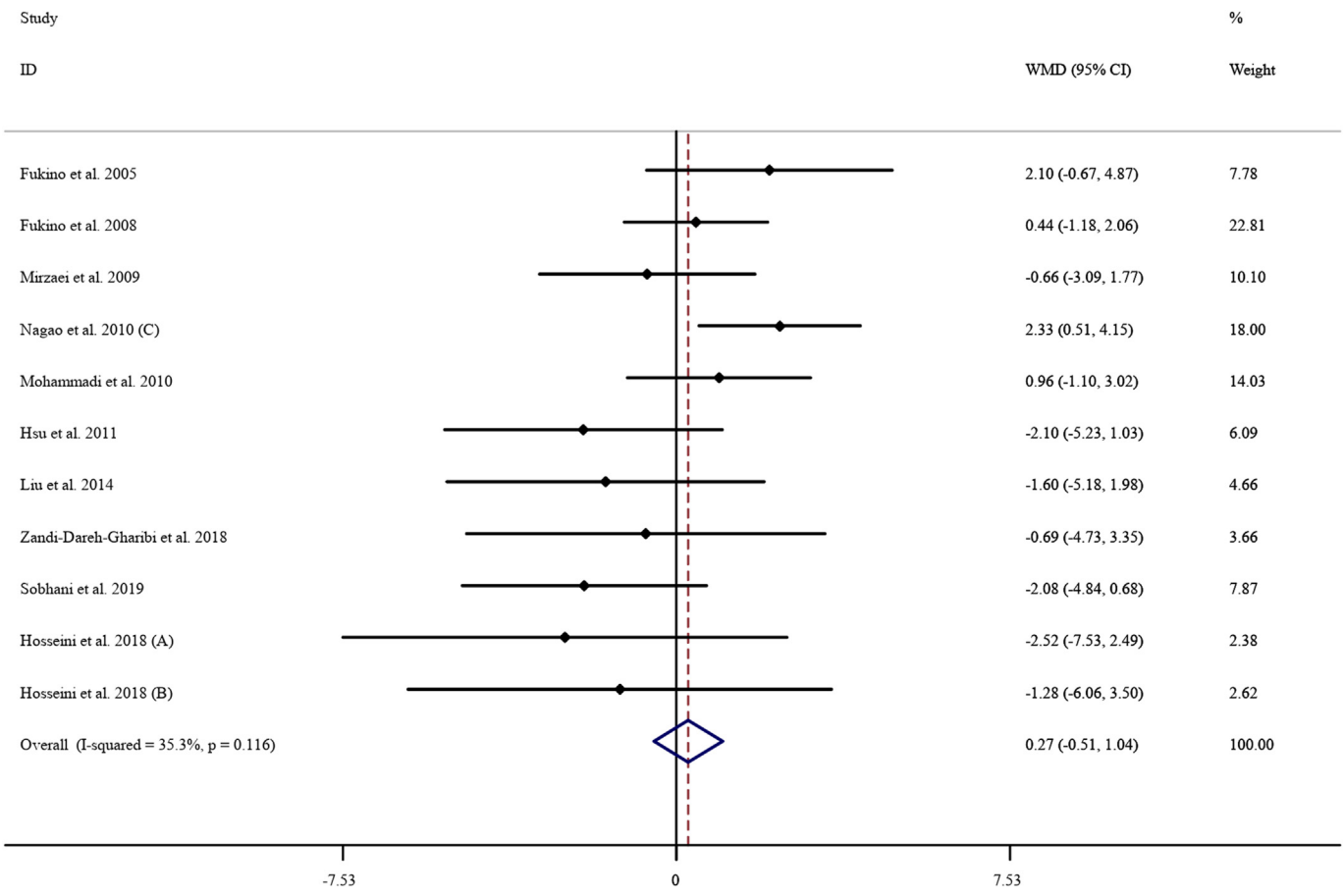

Fig. 5. Forest plot of the fixed-effects meta-analysis of the effect of the green tea on insulin.

Table 2
Subgroup analyses of green tea on glycemic control.

	NO	WMD (95%CI)	P within group	P heterogeneity	I [2] (%)
Subgroup analyses of green tea supplementation on FBG.					
Trial duration (week)					
≤8	9	3.90 (−1.41, 9.20)	0.150	0.439	0.0%
>8	7	−8.61 (−15.57, −1.66)	**0.015**	0.047	52.9%
Green tea dosage (mg)					
≥800	9	−4.89 (−11.80, 2.00)	0.164	0.002	66.9%
<800	7	3.57 (−5.48, 12.62)	0.439	0.162	34.8%
Subgroup analyses of green tea supplementation on insulin level					
Trial duration (week)					
≤8	7	0.11 (−0.83, 1.05)	0.819	0.322	14.1%
>8	4	0.59 (−0.76, 1.95)	0.393	0.043	63.2%
Green tea dosage (mg)					
≥800	6	0.88 (−0.12, 1.89)	0.087	0.164	36.3%
<800	5	−0.59 (−1.79, 0.60)	0.329	0.381	4.4%
Subgroup analyses of green tea supplementation on hemoglobin A1C					
Trial duration (week)					
≤8	4	−0.40 (−0.72, −0.08)	**0.013**	0.166	41.0%
>8	9	−0.00 (−0.28, 0.26)	0.952	0.000	73.6%
Green tea dosage (mg)					
≥800	9	−0.14 (−0.28, 0.00)	0.056	0.543	0.0%
<800	4	−0.25 (−0.98, 0.47)	0.493	0.000	90.2%
Subgroup analyses of green tea supplementation on HOMA-IR					
Trial duration (week)					
≤8	6	0.28 (−0.10, 0.66)	0.155	0.382	5.4%
>8	3	−0.47 (−1.26, 0.32)	0.244	0.735	0.0%
Green tea dosage (mg)					
≥800	5	0.13 (−0.32, 0.60)	0.562	0.411	0.0%
<800	4	−0.11 (−0.91, 0.69)	0.782	0.182	38.3%

FBG, fasting plasma glucose; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; WMD, weighted mean difference; CI, confidence interval.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2020.11.004.

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