

Effects of coenzyme Q₁₀ on cardiovascular and metabolic biomarkers in overweight and obese patients with type 2 diabetes mellitus: a pooled analysis

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Background: The potential effects of coenzyme Q10 (CoQ₁₀) supplementation in overweight/obese patients with type 2 diabetes mellitus are not fully established. In this article, we aimed to perform a pooled analysis to investigate the effects of CoQ₁₀ intervention on cardiovascular disease (CVD) risk factors in overweight/obese patients with type 2 diabetes mellitus (T2DM).

Methods: MEDLINE, Embase, and Cochrane databases were searched for randomized controlled trials that evaluated the changes in CVD risk factors among overweight and obese patients with T2DM following CoQ₁₀ supplementation. Two investigators independently assessed articles for inclusion, extracted data, and assessed risk of bias. Major endpoints were synthesized as weighted mean differences (WMDs) with 95% CIs. Subgroup analyses were performed to check the consistency of effect sizes across groups. Publication bias and sensitivity analysis were also performed.

Results: Fourteen eligible trials with 693 overweight/obese diabetic subjects were included for pooling. CoQ₁₀ interventions significantly reduced fasting blood glucose (FBG; -0.59 mmol/L; 95% CI, -1.05 to -0.12 ; $P=0.01$), hemoglobin A1c (HbA1c; -0.28% ; 95% CI -0.53 to -0.03 ; $P=0.03$), and triglyceride (TG) levels (0.17 mmol/L; 95% CI, -0.32 to -0.03 ; $P=0.02$). Subgroup analysis also showed that low-dose consumption of CoQ₁₀ (<200 mg/d) effectively reduces the values of FBG, HbA1c, fasting blood insulin, homeostatic model assessment of insulin resistance, and TG. CoQ₁₀ treatment was well tolerated, and no drug-related adverse reactions were reported.

Conclusion: Our findings provide substantial evidence that daily CoQ₁₀ supplementation has beneficial effects on glucose control and lipid management in overweight and obese patients with T2DM.

Keywords: coenzyme Q10, type 2 diabetes mellitus, cardiovascular risk factors, lipids, glucose, obesity

Introduction

Diabetes is a chronic disease with high rates of disability and mortality. In 2013, it was estimated that globally there were 382 million diabetic adults and is expected to increase to almost 592 million by 2035.¹ Early onset of diabetes leads to longer lifetime exposure to hyperglycemia and consequently a greater propensity to long-term complications.² Poor glycemic control causes long-term adverse outcomes in subjects with diabetes, including microvascular and macrovascular complications.^{3,4} Some researchers have suggested that up to two of every three cases of type 2 diabetes mellitus (T2DM) can be attributed to obesity.⁵ Being overweight and obese increases the risks of diabetes and cardiovascular disease (CVD).⁶ Obesity accentuates the

metabolic and CVD complications in patients with T2DM by increasing insulin resistance, causing a progressive decline of β -cell functions, and subsequently increasing the difficulty in achieving the glycemic targets.^{7,8} The management of diabetes and its CVD-related complications impose enormous medical and economic burdens. Therefore, primary and secondary prevention of diabetes and delaying the onset or progression of diabetes-related complications have become a public health imperative. Treatment strategies for patients with T2DM who are obese should focus equally on glycemic control, weight loss, and the comprehensive management of CVD comorbidities or risk factors. In recent decades, large meta-analyses of randomized controlled trials (RCTs) have suggested that lifestyle modifications, such as dietary micro-nutrients or functional food supplementations, are generally used to improve glycemic management and clinically relevant metabolic biomarkers in patients with diabetes.^{9–11}

Accumulating evidence indicates that mitochondrial dysfunction, inflammation, and oxidative stress contribute to the pathogenesis of diabetes and associated complications.^{12,13} Coenzyme Q10 (CoQ₁₀; also called ubiquinone), a lipid-soluble benzoquinone with 10 isoprenyl units in the side chain, can be synthesized endogenously or obtained naturally from the diet. In clinical applications, oral CoQ₁₀ treatment is a frequent mitochondrial energizer and antioxidant strategy in many diseases that may provide a significant symptomatic benefit. CoQ₁₀ has been used to prevent and treat a wide range of diseases, including primary and secondary CoQ₁₀ deficiencies, mitochondrial diseases, fibromyalgia, CVD, neurodegenerative diseases, cancer, diabetes mellitus, hypertension, and periodontal disease.^{14–16} The plasma levels of CoQ₁₀ in patients with diabetes are significantly lower when compared with the healthy individuals.^{17,18} The deficiency of CoQ₁₀ may further impair the body's defensive mechanisms against oxidative stress induced by hyperglycemia in diabetes.¹⁹ Several studies have demonstrated that the restoration of CoQ₁₀ levels in patients with diabetes by the supplemental use of exogenous CoQ₁₀ could potentially preserve mitochondrial function, alleviate oxidative stress, and eventually lead to improvement of glycemic control.^{20–24} However, the results of whether the supplementation of CoQ₁₀ helps to improve glucose and insulin levels, to modify lipid profiles, and to reduce blood pressure in overweight diabetic patients are inconsistent and have not been fully understood. Therefore, we undertook a comprehensive meta-analysis of RCTs to investigate the effects and safety of CoQ₁₀ supplementation on multiple markers of cardiovascular health in overweight and obese patients with established T2DM.

Materials and methods

Search strategy

The protocol for this pooled analysis was conducted following PRISMA guidelines.²⁵ Two independent investigators performed an electronic literature search of MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) from their inception to December 31, 2017, restricting the search to publications in English and clinical trials that investigated the effects of CoQ₁₀ intervention in patients with established T2DM. We used the following search terms: “Coenzyme Q10” OR “Co-enzyme Q10” OR “CoQ₁₀” OR “ubiquinone” OR “ubiquinol” and combined with “diabetes mellitus” OR “type 2 diabetes” OR “type 2 diabetes mellitus” OR “diabetes” OR “noninsulin-dependent diabetics” OR “NIDDM” OR “T2DM”. To identify any other missing eligible trials, we also performed a manual search of reference citations in relevant review articles and original articles that were selected for full-text retrieval.

Study inclusion criteria

To be included, an original study had to meet the following criteria: 1) population: target population (adults aged ≥ 18 years) with a body mass index (BMI) of ≥ 25 kg/m² and diagnosed with T2DM; 2) intervention: the patients ingested a determined amount of CoQ₁₀ or ubiquinol intervention for ≥ 4 weeks; 3) comparison: placebo or conventional antidiabetic agents were used; 4) outcomes of interest: an assessment of at least one of the following outcome markers, namely fasting blood glucose (FBG), hemoglobin A1c (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), fasting blood insulin (FBI), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), SBP, DBP, and BMI; and 5) study design: study was an RCT conducted in human subjects with either a parallel or crossover design.

Data extraction

Data extraction included information regarding study characteristics (first author's name, year of publication, sample size, details of the study design, and length of follow-up), basic characteristics of participants (such as age, percentage male, duration of diabetes, baseline of BMI, and FBG), and intervention characteristics (such as type of intervention, dose, and type of control) and reported the outcomes of interest.

Assessing the quality of the methodology used

Two of the investigators independently used the Cochrane Collaboration bias risk analysis tool to assess the quality of

the trials included.²⁶ Randomization sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases (defined as baseline imbalance in our present study) were classified as high, low, or unclear for each domain of the studies included.

Grading quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to rate the quality of evidence and generate absolute estimates of the effect of CoQ₁₀ for the primary and secondary outcomes.²⁷

Statistical analyses

We used STATA software (version 12; StataCorp LP, College Station, TX, USA) to combine the individual study results for all outcomes studied. For each marker, we calculated the effect sizes as a weighted mean difference (WMD) and a 95% CI between the CoQ₁₀ intervention and control groups using a random-effects model. We used the *I*² statistic to assess the degree of statistical heterogeneity among studies, with a value of <25%, 26%–50%, and >50% being considered as a low, moderate, and high levels of heterogeneity, respectively.²⁸ To evaluate the robustness of our findings, sensitivity analyses were performed by removing one study each time and repeating the analysis (the “leave-one-out” approach). To explore the influence of various factors on the cardiovascular risk factors of CoQ₁₀ intervention, a priori subgroup analyses were then carried out according to the mean age of the patients, the duration of T2DM, the baseline level of BMI, CoQ₁₀ dose, and intervention duration. We investigated the possibility of publication bias using funnel plot asymmetry and Egger’s weighted regression test.²⁹ A *P*-value of <0.05 was considered to be statistically significant.

Meta-regression

In the present study, we applied a restricted maximum likelihood (REML)-based random-effects meta-regression analysis to explore whether the potential confounders of treatment response, such as the dose (mg/d) and duration (number of weeks) of supplementation with CoQ₁₀, were associated with the source of heterogeneity.³⁰

Results

Search results and trial flow

A PRISMA study flow chart of the selected trials is shown in [Figure S1](#). We initially identified 375 potential records from the original literature search, of which 44 were duplicate articles. Three hundred thirty-one potentially

relevant articles were screened based on their titles and abstracts, and then 45 articles were selected for detailed evaluation. After full-text assessment, 31 of these studies were excluded, most of them due to CoQ₁₀ being mixed with other components (n=3); reported from the same population (n=2); the outcomes of interest not being reported (n=3); duplicate data (n=2); not being an RCT study (n=4); letters, reviews, or meta-analysis (n=6); mixed patients (n=5); subjects being younger than 18 years (n=3); and participants with a BMI < 25 kg/m² (n=3). Overall, a total of 14 studies with 693 participants were finally selected for the meta-analysis.^{20–24,31–39}

Study and participant characteristics

Detailed characteristics of the resulting 14 trials are listed in Table 1. Most studies included were single-center studies published between 1999 and 2018. The mean baseline BMI of the T2DM patients varied from 25.0 to 30.4 kg/m². The population sizes included in these studies ranged from 23 to 80 subjects. Overall, 730 subjects were randomly assigned in these trials, while 693 (94.9%) subjects completed the studies. Of the 14 trials used in the meta-analysis, 10 trials included both men and women,^{20–22,24,31,33–36,39} one included only women,³⁸ and three did not indicate the sex composition of the sample.^{23,32,37} The dose of CoQ₁₀ varied from 100 to 400 mg/d (median, 185.7 mg/d). The follow-up duration of CoQ₁₀ intervention was 8, 12, or 24 weeks (median, 12.86 weeks). The mean age of the participants ranged from 47 to 68 years (median, 55.78 years). The mean baseline FBG ranged from 7.15 to 11.5 mmol/L (median, 8.88 mmol/L). All trials were randomized, with 92.8% (13 trials) utilizing a parallel design and 7.2% (one trials) utilizing a crossover design. Among the studies included, 11 of the 14 studies included subjects with only T2DM. Of the remaining three trials, one was performed on subjects with T2DM and dyslipidemia, one was conducted on T2DM subjects with left ventricular diastolic dysfunction, and one was conducted on T2DM subjects with coronary heart disease.

Assessment of quality and potential bias

A detailed risk-of-bias summary is shown in Figure 1. Among the 14 studies included, only seven studies reported random sequence generation.^{21,22,33–35,37,39} Two trials did not describe whether the blind method was adopted and were categorized as at high risk of bias.^{20,21} Overall, six trials were considered as at low risk of bias,^{22,33–35,37,39} two as at a high risk of bias,^{20,21} and six as unclear.^{23,24,31,32,36,37}

Table 1 Characteristics of the included studies

Reference (years)	Study design	Location	Enrollment/ no. completed	Population	Male (%)	Duration of DM (years)	Mean age (years)
Chew et al ³¹ (2008)	R, DB, P	Australia	36/36	T2DM subjects with LVDD	75.0	4.3±4.0	61.8±7.63
Eriksson et al ²³ (1999)	R, DB, P	Denmark	23/23	Patients with T2DM	NR	NR	64.5±6
Akbari Fakhrabadi et al ³⁹ (2014)	R, DB, P	Iran	74/62	Patients with T2DM	25.8	16.2±7.25	55.7±6.55
Hamilton et al ³² (2009)	R, DB, C	Australia	23/23	Statin-treated T2DM patients	NR	8.0	68.0±6
Hernández-Ojeda et al ³³ (2012)	R, DB, P	Mexico	56/49	Patients with T2DM	22.4	10.7±8.74	56.1±8.66
Hosseinzadeh-Attar et al ³⁴ (2015)	R, DB, P	Iran	64/64	Patients with T2DM	57.8	5.3±3.4	46.1±7.97
Lim et al ³⁵ (2008)	R, DB, P	Singapore	80/80	Patients with T2DM	50	NR	53.5±9
Moazen et al ²¹ (2015)	R, SB, P	Iran	52/52	Patients with T2DM	53.8	4.6±3.91	51.7±7.36
Mohammed-Jawad et al ²⁰ (2014)	R, NB, P	Iraq	38/38	Patients with T2DM	47.4	4.4±3.48	50.5±7.55
Mehrdadi et al ²² (2017)	R, DB, P	Iran	64/56	Overweight/obese T2DM subjects	57.1	5.2±3.5	47.0±8
Playford et al ³⁶ (2003)	R, DB, P	Australia	40/40	Patients with T2DM and dyslipidemia	82.5	NR	53.7±1.85
Raygan et al ³⁷ (2016)	R, DB, P	Iran	60/60	Overweight or obese and T2DM patients with CHD	NR	NR	62.9±12.81
Zahedi et al ²⁴ (2014)	R, DB, P	Iran	40/40	Patients with T2DM	47.5	7.6±6.09	56.1±9.65
Gholami et al ³⁸ (2018)	R, DB, P	Iran	80/70	Women with T2DM	0	4.75±2.60	53.3±6.45

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; C, crossover; CoQ10, coenzyme Q10; CHD, coronary heart disease; DB, double blind; DM, diabetes mellitus; FBG, fasting blood glucose; FBI, fasting blood insulin; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; LVDD, left ventricular diastolic dysfunction; NR, not reported; P, parallel; R, randomized; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus.

Changes in glycemic control, insulin levels, and sensitivity

Overall, the pooled result showed that the consumption of CoQ10 significantly decreased the FBG (12 studies; WMD=−0.59 mmol/L; 95% CI=−1.05 to −0.12; $P=0.01$) and HbA1c levels (13 studies; WMD=−0.28%; 95% CI=−0.53 to −0.03; $P=0.03$) in overweight and obese patients with T2DM. Heterogeneity tests results of these outcomes were 37% and 33%, respectively. However, FBI (five studies; WMD=−1.87 μ IU/mL; 95% CI=−4.51 to 0.77; $P=0.17$; $I^2=71%$) and HOMA-IR (five studies; WMD=−1.03; 95% CI=−2.06 to −0.00; $P=0.05$; $I^2=71%$) levels did not change significantly with the consumption of CoQ10. Forest plots for each measured parameter are shown in Figure 2.

Changes in lipid concentrations, blood pressure, and BMI

As shown in Figure 3, the consumption of CoQ10 by overweight and obese patients with T2DM caused a significant

reduction in TG concentrations compared with the control (eight studies; WMD=−0.17 mmol/L; 95% CI=−0.32 to −0.03; $P=0.02$; $I^2=0%$). However, no significant changes were found in the concentrations of TC (10 studies; WMD=−0.18 mmol/L; 95% CI=−0.33 to 0.16; $P=0.50$; $I^2=40%$), LDL-C (10 studies; WMD=0.05 mmol/L; 95% CI=−0.30 to 0.20; $P=0.69$; $I^2=77%$), and HDL-C (10 studies; WMD=0.03 mmol/L; 95% CI=−0.01 to 0.08; $P=0.17$; $I^2=29%$) values of the diabetic participants.

Six studies investigated the impact of CoQ10 on BP in overweight and obese patients with T2DM. CoQ10 supplementation did not result in a significant reduction in SBP (six studies; WMD=1.84 mmHg; 95% CI=−5.60 to 1.92; $P=0.34$; $I^2=21%$) and DBP levels (five studies; WMD=−1.38 mmHg; 95% CI=−5.48 to 2.72; $P=0.51$; $I^2=80%$). Similarly, no significant difference was seen in BMI with CoQ10 intake in the three studies that evaluated this outcome (WMD=−0.35 kg/m²; 95% CI=−1.58 to 0.88; $P=0.58$; $I^2=0%$).

BMI (kg/m ²)	Baseline of FBG	DM criteria	Intervention		Dose (mg/d)	Duration (weeks)	Main outcomes
			Treatment group	Control group			
30.4±4.81	7.4±1.7	ADA	CoQ ₁₀	Placebo	200	24	FBG, HbA1c, TC, TG, LDL-C, HDL-C
29.4±3.86	11.5±2.47	NR	CoQ ₁₀	Placebo	200	24	FBG, HbA1c, TC, TG, HDL-C, SBP, DBP, BMI
29.1±3.70	9.16±2.78	ADA	CoQ ₁₀	Placebo	100	12	FBG, HbA1c, FBI, HOMA-IR, TC, LDL-C, HDL-C
29.0±4	NR	NR	CoQ ₁₀	Placebo	200	12	HbA1c, LDL-C, SBP, DBP
29.3±6.35	11.6±5.06	ADA	Ubiquinone	Placebo	400	12	FBG, HbA1c, TC, LDL-C, HDL-C, TG
29.5±3.04	8.83±1.74	ADA	CoQ ₁₀	Placebo	200	12	FBG, HbA1c, TC, TG, LDL-C, HDL-C, BMI
25.0±4.81	7.75±2.0	NR	CoQ ₁₀	Placebo	200	12	FBG, HbA1c, SBP, DBP
25.3±2.27	9.75±4.00	NR	CoQ ₁₀	Placebo	200	8	FBG, HbA1c, BMI
28.8±4.19	10.56±3.09	ADA	CoQ ₁₀	Sulfonylurea and metformin	150	8	FBG, HbA1c, TC, LDL-C, HDL-C
29.5±3.10	8.88±1.75	NR	CoQ ₁₀	Placebo	200	12	FBG, HbA1c, FBI, HOMA-IR
30.4±0.89	7.75±0.53	NR	CoQ ₁₀	Placebo	200	12	HbA1c, TC, LDL-C, HDL-C, TG, SBP
29.4±5.58	7.15±2.47	ADA	CoQ ₁₀	Placebo	100	8	FBG, FBI, HbA1c, TC, LDL-C, HDL-C, TG
25.9±3.02	7.34±2.07	NR	CoQ ₁₀	Placebo	150	12	FBG, HbA1c, FBI, HOMA-IR, TC, LDL-C, HDL-C, TG
28.9±3.33	7.78±2.90	WHO	CoQ ₁₀	Placebo (cellulose acetate)	100	12	FBG, HbA1c, FBI, HOMA-IR, TC, LDL-C, HDL-C, TG, SBP, DBP, BMI

Meta-regression analyses

The results from the univariate weighted random-effects meta-regression analysis demonstrate that the duration of CoQ₁₀ supplementation was not a source of heterogeneity of FBG (coefficient=0.068; 95% CI=-0.069 to 0.206; *P*=0.294) and HbA1c levels (coefficient=-0.034; 95% CI=-0.038 to 0.106; *P*=0.294; [Figure S2](#)). Similarly, as shown in [Figure S3](#), the amount of CoQ₁₀ consumed per day was also not a source of heterogeneity of FBG (coefficient=0.002; 95% CI=-0.006 to 0.010; *P*=0.626) and HbA1c levels (coefficient=-0.0003; 95% CI=-0.005 to 0.004; *P*=0.877).

Subgroup analysis and sensitivity analysis

The subgroup analysis results based on the CoQ₁₀ dose demonstrated that CoQ₁₀ consumption significantly decreased the levels of FBG (*P*=0.006), HbA1c (*P*=0.005), FBI (*P*=0.01), HOMA-IR (*P*=0.0001), and TG (*P*=0.02) in the low-dose CoQ₁₀ supplementation group (<200 mg/d). In the subgroup analysis based on the baseline patient BMI, the

pooled result showed that CoQ₁₀ supplementation significantly decreased FBG, HbA1c, and TG levels of overweight and obese patients with diabetes mellitus by 0.67 mmol/L, 0.36%, and 0.16 mmol/L, respectively. We layered the trials according to mean age (<55.7 or ≥55.7 years), and a significant change in FBG (*P*=0.02) and HbA1c levels (*P*=0.01) was observed in subjects with a mean age of <55.7 years, whereas a significant change in FBI (*P*=0.001) and HOMA-IR levels (*P*=0.03) was observed in subjects with mean age of ≥55.7 years. A post hoc subgroup analysis was also performed to examine the effect of intervention duration on the overall effects of CoQ₁₀ on CVD risk factors in overweight and obese patients with T2DM. The post hoc subgroup analysis suggested that CoQ₁₀ consumption significantly decreased the levels of FBG (*P*=0.01), HbA1c (*P*=0.02), and TG (*P*=0.04) at supplemental duration of ≤12 weeks. There were no statistically significant differences in the pooled effects of CoQ₁₀ on CVD risk markers in the subgroups stratified by the duration of diabetes. Complete results of subgroup analysis are shown in [Table S1](#).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incompleted outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chew 2008	?	?	+	+	+	+	+
Eriksson 1999	?	?	+	+	+	+	+
Fakhrabadi 2014	+	+	+	+	+	+	+
Gholami 2018	?	+	+	+	+	+	+
Hamilton 2009	?	?	+	+	+	+	+
Hernández-Ojeda 2012	+	+	+	+	+	+	+
Hosseinzadeh-Attar 2015	+	+	+	+	+	+	+
Lim 2008	+	+	+	+	+	+	+
Mehrdadi 2016	+	+	+	+	+	+	+
Moazen 2015	+	+	+	-	+	+	+
Mohammed-Jawad 2014	?	?	-	-	+	+	+
Playford 2003	?	?	+	+	+	+	+
Raygan 2015	+	+	+	+	+	+	+
Zahedi 2014	?	?	+	+	+	+	+

Figure 1 Quality assessment of the included studies.

Note: Labeling an item as “question mark” indicated a unclear or unknown risk of bias; labeling an item as “negative sign” indicated a high risk of bias; and labeling an item as “positive sign” indicated a low risk of bias.

The sensitivity analysis results show that the exclusion of any single study each time did not influence the significance of our pooled effect size for either outcome (data not shown).

Publication bias

No obvious publication bias was found in the visual inspection of funnel plots. Figure 4 shows the

funnel plots of these study outcomes. Similarly, Egger’s tests showed that no statistical evidence of publication bias was observed in relation to levels of FBG ($P=0.275$), HbA1c ($P=2.53$), FBI ($P=0.836$), HOMA-IR ($P=0.618$), TC ($P=0.518$), LDL-C ($P=0.560$), HDL-C ($P=0.627$), TG ($P=0.069$), SBP ($P=0.977$), DBP ($P=0.896$), or BMI ($P=0.093$).

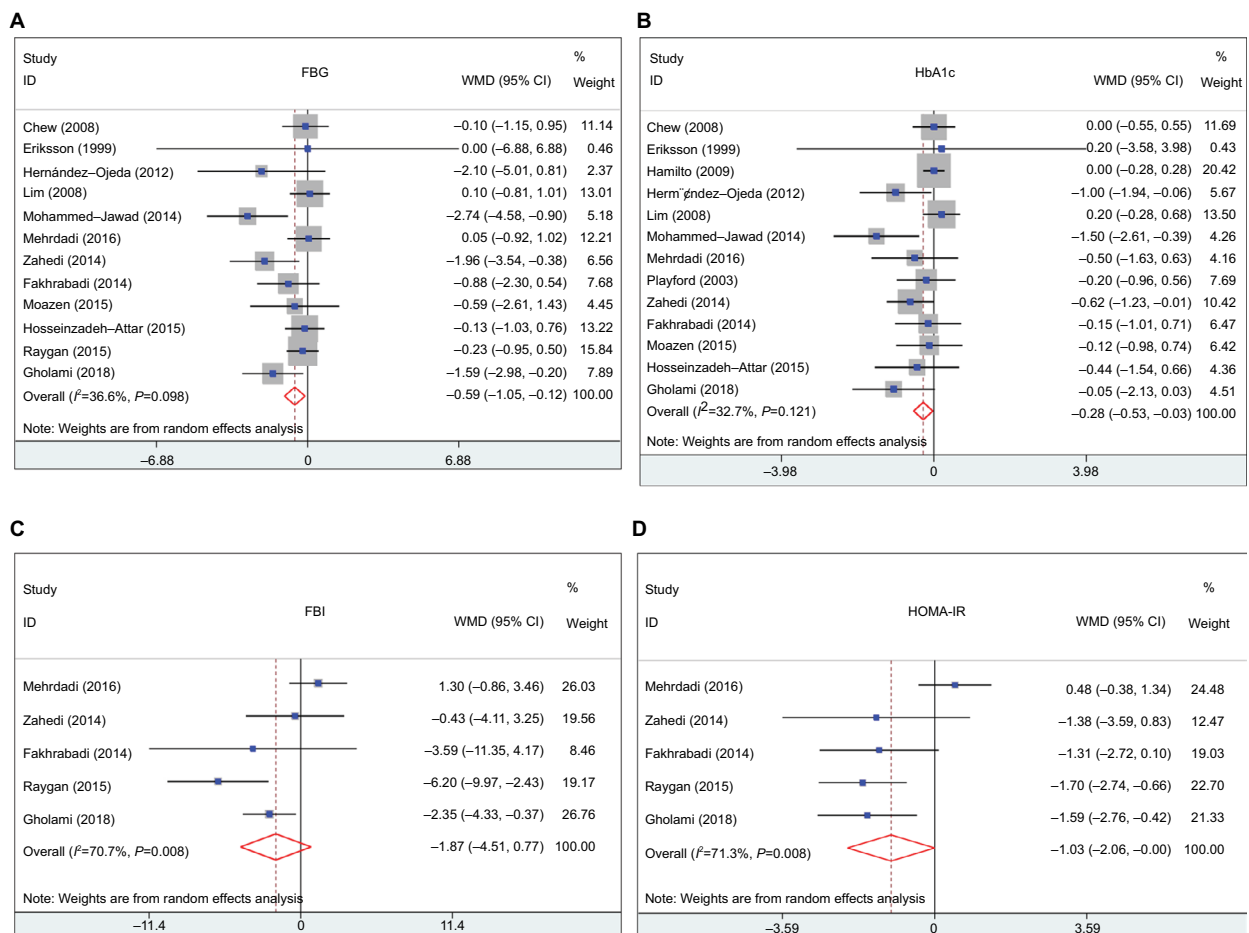


Figure 2 Forest plot detailing WMD and 95% CIs for the impact of CoQ₁₀ supplementation on FBG (A), HbA1c (B), FBI (C), and HOMA-IR (D) in overweight and obese patients with established T2DM.

Abbreviations: CoQ₁₀, coenzyme Q10; FBG, fasting blood glucose; FBI, fasting blood insulin; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference.

GRADE profile evidence evaluation

GRADE evidence profiles for the primary and secondary outcomes are shown in [Table S2](#). There were 11 outcomes regarding efficacy in this meta-analysis. The GRADE Working Group grade levels of evidence are of high quality for levels of TG, SBP and BMI; of moderate quality for levels of FBG, HbA1c, and HDL-C; and low quality for levels of HOMA-IR, FBI, TC, LDL-C, and DBP.

Discussion

Summary of main results

The results from our pooled analysis demonstrate that CoQ₁₀ interventions significantly reduced the levels of FBG, HbA1c, and TG by 0.59 mmol/L, 0.28%, and 0.17 mmol/L, respectively. These changes varied substantially depending on the treatment dose of CoQ₁₀, the intervention duration, the mean age of the subjects, and the initial level of BMI. Subgroup analysis also demonstrated that consumption of lower dose

of CoQ₁₀ (<200 mg/d) caused a significant reduction in levels of FBG, HbA1c, FBI, HOMA-IR, and TG in overweight and obese individuals with T2DM.

Agreements and disagreements with other studies

The impact of CoQ₁₀ supplementation for improving glucose and insulin responses, various lipid parameters, and blood pressure in patients with diabetes have been inconsistent. Therefore, there is not yet sufficient synthesis regarding the efficacy and risks for clinicians to make evidence-based decisions regarding the supplementation of CoQ₁₀ in the management of diabetes, especially in overweight and obese patients with diabetes mellitus. Two meta-analyses regarding this topic have been published.^{40,41} A previous meta-analysis that included seven trials involving 356 patients pointed out that CoQ₁₀ supplementation has no beneficial effects on glycemic control, lipid profile, or blood pressure in patients

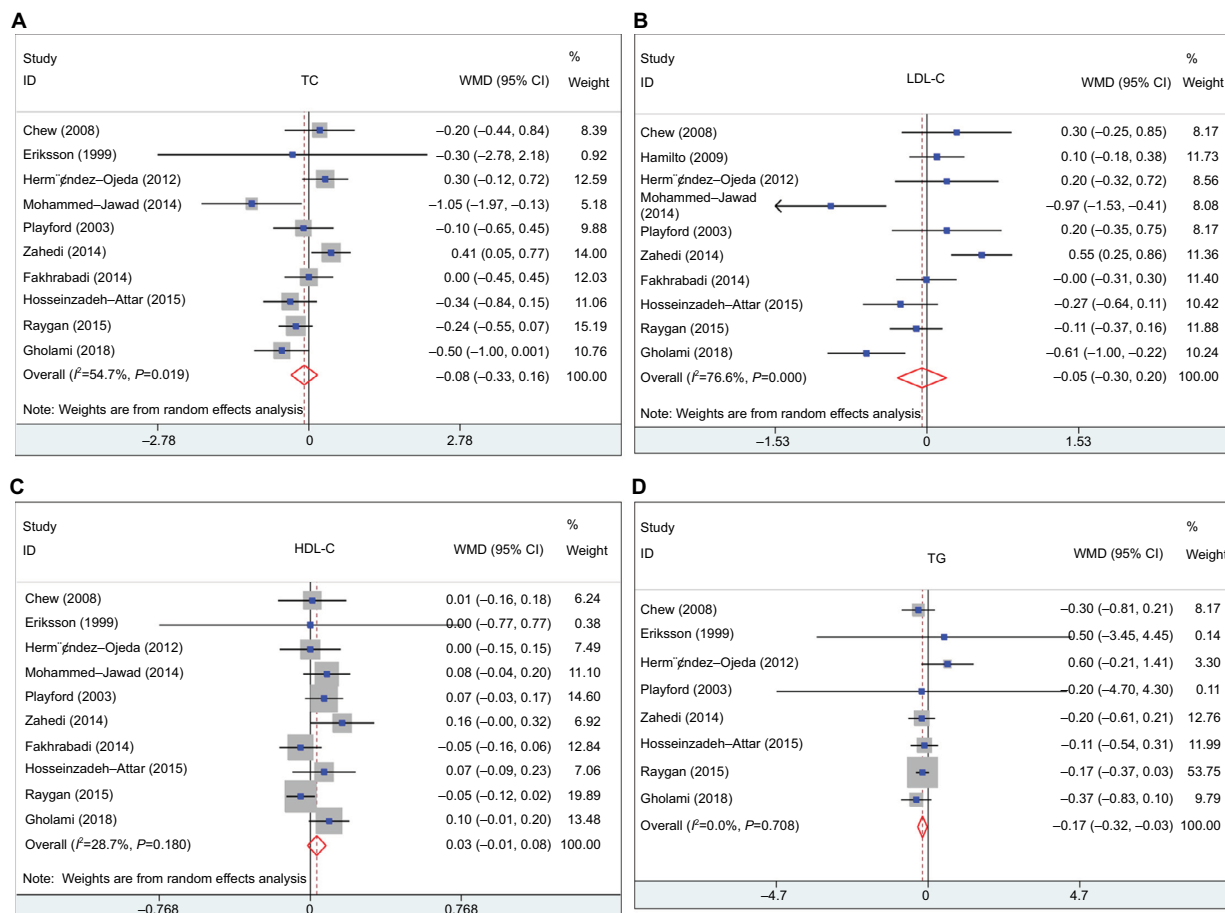


Figure 3 Forest plot detailing WMD and 95% CIs for the impact of CoQ₁₀ supplementation on TC (A), LDL-C (B), HDL-C (C), and TG (D) in overweight and obese patients with established T2DM.

Abbreviations: CoQ₁₀, coenzyme Q10; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference.

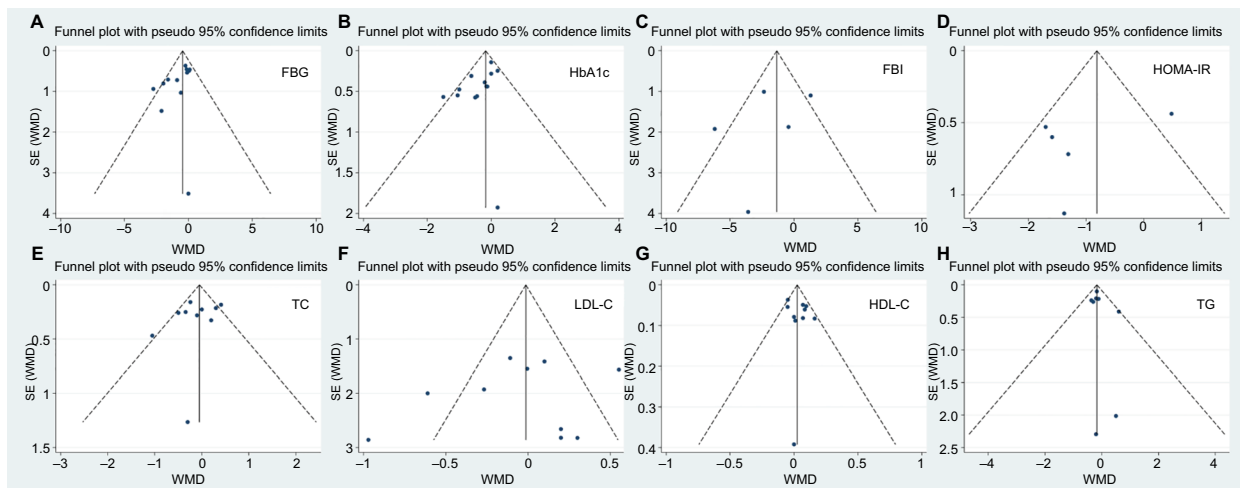


Figure 4 Funnel plot detailing publication bias in the studies reporting the impact of CoQ₁₀ on glucose control, insulin sensitivity, and blood lipid.

Abbreviations: CoQ₁₀, coenzyme Q10; FBG, fasting blood glucose; FBI, fasting blood insulin; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; WMD, weighted mean difference.

with diabetes. However, TG levels may be reduced with CoQ₁₀ ingestion.⁴¹ A further meta-analysis based on 14 eligible studies regarding the effects of CoQ₁₀ supplementation on diabetes biomarkers in healthy (healthy subjects without diabetes mellitus) and unhealthy subjects by Moradi et al⁴⁰ concluded that CoQ₁₀ supplementation slightly but significantly reduced FBG levels, but not fasting insulin and HbA1c levels in the overall analysis. A subgroup analysis based on the type of disease was also performed in this study, with no beneficial effects of CoQ₁₀ on FBG and HbA1c levels being found in patients with diabetes. However, the primary outcomes included were the change in HbA1c, FBI, and FPG levels, while CVD risk factors, such as levels of HOMA-IR, lipid profile and BP, were not determined in this study. In our present study, nine studies included were overlapped with the two previous meta-analyses. By using the previous meta-analysis as a base, we included five other recent RCTs, giving a greater power to identify and quantify the effects of CoQ₁₀ on cardiovascular and metabolic biomarkers in overweight and obese patients with established T2DM. Furthermore, several strengths of our study should be noted: first, our meta-analysis paid attention to only overweight and obese patients with established T2DM and included 14 clinical RCTs totaling 693 patients, which was highly homogeneous and selective. Second, largely due to lenient inclusion criteria, there is indirectness of evidence in terms of the differences in population and the differences in intervention and inconsistency in the effect and effect size across studies. To evaluate the strength of the available evidence and make more objective decisions regarding the results, subgroup analyses according to putative moderators, such as baseline BMI, CoQ₁₀ dose, mean age, and intervention duration, were performed to distinguish the influence of different factors on treatment efficacy. Third, our current meta-analysis was the latest and the most comprehensive one, which generally redefined and reinforces earlier results of previous meta-analyses. We examined the dose response and time response of CoQ₁₀ consumption by using linear meta-regression. Publication bias and sensitivity analysis were also performed to test the robustness of our findings. Furthermore, the GRADE methodology was used to rate the level of evidence. Finally, we further summarized the reported side effects of CoQ₁₀ consumption in the eligible trials, which had not been investigated in previous reviews.

Potential explanation of findings

The exact mechanisms responsible for the glycemic control and lipid-lowering effects of CoQ₁₀ in diabetes are not yet

completely understood. Increasing evidence suggests that oxidative stress contributes to and also results from hyperglycemia, insulin resistance, and malfunction of β -cell function.^{42,43} The β -cell function as well as glucose and fatty acid metabolism in the liver may be deteriorated as a result of CoQ₁₀ deficiency resulting in impaired insulin action and hyperinsulinemia. Supplemental use of CoQ₁₀ improves insulin sensitivity and hyperglycemia- or hyperinsulinemia-associated metabolic disorders by modulating insulin and adiponectin receptors, as well as tyrosine kinase (TK), phosphatidylinositol 3 kinase (PI3K), and glucose transporters 2 (GLUT2), while improving the lipid profile, redox system, soluble receptor of advanced glycosylated end products (sRAGEs), and adipocytokines (eg, adiponectin and visfatin).⁴⁴

Our results also show that participants with established diabetes receiving CoQ₁₀ had statistically significantly lower levels of TG level after treatment compared with control individuals. This positive effect was supported by *in vivo* mechanistic study finding, in which CoQ₁₀ has been shown to increase fatty acid oxidation through AMP-activated protein kinase (AMPK)-mediated peroxisome proliferator-activated receptor alpha (PPAR α) induction.⁴⁵ Moreover, CoQ₁₀ increased the lipolysis of TGs by decreasing the oxidative stresses and endothelial metabolism of the participants.⁴⁶

Supplementation with CoQ₁₀ could also improve hypertension and coronary artery disease. Some investigators found that CoQ₁₀ consumption can decrease BP in subjects with uncontrolled or poorly controlled hypertension.^{47,48} The primary mode of action of CoQ₁₀ in clinical hypertension is vasodilatation, via a direct effect on the endothelium and vascular smooth muscle.⁴⁷ CoQ₁₀ may also reduce BP by reducing peripheral resistance through the preservation of nitric oxide.⁴⁹ In addition, CoQ₁₀ is beneficial in improving prostaglandin prostacyclin production, promoting vasodilation and inhibiting platelet aggregation.⁵⁰ The effect of CoQ₁₀ on the change of BP in diabetes has not yet been systematically examined. Therefore, we further assessed the effect of CoQ₁₀ consumption on SBP and DBP outcomes, but failed to find any significant effects.

Safety concerns

Some adverse events reported to be associated with CoQ₁₀ were gastrointestinal effects (ie, abdominal discomfort, nausea, vomiting, diarrhea, and anorexia), allergic rash, headache, and the risk of bleeding.⁵¹ In our pooled analysis, CoQ₁₀ treatment was well tolerated, and no drug-related

adverse reactions were reported among the eligible trials during the follow-up period.

Implications for clinical practice

The persistence of excess adiposity in children and adults can lead to metabolic abnormality. Insulin resistance and progressive β -cell dysfunction are regarded as the key pathophysiologic mechanisms of T2DM development, and most T2DM patients who are overweight or obese also have CVD comorbidities/risk factors such as hypertension, dyslipidemia, and hypercoagulability.^{52,53} Our findings may have major clinical implications, given that the metabolic biomarkers evaluated in our present study are clinically relevant for monitoring the treatment and progression of diabetes across multiple organ systems. Glycemic control is fundamental to the management of diabetes. The pooled estimates suggest that CoQ₁₀ significantly affected the FBG level. FBG level is considered a key variable in the diagnosis of diabetes and is also adopted by the Food and Drug Administration (FDA) to evaluate the efficacy of dietary supplements and glycemic-lowering drugs. Moreover, our results show a significant benefit for HbA1c levels in overweight and obese individuals with T2DM. Large clinical trials have firmly established that a reduction in HbA1c level, a long-term indicator of glycemic control, is associated with a decreased risk for multiple diabetic complications and death.³ Patients with T2DM also have an increased prevalence of lipid abnormalities in visceral organs and ectopic fat depots that contribute to higher rates of CVD outcomes. Lipid management has been shown to reduce macrovascular disease and mortality in patients with T2DM, particularly in those who have had prior cardiovascular events.⁵⁴ Our pooled result also shows that CoQ₁₀ intervention significantly lowered TG levels. Therefore, our study provided evidence for clinicians and researchers to incorporate CoQ₁₀ treatment into the management of T2DM in overweight and obese patients.

Limitations

Our present meta-analysis has some limitations in interpreting the current results. First, our search was limited to studies published in English, and non-English or unpublished reports may exist. Second, despite the numerous subgroup and sensitivity analyses that were carried out, there was unavoidable heterogeneity in many of the reported outcomes, indicating variation between the studies in the estimates of the effect of CoQ₁₀ on the measured outcomes. Moreover, due to the lack of information in most of the existing studies, influences of other covariates such as the smoking habits could not be fully

determined. Therefore, we hardly considered this point in the subgroup analysis and ruled out heterogeneity thoroughly. Third, our pooled result was obtained with unadjusted estimates, and the precise effect of CoQ₁₀ on CVD biomarkers in overweight and obese patients with T2DM could have been impacted by other confounders (ie, other lifestyle interventions, alcohol consumption). The synergistic effects of other coexisting substances on the clinical outcomes should be excluded during the study period. Finally, since we performed multiple comparisons in this meta-analysis, the Bonferroni method, which controls false-positive error rate, was used to adjust for multiple comparisons. The threshold for significance was set at a *P*-value of <0.015. After Bonferroni correction, no significant effect was observed for the HbA1c and TG outcomes.

Conclusion

The present pooled analysis provides evidence for the beneficial effects of daily CoQ₁₀ supplementation on concentrations of FBG, HbA1c, and TG levels in overweight and obese patients with established T2DM. In a subgroup analysis, CoQ₁₀ effectively reduced the values of FBG, HbA1c, FBI, HOMA-IR, and TG in the low-dose of CoQ₁₀ (<200 mg/d) consumption group. CoQ₁₀ was well tolerated, and drug-related adverse reactions were not reported among the eligible trials during the follow-up period. The present results should be interpreted cautiously due to the unadjusted estimates (Bonferroni correction). Further adequately powered studies investigating the effects of CoQ₁₀ consumption on clinical endpoints, such as diabetes-related complications morbidity (ie, coronary artery disease, stroke, blindness, and end-stage kidney disease) and all-cause mortality, are needed.

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Disclosure

Haohai Huang and Honggang Chi contributed equally to this work. The authors report no conflicts of interest in this work.

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