International Urology and Nephrology (2022) 54:173–184
https://doi.org/10.1007/s11255-021-02838-2

NEPHROLOGY - ORIGINAL PAPER

A systematic review for the efficacy of coenzyme Q10 in patients with chronic kidney disease

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Received: 5 October 2020 / Accepted: 6 March 2021 / Published online: 29 March 2021

Abstract

Background The effects of coenzyme Q10 (CoQ10) supplementation in chronic kidney disease (CKD) patients remain controversial.

Objective A systematic review of current evidence was performed to systematically and comprehensively summarize the effects of CoQ10 on cardiovascular outcomes, oxidative stress, inflammation, lipid profiles, and glucose metabolism.

Methods MEDLINE, EMBASE, and the Cochrane Library database (Cochrane Central Register of Controlled Trials) were searched to identify eligible studies investigating the effects of CoQ10 supplementation on patients with CKD.

Results Twelve independent studies (including seventeen publications) were included in this systematic review. For CKD patients, six studies reported variable cardiovascular outcomes, which yielded inconsistent results. Regarding oxidative stress and inflammation, pooled analysis showed that CoQ10 supplementation significantly reduced malonaldehyde (WMD: − 1.15 95% CI − 1.48 to − 0.81) and high-sensitivity C reactive protein levels (WMD: − 1.18 95% CI − 2.21 to − 0.15). Regarding glucose metabolism, we found that CoQ10 supplementation resulted in significant improvements in HbA1c (WMD: − 0.80; 95% CI: − 1.35 to − 0.24) and QUICKI (WMD: 0.02; 95% CI: 0.01 to 0.03). The pooled results indicated that CoQ10 supplementation had no effects on total cholesterol, or LDL-cholesterol, or on HDL-cholesterol, and triglycerides.

Conclusions Our systematic review demonstrated that CoQ10 supplementation might have promising effects on oxidative stress. This work provided some clues that CoQ10 supplementation might have the potential to improve inflammation levels, glucose metabolism, cardiac structure, and cardiac biomarkers. However, the effects of CoQ10 supplementation should be confirmed in larger high-quality studies.

Keywords Coenzyme Q10 · Chronic kidney disease · Cardiovascular effects · Oxidative stress · Inflammation · Glucose metabolism

Abbreviations

CKD	Chronic kidney disease
CoQ10	Coenzyme Q10
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
hs-CRP	High sensitivity C-reactive protein

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HOMA-B	Homeostatic model assessment for B-cell function
HOMA-IR	Homeostasis model assessment of insulin resistance
LDL	Low-density lipoprotein
MDA	Malonaldehyde
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
PPAR-γ	Peroxisome proliferator-activated receptor-γ
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QUICKI	Quantitative insulin sensitivity check index
VLDL	Very low-density lipoprotein

Background

CoQ10 is a kind of fat-soluble vitamin-like quinone that transports electrons from complexes 1 or 2 to complex 3 in mitochondria [1]. In addition to its critical role as a component of the electron transport chain, CoQ10 might act as a reactive oxygen species scavenger [2]. It has been demonstrated that CoQ10 can inhibit lipid peroxidation in biological membranes, protect mitochondrial proteins and DNA from oxidative damage, and reduce lipid oxidation [3, 4]. In addition to its antioxidant activity, CoQ10 also attenuates the oxidized low-density lipoprotein (oxLDL)-mediated downregulation of endothelial nitric oxide synthase and the upregulation of inducible nitric oxide synthase [5].

Oxidative stress is characterized by an imbalance between the production of pro-oxidants and antioxidant defense mechanisms [6, 7]. Already existing in the early stage of CKD, oxidative stress deteriorates along with the decline of kidney function, and this state is further exacerbated in hemodialysis patients [2]. The accumulation of uric toxins and hemodialysis itself might contribute to oxidative stress [7]. In CKD and hemodialysis patients, oxidative stress promotes the development of atherosclerosis and is a predictor of all-cause and CVD mortality [7, 8].

In the general population, it has been shown that CoQ10 treatment decreases superoxide production in endothelial cells, improves endothelial function, enhances cardiac capacity, and reduces major adverse cardiovascular events [9–11]. In patients with nondialysis CKD and undergoing dialysis, the plasma concentrations of CoQ10 are reduced [12, 13]. Consumption of CoQ10 results in increased electron transport and inefficient active oxygen. CoQ10 can improve mitochondrial function and reduce oxidative stress in hemodialysis patients [13]. In patients with CKD, CoQ10 may have the potential to prevent and treat cardiovascular disease, improve cardiac function, and reduce oxidative stress. Coenzyme Q10 may have benefits for heart function, blood pressure, glucose metabolism, lipids, inflammation, and oxidative stress in patients with nondialysis CKD and those undergoing dialysis, but the results are still controversial. One recent meta-analysis showed that CoQ10 supplementation significantly improved the metabolic profile of CKD patients [14]. However, no published study has systematically and comprehensively summarized the effects of CoQ10 on cardiovascular outcomes, oxidative stress, inflammation, glucose metabolism, and lipid profiles in CKD patients.

The purpose of this systematic review was to systematically assess the impact of CoQ10 supplementation on cardiovascular function, oxidative stress, inflammation, glucose metabolism, lipid profiles and others in patients with CKD.

Methods

Protocol design and eligibility criteria

This systematic review was advanced by using a published protocol [15] and was reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [16]. The protocol of this systematic review was also registered in the International Prospective Register of Systematic Reviews (PROSPERO) and was assigned the registration number CRD42019120201 (website: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD4201912021). The included trials met the following criteria: (1) randomized controlled, quasi-randomized trial, nonrandomized trial or observational study; (2) participants with CKD; (3) the intervention or exposure of interest was CoQ10; and (4) adult patients without intervention or with placebo in trials or without exposure to CoQ10 in the cohort study were comparators.

Prespecified outcomes

The primary outcomes were cardiovascular effects, including (1) cardiac function and structure: left ventricular ejection fraction (determined by echocardiography or contrast or radionuclide angiography); diastolic heart function; cardiac structure (measured by individual trials); (2) biomarkers of cardiac function, such as brain natriuretic peptide and N-terminal pro-b-type natriuretic peptide (NT-pro-BNP); (3) blood pressure and heart rate; (4) symptom improvement (measured by individual trials and/or by exercise capacity), quality of life (measured by individual trials); (5) major cardiovascular events (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and revascularization procedures). Secondary outcomes of interest included effects on oxidative stress, inflammation, glucose metabolism, lipid profiles, all-cause mortality, safety, and tolerability.

Database and search strategy

We performed an electronic search of MEDLINE via Ovid, EMBASE via Ovid and Cochrane Library (Cochrane Central Register of Controlled Trials) in December 2018. We updated our search in August 2019. Relevant text words and medical subject headings were used as follows: kidney diseases, renal replacement therapy, renal insufficiency, dialysis, predialysis, diabetic nephropathies, ubiquinone, ubidecarenone, coenzyme Q10, co-enzyme Q10 and quinone. The clinicaltrials.gov website was searched for relevant studies that have been registered and completed but remain to be published. The reference lists of articles and other reviews retrieved during the search or known to the authors were searched for relevant articles. There were no language restrictions.

Study selection and data extraction

Two independent reviewers assessed the eligibility of the trials with a standardized approach. Discrepancies were resolved by discussion with a third individual. Two authors independently extracted data, including baseline patient characteristics, follow-up duration, intervention, outcome events, and adverse events using a standardized data collection form.

Assessing the risk of bias

Two authors independently assessed the risk of bias of the randomized controlled trials according to the standard criteria. Seven different bias domains, including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and any other potential biases were categorized as low risk of bias, high risk of bias or unclear risk of bias [17]. Observational studies were evaluated with the Newcastle–Ottawa Scale [18].

Statistical analysis

It is possible for baseline imbalances to occur between treatment groups for one or more variables in a randomized controlled trial by chance (especially if a trial's sample size is small) or through an inadequate randomization strategy [19, 20]. If trials with baseline imbalances are combined in a meta-analysis, then this may result in misleading conclusions [21, 22]. As analysis based on change scores (also called changes from baseline) removes a component of between-person variability, it is more efficient and powerful than the comparison of final values in some circumstances [20]. Given most studies with small sample sizes or (and) poor quality, we conducted a meta-analysis of change scores for continuous variables in our work. The method of imputing standard deviations for changes from baseline outlined in the Cochrane Handbook for Systematic Reviews of Interventions was accepted [20]. The results of dichotomous outcomes were expressed as risk ratios (RRs) with 95% CIs for individual studies. We used first-period data from cross-over trials and combined them with data obtained from parallel studies [23]. There is no reason to assume that the effects being estimated in the different studies will not be identical; therefore, the random-effect model was the most appropriate choice for most meta-analyses [24]. Accordingly, a Dersimonian–Laird random-effect model was used [25]. The heterogeneity of treatment effects between studies was investigated statistically using the test and I^2 statistic. I^2 values of 25, 50, and 75% correspond to low, medium and high levels of heterogeneity, respectively [26]. If heterogeneity existed and there were a substantial number of studies, subgroup analyses and meta-regression will be undertaken. Funnel plots, Egger's regression asymmetry test, and Begg's test were used to evaluate publication bias if appropriate [27, 28]. A two-sided p value < 0.05 was regarded as significant for all analyses. All analyses were calculated using Stata software (V.12.0; StataCorp, College Station, Texas, USA). When there were insufficient clinically homogeneous trials to perform a meta-analysis for some outcomes, we presented a narrative synthesis.

Results

Characteristics of the included studies

Briefly, we identified 1252 potentially relevant records, of which 207 were removed because they were duplicates. After screening the titles and abstracts and full-text browsing, 12 independent studies (including 17 publications) were included in this systematic review (Fig. 1). No observational studies were included. One trial was presented by two publications [29, 30], and another trial was presented by five publications [31–35]. The basic characteristics of the included studies were shown in Table 1. Nine trials adopted a parallel study design, and three trials had a randomized crossover design. The studies involved participants with non-dialysis-dependent CKD, dialysis-dependent CKD, or both. The study sample size ranged from 21 to 97. The daily dosage of CoQ10 used also differed among studies, and ranged from 30 to 1200 mg/day. The treatment

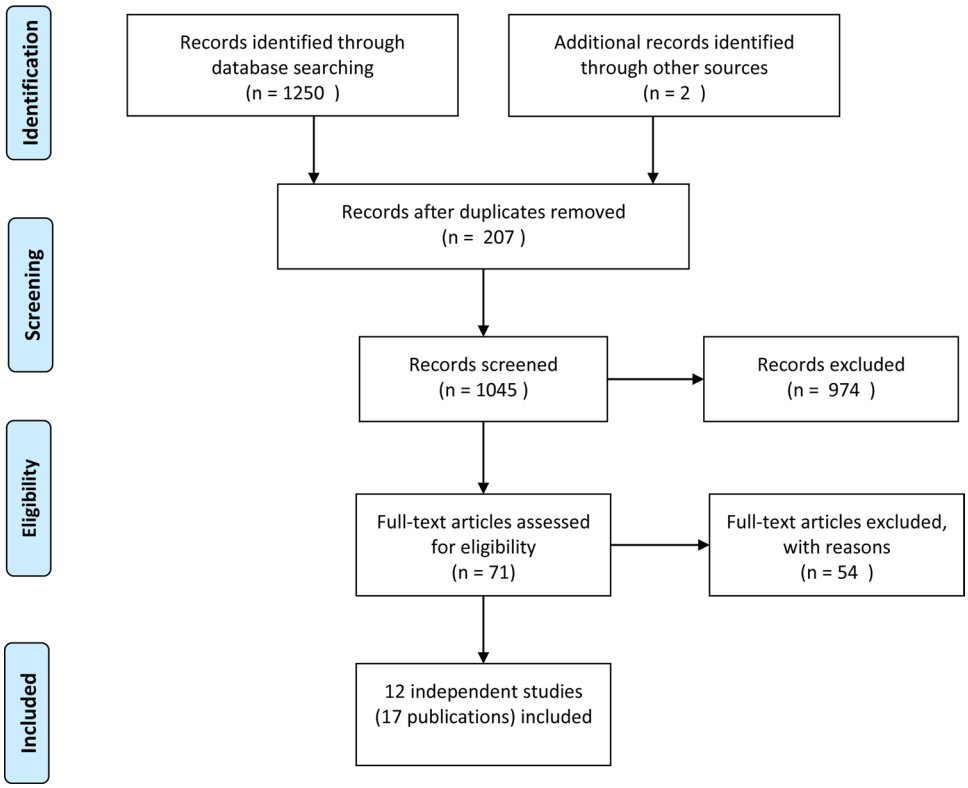

Fig. 1 The flowchart of study identification and selection

duration of the included studies ranged from 4 weeks to 6 months. The quality assessment for each included trial, based on the authors' judgments on the risk of bias, was presented in Figure S1 in the Supplementary File. Overall, study quality was varied, and high-quality studies were lacking. We planned to use funnel plots, Egger's regression asymmetry test and Begg's test to evaluate publication bias. However, because there were no adequate studies for each outcome, these tests were not performed.

Cardiovascular effects

Six studies evaluated the cardiovascular effects of CoQ10 on patients with CKD, which included cardiac function and structure, blood pressure and heart rate, biomarkers of cardiac function, and symptom improvement (Table 2). In one prospective, double-blind, placebo-controlled, crossover study, the hemodialysis patients received CoQ10 200 mg/d or placebo during the 8 weeks in each phase. Echocardiographic findings showed that intraventricular septum (IVS) thickness and left ventricle mass (LVM) were significantly decreased in the CoQ10 group ($p=0.03$ and $p=0.01$) compared with the placebo group. However, the results suggested that CoQ10 supplementation did not significantly improve diastolic heart function in hemodialysis patients [36]. A study conducted by Rivara et al. demonstrated a significant reduction in troponin T and NT-pro-BNP concentrations with 1200 mg daily CoQ10 supplementation in a pre-specified per-protocol analysis. However, in the intention-to-treat analysis, the reductions in troponin T ($p=0.09$) and NT-pro-BNP ($p=0.10$) levels did not reach statistical significance [37]. One abstract of congress reported that after 8 weeks of treatment with CoQ10, ST-segment depression during hemodialysis was significantly improved [1.86 ± 0.54 to 1.76 ± 0.66 (60 mg CoQ10), and 2.55 ± 0.75 to 2.11 ± 0.70 (90 mg CoQ10)], but no significant change was noted in the placebo group [38]. One study evaluated the effect of CoQ10 supplementation on exercise performance measures. The results showed no effect of CoQ10 on the 6-min walk test (6MWT) and maximal oxygen consumption (VO_2max) at 1 min with submaximal exercise in a cycle ergometer in maintenance hemodialysis patients [39]. Three studies [31, 37, 40] investigated the efficacy of CoQ10 supplementation on blood pressure and found no effects on blood pressure. No study reported major cardiovascular events (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and revascularization procedures).

Oxidative stress

Seven studies [29, 33, 37, 39, 41–43] reported the effects of CQ10 supplementation on biomarkers of oxidative stress. Markers of oxidative stress were variable in different studies (Table S1 in Supplementary File). Four studies [29, 39, 41–43] reported data on the effects of coenzyme Q10

Table 1 Basic characteristics of the included studies

Authors (refs)	Year	Design	Sample size (control/treatment)	Population	CoQ doses	Duration	Age	Presented data
Kirigaya [38]	1983	Parallel RCT	10/9/9/10	Hemodialysis	30 mg/60 mg/ 9 0 mg Qd	8 weeks	NA	ST-segment depression
Singh [41]	2000	Parallel RCT	10/11	Chronic renal failure	60 mg Tid	4 weeks	NA	MDA
Singh [42]	2003	Parallel RCT	49/48	End-stage renal failure	60 mg Tid	12 weeks	NA	MDA
Mori [31–35]	2009	Parallel RCT	19/23	Chronic kidney disease	200 mg Qd	8 weeks	56.5 ± 1.4	Blood pressure, triglycerides, cholesterol, HDL-cholesterol (c), LDL-C, FPG, insulin, HOMA-IR, CRP, F2-isoprostanes
Shojaei [45]	2011	Parallel RCT	13/13	Hemodialysis	100 mg Qd	3 months	53.3 ± 14.2	Lipoprotein (a)
Turk [36]	2013	Cross-over RCT	14/14	Hemodialysis	200 mg Qd*	20 weeks	47.4 ± 11.1	Intraventricular septum, LV mass, left ventricular posterior wall, Sm, Em, IRT time, DT, E/Em ratio
Gokbel [39]	2016	Cross-over RCT	14/14	Hemodialysis	200 mg Qd[#]	24 weeks	46.6 ± 11.9	6MWT, VO_{2max}, MDA, Ox-LDL, SOD, GPx
Zahed [40]	2016	Cross-over RCT	17/17	Hemodialysis	100 mg Qd[$]	6 months	66.3 ± 11.3	Systolic blood pressure, hs-CRP
Rivara [37]	2017	Parallel RCT	28/26/26	Hemodialysis	600/1200 mg Qd	4 months	54 ± 13	F2-isoprostanes, cardiac biomarker, pre-dialysis blood pressure
Gholnari [43]	2018	Parallel RCT	25/25	Diabetic nephropathy	100 mg Qd	12 weeks	NA	Insulin, HOMA-IR, and B cell function, insulin sensitivity check index, MDA, AGEs, FPG, lipid profiles,
Heidari [44]	2018	Parallel RCT	20/20	Diabetic nephropathy	100 mg Qd	12 weeks	40–85	Gene expression of PPAR-γ, interleukin-1, TNF-α, oxidized low-density lipoprotein, lipoprotein(a), glucose transporter-1, TGF-β
Fallah [29, 30]	2018	Parallel RCT	30/30	Diabetic hemodialysis	60 mg Bid	12 weeks	NA	Serum insulin, HOMA-IR, insulin sensitivity check index, triglycerides, VLDL-cholesterol, FPG, HbA1c, lipid profiles,TAC, NO, hs-CRP, MDA, and GSH

Table 1 (continued)

MDA malondialdehyde, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *FPG* fasting plasma glucose, *HOMA-IR* homeostasis model assessment of insulin resistance, *hs-CRP* high sensitivity C-reactive protein, *LV* left ventricular, *IRT* isovolumetric relaxation time, *DT* E-wave deceleration time, *6MWT* 6-min walk test, VO_{2max} estimated maximal oxygen consumption, *Ox-LDL* oxidized low-density lipoprotein cholesterol, *SOD* superoxide dismutase, *GPx* glutathione peroxidase, *hs-CRP* high-sensitivity C-reactive protein, *CRP* C-reactive protein, *AGEs* advanced glycation end products, *PPAR-γ* peroxisome proliferator-activated receptor-γ, *IL-1* interleukin-1, *TNF-α* tumor necrosis factor-α, *TGF-β* transforming growth factor-β, *VLDL* very low density lipoprotein, *HbA1c* glycosylated hemoglobin A1c, *TAC* total antioxidant, *NO* nitric oxide, *GSH* glutathione, *QD* once daily, *Bid* twice daily, *Tid* thrice daily, *RCT* randomized controlled trial

[*] All patients received placebo and oral CoQ10 200 mg/d during the 8 weeks in each phase, with a 4-week washout period

[#] All patients received placebo and oral CoQ10 200 mg/d during the 12 weeks in each phase, with a 4-week washout period

[$] All patients received placebo and CoQ10 100 mg/d during the 3 months in each stage, with 2-week washout period

Table 2 Cardiovascular effects of CoQ10 on patients with chronic kidney disease

Study	Cardiovascular effects
Kirigaya (1983) [38]	After 8 weeks of treatment with CoQ10, ST-segment depression during hemodialysis was significantly improved [1.86 ± 0.54 to 1.76 ± 0.66 (60 mg CoQ10), 2.55 ± 0.75 to 2.11 ± 0.70 (90 mg CoQ10)], but no significant change was noted in placebo group
Mori (2009) [31]	CoQ10 supplementation had no effect on blood pressure
Turk (2013) [36]	CoQ10 supplementation decreased intraventricular septum thickness and left ventricle mass. Myocardial peak systolic and early diastolic velocities derived from the intraventricular septum were increased. Isovolumetric relaxation time and E/Em ratio calculated for IVS were also significantly reduced
Gokbel (2016) [39]	Neither walking distance in 6MWT nor VO_2max showed a significant change when compared with baseline values after 24-week supplementation with CoQ10. There was no significant difference between the supplementation and placebo group in terms of exercise performance parameters
Zahed (2016) [40]	Systolic blood pressure was not reduced significantly
Rivara (2017) [37]	Significant reductions in troponin T and NT-pro-BNP concentrations with CoQ10 supplementation was found in a pre-specified per-protocol analysis. However, in intention-to-treat analysis, the reduction of troponin T ($p = 0.09$) and NT-pro-BNP ($p = 0.10$) level did not reach significant difference. No significant effects on pre-dialysis blood pressures were found

CoQ10 coenzyme Q10, *6MWT* 6-min walk test, *VO_2max* maximal oxygen consumption, *IVS* interventricular septum, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide

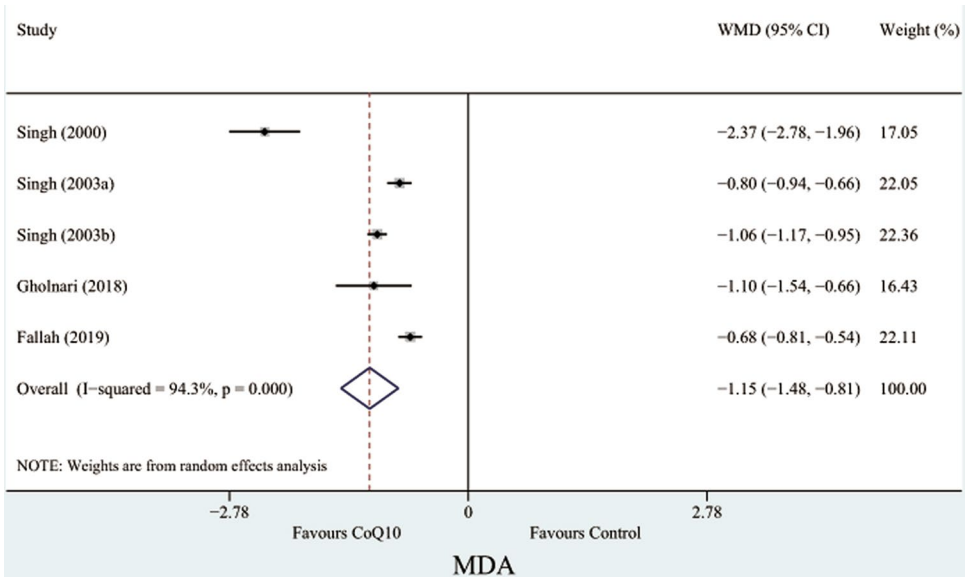

Fig. 2 Meta-analysis of CoQ10 treatment on changes (95% CI) in MDA. The horizontal lines denote the 95% CIs. The square represents the point estimate of each study. The diamond represents the overall pooled estimate of the treatment effect. *CoQ10* coenzyme Q10, *CI* confidence interval, *WMD* weighted mean difference

supplementation on MDA levels (Fig. 2). In a pooled analysis of these studies using the random-effect model, CoQ10 significantly decreased the MDA level (WMD: − 1.15 95% CI − 1.48 to − 0.81; Fig. 2) compared with the control group. When excluding the study [41] with imputed change scores, similar results were noted (WMD: − 0.88 95% CI − 1.10 to − 0.67). One study reported the efficacy of CoQ10 supplementation on increases in MDA with exercise [43]. However, there was no significant difference between the placebo and CoQ10 groups in terms of increases in MDA with exercise (data not shown).

Two studies indicated the effects of CoQ10 on F2-isoprostane and showed that small doses of CoQ10 (100 mg or 600 mg/d) had no effect on F2-isoprostanes [33, 37]. In contrast, large doses (1200 mg/d) have an effect on patients under hemodialysis [37]. Regarding advanced glycation end products (AGEs), one study demonstrated that CoQ10 supplementation for 12 weeks had favorable effects [43]. One recent study reported that CoQ10 can increase the levels of total antioxidant (TAC) and nitric oxide (NO), but did not have any beneficial effects on glutathione (GSH) [29]. There was no significant difference between the placebo and CoQ10 supplementation groups in terms of changes in superoxide dismutase (SOD) activity, glutathione peroxidase (GPx) activity, and serum oxidized low-density lipoprotein cholesterol levels with exercise [39].

Inflammation

Two studies [29] [40] reported information on high sensitivity C-reactive protein (hs-CRP), one of which was a cross-over trial. As stated above, we include only data from the first period of this study. The changes in hs-CRP from baseline were estimated. When combining data from two studies on hs-CRP, we found that CoQ10 supplementation significantly decreased hs-CRP levels (WMD: − 1.18 95% CI − 2.21 to − 0.15; Figure S2 in Supplementary File). Removing the cross-over trial, which also had imputed change scores, did not alter the conclusion (WMD: − 1.65 95% CI − 1.94 to − 1.35). Mori et al. determined the effects of CoQ10 on C-reactive protein (CRP) and found CRP was not different between groups [31]. One study found that CQ10 supplementation in CKD patients significantly improved the gene expression of interleukin-1, and tumor necrosis factor-α [44].

Glucose metabolism

Data on glucose metabolism were obtained from four studies [30, 31, 43, 44]. Two studies [30, 43] investigated the efficacy of CoQ10 supplementation on hemoglobin A1c (HbA1c) and the quantitative insulin sensitivity check index (QUICKI). By a pooled analysis, we found CoQ10 supplementation resulted in significant improvement in HbA1c (WMD: − 0.80; 95% CI: − 1.35 to − 0.24; Fig. 3a) and QUICKI (WMD: 0.02; 95% CI: 0.01 to 0.03; Fig. 3b). Three studies [30, 31, 43] provided intervention effects of CoQ10 on fasting plasma glucose (FPG), insulin, and homeostasis model assessment of insulin resistance (HOMA-IR). However, changes from baseline were imputed in one study [31], in which the investigators enrolled nondiabetic patients. A pooled analysis of these three studies found that CoQ10 supplementation had no effects on FPG (WMD: − 4.23; 95% CI: − 17.88 to 9.42; Fig. 3c), insulin (WMD: − 3.02; 95% CI: − 6.74 to 0.71; Fig. 3d) or HOMA-IR (WMD: − 0.31; 95% CI: − 1.33 to 0.72; Fig. 3e).

When excluding the study with imputed change scores, the results of FPG (WMD: − 14.52; 95% CI: − 31.87 to 2.82) and HOMA-IR (WMD: − 0.84; 95% CI: − 1.70 to 0.03) did not alter the initial qualitative interpretations. However, the sensitivity analysis showed that CoQ10 supplementation decreased insulin levels compared with the control group (WMD: − 4.97; 95% CI: − 6.97 to − 2.98). One study [43] found that CoQ10 could improve homeostatic model assessment for B-cell function (HOMA-B) (WMD: − 15.80; 95% CI: − 29.52 to − 2.08; Fig. 3f). Heidari explored the effects of CoQ10 on gene expression related to insulin and found that CQ10 supplementation for 12 weeks in patients with diabetic nephropathy significantly improved the gene expression of peroxisome proliferator-activated receptor-γ (PPAR-γ), which is known to be a key regulator of insulin resistance [44].

Lipid metabolism

A total of five studies [30, 31, 43–45] reported the effects of CoQ10 supplementation on lipid profiles (Figure S3 in Supplementary File). Four studies [30, 31, 43, 45] reported the effects of CoQ10 supplementation on total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. Changes from baseline were available from two studies [30, 43]. The remaining two studies [31, 45] provided baseline and final values, so change scores were imputed according to the above-mentioned method. Meta-analysis suggested that CoQ10 supplementation did not significantly affect the levels of total cholesterol (WMD: − 8.56; 95% CI: − 17.81 to 0.69), LDL-cholesterol (WMD: − 4.56; 95% CI: − 12.00 to 2.88), HDL-cholesterol (WMD: 0.15; 95% CI: − 1.56 to 1.86) or triglycerides (WMD: − 10.91; 95% CI: − 25.12 to 3.31). Sensitivity analysis was performed by removing studies in which change scores were imputed. The conclusion remained unchanged (data not shown) regarding total cholesterol, LDL-cholesterol, and HDL-cholesterol. However, regarding triglycerides, when we removed studies with imputed change scores, the result showed that CoQ10 supplementation could decrease the levels of triglycerides

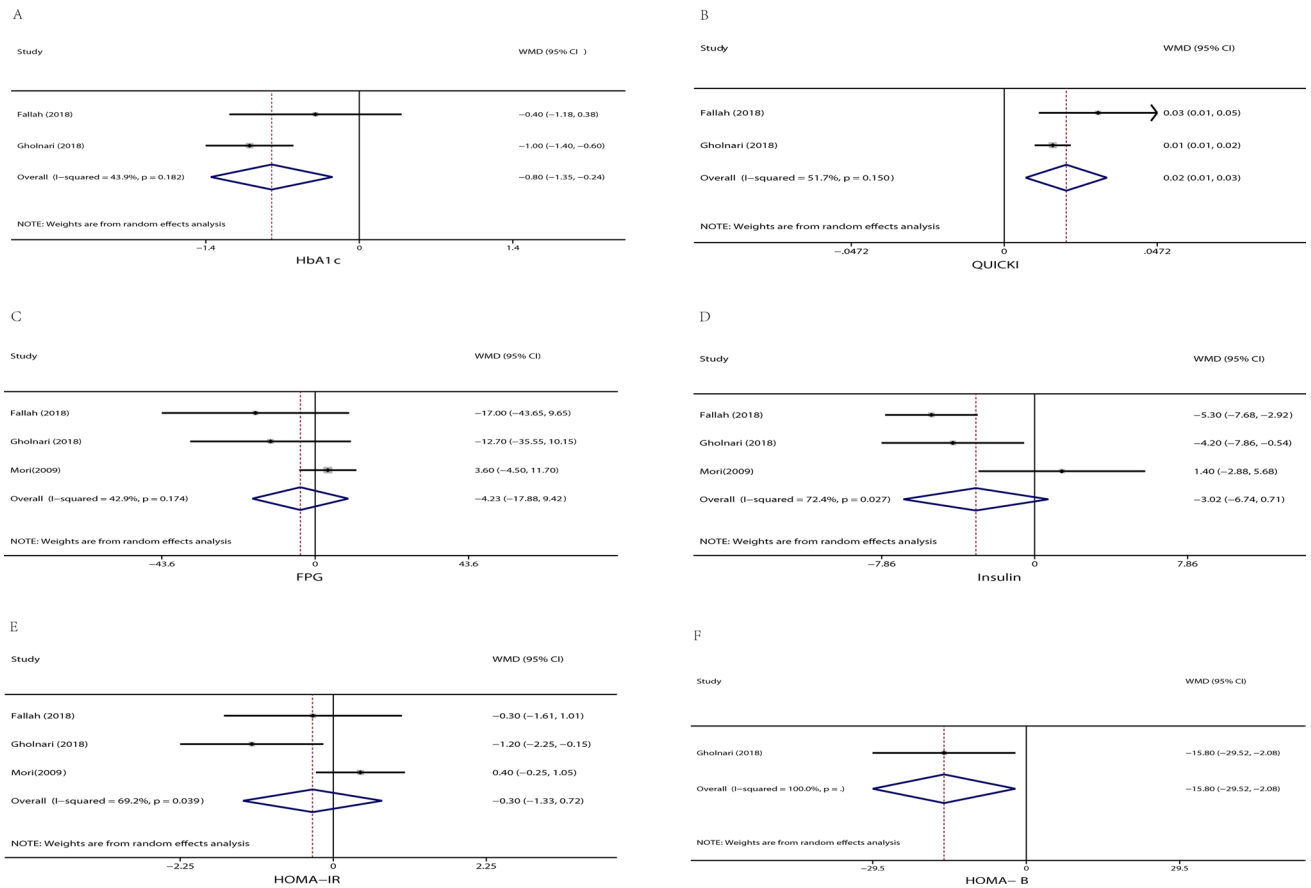

Fig. 3 Forest plot detailing the WMD and 95% CI for the impact of CoQ10 supplementation on changes in HbA1c (**a**), QUICKI (**b**), FPG (**c**), insulin (**d**), HOMA-IR (**e**), and HOMA-IR (**f**) in patients with chronic kidney disease. The horizontal lines denote the 95% CIs. The square represents the point estimate of each study. The diamond represents the overall pooled estimate of the treatment effect. *CoQ10* coenzyme Q10, *WMD* weighted mean difference, *CI* confidence interval, *HbA1c* hemoglobin A1c, *QUICKI* quantitative insulin sensitivity check index, *FPG* fasting plasma glucose, *HOMA-IR* homeostasis model assessment of insulin resistance, *HOMA-B* homeostatic model assessment for B-cell function

(WMD: − 21.05; 95% CI: − 40.68 to − 1.42). Data on VLDL-C were reported from two studies [30, 43]. When combining the two studies, the mean change in VLDL-C concentrations in the treated group compared with the control group was − 3.90 mg/dL (95% CI: − 7.76 to − 0.04). One study provided an intervention effect of CoQ10 on lipoprotein(a) [45]. After 3 months of therapy, serum levels of lipoprotein(a) showed a significant decrease compared with the placebo group (data not shown). One study [44] determining the effects of CoQ10 supplementation on gene expression related to lipids found that CoQ10 supplementation had no effect in this respect.

Safety and tolerability

Only one study reported the safety and tolerability of CoQ10 among the included studies. In Rivara et al.'s study [37], three patients discontinued treatment for abdominal pain and gastrointestinal discomfort or difficulty chewing the study agent; CoQ10 was usually well tolerated.

Discussion

Our work systematically appraised the evidence of CoQ10 supplementation regarding cardiovascular effects, oxidative stress, inflammation, carbohydrate metabolism, and lipid profiles in patients with CKD. The results showed that CoQ10 supplementation might have the potential to improve oxidative stress, glucose metabolism, inflammation levels, cardiac structure, and functional biomarkers.

CoQ10 has important roles in myocardial function. In the general population, there is some evidence that has suggested that decreased CoQ10 concentration in myocardial tissue is associated with impared myocardial function and increasing severity of heart failure [46]. The results of one meta-analysis suggested that CoQ10 supplementation

may improve the ejection fraction (EF) in patients with chronic heart failure (CHF) [47]. The benefits tended to be greater in patients with less severe stages of CHF, such as patients with an EF ≥ 30% or those with New York Heart Association (NYHA) class of II or III heart failure. There were some clues that patients with CKD might benefit from CoQ10 treatment. The CoQ10 level was lower and related to coronary flow reserve in hemodialysis patients [48, 49]. Our cross-sectional study showed that the CoQ10 level was independently associated with endothelial dysfunction [50]. CoQ10 treatment might reduce oxidative stress [51, 52], and oxidative stress may constitute a link between CoQ10 levels and endothelial dysfunction in hemodialysis patients [50]. CoQ10 administration might result in a decrease in intraventricular septum thickness, left ventricle mass, and the ratio of velocity early diastolic transmitral blood flow/early diastolic myocardial velocity [36]. In a randomized trial, high doses of CoQ10 might have the potential to reduce biomarkers of cardiac function (troponin T and NT-pro-BNP) in a pre-specified per-protocol analysis [37]. But the results of the intention-to-treat analysis showed that the reductions in troponin T and NT-pro-BNP level did not reach statistical significance ($p = 0.09$ and 0.10, respectively) [37]. However, not all data support this benefit which might be partly explained by the small sample size. Therefore, large-scale randomized controlled studies are needed to observe the effects of CoQ10 on cardiac function and structure or the long-term cardiovascular prognosis in patients with CKD.

Our meta-analysis showed that CoQ10 supplementation had favorable effects on MDA and other biomarkers of oxidative stress. Previous systematic reviews also demonstrated that CoQ10 supplementation significantly decreased MDA in both the general population and CKD patients [14, 53]. Studies have shown that oxidative stress is associated with kidney disease progression [54, 55]. Several complications of CKD, such as inflammation and cardiovascular disease (CVD), are also linked to an increased level of oxidative stress. Patients with CKD showed increasing concentrations of oxidative stress markers such as mitochondrial superoxide and oxidized LDL [56, 57], homocysteine [58], F2-isoprostanes, MDA and asymmetric dimethylarginine [59, 60]. F2-isoprostanes formation is favored in low oxygen cellular environments, which is aggravated by rarefication of postglomerular capillaries in patients undergoing maintenance dialysis [61]. CoQ10 is an electron carrier and might decrease the oxidative stress status as a reactive oxygen species scavenger [62]. CoQ10 can also improve oxidative stress by reacting with lipids or oxygen radicals through a direct reduction back to tocopherol [63].

Although one previous systematic review [14] found that CRP concentrations did not change following CoQ10 supplementation, our study showed that CoQ10 supplementation could improve hs-CRP levels in hemodialysis patients. The improvement effects of treatment with CoQ10 on inflammation markers were also found in the general population [64]. One recent systematic review [65] assessed the efficacy of CoQ10 supplementation on tumor necrosis factor- α (TNF-α) and interleukin-6 (IL-6) levels in the general population. Overall, nine RCTs were included in the analysis and the results indicated that CoQ10 supplementation resulted in a significant reduction in TNF-α (SMD: − 0.44, 95% CI: [− 0.81 to − 0.07] mg/dl; $p = 0.00$) and IL-6 levels (SMD: − 0.37, 95% CI: [− 0.65 to − 0.09]; $p = 0.01$). However, the evidence of the improvement of inflammation markers in CKD patients is relatively nonrobust due to inadequate studies and small sample sizes.

Our review found that CoQ10 supplementation might have the potential to improve glucose metabolism such as HbA1c and QUICKI. In the general population, recent studies also found that coenzyme Q10 may assist glycemic control [66, 67]. There are several mechanisms by which CoQ10 improves glucose metabolism. CoQ10 supplementation may induce the gene expression of PPAR-γ by activating the calcium-mediated AMPK pathway and inhibiting differentiation-induced adipogenesis [68]. PPAR-γ, a nuclear receptor protein, is a ligand-activated transcription factor that regulates the expression of genes involved in insulin [69]. CoQ10 may improve indices of insulin metabolism through modulation of insulin and adiponectin receptors, as well as tyrosine kinase (TK), phosphatidylinositol kinase (PI3K), and glucose transporters. However, not all data supported the benefits. The possible reasons for the discrepancy included differences in study design, study population characteristics, the dosage of CoQ10 used for intervention, and the duration of the intervention.

This meta-analysis suggested that CoQ10 supplementation did not significantly affect the levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, or triglycerides. However, a previous study showed that CoQ10 supplementation significantly improved total cholesterol and LDL-cholesterol [14]. The difference can be partly explained by different inclusion and exclusion criteria. The study conducted by Bakhshayeshkaram et al. included trials combining CoQ10 and other agents [14]. In contrast, we included studies with CoQ10 supplementation alone. Bakhshayeshkaram's analysis was based on final values [14], and we performed the meta-analysis based on changes from baseline, which seems more appropriate.

This systematic review has several important strengths. First, compared with previous systematic reviews, our review is the first to comprehensively analyze the effects of CoQ10 supplementation on cardiovascular function, oxidative stress, inflammation, glucose metabolism, lipid profiles, and others in patients with CKD. Second, our analysis was based on changes from baseline, which removed a component of between-person variability. Hence, it is more efficient

and powerful than the previous study that performed analyses of final values. Third, we only included RCTs using CoQ10 alone, excluding the trials with the combination of CoQ10 with other agents. The pooled results showed the effects of CoQ10 itself, excluding confounders resulting from other agents.

Despite its strengths, this systematic review has several limitations. First, the numbers of trial participants were relatively small, and no studies had sample sizes of more than 100 participants. Second, in some studies, change scores were not available and were imputed. However, sensitivity analyses were performed by excluding the studies with imputed change scores. Third, for each individual outcome, there are relatively few studies. Even though some treatment effects were observed, these were not robust. Due to these limitations, the interpretation of the results should be cautious and further high-quality RCTs are required.

To investigate the cardiovascular effects of CoQ10 supplementation, our pilot study is ongoing, which was previously registered with the Chinese Clinical Trial Registry (ChiCTR) and assigned the registration number ChiCTR1900022258 (available at http://www.chictr.org.cn/edit.aspx?pid=36344&htm=4). This pilot study is focused on the endothelial and cardiac function in hemodialysis patients. We hope that more clues on this issue will be provided.

Conclusion

In conclusion, this systematic review demonstrated that CoQ10 supplementation might have promising effects on oxidative stress. In addition, this work provided some clues that CoQ10 supplementation might have the potential to improve glucose metabolism, inflammation levels, cardiac structure and function biomarkers. However, the effects of CoQ10 supplementation should be confirmed by larger high-quality studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11255-021-02838-2.

Author contributions YX, JG and JL contributed in conception and design. GY, YX contributed to electronic search. YX and YW contributed in study selection and data collection. GY, YX, and XZ contributed in statistical analysis. YX, GY, EH and HY interpreted data. GY, YX, XZ, JG, and HJ drafted the initial and final manuscript. All authors approved the final version for submission. JG and HJ supervised the study.

Funding This study was supported in part by a grant (No. 19ZX47) from Chinese PLA Strategic Support Force Characteristic Medical Center (the 306th Hospital of the Chinese PLA).

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability The code used in this paper are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Yongxing Xu, Guolei Yang, Xiaowen Zuo, Jianjun Gao, Huaping Jia, Enhong Han, Juan Liu, Yan Wang, and Hong Yan declare that they have no competing interests.

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