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Keywords:	Coenzyme Q10, chronic kidney disease, cardiovascular, oxidative stress, inflammation, glucose metabolism

Efficacy of coenzyme Q10 in patients with chronic kidney disease: Protocol for a systematic review

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Abstract

Introduction Coenzyme Q10 (CoQ10) is a fat-soluble vitamin-like quinone that exerts antioxidative functions and is also an important factor in mitochondrial metabolism. Plasma concentrations of CoQ10 are depressed in patients with chronic kidney disease (CKD). A CoQ10 supplement can reduce adverse cardiovascular events, improve mitochondrial function, and decrease oxidative stress in patients with non-dialysis CKD and dialysis CKD. We performed this study as a systematic review to comprehensively assess the effect of a CoQ10 supplement on patients with CKD.

Methods and analysis The present systematic review protocol will be conducted following the PRISMA-P guidelines. The MEDLINE, EMBASE, and Cochrane library databases will be searched without language restrictions. Two reviewers will independently screen the references in two stages: screening of the title/abstract and then of the full-text, to identify references meeting the inclusion criteria. A descriptive overview and tabular and/or graphical summaries will be generated, and directed content analysis will be carried out on the extracted data.

Ethics and dissemination This systematic review will evaluate the efficacy and safety of CoQ10 in patients with CKD. Because all data used in this systematic review and meta-analysis will have been published, this review will not require ethical approval. Furthermore, all data will be analyzed anonymously during the review trial.

Keywords: Coenzyme Q10; chronic kidney disease; cardiovascular; oxidative stress; inflammation; glucose metabolism, lipid profiles

Strengths and limitations of this study

- The first comprehensive systematic review of the effects of a CoQ10 supplement on cardiovascular, oxidative stress, inflammation, glucose metabolism, lipid profiles, all-cause mortality, safety and tolerability in patients with CKD.
- The methodological design and statistical analysis are very strong and robust.
- Both patients with non-dialysis CKD and those undergoing dialysis are to be included.
- The review is restricted to articles published between January 2008 and February 2019.

Introduction

The mortality rate of patients with chronic kidney disease (CKD) increases with a decrease in the glomerular filtration rate. Cardiovascular diseases, such as coronary artery disease, congestive heart failure and sudden cardiac death, represent the leading cause of morbidity and mortality in patients with CKD, particularly those who have reached end-stage renal disease.[1] Diabetes, hypertension, and obesity are traditional risk factors for cardiovascular disease, which are all more prevalent in patients with CKD.[2] In addition to the traditional risk factors, oxidative stress is also a key contributor to the pathogenesis of atherosclerosis and other cardiovascular diseases in patients undergoing maintenance hemodialysis.[3] Oxidative stress originates from multiple sources, including decoupling of the electron transport chain in the mitochondria and inflammation-mediated production of superoxide via NADPH oxidase. Oxidative stress, inflammation, and endothelial dysfunction are detectable even at the very early stage of CKD.[4]

Coenzyme Q10 (CoQ10) is a fat-soluble vitamin-like quinone, also known as ubiquinone, that exerts antioxidative functions. CoQ10 transports electrons from complexes 1 or 2 to complex 3 in mitochondria.[5] CoQ10 treatment decreases superoxide production in endothelial cells and improves cardiac capacity in patients with heart failure.[6] Long-term therapy with CoQ10 can reduce major adverse cardiovascular events, and is safe and well-tolerated by the general population.[7] Plasma concentrations of CoQ10 are depressed in patients with non-dialysis CKD, and in those undergoing dialysis.[8,9] Depleting CoQ10 leads to inefficient electron transport and increased reactive oxygen species production. CoQ10 supplementation may improve mitochondrial function and decrease oxidative stress in patients undergoing hemodialysis.[7,10] CoQ10 may have potential for preventing and treating cardiovascular disease, improving cardiac function, and decreasing oxidative stress in patients with CKD. CoQ10 may have favorable effects on cardiac function, hypertension, glucose metabolism, lipid profiles, inflammation, and oxidative stress in patients with non-dialysis CKD and those undergoing dialysis, but the results remain

controversial. One recent meta-analysis showed that CoQ10 supplementation significantly improves the metabolic prolife of patients with CKD.[11] However, no published study has systematically and comprehensively summarized the effects of CoQ10 on cardiovascular outcomes, inflammation, oxidative stress, glucose metabolism, and lipid profiles.

The aim of this systematic review will be to systematically appraise the evidence regarding the effects of CoQ10 supplementation in patients with CKD.

Objectives

The primary objective of this systematic review will be to assess the benefit of administering CoQ10 to patients with CKD. This protocol is reported in accordance with the PRISMA-P 2015 checklist [12]. This protocol was previously registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Methods

Inclusion criteria, exclusion criteria, and pre-specified outcomes

The included trials will meet the following criteria: (1) randomized-controlled, quasi-randomized, non-randomized trial, or observational study; (2) participants with CKD; (3) the intervention of interest was CoQ10 treatment; (4) the comparator was adult patients with CKD who did not receive the intervention.

The primary outcomes will be 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;

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 event (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and re-vascularization procedures);

Secondary outcomes of interest include effects on oxidative stress, inflammation, glucose metabolism, lipid profiles, all-cause mortality, safety, and tolerability.

Database and search strategy

Searches will be performed, with no date restrictions, of the MEDLINE via Ovid, EMBASE via Ovid, and Cochrane Library (Cochrane Central Register of Controlled Trials) electronic databases, using relevant text words and medical subject headings, 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 will be 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 will be searched for relevant articles. There will be no language restrictions.

Study selection and data extraction

Two independent reviewers will assess the eligibility of the trials with a standardized approach. Discrepancies will be resolved by discussion with a third individual. Two authors will independently extract data, including baseline patient characteristics, follow-up duration, intervention, outcome events, and adverse events using a standardized data collection form. Any further information required from the original investigators will be requested by written correspondence, and any relevant information obtained in this manner will be included in the review.

Assessing the risk of bias

Two authors will independently assess 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 will be categorized as low risk of bias, high risk of bias, or unclear risk of bias [13]. Observational studies will be evaluated with the Newcastle–Ottawa Scale [14].

Statistical analysis

A meta-analysis will be performed if sufficient data are available. The results of dichotomous outcomes will be expressed as risk ratios (RRs) or odds ratios (OR) with 95% confidence intervals (CIs) for individual studies. For outcomes measured by continuous scales of measurement, the mean difference (MD) and 95% CI will be used. For trials with endpoints with zero events in the treatment arm, RRs will be calculated using a 0.5 cell correction.[15] There is no reason to assume that the effects being estimated in the different studies will not be identical; therefore, the random-effect model is the most appropriate choice for most meta-analyses.[16] Accordingly, a Dersimonian–Laird random-effect model will be used.[17] The heterogeneity of treatment effects between studies will be investigated statistically using the chi-square test and I^2 statistic. I^2 values of 25, 50, and 75% correspond to low, medium, and high levels of heterogeneity, respectively.[18] If heterogeneity exists and there are a substantial number of studies, subgroup analyses and meta-regressions will be undertaken. A sensitivity analysis will be performed to exclude low-quality trials. Funnel plots, Egger's regression asymmetry test, and Begg's test will be used to evaluate publication bias.[14,19] A two-sided P-value < 0.05 will be regarded as significant for all analyses. All analyses will be calculated using Stata software (ver. 12.0; StataCorp, College Station, TX, USA). When there are insufficient clinically

homogeneous trials to perform a meta-analysis, we will present a narrative synthesis.

Assessment of quality of evidence

An assessment of the quality of the evidence for the primary outcome will be made in accordance with the criteria suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Workgroup.[20] The GRADE system rates the quality of evidence across studies as very low, low, moderate, or high.

Ethics and dissemination

No human subject participants will be involved in this study. On completion of the analysis, we will prepare a manuscript for publication in a peer-reviewed journal and present the results at a conference.

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The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see:

http://www.textcheck.com/certificate/CKDMf2

Table 1 MEDLINE search terms

Search for coenzyme Q10	1	Ubiquinone/
	2	(ubiquinon$ or caomet or decorenone or mitocor or neuquinon$ or ubidecarenone or ubimaior or ubiquinol or ubiten).tw.
	3	((bioquinone or bio-quinone or coenzyme or co-enzyme or quinone) adj (q$ or "910")).tw.
	4	Ubiquinol-10.tw.
	5	q 10.tw.
	6	coq 10.tw.
	7	(coq10 or q10).tw.
	8	1 or 2 or 3 or 4 or 5 or 6 or 7
Search for chronic kidney disease	9	Kidney Diseases/
	10	exp Renal Replacement Therapy/
	11	Renal Insufficiency/
	12	exp Renal Insufficiency, Chronic/
	13	dialysis.tw.
	14	(hemodialysis or haemodialysis or hemodiafiltration or haemodiafiltration or hemofiltration or haemofiltration).tw.
	15	(kidney disease* or renal disease* or kidney failure or renal failure).tw.
	16	(ESRF or ESKF or ESRD or ESKD).tw.
	17	(CKF or CKD or CRF or CRD).tw.
	18	(PD or CAPD or CCPD or APD).tw.
	19	Diabetic Nephropathies/
	20	diabetic nephropath$.tw.
	21	diabetic kidney disease$.tw.
	22	Uremia/
	23	ur?emi$.tw.
	24	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
Search for combinations	25	8 and 24
Excluding animal studies	26	exp animals/ not humans.sh.
	27	25 not 26

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Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Medical management
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Methods and analysis The present systematic review protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) guidelines. The MEDLINE, EMBASE, and Cochrane library databases will be searched without language restrictions. Two reviewers will independently screen the references in two stages: screening of the title/abstract and then of the full-text, to identify references meeting the inclusion criteria. A descriptive overview and tabular and/or graphical summaries will be generated, and directed content analysis will be carried out on the extracted data.

Ethics and dissemination This systematic review will evaluate the efficacy and safety of CoQ10 in patients with CKD. Ethical approval is not required for this study. The results of this systematic review will be presented in relevant conferences and published in a peer-review journal. PROSPERO registration number CRD42019120201

Keywords: Coenzyme Q10; chronic kidney disease; cardiovascular; oxidative stress; inflammation; glucose metabolism, lipid profiles

Strengths and limitations of this study

- The first comprehensive systematic review of the effects of a CoQ10 supplement on cardiovascular, oxidative stress, inflammation, glucose metabolism, lipid profiles, all-cause mortality, safety and tolerability in patients with CKD.
- The methodological design is very strong and robust.
- Both patients with non-dialysis CKD and those undergoing dialysis are to be included.
- In cases where it is not possible to pool data through meta-analysis, we will present outcome data in a narrative way.

Introduction

The mortality rate of patients with chronic kidney disease (CKD) increases with a decrease in the glomerular filtration rate. Cardiovascular diseases, such as coronary artery disease, congestive heart failure and sudden cardiac death, represent the leading cause of morbidity and mortality in patients with CKD, particularly those who have reached end-stage renal disease.[1] Diabetes, hypertension, and obesity are traditional risk factors for cardiovascular disease, which are all more prevalent in patients with CKD.[2] In addition to the traditional risk factors, oxidative stress is also a key contributor to the pathogenesis of atherosclerosis and other cardiovascular diseases in patients undergoing maintenance hemodialysis.[3] Oxidative stress originates from multiple sources, including decoupling of the electron transport chain in the mitochondria and inflammation-mediated production of superoxide via NADPH oxidase. Oxidative stress, inflammation, and endothelial dysfunction are detectable even at the very early stage of CKD.[4]

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controversial. One recent meta-analysis showed that CoQ10 supplementation significantly improves the metabolic prolife of patients with CKD.[11] However, no published study has systematically and comprehensively summarized the effects of CoQ10 on cardiovascular outcomes, inflammation, oxidative stress, glucose metabolism, and lipid profiles.

The aim of this systematic review will be to systematically appraise the evidence regarding the effects of CoQ10 supplementation in patients with CKD.

Methods

Protocol design and registration

This protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol (PRISMA-P) checklist (Supplementary File S1) [12]. To minimize reporting bias, this protocol was previously registered with the International Prospective Register of Systematic Reviews (PROSPERO), a platform for the international registration of prospective systematic reviews, and assigned the registration number CRD42019120201 (available at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD4201912021). We started this study in December 2018 and anticipate to complete the study in August 2019.

Eligibility criteria The included trials will meet the following criteria: (1) randomized-controlled, quasi-randomized, non-randomized trial, or observational study (S); (2) participants with CKD (P); (3) the intervention of interest was CoQ10 treatment (I); (4) the comparator was adult patients with CKD who did not receive the intervention (C).

Pre-specified outcomes

The primary outcomes will be 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;

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 event (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and re-vascularization procedures);

Secondary outcomes of interest include effects on oxidative stress, inflammation, glucose metabolism, lipid profiles, all-cause mortality, safety, and tolerability.

Database and search strategy

Searches will be performed, with no date restrictions, of the MEDLINE via Ovid, EMBASE via Ovid, and Cochrane Library (Cochrane Central Register of Controlled Trials) electronic databases, using relevant text words and medical subject headings, 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 will be 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 will be searched for relevant articles. Elsewhere (Supplementary File S2), the full electronic search strategy for MEDLINE through Ovid is presented. There will be no language restrictions.

Records and data management

All citations identified by our search strategy will be exported to EndNote X9, a bibliographic management software and duplicates removed. The screening of

remaining citations will be conducted by using Endnote X9, too. The data extraction will be performed on Microsoft Excel 2016.

Study selection and data extraction

Two independent reviewers will assess the eligibility of the trials with a standardized approach. Discrepancies will be resolved by discussion with a third individual. Two authors will independently extract data, including baseline patient characteristics, follow-up duration, intervention, outcome events, and adverse events using a standardized data collection form. Any further information required from the original investigators will be requested by written correspondence, and any relevant information obtained in this manner will be included in the review.

Assessing the risk of bias

Two authors will independently assess 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 will be categorized as low risk of bias, high risk of bias, or unclear risk of bias [13]. Observational studies will be evaluated with the Newcastle–Ottawa Scale [14].

Statistical analysis

A meta-analysis will be performed if sufficient data are available. The results of dichotomous outcomes will be expressed as risk ratios (RRs) or odds ratios (OR) with 95% confidence intervals (CIs) for individual studies. For outcomes measured by continuous scales of measurement, the mean difference (MD) and 95% CI will be used. For trials with endpoints with zero events in the treatment arm, RRs will be calculated using a 0.5 cell correction.[15] There is no reason to assume that the effects

being estimated in the different studies will not be identical; therefore, the random-effect model is the most appropriate choice for most meta-analyses.[16] Accordingly, a Dersimonian–Laird random-effect model will be used.[17] The heterogeneity of treatment effects between studies will be investigated statistically using the chi-square test and I^2 statistic. I^2 values of 25, 50, and 75% correspond to low, medium, and high levels of heterogeneity, respectively.[18] If heterogeneity exists and there are a substantial number of studies, subgroup analyses and meta-regressions will be undertaken. A sensitivity analysis will be performed to exclude low-quality trials. Funnel plots, Egger's regression asymmetry test, and Begg's test will be used to evaluate publication bias.[14,19] A two-sided P-value < 0.05 will be regarded as significant for all analyses. All analyses will be calculated using Stata software (ver. 12.0; StataCorp, College Station, TX, USA). When there are insufficient clinically homogeneous trials to perform a meta-analysis, we will present a narrative synthesis.

Assessment of quality of evidence

An assessment of the quality of the evidence for the primary outcome will be made in accordance with the criteria suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Workgroup.[20] The GRADE system rates the quality of evidence across studies as very low, low, moderate, or high.

Ethics and dissemination

No human subject participants will be involved. On completion of the analysis, we will prepare a manuscript for publication in a peer-reviewed journal and present the results at conferences.

Discussion

This protocol presents an explicit plan of a systematic review to identify and summarize studies reporting the effects of CoQ10 in CKD patients. To assess the

quality of the evidence, the GRADE guidelines will be applied. In cases where it is not possible to pool data through meta-analysis, we will present outcome data in a narrative way, which will be a likely limitation. The existing evidence may be insufficient to make some robust conclusions; however, the results of this systematic review will provide important additional information relevant to the design of future trials.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measure and study design.

Contributors YX Xu is the first author, JJ Gao is the corresponding author; YX Xu and JJ Gao designed the study; YX Xu, J Lu and EH Han will acquire data; YX Xu and JJ Gao will analyze and interpret data; YX Xu, J Lu, Y wang and JJ Gao drafted the initial and final manuscript; All authors approved the final version of the manuscript.

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Competing interests None declared

Patient consent for publication Not required

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support:			
Sources	5a	Indicate sources of financial or other support for the review	None
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6 and Appendix-A

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
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Supplementary file S2

Search for coenzyme Q10	1	Ubiquinone/
	2	(ubiquinon$ or caomet or decorenone or mitocor or neuquinon$ or ubidecarenone or ubimaior or ubiquinol or ubiten).tw.
	3	((bioquinone or bio-quinone or coenzyme or co-enzyme or quinone) adj (q$ or "910")).tw.
	4	Ubiquinol-10.tw.
	5	q 10.tw.
	6	coq 10.tw.
	7	(coq10 or q10).tw.
	8	1 or 2 or 3 or 4 or 5 or 6 or 7
Search for chronic kidney disease	9	Kidney Diseases/
	10	exp Renal Replacement Therapy/
	11	Renal Insufficiency/
	12	exp Renal Insufficiency, Chronic/
	13	dialysis.tw.
	14	(hemodialysis or haemodialysis or hemodiafiltration or haemodiafiltration or hemofiltration or haemofiltration).tw.
	15	(kidney disease* or renal disease* or kidney failure or renal failure).tw.
	16	(ESRF or ESKF or ESRD or ESKD).tw.
	17	(CKF or CKD or CRF or CRD).tw.
	18	(PD or CAPD or CCPD or APD).tw.
	19	Diabetic Nephropathies/
	20	diabetic nephropath$.tw.
	21	diabetic kidney disease$.tw.
	22	Uremia/
	23	ur?emi$.tw.
	24	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
Search for combinations	25	8 and 24
Excluding animal studies	26	exp animals/ not humans.sh.
	27	25 not 26

BMJ Open

Efficacy of coenzyme Q10 in patients with chronic kidney disease: protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-029053.R2
Article Type:	Protocol
Date Submitted by the Author:	19-Apr-2019
Complete List of Authors:	Xu, Yongxing; the 306th hospital of Chinese PLA, Liu, Juan; the 306th hospital of Chinese PLA Han, Enhong; the 306th hospital of Chinese PLA Wang, Yan; the 306th hospital of Chinese PLA Gao, jianjun; the 306th hospital of Chinese PLA,
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Medical management
Keywords:	Coenzyme Q10, chronic kidney disease, cardiovascular, oxidative stress, inflammation, glucose metabolism

Efficacy of coenzyme Q10 in patients with chronic kidney disease: protocol for a systematic review

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Abstract

Introduction Coenzyme Q10 (CoQ10) is a fat-soluble vitamin-like quinone that exerts antioxidative functions and is also an important factor in mitochondrial metabolism. Plasma concentrations of CoQ10 are depressed in patients with chronic kidney disease (CKD). A CoQ10 supplement can reduce adverse cardiovascular events, improve mitochondrial function, and decrease oxidative stress in patients with non-dialysis CKD and dialysis CKD. We performed this study as a systematic review to comprehensively assess the effect of a CoQ10 supplement on patients with CKD.

Methods and analysis The present systematic review protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) guidelines. The MEDLINE, EMBASE, and Cochrane library databases will be searched without language restrictions in December 2018. Two reviewers will independently screen the references in two stages: screening of the title/abstract and then of the full-text, to identify references meeting the inclusion criteria. A descriptive overview and tabular and/or graphical summaries will be generated, and directed content analysis will be carried out on the extracted data.

Ethics and dissemination This systematic review will evaluate the efficacy and safety of CoQ10 in patients with CKD. Ethical approval is not required for this study. The results of this systematic review will be presented in relevant conferences and published in a peer-review journal. PROSPERO registration number CRD42019120201

Keywords: Coenzyme Q10; chronic kidney disease; cardiovascular; oxidative stress; inflammation; glucose metabolism, lipid profiles

Strengths and limitations of this study

- The systematic review is noncommercial and will comprehensively summarize the effects of a CoQ10 supplement on cardiovascular, oxidative stress, inflammation, glucose metabolism, lipid profiles in patients with CKD.
- The present systematic review protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.
- Our review benefits from a sensitive search strategy including key terms, synonyms and medical subject headings.
- Both patients with non-dialysis CKD and those undergoing dialysis are to be included.
- In cases where it is not possible to pool data through meta-analysis, we will present outcome data in a narrative way, which will be a likely limitation.

Introduction

The mortality rate of patients with chronic kidney disease (CKD) increases with a decrease in the glomerular filtration rate. Cardiovascular diseases, such as coronary artery disease, congestive heart failure and sudden cardiac death, represent the leading cause of morbidity and mortality in patients with CKD, particularly those who have reached end-stage renal disease.[1] Diabetes, hypertension, and obesity are traditional risk factors for cardiovascular disease, which are all more prevalent in patients with CKD.[2] In addition to the traditional risk factors, oxidative stress is also a key contributor to the pathogenesis of atherosclerosis and other cardiovascular diseases in patients undergoing maintenance hemodialysis.[3] Oxidative stress originates from multiple sources, including decoupling of the electron transport chain in the mitochondria and inflammation-mediated production of superoxide via NADPH oxidase. Oxidative stress, inflammation, and endothelial dysfunction are detectable even at the very early stage of CKD.[4]

Coenzyme Q10 (CoQ10) is a fat-soluble vitamin-like quinone, also known as ubiquinone, that exerts antioxidative functions. CoQ10 transports electrons from complexes 1 or 2 to complex 3 in mitochondria.[5] CoQ10 treatment decreases superoxide production in endothelial cells and improves cardiac capacity in patients with heart failure.[6] Long-term therapy with CoQ10 can reduce major adverse cardiovascular events, and is safe and well-tolerated by the general population.[7] Plasma concentrations of CoQ10 are depressed in patients with non-dialysis CKD, and in those undergoing dialysis.[8,9] Depleting CoQ10 leads to inefficient electron transport and increased reactive oxygen species production. CoQ10 supplementation may improve mitochondrial function and decrease oxidative stress in patients undergoing hemodialysis.[7,10] CoQ10 may have potential for preventing and treating cardiovascular disease, improving cardiac function, and decreasing oxidative stress in patients with CKD. CoQ10 may have favorable effects on cardiac function, hypertension, glucose metabolism, lipid profiles, inflammation, and oxidative stress in patients with non-dialysis CKD and those undergoing dialysis, but the results remain

controversial. One recent meta-analysis showed that CoQ10 supplementation significantly improves the metabolic prolife of patients with CKD.[11] However, no published study has systematically and comprehensively summarized the effects of CoQ10 on cardiovascular outcomes, inflammation, oxidative stress, glucose metabolism, and lipid profiles.

The aim of this systematic review will be to systematically appraise the evidence regarding the effects of CoQ10 supplementation in patients with CKD.

Methods

Protocol design and registration

This protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol (PRISMA-P) checklist (Supplementary File S1) [12]. To minimize reporting bias, this protocol was previously registered with the International Prospective Register of Systematic Reviews (PROSPERO), a platform for the international registration of prospective systematic reviews, and assigned the registration number CRD42019120201 (available at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD4201912021). We started this study in December 2018 and anticipate to complete the study in August 2019.

Eligibility criteria The included trials will meet the following criteria: (1) randomized-controlled, quasi-randomized, non-randomized trial, or observational study (S); (2) participants with CKD (P); (3) the intervention of interest was CoQ10 treatment (I); (4) the comparator was adult patients with CKD who did not receive the intervention (C).

Pre-specified outcomes

The primary outcomes will be 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;

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 event (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and re-vascularization procedures);

Secondary outcomes of interest include effects on oxidative stress, inflammation, glucose metabolism, lipid profiles, all-cause mortality, safety, and tolerability.

Database and search strategy

Searches will be performed, with no date restrictions, of the MEDLINE via Ovid, EMBASE via Ovid, and Cochrane Library (Cochrane Central Register of Controlled Trials) electronic databases, using relevant text words and medical subject headings, 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 will be 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 will be searched for relevant articles. Elsewhere (Supplementary File S2), the full electronic search strategy for MEDLINE through Ovid is presented. There will be no language restrictions.

Records and data management

All citations identified by our search strategy will be exported to EndNote X9, a bibliographic management software and duplicates removed. The screening of

remaining citations will be conducted by using Endnote X9, too. The data extraction will be performed on Microsoft Excel 2016.

Study selection and data extraction

Two independent reviewers will assess the eligibility of the trials with a standardized approach. Discrepancies will be resolved by discussion with a third individual. Two authors will independently extract data, including baseline patient characteristics, follow-up duration, intervention, outcome events, and adverse events using a standardized data collection form. Any further information required from the original investigators will be requested by written correspondence, and any relevant information obtained in this manner will be included in the review.

Assessing the risk of bias

Two authors will independently assess 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 will be categorized as low risk of bias, high risk of bias, or unclear risk of bias [13]. Observational studies will be evaluated with the Newcastle–Ottawa Scale [14].

Statistical analysis

A meta-analysis will be performed if sufficient data are available. The results of dichotomous outcomes will be expressed as risk ratios (RRs) or odds ratios (OR) with 95% confidence intervals (CIs) for individual studies. For outcomes measured by continuous scales of measurement, the mean difference (MD) and 95% CI will be used. For trials with endpoints with zero events in the treatment arm, RRs will be calculated using a 0.5 cell correction.[15] There is no reason to assume that the effects

being estimated in the different studies will not be identical; therefore, the random-effect model is the most appropriate choice for most meta-analyses.[16] Accordingly, a Dersimonian–Laird random-effect model will be used.[17] The heterogeneity of treatment effects between studies will be investigated statistically using the chi-square test and I^2 statistic. I^2 values of 25, 50, and 75% correspond to low, medium, and high levels of heterogeneity, respectively.[18] If heterogeneity exists and there are a substantial number of studies, subgroup analyses and meta-regressions will be undertaken. A sensitivity analysis will be performed to exclude low-quality trials. Funnel plots, Egger's regression asymmetry test, and Begg's test will be used to evaluate publication bias.[14,19] A two-sided P-value < 0.05 will be regarded as significant for all analyses. All analyses will be calculated using Stata software (ver. 12.0; StataCorp, College Station, TX, USA). When there are insufficient clinically homogeneous trials to perform a meta-analysis, we will present a narrative synthesis.

Assessment of quality of evidence

An assessment of the quality of the evidence for the primary outcome will be made in accordance with the criteria suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Workgroup.[20] The GRADE system rates the quality of evidence across studies as very low, low, moderate, or high.

Ethics and dissemination

No human subject participants will be involved. On completion of the analysis, we will prepare a manuscript for publication in a peer-reviewed journal and present the results at conferences.

Discussion

This protocol presents an explicit plan of a systematic review to identify and summarize studies reporting the effects of CoQ10 in CKD patients. To assess the

quality of the evidence, the GRADE guidelines will be applied. In cases where it is not possible to pool data through meta-analysis, we will present outcome data in a narrative way, which will be a likely limitation. The existing evidence may be insufficient to make some robust conclusions; however, the results of this systematic review will provide important additional information relevant to the design of future trials.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measure and study design.

Contributors YX Xu is the first author, JJ Gao is the corresponding author; YX Xu and JJ Gao designed the study; YX Xu, J Lu and EH Han will acquire data; YX Xu and JJ Gao will analyze and interpret data; YX Xu, J Lu, Y wang and JJ Gao drafted the initial and final manuscript; All authors approved the final version of the manuscript.

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Competing interests None declared

Patient consent for publication Not required

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	4	Ubiquinol-10.tw.
	5	q 10.tw.
	6	coq 10.tw.
	7	(coq10 or q10).tw.
	8	1 or 2 or 3 or 4 or 5 or 6 or 7
Search for chronic kidney disease	9	Kidney Diseases/
	10	exp Renal Replacement Therapy/
	11	Renal Insufficiency/
	12	exp Renal Insufficiency, Chronic/
	13	dialysis.tw.
	14	(hemodialysis or haemodialysis or hemodiafiltration or haemodiafiltration or hemofiltration or haemofiltration).tw.
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	24	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
Search for combinations	25	8 and 24
Excluding animal studies	26	exp animals/ not humans.sh.
	27	25 not 26