BMJ Open

Renoprotective effects of coenzyme Q10 supplementation in patients with chronic kidney disease: a protocol for a systematic review

Yoshifusa Abe ,[1] Hiroki Nishiwaki ,[2] Taihei Suzuki ,[3] Hisashi Noma ,[4] Yoshitaka Watanabe,[5] Erika Ota ,[6] Takeshi Hasegawa[3,7,8,9]

To cite: Abe Y, Nishiwaki H, Suzuki T, *et al*. Renoprotective effects of coenzyme Q10 supplementation in patients with chronic kidney disease: a protocol for a systematic review. *BMJ Open* 2024;**14**:e084088. doi:10.1136/bmjopen-2024-084088

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-084088).

Received 08 January 2024
Accepted 15 November 2024

For numbered affiliations see end of article.

Correspondence to
Dr Yoshifusa Abe;
yoshifusa@med.showa-u.ac.jp

ABSTRACT

Introduction Coenzyme Q10 (CoQ10) is a fat-soluble vitamin-like quinone. The plasma levels of CoQ10 are reduced in patients with chronic kidney disease (CKD). CoQ10 supplementation can improve mitochondrial function and decrease oxidative stress in these patients. This systematic review will assess the renoprotective effects of CoQ10 supplementation in patients with CKD.

Methods and analysis We will include the following studies: (1) randomised-controlled trials, (2) participants with CKD and (3) participants treated with CoQ10 as an intervention. The systematic review protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and International Clinical Trials Register databases will be searched for articles without language restrictions in December 2024. The authors will be divided into two groups. Two independent authors will screen the titles and abstracts of all reports extracted via an electronic search. After the initial screening, the authors will independently review the full-text articles and perform a directed content analysis of the extracted data. For outcomes measured using continuous scales of measurement, we will adopt standardised mean differences as the effect measures. We will pool the data using the random-effects model.

Ethics and dissemination No human participants will be involved in the study. On completion of the analysis, the manuscript will be prepared for publication in a peer-reviewed journal.

PROSPERO registration number CRD42021241085.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will focus on the renoprotective effects of coenzyme Q10 supplementation in patients with chronic kidney disease.
⇒ This systematic review protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.
⇒ Coenzyme Q10 dosage or duration of administration may affect the outcome, while there is currently no intravenous formulation.
⇒ The search strategy is conducted in English. Therefore, there may be selection bias.

INTRODUCTION

Chronic kidney disease (CKD) is a growing public health concern worldwide. It is associated with an increased prevalence of all-cause mortality, diabetic nephropathy, cardiovascular events and hospitalisation.[1] In addition to traditional risk factors, including diabetes, hypertension, obesity, smoking and alcohol consumption, oxidative stress is a key contributor to the pathogenesis of CKD.[2]

The kidneys are highly metabolically active, with abundant oxidative reactions occurring in the mitochondria.[3] Reactive oxygen species (ROS) and reactive nitrogen species are formed under physiological conditions and removed by antioxidant defence mechanisms. An imbalance between pro-oxidants and antioxidants can lead to oxidative stress, resulting in metabolic abnormalities, oxidation of lipids, DNA and proteins; and oxidative damage to cells, tissues and organs.[3] Oxidative stress contributes to the vicious cycle between CKD and the development of hypertension, cardiovascular remodelling and cardiovascular events.[2 3] Coenzyme Q10 (CoQ10) is a lipophilic vitamin-like quinone that plays a crucial role in ATP production in the mitochondrial respiratory chain, ROS reduction and activation of mitochondrial dehydrogenases and enzymes.[4 5] Patients with diabetes have lower levels of CoQ10 than healthy individuals, and patients with CKD also exhibit decreased circulating levels of CoQ10.[4 6 7] Mutations in genes encoding enzymes involved in the CoQ10 biosynthesis pathway (*COQ2*, *COQ6*, *COQ9*, *PDSS2* and *COQ8B*) are associated with glomerular phenotypes, and CoQ10 deficiency is linked to proteinuria and progressive kidney disease.[5 8]

Thus, CoQ10 supplementation may improve mitochondrial function and decrease oxidative stress in affected patients. Small-scale studies have reported that CoQ10 administration effectively reduces proteinuria and may exert nephroprotective effects against *COQ8B*-related glomerulopathy, which causes steroid-resistant nephrotic syndrome and/or CKD.[9] A recent meta-analysis also showed that CoQ10 supplementation significantly improved the metabolic profile of patients with CKD.[10] In contrast, response to CoQ10 supplementation is variable and depends on both the specific genetic defect and disease severity.[11] Further, the severe neurological and/or renal damage cannot be reversed,[11] especially in patients with severe encephalocardiomyopathy due to *COQ4*-related CoQ10.[11 12] However, no studies have systematically summarised the renoprotective effects of CoQ10 supplementation in patients with CKD.

This systematic review aims to demonstrate the renoprotective effects of CoQ10 supplementation in patients with CKD through a meta-analysis of randomised-controlled trials (RCTs).

METHODS AND ANALYSES

Protocol and registration

This protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) .[13] To minimise reporting bias, we registered this protocol in the International Prospective Register of Systematic Reviews (registration number: CRD42021241085; available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=241085).

Eligibility criteria for considering studies for this review

Type of studies

We will include clinical trials with randomised, placebo-controlled, individual and cluster RCTs.

Types of participants

The inclusion criteria are patients with CKD, including predialysis patients. Exclusion criteria are patients undergoing haemodialysis, peritoneal dialysis or kidney transplantation.

Type of interventions

Studies in which patients with CKD were orally treated with CoQ10 supplementation as there is currently no intravenous formulation. There are no restrictions on the dosage or duration of administration.

Comparison

Patients with CKD not treated with CoQ10.

Prespecified outcomes

The primary outcomes will include renoprotective effects in terms of the following: kidney function such as the estimated glomerular filtration rate, serum creatinine level, serum cystatin C level, blood urea nitrogen level, urine output and blood pressure.

Secondary outcomes will include oxidative stress markers, inflammation, glucose metabolism and lipid profiles. Safety and tolerability outcomes will include the incidence and severity of adverse events, categorised using the Common Terminology Criteria for Adverse Events as grade 1 or grade 2, and treatment discontinuation rates due to adverse effects. Patient-reported tolerability will be assessed using surveys and scoring systems. Any other adverse effects not specifically listed will be recorded as 'Defined by authors' to capture unexpected events.

Database and search strategy

Searches will be performed using electronic databases, including the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, International Clinical Trials Register and ClinicalTrials.gov, with no date or language restrictions until December 2024. We will also search reference lists of review articles, relevant studies and clinical practice guidelines, and grey literature sources (eg, abstracts, dissertations and theses). The following relevant key terms and Medical Subject Headings will be used: kidney diseases, renal replacement therapy, renal insufficiency, dialysis, predialysis, diabetic nephropathies, ubiquinone, ubidecarenone, coenzyme Q10, and quinone. The search strategy was designed with the assistance from experienced librarians (online supplemental material 1).

Study selection

Two groups of authors (YA and HNi; TS and YW) will independently screen the titles and abstracts of all the reports extracted via an electronic search. After the initial screening, the authors will independently review the full-text articles. Discrepancies will be resolved by discussion with another author (TH). Further information required from the original investigators will be requested through written correspondence, and any relevant information obtained in this manner will be included in the review. A PRISMA-P flowchart illustrated the study selection process.

Data extraction and management

Four authors will independently extract the following data: study information (authors, country, publication year and journal titles), trial period, definition of CKD, participants (number of participants, number of participants who dropped out, eligibility and exclusion criteria, age and sex, and background of CKD), interventions (name of drug, dosage of drug and administration period), control details, outcomes, analytical methods and results. Data extraction will be standardised using a predesigned sheet. In case of missing values, we will contact the authors. If a disagreement arises among the primary reviewers, it will be discussed and resolved; however, if no resolution is reached, it will be discussed and resolved by the fifth author. Additionally, a description

of the intention-to-treat analysis related to the processing of missing values was added to the strategy for data analysis and synthesis. Important numerical data, such as screened, randomised patients, as well as intention-to-treat, as-treated and per-protocol populations, will be carefully evaluated. Attrition rates (eg, dropouts, losses to follow-up and withdrawals) will be also investigated. Issues of missing data and imputation methods (eg, last observation-carried-forward) were critically appraised.

Assessment of risk-of-bias assessment

The risk of bias in all included reports will be independently assessed by four authors (YA, HNi, TS and YW) using the tools described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions V.6.2.[14] Any disparities between the primary reviewers or differences in the assessment of the risk of bias will be resolved by a fifth reviewer (TH). The following domains of risk of bias will be assessed: (1) sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting and (7) other biases such as baseline imbalance. Trials with a high risk of bias will be excluded to explore the effect of the methodological quality of trials on the overestimation of the treatment effect. We will use the Cochrane risk of bias 1.0 tool.[15]

Strategy for data analysis and synthesis

Synthetic analyses will be performed when sufficient data will be available. Review Manager software V.5.4 (Cochrane Collaboration, Oxford, UK) will be used for data analyses. For dichotomous outcomes, we will use risk ratios as effect measures due to its ease of interpretation. We will adopt standardised mean differences as the effect measures for outcomes measured using continuous scales.[16] We will use the DerSimonian-Laird-type random-effects model for the synthesis analyses to address heterogeneity among the studies. Statistical heterogeneity among the trials will be evaluated using the heterogeneity variance τ^2, Higgins' I^2 statistic and Q-statistic (Cochrane's Q-test). Furthermore, we will perform graphical analyses using forest plots to assess the overlap of the confidence intervals for individual studies in order to assess possible heterogeneity. We will also provide funnel plots to assess the potential publication bias. Egger's tests will be used to evaluate the asymmetries of the funnel plots.

Analysis of subgroups

CoQ10 affects glucose and lipid metabolisms.[17 18] Further, CoQ10 supplementation may be effective in reducing blood pressure in patients with cardiometabolic disorders, and these effects are more pronounced in patients with diabetes or dyslipidaemia.[19] To assess the clinical heterogeneity based on the potential effect of CoQ10, we will conduct subgroup or meta-regression analyses. Subgroup analyses will be performed for patients with CKD or without diabetes mellitus, patients with CKD with/without dyslipidaemia and patients with CKD with/without hypertension.

Summary of findings and assessment of certainty of the evidence

A table containing a summary of the findings for primary and secondary outcomes will be created according to the procedures described in the Cochrane Handbook for Systematic Reviews of Interventions. Certainty of the evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE system rates the quality of evidence across studies as very low, low, moderate or high. The GRADE assesses the risk of bias.

Patient and public involvement

Patients and/or the general public were not involved in the development of the research question, outcome measures or study design.

DISCUSSION

This protocol presents an explicit plan for a systematic review to identify and summarise studies reporting the renoprotective effects of CoQ10 supplementation in patients with CKD. The average daily nutritional intake and lack of drug-related toxicity of CoQ10 are described in the ESPEN micronutrient guidelines.[20] However, no guidelines mention the effects of CoQ10 on renal protection or proteinuria reduction, and the renoprotective effects of CoQ10 have not been sufficiently evaluated in previous systematic reviews. The findings of this systematic review will provide insights into the establishment of guidelines for renoprotection in patients with CKD without serious side effects.

Ethics and dissemination

No human participants will be included in the study. On completion of the analysis, the manuscript will be prepared for publication in a peer-reviewed journal.

Author affiliations
[1]Children's Medical Center, Showa University Koto Toyosu Hospital, Koto-ku, Tokyo, Japan
[2]Division of Nephrology, Department of Internal Medicine, Showa University Fujigaoka Hospital, Yokohama, Kanagawa, Japan
[3]Division of Nephrology, Department of Internal Medicine, Showa University Graduate School of Medicine, Shinagawa-ku, Tokyo, Japan
[4]Department of Data Science, The Institute of Statistical Mathematics, Tachikawa, Japan
[5]Children's Medical Center, Showa University Northern Yokohama Hospital, Yokohama, Kanagawa, Japan
[6]Global Health Nursing, Global School of Nursing Science, St Luke's International University, Chuo-ku, Japan
[7]Institute of Clinical Epidemiology (iCE), Showa University, Shinagawa-ku, Japan
[8]Department of Hygiene, Public Health, and Preventive Medicine, Graduate School of Medicine, Showa University, Tokyo, Japan
[9]Showa University Research Administration Center (SURAC), Showa University, Shinagawa-ku, Japan

Acknowledgements We thank Asae Ito and Tomoko Morimasa, librarians at Showa University and Dr Noyuri Yamaji at the Institute of Clinical Epidemiology, Showa University, for contributing to the establishment of the search formula.

Contributors YA conceived the study. YA, HNi, TS, YW, HNo, EO and TH designed the study. YA, HNi, TS, YW and TH will select the articles. YA, HNi, TS, YW and TH will assess the risks of bias. YA, HNi, TS, YW and TH will conduct the statistical analysis. YA, HNi, TS, YW, HNo, EO and TH will interpret the data. YA, HNi, TS, YW, HNo, EO and TH will draft and revise the manuscript. All authors have read and approved the final manuscript. TH is the guarantor. TH accepts full responsibility for the finished work and the conduct of the study, has access to the data and controlled the decision to publish.

Funding This systematic review will be performed as part of a project organised by the Showa University Research Administration Center and was supported by JSPS KAKENHI (grant number 19K03092).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Yoshifusa Abe http://orcid.org/0000-0002-4861-8200
Hiroki Nishiwaki http://orcid.org/0000-0001-7365-7685
Taihei Suzuki http://orcid.org/0000-0002-9531-7814
Hisashi Noma http://orcid.org/0000-0002-2520-9949
Erika Ota http://orcid.org/0000-0002-3945-7441

REFERENCES

1 Provenzano M, Coppolino G, Faga T, *et al*. Epidemiology of cardiovascular risk in chronic kidney disease patients: the real silent killer. *Rev Cardiovasc Med* 2019;20:209–20.
2 Ravarotto V, Simioni F, Pagnin E, *et al*. Oxidative stress - chronic kidney disease - cardiovascular disease: A vicious circle. *Life Sci* 2018;210:125–31.
3 Daenen K, Andries A, Mekahli D, *et al*. Oxidative stress in chronic kidney disease. *Pediatr Nephrol* 2019;34:975–91.
4 Gutierrez-Mariscal FM, Arenas-de Larriva AP, Limia-Perez L, *et al*. Coenzyme Q_{10} Supplementation for the Reduction of Oxidative Stress: Clinical Implications in the Treatment of Chronic Diseases. *Int J Mol Sci* 2020;21:7870.
5 Ozaltin F. Primary coenzyme Q10 (CoQ 10) deficiencies and related nephropathies. *Pediatr Nephrol* 2014;29:961–9.
6 Gazdíková K, Gvozdjáková A, Kucharská J, *et al*. Oxidative stress and plasma concentrations of coenzyme Q10, alpha-tocopherol, and beta-carotene in patients with a mild to moderate decrease of kidney function. *Nephron* 2001;88:285.
7 Lippa S, Colacicco L, Bondanini F, *et al*. Plasma levels of coenzyme Q(10), vitamin E and lipids in uremic patients on conservative therapy and hemodialysis treatment: some possible biochemical and clinical implications. *Clin Chim Acta* 2000;292:81–91.
8 Korkmaz E, Lipska-Zi̧etkiewicz BS, Boyer O, *et al*. ADCK4-Associated Glomerulopathy Causes Adolescence-Onset FSGS. *J Am Soc Nephrol* 2016;27:63–8.
9 Atmaca M, Gülhan B, Atayar E, *et al*. Long-term follow-up results of patients with ADCK4 mutations who have been diagnosed in the asymptomatic period: effects of early initiation of CoQ10 supplementation. *Turk J Pediatr* 2019;61:2041:657–63:.
10 Xu Y, Yang G, Zuo X, *et al*. A systematic review for the efficacy of coenzyme Q10 in patients with chronic kidney disease. *Int Urol Nephrol* 2022;54:173–84.
11 Salviati L, Trevisson E, Agosto C, *et al*. Primary coenzyme q(10) deficiency overview. In: *GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved*. Seattle (WA): University of Washington, Seattle, 1993.
12 Laugwitz L, Seibt A, Herebian D, *et al*. Human COQ4 deficiency: delineating the clinical, metabolic and neuroimaging phenotypes. *J Med Genet* 2022;59:878–87.
13 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
14 Higgins JPT, Savović J, Page MJ, *et al*. Chapter 8: assessing risk of bias in a randomized trial. In: *www.training.cochrane.org/handbook*. . Cochrane, 2021: 6. 2.
15 Higgins JPT, Altman DG, Gotzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
16 Higgiins JPT, Li T, Deeks JJ. Chapter 6: choosing effect measures and computing estimates of effect. In: *Cochrane Handb Syst Rev Interv Ver*. 2024: 6. 5. Available: www.training.cochrane.org/handbook [accessed 29 Sep 2024].
17 Bakhshayeshkaram M, Lankarani KB, Mirhosseini N, *et al*. The Effects of Coenzyme Q10 Supplementation on Metabolic Profiles of Patients with Chronic Kidney Disease: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Curr Pharm Des* 2018;24:3710–23.
18 Zhang S-Y, Yang K-L, Zeng L-T, *et al*. Effectiveness of Coenzyme Q10 Supplementation for Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Int J Endocrinol* 2018;2018:6484839.
19 Zhao D, Liang Y, Dai S, *et al*. Dose-Response Effect of Coenzyme Q10 Supplementation on Blood Pressure among Patients with Cardiometabolic Disorders: A Grading of Recommendations Assessment, Development, and Evaluation (GRADE)-Assessed Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Adv Nutr* 2022;13:2180–94.
20 Berger MM, Shenkin A, Schweinlin A, *et al*. ESPEN micronutrient guideline. *Clin Nutr* 2022;41:1357–424.