

BMJ Open Effects of coenzyme Q10 on endothelial and cardiac function in patients undergoing haemodialysis: study protocol for a pilot randomised controlled trial

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ABSTRACT

Introduction Endothelial and cardiac dysfunction are highly prevalent and are associated with cardiovascular morbidity and mortality among patients undergoing dialysis. For patients undergoing dialysis, no study has explored the effect of supplementation of coenzyme Q10 (CoQ10) on endothelial function. To our best of knowledge, only two small sample studies focused on the efficacy of supplementation of CoQ10 on cardiac function. However, the effect of CoQ10 supplementation on cardiac function remains uncertain in patients who undergo haemodialysis. The aim of this study is to explore whether CoQ10 supplementation can improve endothelial and cardiac function in patients undergoing haemodialysis.

Methods and analysis This is a pilot randomised controlled study. Eligible patients undergoing haemodialysis in our haemodialysis centre will be randomly allocated to the CoQ10 and control groups. The follow-up time is 12 months. The primary outcome is to assess the change of brachial artery endothelial-dependent flow-mediated dilation, left ventricular systolic function, diastolic function and Myocardial Performance Index at 12 months from baseline. Secondary outcomes are death or hospitalisation due to cardiovascular events, all-cause mortality, change of CoQ10 concentration, the ratio of ubiquinol to ubiquinone, the change of oxidative stress markers (including malondialdehyde and 8-hydroxy-deoxyguanosine) and Left Ventricular Mass Index.

Ethics and dissemination Risks associated with CoQ10 are minor, even at doses as high as 1800 mg according to previous studies. The trial has received ethics approval from the Medical Ethics Committee for Clinical Trials of Drugs, the 306th Hospital of Chinese PLA. The results of the study are expected to be published in a peer-reviewed journal and presented at academic conferences.

Trial registration number ChiCTR1900022258.

INTRODUCTION

Cardiovascular events are prevalent and the leading cause of death for patients undergoing haemodialysis.^{1 2} Endothelial cells play an important role in maintaining

Strengths and limitations of this study

- A major strength of the proposed study is that we will first evaluate the effect of coenzyme Q10 on endothelial function in patients undergoing haemodialysis.
- We will use hard endpoints including cardiovascular events and all-cause mortality as prespecified outcomes.
- A limitation of the study is that the sample size is relatively small, which can result in insufficient power to determine effects.

cardiovascular homeostasis and the development of cardiovascular pathologies.³ Flow-mediated dilation (FMD) test has been established as a valid method for non-invasive assessment of endothelial function.⁴ The systolic dysfunction, diastolic dysfunction and left ventricular hypertrophy are frequent occurrences in patients undergoing dialysis, which are related to higher cardiovascular morbidity and mortality among patients undergoing dialysis.^{5–9} Echocardiography is commonly used and can provide accurate information on left ventricular function, chamber dimension and geometry, and presence of left ventricular hypertrophy.⁵

Coenzyme Q10 (CoQ10), as an important in vivo antioxidant, is an essential component of the mitochondrial electron transport chain.¹⁰ Supplementation with CoQ10 may be of benefit to the general population. Previous studies have demonstrated that oral CoQ10 supplementation improved endothelial dysfunction in the general population.^{11 12} Meanwhile, treatment with CoQ10 can result in improvement in the left ventricular ejection fraction and reducing cardiovascular events and mortality.^{13–15}

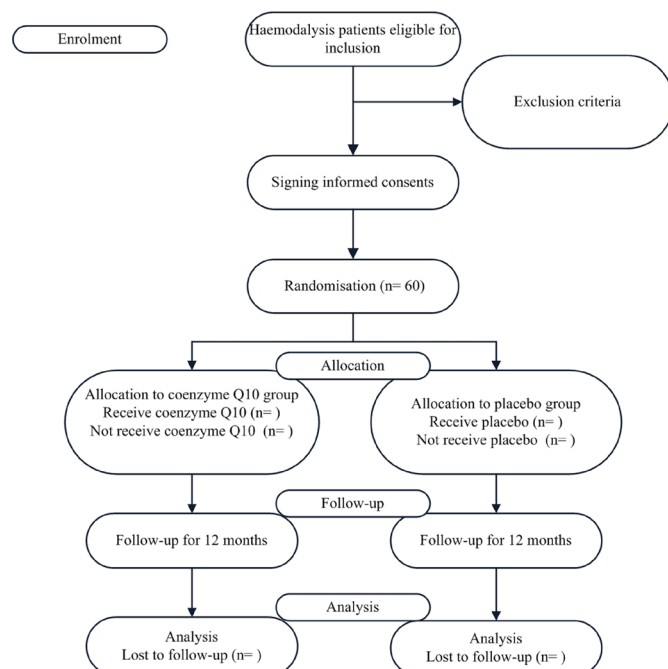


Figure 1 Study flowchart.

For patients undergoing haemodialysis, no study has explored the effects of supplementation of CoQ10 on endothelial function. To the best of our knowledge, only two small sample studies focused on the efficacy of supplementation of CoQ10 on cardiac function.^{16 17} However, the effect of CoQ10 supplementation on cardiac function remains uncertain in patients undergoing haemodialysis.

Thus, we will conduct this pilot randomised controlled study to evaluate the efficacy and safety of CoQ10 in patients undergoing haemodialysis and explore some parameters for a future clinical trial with large sample size.

The trial protocol was written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement.¹⁸ A SPIRIT checklist is provided in the online supplementary additional file 1.

METHODS AND ANALYSIS

Study design

This pilot study is a parallel, single-centre, randomised controlled trial. The study will be carried out in the haemodialysis centre of the 306th Hospital of Chinese PLA. The study will be sequentially conducted as follows: enrolment according to prespecified inclusion and exclusion criteria, randomisation and follow-up for 12 months, and assessment. **Figure 1** demonstrates the flowchart of the study.

Participants and eligibility

All patients in our haemodialysis centre will be eligible for screening according to the inclusion and exclusion criteria.

Inclusion criteria

The inclusion criteria are as follows: undergoing haemodialysis three times per week for at least 3 months, aged more than 18 years and less than 85 years, and life expectancy more than 1 year.

Exclusion criteria

Patients will be excluded if they have any of the following: poor adherence of dialysis or medications; severe systemic or local infection; malignancy; planning to receive kidney transplant within 12 months; hospitalisation within 30 days; history of a major atherosclerotic event within 3 months; pregnancy or lactation; current use antioxidant other than vitamin C; use of haemodialysis catheter.

Randomisation procedure, allocation concealment and intervention

An independent biometrician with no relationship with the data management and data statistical analysis will use the Stata software (V.16.0) to generate random numbers. The allocation ratio is 1:1. The allocation codes will be placed in sealed opaque envelopes until participants are randomised. The participants and echocardiographer will be blind to group allocation. If there is a serious adverse reaction, an emergency unblinding procedure will be initiated. Participants will be randomised to CoQ10 or placebo group. The CoQ10 group will receive oral CoQ10 (Puritan's Pride, USA) 400mg once daily. Both CoQ10 and placebo will be orally administered for 12 months. Patients enrolled in the trial will continue to receive and undergo all usual clinical care activities.

Participants can withdraw from the trial for any reason at any time. Participants will be withdrawn from the study if they violate any of the key inclusion or exclusion criteria or they refuse to continue to participate or withdraw their consent, or the investigators judge that they need to be withdrawn from the study.

Sample size

Because of the lack of adequate preliminary studies in patients undergoing haemodialysis and the pilot nature of this study, we have adopted 30 participants in each group.^{19 20} Posters to encourage patients to enrol in the clinical trial will be posted in our haemodialysis centre.

Study outcomes

Primary outcomes

The primary outcomes are the change in brachial artery endothelial-dependent FMD, left ventricular systolic function, diastolic function and myocardial performance index from baseline after 12 months of treatment. The endothelial function will be assessed by brachial artery FMD with ultrasound equipment on the arm free of vascular access.^{21–23} FMD will be assessed by an observer who is blinded to treatment allocation and will be tested at baseline and every 6 months. All vasodilation medication will have to be interrupted for at least 4 hours before the examination, if possible. Patients were instructed to avoid heavy meals, caffeine, or smoking 12 hours prior to

the FMD measurements. The measurements will be in a temperature-controlled room and will start after 15 min of rest in the supine position. A baseline image of the brachial artery will be obtained above the antecubital fossa in a longitudinal plane. Then a sphygmomanometer will be inflated for 5 min, at least 50 mm Hg above the systolic pressure and no more than 300 mm Hg. The brachial diameter was measured at 60 s following cuff deflation at the same position. The FMD is defined as at the 60 s time point as $[(\text{postinflation diameter} - \text{baseline diameter}) / (\text{baseline diameter}) \times 100\%]$.

Left ventricular systolic function will be assessed by left ventricular ejection fraction determined as: $(\text{LVEDV} - \text{LVESV}) / \text{LVEDV} \times 100$, where LVEDV and LVESV represent the left ventricular end-diastolic volume and left ventricular end-systolic volume.

Left ventricular diastolic function will be assessed by peak early mitral annulus velocity (e'), E/e' (ie, the ratio between peak early mitral inflow velocity (E) and peak early mitral annulus velocity (e')) and grade of diastolic dysfunction. Evaluation of left ventricular diastolic function will be according to updated recommendations from the European Association of Cardiovascular Imaging and American Society of Echocardiography for the evaluation of diastolic function by echocardiography published in 2016.²⁴ Peak early mitral inflow velocity (E) and peak late mitral inflow velocity (A) will be measured from the tip of the mitral leaflets of the left ventricular apical four-chamber view. Peak tricuspid regurgitation systolic jet velocity will be obtained during systole at the leading edge of the spectral waveform from the four-chamber view, with the angle-adjusted alignment of continuous-wave Doppler echo beam. Tissue Doppler imaging technique will be used to determine e' (both septal and lateral mitral annular areas were evaluated). E/e' and E/A were also calculated. Left atrial volumes were determined using two-dimensional echocardiography. Indexed left atrial volume will be calculated by dividing left atrial volume by body surface area.

The Myocardial Performance Index is a combined index of systolic and diastolic functions and is calculated as $(a-b)/b$ where interval (a) is equal to the sum of isovolumic contraction, isovolumic relaxation time and ejection time (from the cessation to the onset of mitral inflow) and interval (b) represents the ejection time (obtained at the ventricular outflow tract). Thus, the sum of isovolumic contraction and relaxation time was obtained by subtracting (b) from (a).^{25 26}

All echocardiographic examinations will be performed by an observer who is blinded to treatment allocation.

Secondary outcomes

Secondary outcomes are death or hospitalisation due to cardiovascular events, all-cause mortality, the change of CoQ10 concentration, the ratio of the reduced form of CoQ10 (ubiquinol) to oxidised CoQ10 (ubiquinone), the change of oxidative stress markers (including

malondialdehyde and 8-hydroxy-deoxyguanosine) and Left Ventricular Mass Index (LVMI).

Left ventricular mass (LVM) will be calculated according to a previously published methodology. $\text{LVM (g)} = 0.8 \{ 1.04 \times [(\text{LVEDD} + \text{IVST} + \text{PWT})^3 - (\text{LVEDD})^3] \} + 0.6$, where LVEDD, IVST and PWT are left ventricular end-diastole diameter, interventricular septum thickness and posterior wall thickness at end-diastole, respectively. $\text{LVMI (g/m}^2\text{)}$ was calculated as follows: $\text{LVMI} = \text{LVM} / \text{body surface area}$.²⁷ LVMI will be performed by an observer who is blinded to treatment allocation.

Adverse events

All adverse events related to CoQ10 and severe adverse events will be reported to the ethics committee in the written case report form. Safety will be monitored using routine blood examination, liver function, blood electrolytes and so on.

Follow-up protocol

Patients will be followed-up clinically every 3 months until the end of the study at 12 months. Biochemical data will be collected at baseline and every 3 months including haemoglobin, urea, creatinine, albumin, calcium, phosphate, intact parathyroid hormone, brain natriuretic peptide and high-sensitivity C-reactive protein measured by standard methods. Kt/V values will be also calculated and collected. The inferior vena cava collapsibility index was used to evaluate volume status.²⁸ The inferior vena cava will be measured by one observer who will be blinded to treatment allocation in a supine position during expiration and maximal inspiration, avoiding Valsalva-like manoeuvres. The Inferior Vena Cava Collapsibility Index will be calculated using the standard formula: $(\text{maximal diameter on expiration} - \text{minimal diameter on deep inspiration}) / \text{maximal diameter on expiration} \times 100\%$. The Inferior Vena Cava Collapsibility Index, FMD test and echocardiographic examinations will be performed at baseline, 6, and 12 months.

Participant adherence to the protocol will be monitored by interviews at study check-up visits to promote participant retention and complete follow-up. In order to assess medication adherence, the participants will be asked to take the study medication that is left over for weighing at each clinical visit.

Data collection, management and monitoring

The data collected at baseline and follow-up visits will fill in the case report forms. Original medical records and informed consents are archived in the participating centre and saved for at least 5 years after the clinical trials finish. All data will be transferred to the data statistical units for data entry and management with the EpiData3.1 database. The data will be entered independently into the database by two researchers and will be checked separately by different trained researchers. The privacy of the participants is guaranteed. Each participant will receive a participation identity number in this study, with which

personal information of participants is labelled in papers. Personal information will be kept in a locked storage unit by one researcher who has and will have access to the final trial dataset.

An independent data and safety monitoring board, who will oversee all aspects of the study, will meet regularly during the trial to monitor safety. Recommendations will be made on study progress and performance, identify any major adverse outcomes or adverse outcomes due to the therapy by this board. Advice will be given regarding whether the study should continue or a protocol change should be made.

Harms

For patients undergoing haemodialysis, daily CoQ10 supplementation at doses as high as 1800 mg was safe and well tolerated.^{17 29} Potential adverse events include gastrointestinal discomfort, loss of appetite, nausea, diarrhoea and rash. In the process of the clinical trial, any severe adverse events must be immediately reported to the ethics committee within 24 hours and recorded including the time of occurrence, severity, duration, measures and outcome.

Statistical methods

The intent-to-treat analysis set will be used as the principal analysis for efficacy analyses. All participants who have begun treatment will be included irrespective of their protocol adherence and whether they will continue participating in the study. Patients who complete the study and comply well with the study protocol without major protocol violations will constitute the per-protocol set. The per-protocol analysis will be used as the secondary analysis for efficacy analyses. Missing data will be handled using the last observation carried forward method. Analysis of covariance will be used to analyse the change from baseline in primary and secondary outcomes adjusted for baseline values and treatment assignment. A two-tailed $p < 0.05$ will be used as the cut-off for statistical significance. All statistical analyses will be performed using Stata software (V.16.0).

Patient and public involvement

The study participants were not involved beyond the standard roles as the subjects of the proposed trial. The public was not involved.

Ethics and dissemination

This study will be performed following the principles of the Declaration of Helsinki. All patients must provide written informed consent (online supplementary additional file 2) before undergoing any study-related procedures. The study protocol has been approved by the Medical Ethics Committee for Clinical Trials of Drugs, the 306th Hospital of Chinese PLA. If any significant changes must be made to the protocol, a draft of the new version will be submitted for approval.

We plan to report the trial results for publication in an appropriate journal and to communicate the results at

an academic conference. Our final report will follow the Consolidated Standards of Reporting Trials guidelines.³⁰

DISCUSSION

CoQ10 is a key component in energy transduction and the antioxidant process.³¹ CoQ10 supplementation can be used for the treatment of endothelial dysfunction. For patients with ischaemic heart disease, a 1-month treatment of CoQ10 significantly improved FMD from $4.6\% \pm 0.6\%$ to $7.8\% \pm 0.6\%$, whereas there was no change in the control group.¹² Hamilton *et al* found brachial artery FMD to be improved by 1% after CoQ10 supplementation for 12 weeks in patients with type 2 diabetes.³² A meta-analysis combined five eligible randomised controlled trials showed that treatment with CoQ10 significantly improved in endothelial function assessed peripherally by FMD (standard mean difference 1.70, 95% CI 1.00 to 2.4, $p < 0.0001$).¹¹

The detailed mechanism might involve altering local vascular oxidative stress.^{12 32} Tiano *et al*'s study indicated that improvements of extracellular superoxide dismutase (ecSOD) activity might be related to CoQ10 capability of enhancing endothelial function.¹² In this study, patients with lower levels of ecSOD had greater improvement in endothelial function.

Excessive oxidative stress is highly prevalent and correlated with cardiovascular morbidity and mortality for patients undergoing haemodialysis.³³ Excessive oxidative stress might result from loss of antioxidants during dialysis and activation of white blood cells triggering the production of reactive oxygen species.³⁴ Although no study has investigated the effect of CoQ10 supplementation on endothelial function in patients undergoing dialysis, increasing evidence has indicated that CoQ10 supplementation can effectively decrease oxidative stress in this special population.^{17 35–37}

Regarding cardiac function, for the general population, a meta-analysis showed that treatment with CoQ10 had a favourable effect on left ventricular ejection fraction.¹⁵ One randomised controlled trial (Q-SYMBIO trial)¹⁴ and one recent meta-analysis¹³ found that CoQ10 treatment significantly reduced major adverse cardiovascular events and mortality.

For patients undergoing haemodialysis, to our best of knowledge, only two small sample studies focused on the efficacy of supplementation of CoQ10 on cardiac function or biomarker of cardiac function.^{16 17} One randomised controlled trial has explored the efficacy of CoQ10 supplementation on cardiac function and found that CoQ10 supplementation decreased LVM and left ventricular posterior wall as well as IVST and did not improve diastolic heart function in this special population.¹⁶ However, this study, being a cross-over trial, only had a sample size with a total of 28 participants and short follow-up time with only 8 weeks in each phase and 4-week washout period. Another small sample study¹⁷ indicated that no significant effect of CoQ10 treatment on N-terminal pro-B-type

natriuretic peptide (NT-proBNP) was found. However, in the per-protocol analysis, significantly lower levels of NT-proBNP among patients assigned to 1200 mg CoQ10 compared with placebo were found. To date, no study has focused on the effects of CoQ10 treatment on cardiovascular events and mortality.

Based on existing evidence, we hypothesise that the administration of CoQ10 will have a favourable effect on endothelial dysfunction and cardiac function in patients undergoing haemodialysis. Compared with the existing studies, we will first evaluate the effect of CoQ10 treatment on endothelial dysfunction in patients undergoing haemodialysis. We will evaluate the cardiac effect of CoQ10. Hard endpoints including cardiovascular events and mortality will be also prespecified outcomes in our study.

However, this is a pilot trial with small sample size. Hence, this study may not be able to result in significant therapeutic effects. The present trial is a study of great value for it will provide important parameters, which can be used to evaluate the feasibility and safety of the protocol and calculate the sample size for a future trial with a larger sample size to determine whether CoQ10 supplementation confers improved survival and reduced cardiovascular events in patients undergoing haemodialysis.

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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.

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