

BMJ Open Can coenzyme Q10 supplementation effectively reduce human tumour necrosis factor- α and interleukin-6 levels in chronic diseases? Protocol for a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Inflammation, as a critical factor, can cause numerous chronic diseases by creating various proinflammatory cytokines. Coenzyme Q10 (CoQ10) can potentially exert an anti-inflammatory agent; in turn, this agent can reduce the systemic inflammatory response. The aims of this study are to conduct a comprehensive systematic review and a meta-analysis for the determination of the CoQ10 efficacy on the changes in serum interleukin-6 (IL-6) and the tumour necrosis factor- α (TNF- α) levels in unhealthy subjects.

Method and analysis We will conduct an electronic search for articles published between January 1990 and January 2017 using a prespecified search strategy in MEDLINE, SCOPUS, EMBASE, CENTRAL and Web of Science. Our search will focus only on randomised controlled clinical trials in unhealthy subjects that employ either a parallel or a crossover design; this search will involve concurrent control groups. The primary outcomes of the literature are to determine the CoQ10 efficacy on the changes in the serum IL-6 and the TNF- α levels in unhealthy subjects. Secondary outcomes such as body mass index, serum adiponectin and high-sensitivity C-reactive protein levels, lipid profile and the heterogeneity assessment of the primary studies will be evaluated. The stages of screen articles, the extracts of relevant data and the assessment of study quality using the Cochrane risk of bias tool will be conducted independently by the two reviewers. Any disagreement will be resolved by discussion with a third person. If the number of eligible studies is sufficient, we will carry out a meta-analysis according to both outcomes.

Ethics and dissemination This study is the protocol for a systematic review and no ethics approval is needed. The findings from the full systematic review will be published in a peer-reviewed journal, and they will also be exhibited at national/international academic and clinical conferences.

Trial registration number CRD42016052200.

Strengths and limitations of this study

- The benefits of this systematic review with meta-analysis are due to a comprehensive search strategy, designed to retrieve as many articles relevant to our primary and secondary objectives as possible.
- The evidence of highest levels for informed decisions about the role of coenzyme Q10 in chronic disease will be provided from results of this study.
- The protocol of this study has been prepared in accordance with the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols) guidelines, including description of key methodological steps.
- The main limitation of this study is that the conclusions will be limited by the number and quality of primary studies.
- One limitation of this study is related to published articles in other languages that needs to a translator.

INTRODUCTION

Much evidence indicates that systematic inflammation has a major role in many human chronic disease pathogenesises, such as cardiovascular, pulmonary, autoimmune and degenerative diseases, as well as cancer and metabolic diseases.¹⁻³ Elevated levels of interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α), as inflammation mediators, are closely linked to numerous chronic diseases.³⁻⁵ Due to adverse effects and health problems of existing anti-inflammatory therapies, the use of natural compounds as antioxidant and anti-inflammatory agents has considered more attention in scientific research.⁶

Coenzyme Q10 (CoQ10), referred to as 'ubiquinone',⁷ is composed of a lipophilic benzoquinone structure with a side chain of 10 isoprenoid units.⁸ It is endogenously synthesised by the mevalonate pathway in the human body⁹ and it is obtained in much of human diet.¹⁰ CoQ10 is a critical intermediate of the mitochondrial electron transport chain for the synthesis of adenosine triphosphate.^{8,11} The biological importance of CoQ10 is related to antioxidant activity, which can scavenge free radicals as well as restore the antioxidant defence system.¹⁰ Furthermore, several studies from both in vitro and animal models have suggested that CoQ10 acts as an anti-inflammatory agent, inhibiting the inflammatory response¹⁰ by blocking the expression of nuclear factor-kappa B¹¹ as well as activating the peroxisome proliferator-activated receptor-mediated anti-inflammatory responses.¹⁰

As previously mentioned, CoQ10 supplementation, a natural dietary antioxidant, possessing anti-inflammatory activity, would be beneficial for numerous human chronic diseases.⁸⁻¹⁵ However, a recent study by Liu *et al* indicated that CoQ10 (300 mg/day) could not significantly decrease the inflammatory cytokines in the progression of the hepatocellular carcinoma after 12 weeks of performing surgery.⁸ Another recent clinical trial showed that the serum level of TNF- α was significantly reduced in patients with rheumatoid arthritis who received capsules of CoQ₁₀ (100 mg/day) for 8 weeks, but no significant effect was seen on serum IL-6 concentration.¹⁵ Consistent with the results of this study, Farsi *et al* observed that CoQ10 supplement at a dose of 100 mg/day could significantly reduce the serum levels of TNF- α ($p=0.04$) after 3 months of treatment in patients suffering from non-alcoholic fatty liver disease. IL-6 blood levels, however, had significantly changed after the intervention duration.¹² In this regard, Sanoobar *et al* examined the efficacy of CoQ10 administration in patients with multiple sclerosis. The researchers observed that the daily intake of CoQ10 supplement at a dosage of 500 mg has favourable effects on the reduction of the plasma inflammatory marker levels (TNF- α , $p=0.003$; IL-6, $p=0.03$) after 12 weeks of intervention.⁹ Overall, on the basis of the available evidence, researchers have reported inconclusive results of CoQ10 supplement effectiveness on TNF- α and IL-6 serum levels.⁹⁻¹⁶ These discrepancies might be related to the various dosing regimens of CoQ10 and the differences in supplementation duration, a variation of the clinical inclusion criteria in the studied samples as a result of using small sample sizes, and plasma TNF- α and IL-6 levels at the baseline. Despite several clinical trials, the efficacy of CoQ10 on circulating TNF- α and IL-6 levels remains questionable and ambiguous. Based on our knowledge and understanding, until now, we have found two systematic reviews and meta-analyses of the evidence in relation to the CoQ10 efficacy for changing the proinflammatory factor levels (C-reactive protein (CRP), IL-6 or TNF- α).^{17,18} Fan *et al*, in this issue, observed the significant lowering effects of CoQ10 on CRP, IL-6 or TNF- α .¹⁷ Another recent review reported that CoQ10 was helpful in significantly decreasing TNF- α

levels, but found no substantial change in IL-6 and CRP serum levels.¹⁸

However, they were based on a limited database search and were restricted to studies published in English.^{17,18} Therefore, based on the available literature, we believe that a systematic review and meta-analysis is required only for the CoQ10 supplementation efficacy on the concurrent changes in serum TNF- α and IL-6 levels in unhealthy subjects. In order to extend our work, we will review more database and grey literature without setting a language limitation on publications. It, therefore, appears that the results of this study can potentially help determine the net effect of the oral CoQ10 supplementation on the TNF- α and the IL-6 serum levels.

OBJECTIVES

The primary objective of this study of the literature is, therefore, to evaluate the CoQ10 supplementation efficacy on the changes in serum TNF- α and IL-6 levels in unhealthy subjects.

The secondary aims of our study are as follows:

1. To evaluate CoQ10 supplementation efficacy on body mass index (BMI) in comparison to the control group in unhealthy subjects.
2. To evaluate CoQ10 supplementation efficacy on the changes in serum adiponectin concentrations in comparison to the control group in unhealthy subjects.
3. To assess CoQ10 supplementation efficacy on the changes in serum high-sensitivity CRP (hs-CRP) levels in comparison to the control group in unhealthy subjects.
4. To determine and summarise the evidence about the efficacy of CoQ10 supplementation to reduce the lipid profile (low-density lipoprotein (LDL), cholesterol and triglyceride (TG)) in comparison to the control group in unhealthy subjects.
5. To investigate the heterogeneity assessment of primary studies and other sources.

METHOD AND ANALYSIS

The design of this systematic review has been developed according to the recommended details presented on the 2015 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines checklist.¹⁹ Moreover, the flow chart of PRISMA will be applied to explain the number of included and excluded primary studies in the different stages of this systematic review (online supplementary appendix 1). This systematic review protocol has been prepared in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines.¹⁹ This protocol is registered in the international prospective register of systematic reviews (PROSPERO 2016: CRD42016052200; website: <http://www.crd.york.ac.uk/PROSPERO>).

ELIGIBILITY CRITERIA

Study design/characteristics

Primary studies will be included in the systematic review if they contain randomised clinical trials (RCT) at least single blind with either parallel or crossover designs, comprising concurrent control groups, which were published in any language between January 1990 and January 2017. Reviewers will exclude methods other than RCTs conducted on humans, such as review articles, case studies, case series, observational studies (cross-sectional, case-control and cohort), experimental studies with animals or in vitro, and studies on healthy subjects, proceedings, editorials/commentaries, letters as well as reports comprising insufficient data on baseline or follow-up TNF- α and IL-6 in each group. We will exclude studies reporting CoQ10 in combination with other substances.

Subject types

In order to be eligible for inclusion, primary studies will be considered if the tested intervention targets non-athlete adult subjects (≥ 18 years) or at least one of the population subgroups, with various chronic inflammatory conditions or non-communicable diseases (such as diabetes, hypertension, obesity, and so on), and at least one of the two sexes.

Intervention(s)

Our target will be RCT studies that used oral CoQ10 supplementation (in capsule form or in any other form) daily in divided dosage or single doses (amount/day) for any intervention duration.

Comparator(s)/control

Studies will be eligible that compared oral CoQ10 supplementation versus control that placebo, standard therapy alone, no intervention and other natural or pharmacological agents will be accepted as controls.

Outcome(s)

Studies will be included in the review if they report the effect of the intervention on the primary outcomes in terms of serum/plasma TNF- α and IL-6 levels at the baseline and at the end of treatment duration in the study groups.

Secondary outcomes of project

We will also record the results of intervention effectiveness on one or several of the following outcomes if available:

- ▶ BMI
- ▶ serum adiponectin and levels
- ▶ serum hs-CRP levels
- ▶ lipid profile measurements (TG, cholesterol and LDL)
- ▶ the heterogeneity assessment of primary studies and other sources.

Data sources

Searching electronic bibliographic databases for this systematic review will be conducted by two reviewers between January 1990 and January 2017. Bibliographic and electronic databases will be searched using the following assess words within topics and abstracts:

1. Cochrane Central Register of Controlled Trials (CENTRAL)
2. Web of Science
3. Medline (<http://www.ncbi.nlm.nih.gov/pubmed>)
4. SCOPUS
5. EMBASE.

Database of ongoing clinical trials

Registers of clinical trials will be searched for in the following databases:

- ▶ www.clinicaltrials.gov
- ▶ ISRCTN registry
- ▶ www.who.int/trialsearch/.

Other resources

To ensure research saturation, the other resources will be manually reviewed to find additional eligible studies such as key journals and the reference list of all the included relevant research articles, meta-analyses and review publications on CoQ10. In regard to the recommendations of the Institute of Medicine Standards and the Cochrane Handbook for Systematic Reviews of Interventions, we will evaluate some of informally published content in academic sources (the grey literature), including thesis data and abstracts of papers presented at different conferences. For further comprehensiveness, we will contact the authors of these papers by email on the basis of the available abstracts; we will request for the full text if necessary.

Search strategy

The aims of literature search strategies will be to find all the relevant RCTs conducted on humans using an appropriate set of key search terms to delimit the concepts 'Coenzyme Q10', 'IL-6', 'TNF- α ' and 'Inflammation'. The search terms of any component of this study were found in the MeSH (Medical Subject Headings) tags of the PubMed database, Emtree and a free text word; a combination of these was used to create a proper electronic search strategy. In regard to each database, a search strategy will be adopted. The search strategy and the syntax of the PubMed database are presented in detail in the online supplementary appendix 2.

STUDY RECORDS

Data management

Two primary researchers (FF and JH) will perform the initial search of the electronic databases using the strategy search and guided by the PRISMA-P statement. FF and JH will also manually review the reference lists of all the included studies. In order to conduct data management, the EndNote X7 software will be used. The main reviewer

will import the results of literature searches into an EndNote library and then delete the duplicate records.

Selection process

The selection phase of this systematic review is compliant with the PRISMA guidelines. The selection of relevant studies for inclusion in the review will be performed in a three-step process. The two independent reviewers (FF and PI) will first screen the titles and the abstracts of all the records identified by the database searches in line with the inclusion/exclusion criteria in order to identify a subset of potentially eligible articles. Any discrepancies relating to inclusion in each step of the screen process (title/abstract, and then full-text review) will be resolved by discussion and/or consultation with a third researcher with specific expertise in chronic diseases and CoQ10.

We will then obtain the full texts of potentially eligible articles that appear to meet our inclusion criteria on the basis of their title/abstract. The full-text screening process of the included abstracts will be carried out by two independent reviewers (FF and PI). At each step of the selection process, a record of the reasons behind excluding certain studies will be maintained.

Data extraction

A standard data extraction form designed by the primary reviewer will be used for data extraction from all the selected studies (see online supplementary appendix 2). The data extraction form will be pilot tested by our team on three selected studies and will be refined as necessary in order to ensure the reliability of the data extraction process. The two reviewers (FF and NM) will independently extract the information from the included studies. Data extraction will be completed using the full text of the published reports or via correspondence with the study authors if the data provided in the published articles were inadequate to complete the extraction process. The principal investigator involved in the process of data extraction will have practice using the form and will receive appropriate training if deemed necessary. Similarly, any disagreement in the extracted data process which cannot be resolved through consultation will be referred to a third reviewer with specific expertise in order to reach a consensus.

Data items

The PICOS (Participants, Interventions, Comparisons, Outcomes, Study characteristics) criteria will be applied to systematise our information extraction:

- ▶ Study characteristics: name of the first author, study design, place and time of the study, country of origin, year of publication and size of the sample divided into separate groups.
- ▶ Participant sociodemographic characteristics: age, ethnicity, sex, number of participants, disease type and initial healthy status.
- ▶ Intervention and their specific: dosage, length of follow-up, type of administration, treatment group

sample size, blinding procedure, withdrawals and dropouts.

- ▶ Outcomes: definition and measures of primary (TNF- α and IL-6 levels) and secondary outcomes (BMI, serum adiponectin, hs-CRP levels, lipid profile, heterogeneity assessment in primary studies and other miscellaneous points).

Outcomes and prioritisation

We will consider pooling studies that include TNF- α and IL-6 levels in unhealthy subjects as our primary clinical outcomes and other outcomes as secondary outcomes. Our prioritisation will also be given to studies with an RCT design, which examined the effect of CoQ10 supplementation alone under inflammation conditions. Article presentation in the review will be ultimately improved by prioritisation of the search strategy items.

Missing data

In order to perform data management in certain conditions set by the Cochrane Institute, our investigators will contact the corresponding authors of the studies by email to obtain clarification if the data provided are incomplete in the study reports. We will have to send reminder emails (up to three times) if the authors do not reply to the initial email. Reviewers will consider the incomplete information as missing data if a response is not received after three emails.

Risk of bias assessment (in individual studies)

Risk of bias assessment of the individual studies will be carried out by two independent review authors (FF, JH) using the guidelines of a tool developed by Cochrane Collaboration to assess and report the risk of bias in the following seven criteria:

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
7. other potential sources of biases.

Two principal investigators (FF, JH) will first test pilot the Cochrane tool items on three primary articles. In case of disagreement on the risk of bias assessment, consultation with the third person will be employed to reach a resolution. The options of yes, no or unclear will be used for each component of our chosen domains, and then, the risk of bias will be documented as a risk of bias category from the following: low, unclear or high. We will then describe reasons for each assessment.

Data synthesis

If the number of eligible studies is an adequate, we will carry out a meta-analysis according to both outcomes. Based on the conditions of the primary studies in terms of methodology, one of the two models (fixed or random effects model) will be used.

A narrative data synthesis of all the included studies after a systemic review will be performed and it will be assigned in a text as well as separate tables. For the purposes of data synthesis, all the data from continuous outcomes analyses will be presented as mean difference or standardised mean difference (SMD), both with 95% CI; the risk ratio index will be calculated for the qualitative and the categorical data.

To investigate clinical and methodological heterogeneity, we will undertake the determination of the feasibility of meta-analysis. For this purpose, we will consider the main sources of heterogeneity including different study design (crossover or parallel and year of publication), population characteristics (gender, ethnicity, age, disease types and stage distribution), duration of follow-up, sampling interval and test characteristics. The Q Cochrane test will be applied to statistically check the extent of heterogeneity among primary studies as recommended by the Cochrane Handbook for Systematic Reviews of RCT. The I^2 statistic will also be used to determine the extent of heterogeneity between studies and to guide our choice of the model (fixed or random effects model). $I^2 > 50\%$ will be considered as severe heterogeneity. However, if we find substantial heterogeneity and a sufficient number of eligible studies, meta-regression and subgroup analyses according to gender, BMI and the sample size, SMD will be conducted in order to identify the heterogeneity of the sources. If some studies are at high risk of bias, we will conduct a sensitivity analysis in order to assess the impact of the methodological quality and the effect of studies with a lower sample size on the power of review conclusions. All data from sensitivity analyses will be presented and summarised in tables. The forest plots will be used for the graphical representation and the final synthesis of primary studies. The Stata (V.12) software (StataCorp, College Station, Texas, USA) will be used for all the mentioned analyses.

Assessment of possible reporting bias

We will investigate the likelihood of outcome reporting bias (publication and other reporting biases) using funnel plots (ie, plots of study results against precision) if the number of studies included in a meta-analysis is sufficient (~10 studies). Begg's test and Egger's test will also be used in order to assess for asymmetry. When this is non-negligible, we will use the trim and fill method to correct the results. The statistically significant correlation will be indicated using a p value of ≤ 0.05 .

Ethics and dissemination

This research is a protocol for a systematic review and no ethics approval is needed. The findings from the full systematic review will be published in a peer-reviewed journal and will also be exhibited at national/international academic and clinical conferences.

As previously mentioned, inflammation is recognised as a common cause of numerous chronic disease pathogenesis in humans.^{17 18} Among the constituents of

pharmacotherapy, as anti-inflammatory medicines or inflammatory blockers are currently being applied in extended ranges, these blockers are highly expensive and have more side effects.^{17 18} Hence, a natural component such as CoQ10 is needed, which is safe and cost-effective and readily available.¹⁷ CoQ10 can also be considered as an important agent for the conservative management of this condition.

The purpose of this systematic review will be comprehensively identified and summarised in studies reporting whether CoQ10 supplementation effectively can reduce serum TNF- α and IL-6 levels in unhealthy subjects. The results of this study will assist future research that studies the anti-inflammatory effect of CoQ10 as a treatment approach in many human chronic diseases. Furthermore, the results of this systematic review with meta-analysis will be important to create awareness among clinicians, therapists and patients on the topic of CoQ10 effectiveness.

Confidence in cumulative evidence

The GRADE (Grading of Recommendations Assessment, Development and Evaluation)²⁰ guidelines will be applied in order to assess the quality of the evidence in relation to the effect of CoQ10 on the primary and secondary outcomes. The quality assessment of evidence will be performed based on the following domains: design and risk of bias, consistency, directness, precision and publication bias.

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Contributors AA, MV, AK and LJ were responsible for the systematic review protocol design process and the formulation of the research question for this work. FF and JH searched the electronic databases and reviewed the collected data. MMA and PI participated in the assessment of the full-text papers and data collection.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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