BMJ Open

Efficacy of coenzyme Q10 supplementation for male infertility with high sperm DNA fragmentation index: a protocol for a systematic review and meta-analysis

Yu Zhao ,[1,2] Xiaoli Zhao,[3,4] Guangyin Zhang,[5,6] Ruihong Ma,[3,4] Qiang Geng,[1,2] Bin Ouyang,[1,2] Tian Xia[3,4]

To cite: Zhao Y, Zhao X, Zhang G, *et al*. Efficacy of coenzyme Q10 supplementation for male infertility with high sperm DNA fragmentation index: a protocol for a systematic review and meta-analysis. *BMJ Open* 2023;**13**:e068368. doi:10.1136/bmjopen-2022-068368

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-068368).

Received 15 September 2022
Accepted 18 May 2023

For numbered affiliations see end of article.

Correspondence to
Dr Guangyin Zhang; tj_zhang120@163.com and Dr Tian Xia; xiatian76@163.com

ABSTRACT

Introduction Infertility is a focal issue in public health and affects human reproduction and survival. Notably, an increasing number of studies in recent decades have found that sperm DNA integrity plays a critical role in the development of healthy embryos. Among the multiple pathogenic factors of sperm DNA fragmentation, oxidative stress has proven to be predominant. Coenzyme Q10 supplementation, which has been used for the treatment of male infertility, has shown good clinical efficacy due to its oxidation resistance, but its efficacy as measured by the sperm DNA fragmentation index remains controversial. To address this issue, we will perform a systematic review and meta-analysis to evaluate the efficacy of coenzyme Q10 for male infertility patients with a high sperm DNA fragmentation index.

Methods and analysis The PubMed, Embase, Cochrane Central Register of Studies and Web of Science databases will be comprehensively searched from inception to 31 December 2022 to identify relevant studies published in the English language using appropriate search strategies. The search terms will be derived from the following concepts: sperm DNA fragmentation, coenzyme Q10 and randomised controlled trials. Two review stages, that is, title and abstract screening and full-text screening, will be performed by two reviewers. The risk of bias, publication bias and evidence grade of the included studies will be assessed using a standardised protocol. Data will be used to calculate effect sizes. Heterogeneity among the studies will be evaluated graphically. Subgroup analysis and sensitivity analysis will be performed if necessary to validate the results.

Ethics and dissemination No ethical approval will be needed, as there will be no participants in this study. We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to disseminate the findings through publication and conference presentation.

PROSPERO registration number CRD42022293340.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will systematically review the efficacy of coenzyme Q10 supplementation for male infertility patients with a high sperm DNA fragmentation index.
⇒ This study will be compiled and reported following the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.
⇒ Risk of bias, evidence evaluation, subgroup analysis and sensitivity analysis will be conducted to validate the results.
⇒ As we will only include articles published in English, this limitation may lead to missing related research in other languages, thus causing further publication bias.
⇒ Although important databases were selected, there are others that we did not use, and thus, we may miss related studies.

INTRODUCTION

It is well known that normal embryonic development depends on the integrity of complete genetic material from both sperm and oocytes.[1] Among the factors that influence the normal development of embryos and fetuses, the integrity of sperm DNA is important.[2] Multiple studies have demonstrated that sperm DNA integrity plays a crucial role in embryo development[3–5] and has the capacity to predict the final pregnancy outcome.[6] However, the current evaluation of infertile men commonly relies on semen analysis, which still has a limitation of inaccuracy in predicting male fertility potential and final pregnancy outcome from assisted reproductive technology (ART).[7] The Sperm DNA Fragmentation Index (SDFI), as an indicator reflecting sperm DNA integrity, can offset this limitation.[8 9]

Oxidative stress (OS) is defined as 'an imbalance between oxidants and antioxidants in favour of the oxidants, leading to a

disruption of redox signalling and control and/or molecular damage'.[10] This biological process participates in the onset of dozens of diseases at the molecular level,[11 12] especially sperm DNA fragmentation (SDF).[1 13 14] Hence, there is an urgent need to identify an effective treatment for male infertility patients with high SDFI by regulating OS status in vivo.

Coenzyme Q10 (CoQ10), a well-known exogenous antioxidant supplement, is an isoprenylated benzoquinone that works by transporting electrons from complexes I and II to complex III.[15] The antioxidant effect of CoQ10 manifests as preventing membrane phospholipid peroxidation and free radical oxidation.[16] Given its excellent antioxidation, CoQ10 supplementation has been applied for decades to improve semen parameters with good clinical efficacy.[17–19] Although a certain number of clinical studies have confirmed that coenzyme Q10 can improve sperm quality, whether oral CoQ10 can improve SDFI remains controversial. Therefore, we hypothesised that oral coenzyme Q10 alone could improve the SDFI and increase the probability of conception in male infertility patients. The purpose of this study is to systematically review the clinical evidence that CoQ10 supplementation improves SDFI and assess its clinical effect on SDFI through meta-analysis.

This systematic review and meta-analysis will be completed and reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[20] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[21]

METHODS AND ANALYSIS

Patient and public involvement

This study will have no patient or public involvement.

Protocol and registration

In accordance with guidelines, this protocol will be conducted by following the PRISMA-Protocols (PRISMA-P)[22] (online supplemental table 1) and registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 14 August 2022 (registration number CRD42022293340).

Criteria for study selection

Inclusion criteria

This study will include published randomised controlled clinical trials on male infertility patients with a high SDF index. It will exclude animal studies, conference papers, case reports and reviews.

Comparators

The intervention will be administration of coenzyme Q10 supplementation alone, in any form (eg, tablet, powder, capsule). Trials whose only intervention combined coenzyme Q10 with other antioxidants (L-carnitine, vitamin E, Zn, etc) will be excluded. The control will be placebo or no intervention.

Literature Search

Two authors will independently search the PubMed, Embase, Cochrane Central Register of Studies and Web of Science databases from inception to 31 December 2022 to identify relevant articles written in the English language. The two authors will also manually review the reference lists of the selected articles to identify additional eligible articles. There will be no limits on publication date. The search strategy will include medical subject heading terms combined with free words (online supplemental table 2).

Article selection

The titles and abstracts will be screened independently by two reviewers in accordance with the inclusion criteria. Next, the full texts of the remaining studies will be carefully read to determine whether they meet the inclusion criteria. Any disagreement between investigators will be resolved through discussion. We will list the reasons for excluding articles (see online supplemental figure 1).

Data extraction and analysis

Data extraction

Two reviewers will perform data extraction independently using a standard data collection form (online supplemental table 3). Excel 2019 software will be used for data recording. Initially, two or three potentially eligible articles will be pilot tested. Divergence will be resolved by consensus. If there is no consensus, a third reviewer will be consulted to resolve the inconsistency.

The following study characteristics will be extracted:

- Study information: author(s) name, title, publication year, lower limit of SDFI (if provided).
- Study methods: study design, total duration of the study, study centres (country).
- Study participants: sample size, age, race, semen parameters at baseline.
- Study intervention: dosage forms of coenzyme Q10, type of oral dose and frequency.
- Study outcomes: primary outcome—SDFI (measured by the sperm chromatin structure assay, terminal deoxynucleotidyl transferase 2'-deoxyuridine 5'-triphosphate (dUTP) nick end labelling and sperm chromatin dispersion); secondary outcome—spouse pregnancy rate (if reported), sperm concentration, normal morphology, total motility and reactive oxygen species level.

Measure of treatment effect

As a change in SDFI is a continuous variable, the treatment effect will be measured using mean difference (MD) with 95% CI. The standardised MD and 95% CI will be used to evaluate effect size because indicators differed in detection methods and units used to measure raw data (such as reactive oxygen species).

Missing data management

If relevant data are missing, corresponding authors will be contacted to obtain, if possible, any data, including source data not presented in the publication. If the data

are not available on request, we will use informative missingness ORs[23] to attribute missing data.

Risk of bias assessment

Two researchers will evaluate the risk of bias (ROB) from the included studies with the Cochrane Collaboration's tool for assessing ROB V.2.0[24] (online supplemental table 4). The main items needed for evaluation will be as follows:

- Bias arising from the randomisation process.
- Bias due to deviations from intended interventions.
- Bias due to missing outcome data.
- Bias in outcome measurement.
- Bias in selection of the reported result.

The possible ROB on each of five domains based on the extracted information will be rated as 'high risk' or 'low risk'. If there was insufficient detail reported in the study, we judged the ROB as 'unclear'.

Publication bias assessment

We will perform the assessment of publication bias using a visual inspection of the funnel plot asymmetry and Egger's test of asymmetry.[25] If there are fewer than 10 studies associated with one outcome, the power of the assessment would be too low to be implemented according to the Cochrane recommendations. Egger's test of asymmetry is also invalid when the number of included studies is fewer than 20.

Evidence evaluation

We will use the Grading of Recommendations Assessment, Development and Evaluation system[26] to assess the strength of evidence from each included study.

Data synthesis

We will extract and summarise the study characteristics and present them in text descriptions and baseline tables. The synthesis describes the characteristics of each of the included studies and shows information about the effective measures for outcomes and quality of study.

A meta-analysis will be performed based on the availability of data, including the MD or OR. The heterogeneity between the included studies will be approached graphically.[27] The metafor package for R (V.4.0-0) will be used to pool the data from the included studies.[28] The final analysis data will also be presented in a forest plot by using the metafor package for R.

Subgroup analysis

Subgroup analysis will be conducted when we have adequate data for each of the following variables:

1. The dosage of coenzyme Q10 supplementation.
2. Duration of intervention.
3. Patient ages.
4. Detection methods of the SDFI.

If an adequate number of included studies (n>2) included an outcome, subgroup analyses will be extended to random effects meta-regression analyses. We will choose MD as the effect size for the data from the included studies.

Sensitivity analysis

A sensitivity analysis will be conducted to account for the ROB through a leave-one-out method operated in the metafor package for R (V.4.0-0).

DISCUSSION

This study will provide a repeatable and transparent procedure to comprehensively explore the efficacy of CoQ10 supplementation in male infertility patients. In this systematic review, the strengths and weaknesses of the included studies will be identified. Additionally, this review will provide estimates for the effectiveness of interventions in terms of improving SDFI and OS status. The different doses, durations and detection methods selected may cause significant heterogeneity among the included studies. To solve this problem, a narrative summary will be presented to provide valid data if possible.

Conclusion

The findings of this review can offer clinicians a new therapeutic approach to treat patients with high SDFI. Considering the higher cost of the combination of antioxidants, administration of CQ10 alone may significantly reduce the healthcare costs of patients.

Author affiliations
[1]Department of Andrology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China
[2]Department of Andrology, National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China
[3]Department of Reproductive Center, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China
[4]Department of Reproductive Center, National Clinical Reasearch Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China
[5]Department of Psychosomatic Medicine, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China
[6]Department of Psychosomatic Medicine, National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, People's Republic of China

Twitter Ruihong Ma @ruihong2550@126.com

Acknowledgements The authors thank Jingyu Xu for contributing to the revision of this manuscript.

Contributors TX is the guarantor. YZ drafted the manuscript. YZ, XZ, GZ, RM, QG, BO and TX contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. XZ developed the search strategy. GZ provided statistical expertise. All authors read, provided feedback and approved the final manuscript.

Funding This work is supported by the National Key Research and Development program(2017YFC1311103).

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 iD

Yu Zhao http://orcid.org/0000-0003-3975-155X

REFERENCES

1 Sakkas D, Alvarez JG. Sperm DNA fragmentation: mechanisms of origin, impact on reproductive outcome, and analysis. *Fertility and Sterility* 2010;93:1027–36.
2 Khadem N, Poorhoseyni A, Jalali M, *et al*. Sperm DNA fragmentation in couples with unexplained recurrent spontaneous abortions. *Andrologia* 2014;46:126–30.
3 Aoki VW, Emery BR, Liu L, *et al*. Protamine levels vary between individual Sperm cells of infertile human males and correlate with viability and DNA integrity. *J Androl* 2006;27:890–8.
4 Khalafalla K, Majzoub A, Elbardisi H, *et al*. The effect of Sperm DNA fragmentation on intracytoplasmic Sperm injection outcome. *Andrologia* 2021;53:e14180.
5 Yifu P, Lei Y, Shaoming L, *et al*. Sperm DNA fragmentation index with unexplained recurrent spontaneous abortion: A systematic review and meta-analysis. *J Gynecol Obstet Hum Reprod* 2020;2020:101740.
6 Li MW, Lloyd KCK. DNA fragmentation index (DFI) as a measure of Sperm quality and fertility in mice. *Sci Rep* 2020;10:3833.
7 Wang C, Swerdloff RS. Limitations of Semen analysis as a test of male fertility and anticipated needs from newer tests. *Fertil Steril* 2014;102:1502–7.
8 Simon L, Emery BR, Carrell DT. Review: diagnosis and impact of Sperm DNA alterations in assisted reproduction. *Best Pract Res Clin Obstet Gynaecol* 2017;44:38–56.
9 Yifu P, Lei Y, Shaoming L, *et al*. Sperm DNA fragmentation index with unexplained recurrent spontaneous abortion: A systematic review and meta-analysis. *J Gynecol Obstet Hum Reprod* 2020:101740.
10 Sies H. Oxidative stress: a concept in redox biology and medicine. *Redox Biol* 2015;4:180–3.
11 Tamagno E, Guglielmotto M, Vasciaveo V, *et al*. Oxidative stress and beta Amyloid in Alzheimer's disease. *Antioxidants (Basel)* 2021;10:1479.
12 Juul F, Vaidean G, Parekh N. Ultra-processed foods and cardiovascular diseases: potential mechanisms of action. *Adv Nutr* 2021;12:1673–80.
13 Kocer A, Henry-Berger J, Noblanc A, *et al*. Oxidative DNA damage in mouse Sperm Chromosomes: size matters. *Free Radic Biol Med* 2015;89:993–1002.
14 Wright C, Milne S, Leeson H. Sperm DNA damage caused by oxidative stress: Modifiable clinical, Lifestyle and nutritional factors in male infertility. *Reprod Biomed Online* 2014;28:684–703.
15 Beharry KD, Cai CL, Henry MM, *et al*. Co-enzyme Q10 and N-3 polyunsaturated fatty acid supplementation reverse intermittent hypoxia-induced growth restriction and improved antioxidant profiles in neonatal rats. *Antioxidants (Basel)* 2017;6:103.
16 Sarmiento A, Diaz-Castro J, Pulido-Moran M, *et al*. Coenzyme Q10 supplementation and exercise in healthy humans: a systematic review. *Curr Drug Metab* 2016;17:345–58.
17 Safarinejad MR. Efficacy of coenzyme Q10 on Semen parameters, Sperm function and reproductive hormones in infertile men. *J Urol* 2009;182:237–48.
18 Alahmar AT, Sengupta P. Impact of coenzyme Q10 and selenium on seminal fluid parameters and antioxidant status in men with idiopathic infertility. *Biol Trace Elem Res* 2021;199:1246–52.
19 Balercia G, Buldreghini E, Vignini A, *et al*. Coenzyme Q10 treatment in infertile men with idiopathic Asthenozoospermia: a placebo-controlled, double-blind randomized trial. *Fertil Steril* 2009;91:1785–92.
20 Higgins J, Thomas J. Cochrane Handbook for systematic reviews of interventions version 6.2.0. *Cochrane Collaboration* 2021. Available: http://handbook.cochrane.org/
21 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
22 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
23 Higgins JPT, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clin Trials* 2008;5:225–39.
24 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019:l4898.
25 Egger M, Smith GD, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
26 Mendoza C, Kraemer P, Herrera P, *et al*. Clinical guidelines using the GRADE system (grading of recommendations assessment, development and evaluation). *Rev Med Chil* 2017;145:1463–70.
27 Olkin I, Dahabreh IJ, Trikalinos TA. GOSH - a graphical display of study heterogeneity. *Res Syn Meth* 2012;3:214–23.
28 Viechtbauer W. Conducting meta-analysis in R with the Metafor package. *J Stat Software* 2010;36:1–48.