

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of supplementation with carnosine and other histidine containing dipeptides on chronic disease risk factors and outcomes: protocol for a systematic review of randomized controlled trials
AUTHORS	Menon, Kirthi; Mousa, Aya; de Courten, Barbora

VERSION 1 – REVIEW

REVIEWER	Katarzyna Kilis-Pstrusinska Department of Pediatric Nephrology, Wroclaw Medical University, Wroclaw, Poland
REVIEW RETURNED	09-Dec-2017

GENERAL COMMENTS	An interest in carnosine and histidine-containing dipeptides (HCDs) in chronic diseases is getting higher. The authors aim to conduct a comprehensive systematic review to examine the effects of supplementation with carnosine and other HCDs on chronic disease risk factors and outcomes. The authors' task is very valuable. The protocol is appropriate, given in detail and based on current search strategy.
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REVIEWER	Maxime Hanssens Ghent University, Belgium (Department of Movement & Sports Sciences)
REVIEW RETURNED	07-Feb-2018

GENERAL COMMENTS	Page 3 line 12 "however the effects of carnosine and other histidine-containing peptides (HCDs) on chronic disease risk factors and outcomes have not been established." □ this sounds like there is no existing research about this topic, whilst it is rather an overview of all the existing research that is lacking (aim of this study). Page 7 line 6: what is this rigorous gold-standard methodology? What key words will be selected? The aim to write a review on carnosine supplementation in humans and its effects in the prevention of chronic disease risk factors is very relevant. Nevertheless, the amount of human HCD supplementation studies is very limited and the authors want to include risk factors for a broad variety of chronic diseases (CVD, T2DM, cancer, etc.). This raises the question if a good meta-analysis can be performed. Since animal research is certainly more advanced in this topic, a slight comparison or projection to animal research might be an added value.
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VERSION 1 – AUTHOR RESPONSE

MS: 2017-020623 entitled "Effects of supplementation with carnosine and other histidine containing dipeptides on chronic disease risk factors and outcomes: protocol for a systematic review of randomized controlled trials".

Response to Reviewers

Reviewer 1

Comment 1: An interest in carnosine and histidine-containing dipeptides (HCDs) in chronic diseases is getting higher. The authors aim to conduct a comprehensive systematic review to examine the effects of supplementation with carnosine and other HCDs on chronic disease risk factors and outcomes.

The authors` task is very valuable. The protocol is appropriate, given in detail and based on current search strategy.

Response: We thank the reviewer for their time and effort in reviewing our manuscript.

Reviewer 2

Comment 1: Page 3 line 12 "however the effects of carnosine and other histidine-containing peptides (HCDs) on chronic disease risk factors and outcomes have not been established." ◊ this sounds like there is no existing research about this topic, whilst it is rather an overview of all the existing research that is lacking (aim of this study).

Response: We thank the reviewer for their feedback on our manuscript. We have now reworded the abstract (page 2, paragraph 1, lines 6-8) and the introduction (page 5, paragraph 2, lines 1-4) sections of the manuscript to clarify that *an overview* of the effects of carnosine and other HCDs on chronic disease risk factors is lacking.

Comment 2: Page 7 line 6: what is this rigorous gold-standard methodology?

Response: The gold standard methodology includes using the PRISMA guidelines, PICO framework and GRADE approach with quality appraisal at both the study and outcome levels. We have now clarified this in the highlights (page 2, paragraph 5, lines 4-5) and discussion (page 10, paragraph 3, line 3) sections of the manuscript.

Comment 3: What key words will be selected?

Response: A full list of key words/search terms is provided in Supplementary Table 2. We have now noted this in the methods section of the manuscript (page 6, paragraph 1, lines 3-4) and it was also noted on page 7, lines 1-2.

Comment 4: The aim to write a review on carnosine supplementation in humans and its effects in the prevention of chronic disease risk factors is very relevant. Nevertheless, the amount of human HCD supplementation studies is very limited and the authors want to include risk factors for a broad variety

of chronic diseases (CVD, T2DM, cancer, etc.). This raises the question if a good meta-analysis can be performed. Since animal research is certainly more advanced in this topic, a slight comparison or projection to animal research might be an added value.

Response: As noted by the reviewer, our aim is to review the effects of carnosine and HCDs on chronic disease risk factors in humans. Hence, animal studies are outside the scope of this review. Our preliminary search has identified a number of human studies (~ 5 RCTs) with outcomes related to CVD and T2DM including HbA1c, fasting and post prandial glucose, serum lipids and inflammatory markers, therefore a meta-analysis can be performed with these data. Nevertheless, we agree with the reviewer that animal research is more advanced in this topic, and when reporting the results from our meta-analyses, we plan to compare these with findings from animal research as suggested by the reviewer.