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OPEN PEER REVIEW

Association Between Serum Nitric Oxide Level and Changes in Thyroid Function Test in a Population-based Study: Tehran Thyroid Study Participants (TTS)

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

4 comments · 5 Nov 2020 – 21 Nov 2020

Referee 1 Reviewer

MAJOR REVISION 5 Nov 2020

Dear AE,
Comments for the authors:
1- Some sentences in the manuscript need to be grammatically corrected.
For example, the use of the definite article "the" before certain names has not been observed. For instance, it is necessary to use the definite article "the" in the first sentense of abstract as following: “Nitric oxide (NO) plays a role in the thyroid function regulation through the inhibition of iodide (I) uptake at the thyroidal sodium-iodide symporter (NIS) and impacts the thyroid vascularity and blood flow”.
2- It is necessary to check punctuations and use them correctly.
3- It is necessary to match the keywords with MeSH terms.
4-It is necessary to specify inclusion/exclusion criteria in methods in population studies.
5- Please specify the gender of the participants in the table header of both table 1 and table 2 with women/men or female/male.
6- Please check the symbol of units in the tables and the manuscript. Some of them are incorrect. For example it is necessary to replace Pmol/L with pmol/L, kg / m2 with kg / m2 with and mg/dl with mg/dL.
7- Please mention the company name of the kits used in the methods.
Thanks.

Samaneh Hosseinzadeh Reviewer

MAJOR REVISION 6 Nov 2020

Dear AE,
Comments for the authors:
- In the last paragraph of the introduction, the goal of the study was to evaluate the correlation between mentioned variables, but why? What is the aim of evaluation? What is the importance of that? Why did the authors attempt to do this research? And so on... Answers to such questions should be mentioned in the last paragraph of the introduction.
- Since the American Association of Clinical Endocrinologists, the American Thyroid Association (ATA), and The Endocrine Society, recommend levothyroxine (LT4) monotherapy as the treatment for hypothyroidism, and also, given that nitric oxide has been suggested as a marker for LT4 therapy in some published articles, why did the authors use this parameter in their research?
- In a very similar study to the present manuscript entitled “Association between serum nitric oxide metabolites and thyroid hormones in a general population: Tehran Thyroid Study”, their results mentioned were different from the results of this study. What is your assessment of that? Is there any cause rather than a difference in the design study?
- The author's assumption that readers are familiar with the parameters of hypothyroidism is understandable, but according to the rules of the abstract, a word should not be mentioned in the result and discussion without prior explanation in the introduction. This rule has not been regarded in the case of “hypothyroidism” in the last sentence of the abstract.
- It is better to mention the intended standard source for hypothyroidism parameters listed in “Definition of terms” Section.
- Given that “Shapiro-Wilk” test has been introduced as a test with higher power compared to other statistical tests, why the authors tend to use the Kolmogorov– Smirnov test?

- According to availability of previous researches, it is suggested that the authors ignore being the first (referring to the last paragraph of the discussion)
- Some references (i.e. 4,14, etc.) need to be reviewed.
- Table captions should be written in the same way (male and female or men and women)
- Standards should be observed in writing units of measurement in the tables (i.e. pmol/L instead of Pmol/L)
- It is better to review the sentences grammatically to improve the article.
- Keywords do not represent the subject of the research. Also, make sure they are valid with the Mesh.
Thanks.

Associate Editor

MAJOR REVISION 15 Nov 2020

Dear EIC,
Thanks to the authors of this manuscript.
In addition to address the reviewers' comments, please add and discuss the following point in the study limitations: Only the serum NO level in phase 3 has been used and its changes have not been considered.
Thanks.

Editor-in-Chief

MAJOR REVISION 21 Nov 2020

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
Thanks.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to reviewer 1:
1- Some sentences in the manuscript need to be grammatically corrected. For example, the use of the definite article "the" before certain names has not been observed. For instance, it is necessary to use the definite article "the" in the first sentence of abstract as following: "Nitric oxide (NO) plays a role in the thyroid function regulation through the inhibition of iodide (I) uptake at the thyroidal sodium-iodide symporter (NIS) and impacts the thyroid vascularity and blood flow".
Response: Agreed and corrected.
2- It is necessary to check punctuations and use them correctly.
Response: Agreed and corrected.
3- It is necessary to match the keywords with MeSH terms.
Response: Agreed and corrected. The new keywords: Nitric oxide, Thyrotropin, Thyroxine, Population.
4-It is necessary to specify inclusion/exclusion criteria in methods in population studies.
Response: Inclusion and exclusion criteria are mentioned in first paragraph of "subject" section. "included 1971 participants over 20 years old from the third phase of TTS, whose data on serum NOx from the third phase and on TSH, FT4 and TPOAb from the third and fourth phases were available." "Members using thyroid and anti-thyroid drugs (n=100), radioactive iodine (n=1), pregnant women (n=23), those with hospitalization history during the past three months (n=69), chronic diarrhea (n=35), weight loss (n=67), malignancy (n=5), estimated Glomerular Filtration Rate <60 ml/min/1.72 m2, and missing data (n=13) in the third and fourth phases of TTS were excluded."
5- Please specify the gender of the participants in the table header of both table 1 and table 2 with women/ men or female/male.
Response: Agreed and corrected. It is women/men in both tables now.
6- Please check the symbol of units in the tables and the manuscript. Some of them are incorrect. For example it is necessary to replace Pmol/L with pmol/L, kg / m2 with kg / m2 with and mg/dl with mg/dL.
Response: Agreed and corrected.
7- Please mention the company name of the kits used in methods.
Response: Agreed and corrected. The company name of the kits has been added to the second paragraph of "Anthropometric, clinical, and laboratory measurements" section.
Response to Reviewer 2:
- In the last paragraph of introduction, the goal of study was to evaluate the correlation between mentioned variables, but why? What is the aim of evaluation? What is the importance of that? Why did the authors attempt to do this research? And so on... Answers to such questions should be mentioned in the last paragraph of introduction.
Response: Agreed and added. The justifications and significance of the study have been added to the last paragraph of the 'introduction' section.
"Among the studies on nitrate as a thyroid disrupter, few have focused on serum nitrate level; therefore, the goal of the present study was to … "
- Since the American Association of Clinical Endocrinologists, the American Thyroid Association (ATA), and The Endocrine Society, recommend levothyroxine (LT4) monotherapy as the treatment for hypothyroidism, and also, given that nitric oxide has been suggested as a marker for LT4 therapy in some published articles, why did the authors use this parameter in their research?
Response: Thank you for your insightful comment, but Only euthyroid participants were included in this study and all thyroid and anti-thyroid drug users were excluded. As you can see, this issue is not directly related to the

scope of this study.
- In a very similar study to the present manuscript entitled "Association between serum nitric oxide metabolites and thyroid hormones in a general population: Tehran Thyroid Study", their results mentioned were different from the results of this study. What is your assessment of that? If there any cause rather than difference in design study?
Response: Agreed and added. Unlike to this study, the mentioned study is a cross-sectional study in which the participants with thyroid function tests in the third phase were included, while in the present study the participants with thyroid function test in the third and fourth phases were included, and unlike the mentioned study, those with eGFR< 60 ml/min/1.72 m2 were excluded; therefore, different results can be expectable. The explanation for this difference has been added to the first paragraph of discussion.
"These conflicting results may be due to several factors such as differences in the study design and participants. Additionally, unlike the study conducted by Bagherpoor et al., the participants with estimated Glomerular Filtration Rate <60 ml/min/1.72 m2 were excluded in this study, since individuals with lower eGFR have higher serum nitrate level(34) and various thyroid function test abnormalities(35)."
- The author's assumption that readers are familiar with the parameters of hypothyroidism is understandable, but according to the rules of the abstract, a word should not be mentioned in the result and discussion without prior explanation in the introduction. This rule has not been regarded in the case of "hypothyroidism" in last sentence of abstract.
Response: Agreed and added. The definition of clinical and subclinical hypothyroidism has been added to the second paragraph of abstract.
"and also; it also aimed at the evaluation of the correlation between serum NOx and the incidence of clinical hypothyroidism, characterized by elevated TSH level and decreased FT4 concentration, and subclinical hypothyroidism, characterized by mildly elevated TSH level despite FT4 concentration within the normal range, over three years of follow up."
- It is better to mention the intended standard source for hypothyroidism parameters listed in "Definition of terms" Section.
Response: The diagnostic criteria of clinical and subclinical hypothyroidism are described clearly in the "Definition of terms" section, and the valid references are mentioned.
"hypothyroidism as TSH > 5.06 mIU/L and FT4 < 11.71 pmol/L, and subclinical hypothyroidism as TSH > 5.06 mIU/L and 11.71 pmol/L< FT4 < 19.95 pmol/L(28)."
- Given that "Shapiro-Wilk" test has been introduced as a test with higher power compared to other statistical tests, why the authors tend to use the Kolmogorov– Smirnov test?
Response: Agreed. Although Shapiro-Wilk test has higher power compared to other statistical tests, as you know, it's using will not change the final results.
- According to availability of previous researches, it is suggested that the authors ignore being the first (referring to the last paragraph of the discussion)
Response: Agreed and corrected. Most of the previous research studies are focused on drinking water and food nitrate level, or are done on animals. This study, however, is certainly one of the few cohort studies with such a large sample size and long follow-up on the serum nitrate level in human.
- Some references (i.e. 4, 14, etc.) need to be reviewed.
Response: Agreed and corrected. References have been reviewed and updated.
- Table captions should be written in the same way (male and female or men

and women)
Response: Agreed and corrected. It is women/men in both tables now.
- Standards should be observed in writing units of measurement in the tables (i.e. pmol/L instead of Pmol/L)
Response: Agreed and corrected.
- It is better to review the sentences grammatically to improve the article.
Response: Agreed and corrected.
- Keywords do not represent the subject of the research. Also, make sure they are valid with the Mesh
Response: Agreed and corrected. The new keywords: Nitric oxide, Thyrotropin, Thyroxine, Population.
Response to Associate Editor's Comments:
Associate Editor 1:
Thanks to the authors of this manuscript.
In addition to address the reviewers' comments, please add and discuss the following point in the study limitations: Only the serum NO level in phase 3 has been used and its changes have not been considered.
Response: Agreed and corrected. This limitation has been added to the last paragraph of the 'discussion' section.
"Third, since we only had data on serum NO level in the third phase, its changes were not calculated, although factors affecting serum NO level such as smoking, BMI, FBS, eGFR, etc. were considered(43)."
I would like to express our sincere gratitude for your careful and wise considerations of our paper and your helpful comments. It is noteworthy to mention that this article has been extracted from the thesis writing by Behnaz Ghazisaeidi in School of Medicine, Shahid Beheshti University of Medical Sciences (Registration No.: 129).

[Translated from Persian by the Brieflands editorial office.]

2 Revision 1

2 comments · 11 Jan 2021 – 18 Jan 2021

Associate Editor

ACCEPT 11 Jan 2021

Dear EIC,
The authors offered acceptable revision and the manuscript can be considered to accepted paper.
Thanks.

Editor-in-Chief

ACCEPT 18 Jan 2021

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.