OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

International Journal of Endocrinology and Metabolism
Article DOI: 10.5812/ijem.95385
Published in: International Journal of Endocrinology and Metabolism: 17(4); e95385

Peer Review Report for "Systemic Thyroid Hormone Status in Treated Graves' Disease"

Author(s): Fereidoun Azizi, Atieh Amouzegar, Maryam Tohidi, Mehdi Hedayati, Leila Cheraghi, Yadollah Mehrabi

Review Timeline:

Submit Date: 15 Jun 2019
Revised Date: 7 Sep 2019
Accepted Date: 29 Sep 2019

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

16 Jul 2019

Dear AE,
In this survey thyroid hormones and metabolic parameters were compared in 3 different groups of treated Graves' disease.
The following issues should be addressed.
1. Although the title of the study is in line with the main aim, all over the text the authors focused on the metabolic parameters and also the final conclusion in the abstract and at the end of the discussion includes results regarding metabolic parameters, so I think the title and aim should be better to change and cover metabolic parameters.
2. In the abstract Group a should be changed to group 1. Please consider the unification of the terms all over the text e.g Group 1, 2, and 3. And thyroid hormones e.g FT4, ft4, etc.
3. Groups all over the texts are initiated with a small letter of g and should be turned to capital letter G e.g Group 1.
4. Keywords should be reworded bases on Mesh terms.
5. Introduction is well written
6. In the method, please more clarify the recruitment of patients. How the investigator allocated treatment for patients? I mean what criteria were considered to select especial treatment for each patient. Also, clarify if any considerations in selecting treatment could interfere with the outcomes (thyroid or metabolic parameters).

7. Blood pressure was measured, although it was not used in the results !!
8. Smoking status of patients was collected without any use, however, as smoking affects thyroid hormones the results should mention in each group. Also, smoking is better to be used for adjustment in the analysis.
9. Family history of diabetes and medication is of no use, these are mentioned in the method section.
10. In the results, there are 2 mistakes under the section of Association Between Variables, which should be corrected:
“In group 1, age, BMI and serum triglycerides, insulin and HOMA-IR and in the Eu-G group, serum FBS, TRAb, and TSH were correlated with serum T3: T4 ratio. While FBS, TRAb, and TSH concentrations correlated with T3: T4 ratio in groups 2 and 3 (Table 3).”
As referred to “Table 4 shows that the mean T3: T4 ratio was significantly higher in the combined groups 2 & 3 compared to group 1 in the presence of BMI and serum FBS, insulin, triglycerides and TSH.”, however, Table 4 did not express the main point. Please correct Table 4. I think in the second row of Table 4 combined group 2&3 is incorrect and should be changed to mean T3/T4 ratio.
11. TPOAb and smoking both should be adjusted in table 4 as the important parameters found to affect thyroid hormones.
12. In the discussion please justify the difference found in the TPOAb and TRAB among the groups.
13. I cannot understand the use of Table 3 or in other words how Table 3 helped the authors in the obtained results or justifications????
14. Please write the complete terms for GHQ-2.
15. In the discussion at the last sentence of the second paragraph, please change the driving of D3 to T3.
16. Following language editing, some points should be addressed:
a) “Although previsions studies”, previous is correct
b) “ Study patients were aged”
c) “is repotted in Graves”, reported is correct
d) This sentence should be rephrased: “The major strength of the present study is that it is the first study that reports differences in and compares some thyroid-related variables in Graves’ patients on L-T4 treatment, compared to euthyroid Graves’ patients with apparently normal thyroid hormone production”
e) The following term should be identical all over the text: LT4 treated/ treatment/monotherapy/suppressed or L-T4. These identifications should be applied for other terms.
Thanks.

REFEREE: Reviewer | **Revision** (0) 3 Aug 2019

Dear AE,
This is a retrospective study from one center trying to compare markers of thyroid hormone status in treated euthyroid and levothyroxine (LT4) treated hypothyroid Graves’ patients. As the authors mentioned, previous studies compared levels of T4, T3, and andT3/T4 ratio between LT4 treated hypothyroid patients and healthy subjects. Therefore we have

conclusive data in this regard. However, studying specifically a spectrum of graves patients makes this study somewhat novel. The main drawback of this study is retrospective design. However, it provides valuable data, helping clinicians in management of graved disease. Some of my suggestion are given below.

Major comments:

1) I have a concern regarding group 3. I think that the inclusion of patients with a history of radioiodine treatment here can be problematic. It would be better to have only patients with a history of MMI treatment who was on remission. This can totally separate group 3 from group 1.

2) As I mentioned before, this study specifically provided data among Graves patients. I am interested to know the possible role of TRAb in determining the T3/T4 ratio. Was there any significant association in the univariate analysis? Even this is not the case, please discuss it

3) To provide quantitative support for the statements given in lines 228-234, it is better to provide R2 of the model. Moreover having the partial contribution of each variable can be informative as well.

4) Patients in group 2 have a higher T3/T4 ratio than group 3. It seems that higher levels of TRAb may play a role. Regarding my first comment, lower levels of TRAb in group 3 can be explained by the inclusion of patients with a remote history of radioiodine treatment. I think that after the exclusion of this subgroup from group 3, the T3/T4 ratio in group 3 will be raised.

Minor comments:

1) line 88, here subheading is “study design “that seems to be irrelevant regarding the following information.

2) line 104,105, reference number 13 is not correct.

3) table 2, there is no comment regarding the mode of data expression in the footnote.

4) table 4, the variables have no units.

5) table 4, it is better to provide the results of the univariate analysis as well.

Thanks.

REFEREE: Associate Editor | **Revision** (0) 5 Aug 2019

Dear EIC,

Regarding reviewers' comments, the manuscript needs some revisions before considering for publication.

Thanks.

REFEREE: EIC | **Revision** (0) 5 Aug 2019

Dear Author,

Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Response to reviewer 1

1. Thank you for comment. Please note that in addition to metabolic parameters, thyroid function tests, TRAb, TPOAb and anthropometric variables are also included in the results and discussion, therefore, I prefer the present title of the manuscript.
2. Agreed and corrected.
3. Many articles in the literature use small letters for group, class, model etc … in the text.
4. Agreed and corrected.
5. Thank you
6. This is a cross-sectional study in 3 groups of patients with Graves' disease. Criteria for recruitment of patients have been described in lines 86-89. We have added criteria for choice of treatment in lines 90-93.
7. Agreed and omitted.
8. Majority of patients (82%) were female and only 5% gave history of smoking. Therefore smoking status was not used for the adjustment in the analysis; Lines 143-146.
9. Insulin, HOMA-IR and FBS values were associated with serum T3 & T4 ratio. Therefore, we searched for variables related to glucose intolerance.
10. Agreed and corrected. The new paragraph is:
    - Table 5 shows that in the presence of BMI and serum FBS, insulin, triglycerides and TSH, combined group 2 & 3 had a significant positive effect on T3:T4 ratio compared to group; lines 187-8.
11. As written in statistical analysis covariate with a p values less than 0.1 in the univariate analysis were sleeted to be adjusted in the multivariate model. Because smoking & TPOAb had higher p values in univariate analysis, they were not selected for adjusting in Table 4.
12. Agreed and added in Discussion, Lines 207-211.

13. Table 3 describes important point. In group 1 (hypothyroid on levothyroxine therapy) BMI, triglycerides, insulin and HOMA-IR correlate with T3:T4 ratio. This has been discussed in pages 10 and 11 of the manuscript.
14. Added.
15. Diiodinase 3 was used instead of D3.
16. Agreed and corrected. However, "Monotherapy" is used in the discussion, because of its importance in showing difference between L-T4 monotherapy and normal thyroid production of both T4 and T3.

Response to Reviewer 2:

Major comments:

1. Agreed. However, all patients in group 3 are euthyroid, meaning that they have normal thyroid functioning tissue. They also differ from group 1, because they are not taking L-T4. We have added a sentence stating that there was no difference within MMI and RAI treated in group 3, lines 160-162.
2. We found no significant association between TRAb and T3/T4 ratio in univariate analysis. Please note that values for TRAb were taken in euthyroid state and not when patients were hyperthyroid. Explanation was added in Discusion, lines 207-210.
3. Agreed and added.
4. Agreed and was replied in items 1 & 2.

Minor comments:

1. Agreed and omitted.
2. Ref. 13. Added.
3. Added.
4. For association tables, adding units is not necessary.
5. Agreed and added.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) — 22 Sep 2019

Dear AE,
The study is reviewed carefully. According to comments and revisions by the author, this manuscript is accepted.
Thanks

Farhad Hosseinpanah: Reviewer | **Revision** (1) — 29 Sep 2019

Dear AE,
The authors responded to all my questions satisfactorily. I have no further comments.
Thanks.

Hengameh Abdi: Associate Editor | **Revision** (1) — 29 Sep 2019

Dear EIC,
The revised manuscript is acceptable for publication.
Thanks.

Fereidoun Azizi & Dr. Azita Zadeh-Vakili: EIC | **Revision** (1) — 29 Sep 2019

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