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Peer Review Report for "Long-Term Antithyroid Drug Treatment: Trends in Serum TSH and TSH Receptor Antibody Changes in Patients with Graves' Disease"

Author(s): Ken Okamura, Sachiko Bandai, Megumi Fujikawa, Kaori Sato, Hiroshi Ikenoue, Takanari Kitazono

Review Timeline:

Submit Date: 10 Feb 2020
Revised Date: 9 May 2020
Accepted Date: 12 May 2020

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 Feb 2020

Dear AE,
Okamura et al. have studied the trend of changes in serum TSH and TRAb in patients with Graves' disease. This manuscript is an extension of the authors' paper in the Endocrine J. However, the importance of the findings would be interesting to the IJEM readers.
Comments:
1. The length of the introduction should be reduced to two-third.
2. Page 7, Lines 8-12: The list of abbreviations should be deleted. Each abbreviation should be described at its first presentation in the manuscript.
3. Table 1: Please describe A1, A2, B1 … in the footnote.
4. Table 4: Please omit (%) throughout all columns. In the footnote denote "data are n (%)".
5. "Discussion" is too lengthy. Please shorten it to one half or as much as you could, without omitting important points.
6. Please add "limitations of the study" at the end of your "Discussion".
Thanks.

REFEREE: Reviewer | **Revision** (0) 16 Feb 2020

Dear AE,
The manuscript entitled “Long-term ATD treatment-Trend of changes in serum TSH and TRAb in patients with Graves’ disease” was reviewed. Please the authors address the following comments:
Abstract:
- The section of “Methods” in the abstract should be rephrased.
Introduction:
- Page 5, lines 9-10: It is not appropriate to cite 16 references for two sentences.
- Page 5, paragraph 2 and page 6, paragraph 1: There are no references.
- Page 6, lines 14-15: The statement is not clear.
- Some parts of the “Introduction” section should be replaced by an overview of findings of other studies regarding TSH and TRAb changes.
- There is no need to include a list of abbreviations.
Methods:
- Page 8, lines 11-18: Please mention numbers (percent) of each group.
- Reference ranges of laboratory measurements should be included.
- Please include a statement regarding the informed consent of the study population.
- The section of statistical analysis is incomplete.
Results:
- Please include numbers of figures in each figure file.
- Tables 1 and 4: Please describe the meaning of arrows used in the tables in their footnotes.
Discussion:
- Overall, the “Discussion” section should be summarized and more structured.
- Page 18: Authors talk about the use of RAIU for evaluation of the thyroid stimulation status; would this test be reliable in the setting of ATD therapy?
- Page 26, the second paragraph: Explaining KI therapy in this study is not relevant.
- Page 26, the last paragraph: I think some sentences should be deleted.
- Authors should explain the strengths and limitations of their study.
- The manuscript should be edited critically for English grammar.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 22 Feb 2020

Dear EIC,
Based on the reviewers' comments, the manuscript needs minor revision.
Regards

REFEREE: EIC | **Revision** (0) 22 Feb 2020

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.

International Journal of Endocrinology and Metabolism

Manuscript ID: 101139

Title: Long-term antithyroid drug treatment - Trend of changes in serum TSH and TRAb in patients with Graves' disease

Title was changed to: Long-term antithyroid drug treatment: Trends in serum TSH and TRAb changes in patients with Graves' disease

Response to Reviewer 1:

Thank you very much for your valuable comments. The manuscript was re-written as you suggested. The title was slightly changed by the advice of our English editor. There was difficulty in changing Excel file to Word file for the Tables, Therefore, Tables were changed deleting former Table 3.

Reviewer 1:
Okamura et al. have studied trend of changes in serum TSH and TRAb in patients with Graves' disease. This manuscript is an extension of authors' paper in the Endocrine J. However, because of importance of the findings would be interesting to the IJEM readers.

1. The length of introduction should be reduced to two third.

The introduction was re-written according to the advice by Reviewer 2.

2. Page 7, Lines 8-12: The list of abbreviations should be deleted. Each abbreviation should be described at its first presentation in the manuscript.

Was there a list of abbreviation in our final manuscript? We deleted the explanation of Group A1 – C from the manuscript.

3. Table 1: Please describe A1, A2, B1 … in the footnote.

Group A1 – C was described in the footnote of Table 1.

4. Table 4: Please omit (%) throughout all columns. In the footnote denote “data are n (%)”.

We omitted (%) in the columns.

5. “Discussion” is too lengthy. Please shorten it to one half or as much as you could, without omitting important points.

We shortened the discussion,

6. Please add “limitations of the study” at the end of your “Discussion”.

We added limitation of the study at the end of discussion, Page 18, Line 11.

Thank you very much for your comments.

Response to Reviewer 2:

Thank you very much for your valuable comments. The manuscript was re-written as you suggested. The title was slightly changed by the advice of our English editor. There was difficulty in changing Excel file to Word file for the Tables, Therefore, Tables were changed deleting former Table 3..

Reviewer 2:
The manuscript entitled “Long-term ATD treatment-Trend of changes in serum TSH and TRAb in patients with Graves’ disease” was reviewed. Please address the following comments:

Abstract:
The section of “Methods” in the abstract should be rephrased.

Methods in the abstract was rephrased in Page 3, Line 4 as :

Methods: In 609 GD patients initially treated with 15 mg of methylmercaptoimidazole (MMI), the changes in serum TSH Receptor Antibody (TRAb) and long-term prognosis were compared in the TSH-normalized group (A) and the TSH-suppressed group (B,C) during the initial 180 days of treatment.

Introduction:
Page 5, lines 9-10: It is not appropriate to cite 16 references for two sentences.

Although we quoted 16 references in the manuscript we sent to Prof Azizi, we extensively re-written the manuscript excluding these references in the final manuscript we sent to the Journal. These 16 references were deleted.

Page 5, paragraph 2 and page 6, paragraph 1: There are no references.

Is the page number included the title page? In our final manuscript, we quoted the reference (#5 in the previous manuscript).

Page 6, lines 14-15: The statement is not clear.

In our final manuscript sent to your Journal, Page 6, line 14-15 was about statistical analysis. Which statement do you mean? If this statement is about the adherence to ATD, we could not rule out the possibility that some of the patients did not take ATD regularly.

Some parts of the “Introduction” section should be replaced by an overview of findings of other studies regarding TSH and TRAb changes.

Introduction was re-written, overviewing the studies regarding TSH and TRAb changes.

There is no need to include a list of abbreviations.

Explanation of Group A-C was deleted from the manuscript and explained in the footnote of Table 1.

Methods:
Page 8, lines 11-18: Please mention numbers (percent) of each group.

It may be Page 7, lines 7 – 18 in our final manuscript. Numbers (percent) of each group was written in the results, Page 9, Line 15 – Page 10, Line 8 of the revised manuscript including title page.

Reference ranges of laboratory measurements should be included.

Reference ranges of laboratory measurements were written in Page 8, Line 14 – 16 of the revised manuscript including title page.

Please include a statement regarding informed consent of the study population.

A statement regarding informed consent of the study population was written in Page 9, Line 7 – 9 of the revised manuscript including title page.

The section of statistical analysis is incomplete.

The section of statistical analysis was re-written in Page 8, Line 18 – Page 9, Line 5 of the revised manuscript including title page.

Results:
Please include numbers of figures in each figure file.

Number of figure was written in Figure 1.

Tables 1 and 4: Please describe meaning of arrows used in the tables in their footnotes.

Table 1, 2, 3, arrows were replaced by the explanation words within the table.

Discussion:
Overall, the “Discussion” section should be summarized and more structured.

Discussion was extensively shortened.

Page 18: Authors talk about use of RAIU for evaluation of the thyroid stimulation status; would this test be reliable in the setting of ATD therapy?

If the patients enter true remission, every step of thyroid hormone synthesis may become normal including NIS. In our previous experience reported 28 years ago (Ref 13 in revised manuscript), the most sensitive predictor of relapse was RAIU. RAIU should be evaluated considering the serum level of TSH (Ref 20 in revised manuscript). In that sense, T3 suppression test may be useful. High uptake even when serum TSH level is suppressed may be a good marker of thyroid stimulation or abnormal thyroid autoregulation, although RAIU is time-consuming using RAI and influenced by iodine intake. Thionamide drugs are not considered to affect NIS function and are used to measure tissue/serum ratio of iodide to evaluate transport activity. Therefore, we believe that high RAIU (if examined), is a reliable marker that the possibility of remission

is low.

Page 26, the second paragraph: Explaining about KI therapy in this study is not relevant.

Our final manuscript sent to your journal was 18 pages without title and references. We believe that KI therapy without severe side effect may be useful for the KI-sensitive GD patients especially for the long-term treatment. However, the discussion about KI therapy was deleted as you suggested.

Page 26, the last paragraph: I think some sentences should be deleted.

The sentences were deleted.

Authors should explain strengths and limitations of their study.

Limitation of the study was explained in the last part of discussion, Page 18, Line 11.

The manuscript should be edited critically for English grammar

The manuscript was edited for English grammar.

Thank you very much for your comments.

Associate Editor's Comments:

Associate Editor 1:
Dear E.I.C
Greetings!

Based on the reviewers comments, the manuscript needs minor revision.
Regards

EIC Decision:

The manuscript needs revision.

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.

Hengameh Abdi: Reviewer | **Revision** (1) 27 Apr 2020

Dear AE,
I read the revised manuscript; some minor amendments are required:
1) Abstract: Please add a summarized description of the study aim in the section of background.
2) Methods: Page 6, line 14, "the thyroid volume 5-20 mL" should be deleted; Line 15, please add units of Tg Ab and TPOAb measurements.
3) Please define the ablative therapy in your study; radioiodine therapy or thyroidectomy?
4) Considering my previous comment, the STRENGTHS and LIMITATIONS of the study should be explained in a separate paragraph before the conclusion paragraph.
Thanks.

REFEREE: Reviewer | **Revision** (1) 28 Apr 2020

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

REFEREE: Associate Editor | **Revision** (1) 28 Apr 2020

Dear EIC
The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.
Kind regards,

REFEREE: EIC | **Revision** (1) 28 Apr 2020

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 (2)

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 Reviewers' Comments:

Reviewer 2: Thank you very much for the comments.
1) Abstract: Please add a summarized description of the study aim in the section of background.

The study aim was added to the background of Abstract, as written in Page 3, Line 2. "Trends in serum TSH and TRAb changes during antithyroid drug treatment and long-term prognosis were evaluated in Graves' hyperthyroidism (GD)."

2) Methods: Page 6, line 14, "the thyroid volume 5-20 mL" should be deleted; Line 15, please add units of Tg Ab and TPOAb measurements.

As you suggested "the thyroid volumne 5-20mL" was deleted. Since Tg-Ab or thyroid microsomal antibody was measured by haemagglutination method, unit was expressed as dilution, as written Page 8, Line 15. "anti-Tg or antithyroid microsomal antibody measured by haemagglutination <100 dilution."

3) Please define the ablative therapy in your study; radioiodine therapy or thyroidectomy?

The ablative therapy was defined as "radioiodine therapy or thyroidectomy" (Page 11 Line 10)
4) Considering my previous comment, the STRENGTHS and LIMITATIONS of the study should be explained in a separate paragraph before the conclusion paragraph.

The strengths and limitations of the study was written in a separate paragraph before the conclusion paragraph (Page 18, Line 9-11).

"The strength of this study is a long-term follow up of a large number of GD patients but the study is limited by the fact that about 30% of the patients dropped out

during the course.”

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Revision (2)

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

REFEREE: Reviewer | **Revision** (2) 12 May 2020

Dear AE,
The revised manuscript is acceptable for publication in the IJEM.
Thanks.

REFEREE: Associate Editor | **Revision** (2) 12 May 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: EIC | **Revision** (2) 12 May 2020

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