OPEN PEER REVIEW

Open Peer Review (OPR)

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- 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

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Peer Review Report for "Remission Rate of Graves' Disease and the Trend of Changes in Serum TSH Receptor Antibodies in Prolonged Antithyroid Drug Treatment"

Author(s): Danilo Villagelin, Roberto Bernardo Santos, João Hamilton Romaldini

Review Timeline:

Submit Date:	10 Feb 2020
Revised Date:	16 May 2020
Accepted Date:	18 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)

3 Mar 2020

Dear AE,
In this manuscript the trend of changes in serum TSH and TRAb in Graves' disease: was reviewed focusing on two aspects of treatment with anti-thyroid drugs: the impact of using anti-thyroid drugs for more than 12-18 months on remission rates and the course of TRAb during prolonged anti-thyroid treatment.
Following points should be addressed by the authors:
- The title is better to be changed "Trend of changes in serum TSH and TRAb in Graves' disease:Treated and untreated" as the authors reviewed the trend of the disease not TSH and also in treated patients; what do the authors mean by assessing trend in untreated Graves????
- In method please clarify the years in which the authors search the subject.
- Please indicate the limitations of your study e.g. the difference in laboratory measurements techniques etc.
Thanks.

Hengameh Abdi: Reviewer | Revision (0)

7 Apr 2020

Dear AE,
The manuscript entitled "Trend of changes in serum TSH and TRAb in Graves' disease: Treated and untreated" was reviewed. My primary concern about this review article is the mismatch present between its title and its aims and the evidence acquisition; firstly, there is no information about the TSH trend throughout the manuscript. Second, using the terms "treated and untreated" is not appropriate. Please match the title with the aims mentioned in the manuscript. Moreover, aims noticed in the section of "Introduction" should be the same as mentioned in the section of "Abstract".
Other comments for the authors are as follows:
1) Abstract: "Context" should be summarized". The section of "Evidence Acquisition" should be revised and include a summarized explanation about the search strategy.
2) The main text of your manuscript should include sections of "Context", "Evidence Acquisition", "Results" and "Conclusions".
3) The section of "Introduction" should be summarized. Some data can be transported to the section of "Results".
4) Page 4, paragraph 2: There are no references for the statements.
5) Page 7: Paragraphs 1 & 2 are related to findings of one study and can be merged in one paragraph.
6) Please cite to the original study related to the Figure 1 in its footnote.
7) I suggest a more comprehensive review to find studies related to changes in TRAb during and after ATD therapy for Graves' disease. Moreover, please organize the section of "Results" for two aims of "the effect of duration of ATD therapy on relapse rate" AND "trend of changes in TRAb in different treatment states".
8) The manuscript needs English grammar editing.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 7 Apr 2020

Dear EIC,
The authors should address the reviewers' comments.
Thanks.

REFEREE: Reviewer | **Revision** (0) 8 Apr 2020

Dear AE,
My comments regarding the manuscript entitled "Trend of changes in serum TSH and TRAb in Graves' disease: Treated and untreated" are as follows:
1) Abstract: The "Context" section is too long. "Methods" is a repetition of the study aim; authors should summarize their study methods mentioned in page 7.
2) Line 68: Add TSH receptor antibodies (TRAb).
3) Please provide references for paragraph 2 of the "Introduction".
4) Change the heading of "Discussion" to "Results".
5) Please consider dividing the "Results" section to few subheadings such as "Autoimmune system and ATD treatment", "Serum TRAb during ATD therapy", "TRAb prediction of remission of GD", etc.
6) Line 197: The statement "approximately 10% of patients will remain TRAb positive after

five years of treatment." may not be correct. I recommend authors to study deeply the following references: PMID: 27521067; PMID: 16571093; PMID: 16187913;
it seems that after 12-18 months of ATD therapy, 24% have persistently elevated (>10 U/L), 64% have TRAb levels of 1.5-10 U/L and <20% have negative TRAb. In addition, according to another study (PMID: 31310160), after long term (>60 months) ATD therapy, normal TRAb is seen in majority of patients.
7) References should be arranged according to “instructions for authors” of the International Journal of Endocrinology and Metabolism.
8) I recommend changing the title of the article to "Trend of changes in serum TSH receptor antibodies during and after treatment with antithyroid drugs".
Thanks.

REFEREE: EIC | **Revision** (0) 8 Apr 2020

Dear Author,
Please address the reviewers' comments carefully.
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.

Reviewers' Comments:

Reviewer 1:
My comments regarding the manuscript entitled "Trend of changes in serum TSH and TRAb in Graves' disease: Treated and untreated" are as follows

:
1) Abstract: The "Context" section is too long. "Methods" is a repetition of the study aim; authors should summarize their study methods mentioned in page 7

We agree and correct de abstract, please see new abstract

.
2) Line 68: Add TSH receptor antibodies (TRAb).

We corrected the sentence, please see line 70

3) Please provide references for paragraph 2 of the "Introduction".
We corrected the paragraph, adding the references 2-4.

4) Change the heading of "Discussion" to "Results".

We altered the heading.

5) Please consider dividing the "Results" section to few subheadings such as "Autoimmune system and ATD treatment", "Serum TRAb during ATD therapy", "TRAb prediction of remission of GD", etc.

We inserted subheadings: *Serum TRAb during ATD therapy and* Prolonged

treatment (more than 18 months) and the impact on remission rates

6) Line 197: The statement "approximately 10% of patients will remain TRAb positive after five years of treatment." may not be correct. I recommend authors to study deeply the following references: PMID: 27521067; PMID: 16571093; PMID: 16187913;
it seems that after 12-18 months of ATD therapy, 24% have persistently elevated (>10 U/L), 64% have TRAb levels of 1.5-10 U/L and <20% have negative TRAb. In addition, according to another study (PMID: 31310160), after long term (>60 months) ATD therapy, normal TRAb is seen in majority of patients.

Thank you for the important commentary. After reviewing the three articles and the hyperthyroidism guideline from the American Thyroid Association, we summarize our impression

TRAb titers usually decline during anti thyroid drugs treatment. This is the rationale after 12-18 months measurement TRAb before anti thyroid drugs treatment stop. Azizi (2019) suggested the patients with higher TRAb titers, after approximately four years had higher chances of relapse. Quadbeck (2005) reported approximately 10% of patients with TRAb titers with twice the reference range after antithyroid drug treatment. Carella studied 58 patients after anti thyroid drug treatment and a higher percentage of patients with TRAb positive.

However, Bandai 2019, studied more than 500 patients and demonstrated 10% of patients will remain with TRAb titers positive after a long period.

7) References should be arranged according to “instructions for authors” of the International Journal of Endocrinology and Metabolism.

Ok, we corrected.

8) I recommend changing the title of the article to "Trend of changes in serum TSH receptor antibodies during and after treatment with antithyroid drugs".

We appreciated the comment and change the article title.

Reviewer 2:
The manuscript entitled "Trend of changes in serum TSH and TRAb in Graves’ disease: Treated and untreated" was reviewed. My primary concern about this review article is the mismatch present between its title and its aims and the evidence acquisition; firstly, there is no information about the TSH trend throughout the manuscript. Second, using the terms "treated and untreated" is not appropriate. Please match the title with the aims mentioned in the manuscript. Moreover, aims noticed in the section of "Introduction" should be the same as mentioned in the section of "Abstract".

We appreciated the comment and change the article title and corrected the abstract

Other comments are as follows:
1) Abstract: "Context" should be summarized". The section of "Evidence Acquisition" should be revised and include a summarized explanation about the search strategy.

We are grateful for the comment, we correct including the period of search and types of study.

2) The main text of your manuscript should include sections of "Context", "Evidence Acquisition", "Results" and "Conclusions".

Ok, we modified the sections.

3) The section of "Introduction" should be summarized. Some data can be transported to the section of "Results".

We summarize the introduction

4) Page 4, paragraph 2: There are no references for the statements.

We corrected the paragraph, adding the references 2-4.

5) Page 7: Paragraphs 1 & 2 are related to findings of one study and can be merged in one paragraph.

We corrected the paragraph, please see line 152-164.

6) Please cite to the original study related to the Figure 1 in its footnote.

We add the references in the footnote.

7) I suggest a more comprehensive review to find studies related to changes in TRAb during and after ATD therapy for Graves' disease. Moreover, please organize the section of "Results" for two aims of "the effect of duration of ATD therapy on relapse rate" AND "trend of changes in TRAb in different treatment states".

We inserted subheadings: *Serum TRAb during ATD therapy and* Prolonged treatment (more than 18 months) and the impact on remission rates.

Also a new review was performed.

8) The manuscript needs English grammar editing.

We performed an English grammar review.

Reviewer 3:
In this manuscript the trend of changes in serum TSH and TRAb in Graves' disease: was reviewed focusing on two aspects of treatment with anti-thyroid drugs: the impact of using anti-thyroid drugs for more than 12-18 months on remission rates and the course of TRAb during prolonged anti-thyroid treatment.
Following points should be addressed
The title is better to be changed "Trend of changes in serum TSH and TRAb in Graves' disease:Treated and untreated" as the authors reviewed the trend of the disease not TSH and also in treated patients; what do the authors mean by assessing trend in untreated Graves????

We appreciated the comment and change the article.

In method please clarify the years in which the authors search the subject.

We inserted the period of the review was done.

Please indicate the limitations of your study e.g. the difference in laboratory measurements techniques etc.

Thank you for the important comment, we add a paragraph regarding limitations. Please see line

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) — 12 May 2020

Dear AE,
Authors have revised the manuscript according to my comments. It is acceptable for publication.
Thanks.

Ladan Mehran: Reviewer | **Revision** (1) — 12 May 2020

Dear AE,
The authors addressed all comments, They just should use trend all over the text instead of course.
Thanks.

REFEREE: Reviewer | **Revision** (1) — 12 May 2020

Dear AE,
Authors have considered all of my comments correctly.
Thanks.

REFEREE: Associate Editor | **Revision** (1) — 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** (1) — 12 May 2020

Dear Author,
The revised manuscript is preliminary acceptable for publication in the IJEM.
- One minor point is that the article title in the journal site has not been modified. Please consider this issue and change the title as follows:
"Trend of changes in serum TSH receptor antibodies during and after treatment with antithyroid drugs"
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.

Reviewers' Comments:

Reviewer 1:
Authors have revised the manuscript according to my comments. It is acceptable for publication.

Reviewer 2:
The authors addressed all comments
Please use trend all over the text instead of course.

We use the word “trend” instead of the word “course”, it is signaled in red

Reviewer 3:
Authors have considered all of my comments correctly.

OPEN PEER REVIEW

Revision (2)

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

REFEREE: EIC | **Revision** (2) 18 May 2020

Dear Author,
You have not replied to the EIC comment regarding change of the article title; however, there is no problem, we can correct the title during the article proofreading. If you are not agreed with the new suggested title mentioned in the previous e-mail, please e-mail us as soon as possible.
The revised manuscript is acceptable for publication.
Thanks.