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# Peer Review Report for "Effect of Correction of Hyperthyroidism with Anti-thyroid Drugs on the Glycated Hemoglobin in Non-diabetic Patients with Primary Hyperthyroidism"

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## Review Timeline:

Submit Date: 26 May 2020
Revised Date: 11 Nov 2020
Accepted Date: 12 Dec 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)

28 Jul 2020

Dear AE,
The manuscript entitled "Effect of Correction of Hyperthyroidism with Anti-thyroid Drugs on the Glycated Hemoglobin in Non- diabetic Patients with Primary Hyperthyroidism" was reviewed. Overall, the manuscript can be considered for publication after revision only as a brief report. My comments are as follows:
- Abstract, Methods: Please mention number of patients.
- Background: The first paragraph should be revised. Five references have been cited for 4 sentences about general and unspecified facts.
- The section of statistical analysis should be completed especially regarding the explanation about the determination of sensitivity/specificity.
- Results, page 7, 3rd paragraph: Please change as follows: 100 ≤ FPG < 126 and 140 ≤ 2-hour OGTT plasma glucose < 200 mg/dL.
- Table 1: Check T3 and T4 units and unify them with the table footnote and in the whole manuscript.
- All abbreviations should be completely written in their first appearance in the manuscript.

- References should be updated.
Thanks.

**Fereidoun Azizi**: Reviewer | **Revision (0)** 26 Aug 2020

Dear AE,
Major Comment:
1. Lack of control group has been unenviable in this study because it was unethical to keep a group of hyperthyroid patients without antithyroid drug therapy. However, authors should add information in FPG, 2hr PG, and glycated hemoglobin in the adult population in their province (or at least in their country).
2. Values for serum T3 are incorrect throughout text and tables; they may be in nmol/l and not ng/dl. Normal serum T3 is 1.1-2.9 nmol/l equal to 70-190 µg/dl, the conversion factor is 0.01129. The same mistake may be pertinent with serum T4 values.
Other Comments:
3. Please convert all serum T4 values to µg/dl and all serum T3 values to ng/dl throughout the text and tables.
4. Abstract, conclusions: Since you have not studied patients with dysglycemia, this statement should be changed.
5. Page 5: Please add laboratory methods for measurement of T4, T3, and TSH and supply CV of all laboratory measurements.
6. Page 6, line 16: Use “weight” instead of “body mass”.
7. Page 7, para 1: It is advisable to compare baseline FPG, 2hr PG, and HBA1c of hyperthyroid patients with values in a group of normal (as requested in comment No. 1).
8. Page 7, Para 3: Please add sensitivity and specificity in normal adults, as well.
9. Page 9, para 1 and 2: There is no need to repeat data of the “results” section; discuss the overall importance of findings and compare those to those of literature.
10. Page 10: Before the conclusion, the authors should provide the “limitations” of this study.
11. Table 1: Values of T4 and T3 should be corrected (see comment No. 2).
12. Table 2: Please add values in normal controls (see comment 7).
Thanks.

**REFEREE**: Reviewer | **Revision (0)** 1 Sep 2020

Dear AE,
Title: Effect of Correction of Hyperthyroidism with Anti-thyroid Drugs on the Glycated Hemoglobin in Non- diabetic Patients with Primary Hyperthyroidism
There are some comments which should be addressed by the author:
1. This is a before-after intervention study on 36 participants. From the design point of view, the main shortcoming of the study is that it has no control group. So, one cannot make sure that the observed change in HbA1c is solely due to the administered treatment.
2. The data have been analyzed using paired t-test or its Nonparametric equivalent, Wilcoxon test. Since weight and BMI had a sharp and significant increase during the follow-up period (Table 1), it is recommended to eliminate the effect of their variation on the parameters that appeared in table 2. This can be done using regression analysis or repeated measures ANOVA adjusted for these and other potential confounding variables such as

age.

3. Results section, 2nd paragraph says: Patients were re-assessed 3 months or more after they initially became euthyroid. Please report the mean or preferably median of the total follow-up period.

Thanks.

**REFEREE**: Associate Editor | **Revision** (0)

22 Sep 2020

Dear EIC,

The manuscript needs to be changed according to the comments of the reviewers before the final decision.

Thanks.

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

23 Sep 2020

Dear Author,

The manuscript needs revision before it can be accepted for publication.

Thanks.

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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.

Reply to Reviewer :

Reviewer 1:

Major Comment:

Q1. **Lack of control group has been unenviable in this study, because it was unethical to keep a group of hyperthyroid patients without antithyroid drug therapy. However, authors should add informations in FPG, 2hr PG and glycated hemoglobin in adult population in their province (or at least in their country).**

Ans 1 :We have selected hyperthyroid patients with non-diabetic fasting and post OGTT glucose to determine their HbA1c. It therefore would make little sense to compare them to data in General Indian Population many of whom may be diabetic. We have therefore included a study from India which reported HbA1c in Indians with **normal fasting glucose**. On page 9 under discussion – following line has been added :

“The HbA1c in our patients with non-diabetes range glucose values during the phase of hyperthyroidism was 5.2 ±0.37 %. In a comparable study from general Indian population, the HbA1c in healthy patients with normal fasting glucose was slightly higher at 5.4 ± 0.04% .

In the present study, while there was an increase in the HbA1c to 5.35 ±0.45% ( a closer approximation to the values found in euglycemic general Indian population noted above) , following the correction of hyperthyroidism , there were no corresponding changes in the mean fasting and the 2hr post OGTT plasma glucose.”

Glucose values in the above cohort were not reported as by definition they were normal. These values in normal population were presented in discussion, rather than in results because of copyright issues.

Following reference has been added for this info :

24. Nair M, Prabhakaran D, Venkat Narayan KM, Sinha R, Lakshmy R, DevasenapathyN et al.HbA1c values for defining diabetes and impaired fasting glucose in Asian Indians. Prim Care Diabetes.2011; 5: 95-102

Q2. **Values for serum T3 are incorrect throughout text and tables; they may be in nmol/l and not ng/dl. Normal serum T3 is 1.1-2.9 nmol/l equal to 70-190 µg/dl, the conversion factor is 0.01129. The same mistake may be pertinent with serum T4 values.**

A2. These have been corrected in text and tables. Changes have been highlighted in red.

Q3. **Please convert all serum T4 values to µg/dl and all serum T3 values to ng/dl throughout the text and tables.**

Ans 3. It has been done. Changes highlighted in red.

4. **Abstract, conclusions: Since you have not studied patients with dysglycemia, this statement should be changed.**

Ans 4: That line has been removed.

5. **Page 5: Please add laboratory methods for measurement of T4, T3 and TSH and supply CV of all laboratory measurements.**

Ans 5. Table 1 containing necessary details as above has been added on page no. 4

Q6. **Page 6, line 16: Use "weight" instead of "body mass".**

Ans 6. Change has been made.

Q7. **Page 7, para 1: It is advisable to compare baseline FPG, 2hr PG and HBA1c of hyperthyroid patients with values in a group of normal (as requested in comment No. 1).**

Ans 7 : This has already been answered – see Ans 1.

Q8. **Page 7, Para 3: Please add sensitivity and specificity in normal adults, as well.**

A8. Data can be added to discussion only and not in results on account of copyright infringement. HbA1c sensitivity and specificity in euthyroid controls has been added from reference no. 24 on page 11.

> The somewhat disappointing sensitivity of 50% and specificity of 78% for detection of prediabetes by HbA1c reported even after restoration to the euthyroid state is comparable to that reported by Nair et al[24] from the general Indian population for the detection of prediabetes ( impaired fasting glucose) of only 59.7% and specificity of 59.9%.

Q9. **Page 9, para 1 and 2: There is no need to repeat data of "results" section; discuss overall importance of findings and compare those to those of literature.**

A9. Results have been removed except for those needed to compare with other studies in literature

Q10. **Page 10: Before conclusion, authors should provide “limitations” of this study.**

A10. Has been done. Page 11

11. **Table 1: Values of T4 and T3 should be corrected (see comment No. 2).**

A11. Has been done

Q12**. Table 2: Please add values in normal controls (see comment 7).**

A12. We have not studied normal controls. Data from other studies cannot be added to table as it would violate copyright. Value of HbA1c in euthyroid Indians with normal fasting has been added to the paragraph in discussion. Please see Answer 1.

Reviewer 2:

The manuscript entitled "Effect of Correction of Hyperthyroidism with Anti-thyroid Drugs on the Glycated Hemoglobin in Non- diabetic Patients with Primary Hyperthyroidism" was reviewed. Overall, the manuscript can be considered for publication after revision only as a brief report.

My comments are as follows:

Q1- **Abstract, Methods: Please mention number of patients.**

A1This has been done. It is highlighted in red under methods in abstract

Q2- **Background: The first paragraph should be revised. Five references have been cited for 4 sentences about general and unspecified facts.**

A2.References have been removed. This section has been suitably pruned.

Q3- **The section of statistical analysis should be completed especially regarding explanation about determination of sensitivity/specificity.**

- A3. Details about calculation of sensitivity and specificity along with formula provided in methods – page no. 6- highlighted in red.

  Q4 - **Results, page 7, 3rd paragraph: Please change as follows: 100 ≤ FPG < 126 and 140 ≤ 2-hour OGTT plasma glucose < 200 mg/dL.**
- A4. Changes as suggested done on page no.7 and highlighted in red.
- Q5. **Table 1: Check T3 and T4 units and unify them with the table footnote and in the whole manuscript.**
- A5. Has been done- highlighted in red.

  Q6**. All abbreviations should be completely written in their first appearance in the manuscript**.
- A6- Has been done

  Q7**. References should be updated.**
- A7. Reference 24 added. Some earlier references removed. No new study related to present topic in current literature.

  Reviewer 3:

  Title: Effect of Correction of Hyperthyroidism with Anti-thyroid Drugs on the Glycated Hemoglobin in Non- diabetic Patients with Primary Hyperthyroidism

  1. **This is a before after intervention study on 36 participants. From the design point of view, the main shortcoming of the study is that it has no control group. So, one cannot make sure that the observed change in HbA1c is solely due to the administered treatment.**

Ans 1 : It would be unethical to have a control group , that has not been treated for hyperthyroidism , in order that the effect of hyperthyroidism treatment can be isolated out and demonstrated. We have acknowledged this in the limitations of the study.

. However the only thing that changed for these patients was that they were treated with thyroxine. Patients were non-diabetic – so they did not receive any advice on diet ,exercise or lifestyle modification; nor did they receive any anti-diabetic medication. Indeed even their glucose levels did not change. As HbA1c depends on both glucose levels and RBC turnover, and since there was no change in the former; it must have been the latter i.e RBC turnover that changed ( got reduced).This is further evident in the rise in Hemoglobin.

2**. The data have been analyzed using paired t-test or its Nonparametric equivalent, Wilcoxon test. Since weight and BMI had sharp and significant increase during the follow-up period (table 1), it is recommended to eliminate the effect of their variation on the parameters appeared in table 2. This can be done using regression analysis or repeated measures ANOVA adjusted for these and other potential confounding variables such as age.**

**A2.** Following line added to para 3 of page 7 :

"Age of the patients or changes in hemoglobin levels , T4 or body weight were not independent determinants of change in HbA1c ,on multiple linear regression analysis".BMI was not tested separately from weight as its formula is weight / (height)$^2$. Since height is not varying in adults between baseline and final assessment, therefore the variation in BMI is entirely due to and is already reflected in the variation in weight.

3. **Results section, 2nd paragraph says: Patients were re-assessed 3 months or more after**

**they initially became euthyroid. Please report the mean or preferably median of total follow-up period.**

A3. Following line added to last paragraph of page 6 "Patients were documented to have become nearly euthyroid at a median of 96 days (8 days interquartile range) from recruitment, initial baseline sampling and the commencement of carbimazole treatment. Patients were re-assessed a further median 129 days (interquartile range of 46 days) after they initially became euthyroid".

## 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) — 21 Nov 2020

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

**REFEREE**: Reviewer | **Revision** (1) — 5 Dec 2020

Dear AE,
Regarding the manuscript of "Effect of Correction of Hyperthyroidism with Anti-thyroid Drugs on the Glycated Hemoglobin in Non- diabetic Patients with Primary Hyperthyroidism" with thanks to the authors, they have answered questions raised by me and corrected sections that I asked in my previous review of the manuscript.
Thanks.

**REFEREE**: Associate Editor | **Revision** (1) — 8 Dec 2020

Dear EIC,
The manuscript is suitable to be accepted.
Thanks.

**Fereidoun Azizi & Dr. Azita Zadeh-Vakili**: EIC | **Revision** (1) — 12 Dec 2020

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