Author's response to reviews

Title: Association between lipids profile and thyroid parameters in euthyroid diabetic subjects: A cross-sectional study

Authors:

Yun ZHANG (wing.1120@163.com)
Ping LU (luping.henan@gmail.com)
Ling ZHANG (zhanglingvip@126.com)
Xinhua XIAO (xiaoxinhua@medmail.com.cn)

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Author's response to reviews: see over
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Dear editor,

Great thanks to you for the time and effort you expend on this paper and important and helpful comments, which makes the manuscript more interesting and informative. We have modified our paper after thinking and discussing your comments. This is our responses (in **BOLD** type). The page and line numbers refer to our revised manuscript.
Referee 1:

Specific comments:
1. Is this a real prospective study? Then why only 106 out of 389 cases had anti-TPO antibody determined?
   Response: This is just a cross-sectional study as described in the manuscript. All the subjects came from inpatients of our department. They were admitted to hospital for diabetes and not all of them wanted to get the information of anti-TPO antibody. So anti-TPO antibody was determined in only 106 of all the 389 cases.

2. Because the purpose of this study is to find one or even more, of the parameters, and finally see the influence of TSH levels in euthyroid type 2 diabetes, it will be very important to tell the readers how the normal range is obtained, and how about the inter-assay and intra-assay of each parameters they determined.
   Response: Our department routine determined more than 200 samples for TSH every day (from patients with hyperthyroidism, hypothyroidism and other patients). The normal range came from 1,000 normal controls determined at first. And the inter-assay and intra-assay imprecisions (CV) were all less than 5%. This data had been added at line 11-13, page 6.

3. If there is no statistically significance, it is not necessary to write out the result, then say the difference is not significant.
   Response: Although there is no statistically significance between the seropositive and seronegative groups, the result could reflect a tendency of major cardiovascular risk factors affected by anti-TPO antibody. So we keep this result in the manuscripts.

4. Only female had relation of TSH levels with total cholesterol in euthyroid type 2 DM is the final results, then the authors should have more strong evidence to convince the readers. Maybe it just occurs due to random occurrence of statistics of so many items.
   Response: Yes we only found a relation of TSH levels with total cholesterol in 128
euthyroid diabetic females. In the revised manuscript, another 32 euthyroid diabetic females (25 percent of formal subjects) were recruited. And the association was still exist and more significant (P=0.005). So we believe that our results have certain significance. And several larger studies in general population also reported sex difference about the associations of TSH with coronary heart disease mortality. The HUNT study reported positive and linear associations of TSH levels within the reference range with coronary heart disease mortality in Norwegian women but not men (Asvold BO, Arch Intern Med 2008,168:855-860). Onat A also reported that TSH levels within normal range, low due to partial assay failure, might manifest as independent predictors of incident CHD, particularly in middle-aged men (Onat A, Endocrine 2014; May 3 [Epub]). Of course this is still a small cross-sectional study. And we call for further investigations to confirm this association.

5. Pearson is the inventor's name of this statistical method. Pearson correlation test is correct, instead of pearson correlation tests.

Response: Yes it has been correct in the revised manuscript. Thanks a lot for your advices.

6. The first paragraph of Discussion is too long.

Response: We have divided it into three paragraphs in the revised manuscript.
Referee 2:

Specific comments:

6. Authors did not care to specify the direction of the association between TSH and TC which seems to be a positive one as may be deduced from the Results.

Response: We gave $\beta$ value in the “Results” paragraph in the manuscript. And we have added this information in the Tables in the revised manuscript.

7. Ascribing the stated association to the postmenopausal state is too general, vague and the analogy of association between subclinical hypothyroidism and MetS is far from convincing to be applicable to euthyroid diabetic women. Authors might consult the paper (Onat A, Endocrine 2014; May 3 [Epub]) wherein evidence was presented that TSH may sustain damage in oxidative stress, escape partly from immunoassay and the ensuing autoimmune activation may lead to CHD risk.

Response: Thanks very much for your comments. It is very helpful for us. We have read the paper by Onat A carefully and revised our manuscript. (Page 9, Paragraph 2)

8. Rather than providing the p values of the correlations, it is more informative to provide the coefficients, preferably both values, because the direction of the coefficient may be either positive or inverse with the same p-value.

Response: We have added this information in all the tables.

9. A trend of correlation between TSH and HDL-C should specify the direction, and would merit commenting upon.

Response: Yes TSH was positive associated with HDL-c in Pearson correlation analyses. However, the association lost its significance when adjusted by sex, age, duration of diabetes, FPG and BMI. So we only show it in Table 2.

10. Significance between difference across variable in the seropositive and seronegative groups need to be provided in Table 2, even if not reaching significance. It appears
that, along with higher TSH and pulse pressure values in the seropositive group, lower triglyceride and lipoprotein concentrations are observed. Might this reflect ……?

**Response:** Table 2 is the correlation of thyroid parameters with lipids profile. So we think it really refers to Table 4. We have added this information in Table 4 and discussed it in Page 9, Paragraph 3.

11. The headings of the tables should be more descriptive such as “p values of correlation of …in the whole sample”

**Response:** Thanks a lot for your advice, and we have revised them.

12. The manuscript contains numerous linguistic errors that need to be corrected.

**Response:** The manuscript had been read again carefully and revised.
Referee 3:

Specific comments:

13. Authors investigated the association of serum lipids and TSH level in euthyroid T2DM. However, the background and the clinical significance were not clearly found from the paper. Also, not much valuable data were obtained from the study. As a cross-sectional study, authors should enlarge the samples to get more exact information.

Response: Thyroid dysfunction is a risk factor for cardiovascular disease mediated by the effects of thyroid hormones on lipids metabolism and blood pressure, yet most subjects at risk for cardiovascular disease are euthyroid in the clinical setting. So the relationship between thyroid hormones and atherosclerosis in the euthyroid population has garnered much interest recently. Both thyroid dysfunction and dyslipidemia are more common in diabetes patient. So we carried out this study to investigate the association of serum lipids and TSH level in euthyroid T2DM. We had introduced it in the Introduction and Discussion. And we had given more in the revised manuscript.

In our revised manuscript, another 73 subjects were recruited in this cross-sectional study and the results were not changed. Of course this was still a small cross-sectional study. We believe that it has certain significance and we want to introduce the result firstly. A larger prospective study is prepared to confirm this association found in the present study.

14. This study was performed in diabetic patients. But blood glucose and the related factors were not considered in statistical analysis, except for the DM duration. This is not fully enough.

Response: FPG had been involved in the revised version, although it was not good enough compared with HbA1c. And co-morbidities and hypoglycemic therapies also should be included in the study. This is a limitation of our study needed to be considered, as we point in the manuscript. So a larger prospective study is prepared to confirm this association, all these will be considered.
15. The title is “the association of serum cholesterol and TSH level”. But authors talked more about the relationship between serum lipids and thyroid hormones in introduction and discussion. Thus either the title or the paper should be revised to keep accordance.

Response: Yes the title had been revised. The new title of the revised manuscript is:

Association between lipids profile and thyroid parameters in euthyroid diabetic subjects: A cross-sectional study.

Minor revisions:
1. In the introduction, depiction about the relationship between lipid abnormality and atherosclerosis and thyroid dysfunction is not consistent.

Response: Yes we had read this paragraph carefully, and corrected them.

2. In page 5, line 2, what is “mild thyroid dysfunction that are still within normal range”?

Response: It had been revised as follow: relative low thyroid functions that are still within normal range.

3. The language needs thorough check-up by native speakers.

Response: The manuscript had been read again carefully and revised.

4. The manuscript contains numerous linguistic errors that need to be corrected.

Response: The manuscript had been read again carefully and revised.
Furthermore, another 73 subjects were recruited in this cross-sectional study and the results were not changed. And a prospective study to confirm the association demonstrated in this study is prepared. Thanks again to you for the thoughtful and thorough review. Hopefully we have addressed all of your concerns. If there are any problems, please don’t hesitate to tell us.

Sincerely yours,

ZHANG Yun and XIAO Xinhua