Author’s response to reviews

Title: Using Hashimoto thyroiditis as gold standard to determine the upper limit value of thyroid stimulating hormone in a Chinese cohort

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Version: 1 Date: 29 Apr 2016

Author’s response to reviews:

Dear Dr. Karaca,

Thank you for your work on our manuscript and for the referees’ comments concerning our manuscript entitled “Using Hashimoto thyroiditis as gold standard to determine the upper limit value of thyroid stimulating hormone in a Chinese cohort” (BEND-D-16-00046). According to the referees’ comments, our data has been cautiously revised, discussed and interpreted. Furthermore, the English language of the manuscript has been checked, edited carefully and revised accordingly.

We are looking forward to hearing from you.

Best regards,

Jin-Kui
Response to Reviewer 1

Reviewer #1:

I read with interest the manuscript entitled "Using Hashimoto thyroiditis as gold standard to determine the upper limit value of thyroid stimulating hormone in a Chinese cohort. In this interesting cross sectional study the authors have attempted to redefine the functional upper limit of the TSH range using sophisticated statistical methods. The authors conclude that currently utilized values of 4.5 mIU/mL should be decreased to 2.6 or 2.9 in order to capture more patients with Hashimoto's thyroiditis. As no interventions were undertaken to assess potential clinical response to LT4 treatment of individuals identified as hypothyroid, the clinical impact of redefining the TSH down to this level other than adding millions (billions?) of patients to the ranks of the hypothyroid is unknown.

RE: This is a good question. In this paper we concluded that currently utilized values of 4.5 mIU/mL should be decreased to 2.6 or 2.9 bas. However, it does not mean to capture more patients with Hashimoto's thyroiditis. We only tried using the prevalence of HASHIMOTO THYROIDITIS as the calibration standard to determine the upper limit of TSH. As mentioned in the National Academy of Clinical Biochemistry (NACB) guideline, more than 95% of normal individuals had TSH below 2.5 mU/L. There were even data showing that African-Americans had very low incidence of HASHIMOTO THYROIDITIS with a mean TSH level of 1.18 mU/L. This value maybe the "true normal" upper limit for TSH, because African-Americans have very low prevalence of Hashimoto thyroiditis to elevate TSH [1]

Subclinical hypothyroidism is defined as normal serum levels of thyroid hormones (T4, T3, FT3, FT4) and elevated TSH, while hypothyroidism is defined as: "a systemic disease due to the deficiency of synthesis and physiological effects of thyroid hormones". Subclinical hypothyroidism has a normal level of thyroid hormones. Therefore, subclinical hypothyroidism is not a disease. It is only a risk factor. This risk factor can increase the risk of cardiovascular disease. Whether treatment is needed for subclinical hypothyroidism is still controversial.

Specific Comments: Numbering the pages is helpful.

Background:

lines 47-56. I understand what the authors are expressing here but the concept is a little different. Glucose is directly involved in the generation of advanced glycation products and therefore the fasting blood sugar and more directly the post prandial blood sugar correlates nicely with this relationship. TSH does not cause hypothyroidism, TSH is a tissue reflection of inadequate thyroid hormone action in the hypothalamus and pituitary so a physiologic response to hypothyroidism rather than the etiology. All that being said, both are clinically used to make these diagnoses.

RE: We agree the reviewer’s comment. Hashimoto thyroiditis is the most common pathogenesis of hypothyroidism. The underlying mechanism of hypothyroidism is the destruction of thyroid cells induced by auto-immune lymphocytic infiltration. The increasing of TSH is the feedback response of hypothyroidism.

Results:

lines 49-53 These subjects are on average very young. Several studies (Surks and Hollowel) have clearly indicated that the age of the patient is critical to interpreting the results of TSH testing. The authors should break out the mean and 2.5th as well as 97.5th percentiles in a table with age in decades being the dividing factor.

RE: 2. The research population was medical staff at working age and young nurses took over a considerable proportion within it, so the subjects were rather young. According to the reviewer’s suggestion, an additional was attached to table 2 to describe the age distribution more detailed.

Prevalence of HT by deciles……..Lines 42-49 and 53-59 These sentences are very unclear, not sure what the authors are communicating.

RE : According to the reviewer’s comment, these sentences have been revised carefully, hopefully with more clear expression.

ROC curve for the value of TSH……..

Lines 7-10 Does this mean that 2.6 is used to designate the upper limit of non-Hashimoto's subjects? This gets confusing. How many subjects with TSH (measured just once correct? What
would happen if TSH were measured 2 or 3 times and averaged or the range was used?) < 2.6 would be found to have Hashimoto's by antibodies or US?

RE: The “prevalence of HT” was only used as a tool to determine the cutoff value of TSH. Also in the ROC curve, we did not aim at using 2.6 to designate the limit between HT and non-HT, but using “prevalence of HT” as an inspection standard to determine the upper limit of normal TSH. It was not expected that below this level the presence of HT should be none, but there should be higher probability of HT if above this level.

It should be certain that if TSH was measured 2 or 3 times, the result can be more convincible, especially for clinical practice. However, it’s a clinical epidemiology survey and doesn't need repeated measurement.

Discussion:

page 2 Line2-3 But this is a Danish population with iodine issues, look at Surks and Hollowel). The Spencer paper has always been difficult to interpret.

Lines 46-54 Again this is a very young population, not sure we are ready to change the worlds practice based on this group.

RE: The reference articles have been further searched and replaced.

Page 3 Lines24-30 This sentence is unclear.

Lines 34-44 This is a big limitation.

Conclusion: Line 56-58 Would suggest that the authors insert the word "Young" between the words for and Chinese.

RE: Many revisions have been made in the discussion and conclusion part according to the reviewer’s valuable suggestion.

Table 1 Creatinine tend to go up in hypothyroidism. The significance of this finding is very unclear to me. Why would uric acid go down in supposedly hypothyroid individuals.

ER: As for the creatinine and uric acid in Table 1, we presume the reason for higher concentration in non-HT group was mainly due to more male individuals in group who have
relatively higher level of creatinine and uric acid than females. And this was discussed in the revised manuscript.

Table 2 The usual statistical approach has been to determine the 95% CI so the upper cut off has been pegged at the 97.5% and the lower cutoff has been placed at the 2.5%. Looking at the numbers here, it would appear that the authors population is very similar to the subjects reported by Surks and Hollowell). This should be reassuring that there is internal validity and comparability with other studies. Would the authors consider comparing the 97.5% TSH values in the non-Hashimoto's subjects with the outcomes of the other approaches? I guess I finally have understood what the authors are trying to point out here, that alternative methods of determining the upper expected TSH in a relatively young population is more likely to uncover underlying Hashimoto's thyroiditis. So looking at this from the perspective of false positives and negative may be helpful for clinical understanding. For example, if the TSH > 2.6 we are likely to find that X% will have Hashimoto's thyroiditis, which may or may not benefit from intervention (LT4 only intervention I would consider) but of course there is no data on LT4 outcomes. OR if TSH < 2.6 we can be reassured that only Y% of Hashimoto's (that would otherwise eventually benefit from LT4 therapy) will be missed. The authors should consider putting these findings into a clinical contest for the sake of the readers understanding.

RE: By your kind requirement we added 2.5th, 97.5th and median of TSH categorized by age in Table 2.

Finally, we didn’t try to confirm out hypothesis from the medication aspect. Because we presumed the upper limit of TSH to be a tool to screen out patients with subclinical thyroid diseases, so that we can exert more closely observation on them, but not to set the treatment threshold for medication.

Missing table Would the authors include a table with the mean and 97.5% of TSH by decade in the HT and non-HT groups?

RE: Table 2 was added to describe the mean and 97.5% of TSH by decade as the reviewer suggested.

Response to Reviewer 2
Reviewer #2:

1) The diagnostic criteria for diagnosing Hashimoto's thyroiditis is not clearly explained. Kindly discuss further.

RE: The gold standard to diagnose Hashimoto thyroiditis may be pathological result, but we can’t perform puncture on normal individuals. In this research, the diagnosis of Hashimoto thyroiditis referred to the diagnostic criteria by Caturegli (reference 8 in the manuscript). More specifically, the diagnosis of Hashimoto thyroiditis was established by a combination of presence of thyroid antibodies mainly being TPAb positive and abnormalities of thyroid sonogram including reduced or diffused heterogeneity echo of thyroid with or without nodularity. And this was discussed in the revised manuscript.

2) The manuscript is not referenced properly.

RE: The reference articles were further searched and revised, hopefully can be more effective.

3) The definition of subclinical hypothyroidism needs revision.

RE: It was properly described in the revised manuscript (line 51).

4) The language used, especially under discussion, is very complex and statistical which is difficult to understand. Kindly revise.

RE: Many revisions have been made in the discussion and conclusion part according to the reviewer’ suggestion, hopefully to express more clearly.

5) It is only mentioned that drug and family history of participants were taken but has not been mentioned anywhere which could be major underlying confounding factors. Kindly discuss further and categorise participants.

RE: It is not an iodine deficient area in Beijing. Therefore, the dietary factor should not be a major factor to influence TSH value in such an area (discussed in line 207).

6) There are other major confounding factors which need explanation especially personal history of autoimmune disorders, dietary habits and daily intake of iodine and total body iodine status.
RE: Patients with autoimmune disorders have been ruled out of the research population (complemented in line 124). As stated in the answer to question 5), the body iodine status is not a major factor to influence TSH value in our research.