Author’s response to reviews

Title: Changes of Serum 25(OH) D3 and IGF-1 Levels in Patients with Thyroid Nodules

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Response letter
We carefully read the revision comments of the two reviewers, and made the following responses to the reviewer's questions and revision comments:

A. The responses to Reviewer 1: The paper "Changes of Serum 25(OH) D3 and IGF-1 Levels in Patients with Thyroid Nodules" is aimed to evaluate the relationship between 25OH vitamin D levels and IGF1 levels and thyroid nodules. The paper is interesting about the topic, but it presents major criticisms in its form and it should be carefully and extensively revised.

1. Page 2, line 17: "The incidence of deficiency of vitamin D has gradually increased worldwide, becoming a universal health problem that cannot be ignored". In my opinion this sentence is out of the context of the paper and should be omitted.
Answer: First of all, thank the judges for your opinions. We accepted your suggestion, deleted the sentence “The incidence of deficiency of vitamin D has gradually increased worldwide, becoming a universal health problem that cannot be ignored.” (1. Background, line 17, Page 2 was omitted).

2. Page 2, line 21: The sentence is not clear and should be rephrased. Please add a reference.
Answer: We accepted your suggestion, rephrased this sentence to “IGF-1 probably plays an important role in the genesis and development of certain solid cold thyroid nodules, including PTC, nodular goiters, and FA.”, and add a reference “Liu Y J , Qiang W , Shi J , et al. Expression and significance of IGF-1 and IGF-1R in thyroid nodules[J]. Endocrine, 2013, 44(1):158-164.” (1. Background, line 21,
Page 2 was rephrased. References, Page 13, line 18 was changed. The changes are indicated in the text by highlighting).

3. Page 2, line 23: The sentence is out of the context. The relationship between vitamin D and IGF1 and cancer is well known. However, the aim of this paper is not focused on thyroid cancer.
Answer: We accepted your suggestion, and deleted this sentence and its reference “Wu et al. [3] studies found that the IGF-1/insulin axis is directly linked to vitamin D3, and some of the growth effects of cancer and newborn tissues in IGF-1 may be mediated by vitamin D3, and IGF-1 may be a risk factor that accelerates the growth of colorectal cancer and inhibits the apoptosis” (1. Background, line 23, Page 2 was omitted. References, Page 13, line 18 was deleted.).

4. Page 2, Line 43: The section is very confused and should be completely rewritten. Why did subjects perform thyroid ultrasound? Screening? Known thyroid disease? Signs or symptoms of thyroid diseases? Is this the first US evaluation? I think that exclusion criteria have been applied for both groups (the so called "nodule group" and control group). However, this should be better specified. Furthermore, it is mandatory to specify that patients (I assume that this is so) do not take therapies that can influence the parameters considered (LT4, cholecalciferol etc.).
Answer: First of all, thank the judge for your opinions. The reviewer is very confused about that subjects performed thyroid ultrasound, the reason is that thyroid ultrasound is a routine project for physical examinations in various units in China. Since there are reports of an increase in the incidence of thyroid nodules at home and abroad, this study sought to explore the relationship between changes in human body vitamin D and IGF1 levels and thyroid nodules. And we accept your suggestion, add the section “All subjects did not take therapies (LT4, cholecalciferol, etc.) that could affect the parameters considered.” (2. Methods, line 55, Page 2. The change is indicated in the text by highlighting).

5. Page 3, line 7: Perhaps the section about the US features of the thyroid nodules should be included in a different paragraph and not in "Collection of general data". Furthermore, technical data about US should be added (probe, frequency etc.). Unfortunately, no information about US characteristic of thyroid nodules has been reported. I think that it is important to add data about the size and the US features of thyroid nodules detected. In fact, the Authors stated that they excluded thyroid nodules with malignant US features.
Answer: In this study, we selected the subjects according to the TI-RADS grading diagnostic criteria for thyroid nodules, and documented the size of the thyroid nodules, but the aim was to quantify the thyroid nodules cross-sectional area by the ultrasound data to explore the correlation of thyroid nodules cross-sectional area and 25(OH)D3/ IGF-1. Meanwhile, in the process of collecting clinical data, we found that most patients had multiple thyroid nodules, and the ultrasound diagnosis results were only used for maximal nodule evaluation and reporting, so ultrasound-related data could not be collected and calculated in detail. This is also the shortcoming of this study.
At the same time, we accepted your suggestion, add the section of technical data about US and set a new section about the US features of the thyroid nodules.“2.2.2 Ultrasound examination Ultrasound examination of thyroid nodules was using PHILIPS EPIQ7 color Doppler ultrasound system, L12-5 probe, frequency 7~12MHz. The size of thyroid nodules was recorded, the ultrasonic data of thyroid nodules were quantified, and the cross-sectional area of thyroid nodules was calculated as well.” (2. Methods, line 11, Page 3. The change is indicated in the text by highlighting).

6. IGF1 levels are different based on age. It should be useful to specify in the text that Authors considered only adult patients and to include the mean age.
Answer: Age may be the influencing factor of IGF1, but the study focuses on the adult population of health checkups, and the age range of the included population is relatively narrow, which is also the
shortcoming of the study.

7. Page 3, line 58: Please check the brackets.
Answer: We accepted your suggestion, checked the brackets and corrected to “control group (111.10(81.53, 165.44) vs. 192.65(96.38, 313.49) ng/L)”(3. Results, line 58, Page 3. The change is indicated in the text by highlighting).

8. Page 3, line 61: Please rephrase the sentence.
Answer: We accepted your suggestion, rephrased the sentence “The FBG, TC, WC, TT3, TT4, and hypertension and drinking histories were different between the two groups (P < 0.05).”(3. Results, line 61, Page 3. The change is indicated in the text by highlighting).

9. Page 10, line 17: What does "thyroid and thyroid nodules" mean?
Answer: We have corrected to “Nathan et al.’s study revealed that deficiency of vitamin D was found in both thyroid cancer and thyroid nodules, however, there was no significant difference in the degree of deficiency of vitamin D between thyroid cancer and thyroid nodules”. The change is indicated in the text by highlighting.

10. The discussion section is too long and confused and should be rewritten focusing on the most important topics. In my opinion, the crucial question is the "protective" role of IGF1 which, considering the conflicting data reported in literature, should be better argued.
Answer: We accepted your suggestion, rephrased the discussion section. After we reviewed the literature again (due to the literature on the relationship between serum IGF-1 and thyroid nodules at home and abroad) and after discussion in the group, I think that the support point of IGF-1 as a direct protective factor is not sufficient, but according to this As a result of the study, IGF-1 may be a potential protective factor for thyroid nodules, and further research is needed to confirm. The change is indicated in the text by highlighting.

11. English language should be carefully revised throughout the text.
Answer: Because we are not good at using and expressing English language, this article was polished by professional English staff. If there are still language problems in the article, we hope to polish it in the relevant companies recommended by your journal.

B. The responses to Reviewer 2: This is a very interesting study on a possible link among the serum 25(OH) D3 and IGF-1 levels and thyroid nodules. Although both D3 and IGF-1 being in the systemic circulation, Authors do not provide a plausible suggestion about their role in a locally occurred pathology, but they performed logistic regression analysis and discovered lower incidence in serums with higher level of D3 and IGF-1.

1. The aim of their work has to be explained. As they mention, 50-60% of the healthy population has thyroid nodules. So, why to suggest D3 supplementation for such conditions? Authors have to discuss the limitation of their study too.
Answer: It is recommended that vitamin D3 supplementation is due to the literature that shows that vitamin D3 has the effect of preventing or reducing metabolic diseases.

Limitations of this paper: There were also some limitations in the course of this study: 1) the study did not consider the age range of the subjects, 2) the pathological typing of thyroid nodules was not performed in this study, and 3) the ultrasound results were not recorded in detail and the relevant statistical analysis was not performed. And we added this part to the end of the discussion section. The
change is indicated in the text by highlighting.

2. Subjects were evaluated from June to December. But, there is also seasonal variation in the D3 level. Does this fact taken into account?
Answer: Thanks to the professional advice from the reviewer. In order to reduce the impact of seasonal changes on the results, we have already considered that D3 changes with the seasons when designing the plan. Therefore, we selected the same number of subjects per month, and controlled the proportion of thyroid nodules and normal controls.

3. The title of the tables have to reflect exactly the statistical methods and results which are displayed.
Answer: We accepted your suggestion, rephrased the title of the tables, “Table 1 Difference analysis of basic clinical information between the nodule group and control group”, “Table 2 The correlation results between the single factors and thyroid nodules”, “Table 3 The correlation analysis results of serum 25(OH)D3 and various factors”, “Table 4 The correlation analysis results of serum IGF-1 and various factors”, “Table 5 The correlation between different 25(OH)D3 concentrations and thyroid nodules incidence”, “Table 6 The correlation between different IGF-1 concentrations and thyroid nodules incidence”. The change is indicated in the text by highlighting.

4. Authors use interchangeably "incidence" and "prevalence", but they means different things. Example: p. 9 "The incidence of thyroid nodules was significantly decreased in Q1 group to Q4 group." But in the figures 1 and 2 there is "prevalence", not incidence". Please, be sure to use the exact term.
Answer: We have changed all "prevalence" to "incidence". The change is indicated in the text by highlighting.