

Point-to-point revision letter

November 12, 2021

Editor-in-Chief, Editorial Office

Re: Manuscript NO: 70822

Title: Prevalence of Hypothyroidism in Patients with Non-alcoholic Fatty Liver Disease: A Population-based Study and Review of Literature.

Dear Editorial Board and Reviewers,

Thank you for your review of our manuscript titled " Prevalence of Hypothyroidism in Patients with Non-alcoholic Fatty Liver Disease: A Population-based Study and Review of Literature"

Below are our point by point responses to the reviewers' comments. We have highlighted all the resultant changes to the manuscript, tables, and figures using track changes and provided a clean copy. Thank you for the comments, we truly believe that the edits have strengthened the manuscript. Please let us know if you have additional questions.

Sincerely,

Ashraf Almomani, MD

Reviewer #1: “This is a compilation of many studies with a very large number of patients. It is very valuable. However, some details need to be clarified: 1. Is hypothyroidism a risk factor leading to NAFLD? Or does persistent NAFLD cause hypothyroidism? 2. Why doesn't thyroid hormone replacement therapy for hypothyroidism improve the risk of NAFLD? 3. The degree of hypothyroidism should be categorized. What degree is the risk factor for NAFLD? 4. How long does the treatment hypothyroidism take to reduce the risk of NAFLD effectively? 5. Each patient group should be analyzed such as obesity, T2DM, DLP, HTN. Which group of patients is more related to hypothyroidism? ”

Reply:

1. Thank you for this point. Based on prospective long-term trials mentioned in the text (ex: Bano et al, citation #19), hypothyroidism itself seems to be a risk factor for the development of NAFLD. We have added a paragraph in text to better point this important point
2. This is another great point brought to our attention. We have added and discussed an additional reference (citation #24) that tackles this point. The data for the thyroid hormone replacement effect is very limited, it might have an actual benefit in protection against NAFLD but this could also be related to the weight loss. We have elaborated more in the text.
3. This is a limitation in our study that was mentioned in the text. We have separated the “limitation” section and further highlighted this point.
4. The duration of effective therapy and goals of treatment remain unclear, however; 15 months were suggested by the only available prospective study. We incorporated this to the text after the kind comment.
5. This point is addressed in the multivariate analysis (Table 2).

Reviewer #2: “Thank you for this work. The authors aimed to investigate the prevalence of hypothyroidism in patients with NAFLD. Above all, the topic the authors are trying to address in this paper is too cliché and described in other papers (PMID: 28181781, PMID: 31153607, PMID: 32824723). My main problem remains the lack of novelty of this study.”

Reply: Thank you for pointing this out. In fact, the novelty of our paper is that it investigates the role of the thyroid hormone replacement therapy in NAFLD patients which is barely described in the medical literature. Furthermore, by its own, our paper has one of the largest sample sizes among published articles in this specific topic and serves to fill the small sample gap. Lastly, our paper also serves as a review article for the published retrospective and prospective literature in this field. We agree with the reviewer that these points have to be clearer throughout the text, and to address this we changed the title from “Prevalence of Hypothyroidism in Patients with Non-alcoholic Fatty Liver Disease: A Population-based Study and Review of Literature.” to “Prevalence of Hypothyroidism and Effect of Thyroid Hormone Replacement Therapy in Patients with Non-alcoholic

Fatty Liver Disease: A Population-based Study and Review of Literature.” and pointed our strength in the discussion section.