Author’s response to reviews

Title: Anti-nuclear Antibody and Rheumatoid Factor Positivity in Temporomandibular Disorders

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Version: 1 Date: 23 Oct 2018

Author’s response to reviews:

Dear Editor:

Thank you for reading our manuscript and considering it for publication.

I am pleased to resubmit for publication the revised version of HAFM-D-18-00050 “Anti-nuclear Antibody and Rheumatoid Factor Positivity in Temporomandibular Disorders”.

The constructive comments of the reviewers have been thoroughly considered and reflected in the revised manuscript.

I have addressed the concerns as outlined below. The answer is described below each reviewer’s comment.

Reviewer 1:

I went through the paper. Authors correlated anti-nuclear antibody (ANA) and rheumatoid factor (RF) positivity with pain-related and hematological indices in temporomandibular disorders (TMD). Out of 257 only 39 (15 %) patients had anti-nuclear antibody (ANA) and rheumatoid factor (RF) detected. Male patients had greater severity of symptoms and sign and a positive correlation was also found with inflammatory markers.

Although the number of the patients detected was just only 39, but the findings in this study are novel. There is only one study relevant to the subject done by Halpen and his colleagues. I think,
this will give future direction for further research with a bigger sample size and longer follow up. I will suggest a little modification of one statement made by the authors. The author mentioned autoimmune hemolytic anemia. Did they really look for hemolysis to say that? It can be anemia of chronic disorder. I think this need clarification. Or one can just say anemia without referring to its etiology if work up for hemolysis was not done.

Re: Thank you for your indication. Patients with autoimmune disorders have been reported to show altered hematologic conditions. In our study, ANA/RF positive male TMD patients also had lower red blood cell counts and hemoglobin levels. There is a possibility to explain this result by the phenomenon immune hemolytic anemia which is a disorder characterized by decreased RBC or RBC-related indices due to autoimmune destruction. But this is one of the possible causes that we can assume as the reviewer pointed out, so we changed the word hemolysis to anemia in the Discussion section as the reviewer suggested.

Furthermore the authors explained the exclusion criteria well, but it will be nice to mention that there was no clinical history of other joint involvement to give message that study cohort did not had first presentation of rheumatoid arthritis or other connective tissue disorder. As a whole it is a good study and can go for publication.

Re: Thank you for your opinion. We added the exclusion criteria as suggested in the Methods section as below.

“Those with a history of other pain disorders within 6 months prior to the study, history of psychiatric or immune diseases, medication intake within 4 months prior to the study that could affect the results, history of recent trauma and orthognathic surgery, clinical history of other joint involvement, presence of inflammation or infection in other body parts were excluded from the study.”

Reviewer 2:

In the manuscript entitled: "Anti-nuclear Antibody and Rheumatoid Factor Positivity in Temporomandibular Disorders" the authors investigated the differences in clinical characteristics and long-term treatment outcomes according to the anti-nuclear antibody (ANA) and rheumatoid factor(RF) positivity and the correlation between pain-related and hematological indices in temporomandibular disorders (TMD) patients.

In their clinical study, 257 patients with TMD were enrolled. In each patient, clinical and comprehensive screening along with psychological and hematological evaluations were
evaluated (ANA, RF, complete blood cell count, C-reactive protein[CRP] and erythrocyte sedimentation rate [ESR]).

The authors found that 39 patients were ANA/RF positivity, Male patients had smaller comfortable mouth opening, and maximum mouth opening range with more painful neck muscles on palpation when RF/ANA positive. Moreover, they found that significant correlation was shown in ESR with pain duration and numeric rating scale (NRS) before treatment, CRP with NRS before treatment, and red blood cell (RBC) with pain intensity, NRS before treatment, CMO, pain on palpation of cervical muscles, CMO and MMO 6 months after treatment.

The authors concluded that RF and ANA could be considered as a screening test for the detection of autoimmune phenomena in TMD. Moreover, they stated that TMD patients might show an autoimmune disposition that is associated with pain of a higher level and more dysfunction followed by poor treatment outcomes. The results of the present study may be considered in the diagnosis and prognosis prediction process of chronic TMD pain.

Major comments:

In general, the idea and innovation of this study, regards the analysis of anti-nuclear antibody and rheumatoid factor positivity in Temporomandibular Disorder through a comprehensive screening along with psychological and hematological evaluations is interesting, because the role of the ANA and RF in TMD patients is validated but further studies on this topic could be an innovative issue in this field could be open an innovative matter of debate in literature by adding new information. Moreover, there are few reports in the literature that studied this interesting topic with this kind of study design.

The study was well conducted by the authors; However, there are some concerns to revise that are described below.

The introduction section resumes the existing knowledge regarding the TMJ involvement as a clinical dysfunction in patients without diseases.

However, as the importance of the topic, the reviewer strongly recommends to update the literature through read, discuss and cites in the references with great attention all of those recent interesting articles, that helps the authors to better introduce and discuss the aim of the study in light also on patients with TMD and juvenile idiopathic arthritis and on the impact of orthodontic treatment on TMJ dysfunction on global JIA assessment:


Re: Thank you for your recommendations. We considered the recent literature including those in the reviewer’s suggestion and have updated the reference list as advised. Sentences have been added in the Introduction section to enhance the understanding of the readers concerning TMD.

The authors should be better specified, at the end of the introduction section, the rational of the study and the aim of the study with the null hypothesis.

Re: Thank you for your kind opinion. We added a null hypothesis to specify the goal of our study as below.

“There is a strong need to develop more reasonable and predictive markers to be applied in the diagnostic process. As in other pain disorders we hypothesized that the presence of ANA and RF would be related to the symptom severity of TMD.”

In the material and methods section, should better clarify the inclusion and exclusion criteria of the analysed sample and the Angle's class of malocclusion of all enrolled subjects.

Re: Thank you for your indication. We revised the manuscript following the reviewer’s advice. We excluded those with a history of orthognathic surgery. The main interest of this study is the relationship between the possible presence of an autoimmune phenomena and clinical TMD symptom severity. The relationship between autoimmunity and malocclusion was not analyzed in this present study. However in future studies grouping according to the subjects’ Angle’s classification will be considered.
Moreover, specify if was performed, the intra-examiner agreement for the clinical assessment of TMD pain analyses. Please specify the test unit chosen for the analysis.

Re: Thank you for your comment. The most reliable diagnostic protocol for temporomandibular muscle and joint disorders (TMD) is known as the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD). In our study, one specialist with more than 10 years of clinical experience examined all subjects according to the RDC/TMD protocol. Hence, we did not evaluate the intra-examiner agreement. This is described in the Methods section with the related reference (Dworkin SF, LeResche L (1992) Research Diagnostic Criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 6(4):301-355).

The discussion section appears well organized with the relevant paper that support the conclusions, even if the authors should better discuss the relationship between TMJ dysfunction and the low quality of life in juvenile idiopathic arthritis patients. The conclusion should reinforce in light of the discussions.

Re: Thank you for your indication. The Conclusion section was reinforced following the reviewer’s comment. In our study the age of the subjects was from 20 to 49 years. Data analysis involving children and adolescent patients of TMD will be considered in future studies. Thank you once again for the intuitive advice.

In conclusion, I am sure that the authors are fine clinicians who achieve very nice results with their adopted protocol. However, this study, in my view does not in its current form satisfy a very high scientific requirement for publication in this journal and requests some revisions

Re: Thank you for your comments. We revised the manuscript following the reviewer’s comments. We hope the revised manuscript will satisfy the requirements for publication. We believe this study could offer an initiative for future studies concerning TMD and autoimmunity which is an area yet to be investigated well.

Minor Comments:

Abstract:

- Better formulate the Materials and Methods section, not really clear

Re: Thank you for your comments. The Materials and Methods section of the Abstract was rewritten to enhance clarity.
Introduction:

- Page 3, line 27: please add the relative sentence

Re: Thank you for your comments. Sentences were added in the Introduction section.

Discussion

- Please add a specific sentence that clarifies the results obtained in the first part of the discussion

Re: Thank you for your comments. A new sentence was added at the beginning of the Discussion section summarizing the results of the study.

- Page 12 last paragraph (lines 39-51): Please reorganize this paragraph that is not clear

Re: Thank you for your comments. The sentences were reorganized as advised to add clarity.

Thank you for your comments. We revised the manuscript following the reviewers’ comments. We believe that the results showing the relationship between ANA and RF positivity and TMD will help the clinicians in the diagnosis and treatment of TMD. Since studies concerning this subject are rare we hope that this study will help investigators in future studies.

Thank you once again for reviewing this manuscript and considering it for publication.

Sincerely,

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