Celiac autoantibody positivity in relation to clinical characteristics in children with type 1 diabetes

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Handeling editor:

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Review timeline:

Received: 24 November, 2019
Editorial decision, 13 December, 2019
Revision received: 20 December, 2019
Editorial decision: 30 January, 2020
Revision received: 10 February, 2020
Editorial decision: 17 February, 2020
Published online: 19 February, 2020

1st Editorial decision

13-Dec-2019

Ref.: Ms. No. JCTRes-D-19-00030
Celiac Autoantibody Frequency and Their Relationship with Clinical Characteristics in the Children with Type 1 Diabetes.
Journal of Clinical and Translational Research

Dear Dr. Siddiqui,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jan 12, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Overall this work contributes to the knowledge that patients with type 1 diabetes have an increased risk of having autoantibody positive for celiac disease by evaluating this in a different population than has been previously reported. It is well done with minor but present English grammar issues.

While the information is not new, the novelty of the work lies in the population which was screened. Despite this novelty, there are majors issues with this work that would need to be addressed before publication.
1. Positive tTG alone is not diagnostic of celiac disease. Therefore, positive tTG should be referred to as antibody positivity. Patients with positive tTG and EMA may be referred to as having celiac disease autoimmunity or serologic evidence of celiac disease.
2. Previous publications report that tTG fluctuates in the first year after diagnosis with T1D. How many patients here, if any, were tested for tTG within 1 year of T1D diagnosis
3. Previous work suggests false positive tTG in patients with T1D. This should be discussed in the paper and this suggests caution regarding the conclusions should be made

Other

Title: Would change to : Celiac autoantibody positivity in relation to clinical characteristics in children with type 1 diabetes

Abstract:
Aim: This study is aimed to determine the celiac autoantibody status and the clinical characteristics of children with type 1 diabetes and autoantibody positivity for celiac disease compared to whose without serologic evidence of celiac disease?.

Materials and methods: Were subjects tested for total IgA? This should be mentioned in the paper.

Results: Here it is reported that 66 patients were diagnosed with celiac disease. This is not appropriate as only 35 had serologic evidence of celiac disease and the other patients only had one positive test which is not diagnostic of celiac disease

Relevance for patients" most of the patients are detected
by serological screening only." This statement should be removed as patients should not be diagnosed by serological screening. Patients should undergo an endoscopy to confirm a diagnosis of celiac disease.

Page 6 line 23 does not make sense- some words must be missing

Discussion : Page 8 lines 24-29 discusses that children positive for these blood tests should undergo referral to GI and endoscopy however there is no mention that any of this occurred in this study. There is no mention of any follow-up in this case.

Page 8- after line 29 is a very general discussion about celiac disease and does not feel related at all to the study. I would remove this as it is not appropriate to include this general background in the discussion.

The discussion should include current recommendation for screening for celiac disease in patients with T1D.

Author's response

Dear Editor and Reviewers:
On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editors and reviewers very much for their positive and constructive comments and suggestions on our manuscript Ref.:JCTRes-D-19-00030 "Celiac Autoantibody Frequency and Their Relationship with Clinical Characteristics in the Children with Type 1 Diabetes". We have studied comments carefully and have made correction which we hope meet approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewers' comments are as flowing

COMMENTS TO THE AUTHOR:

Reviewer #1: Overall this work contributes to the knowledge that patients with type 1 diabetes have an increased risk of having autoantibody positive for celiac disease by evaluating this in a different population than has been previously reported. It is well done with minor but present English grammar issues.
Author`s reply:
Thank you for your valuable comment. We corrected grammatical and typographical errors in the manuscript by native English speaker.

While the information is not new, the novelty of the work lies in the population which was screened. Despite this novelty, there are majors' issues with this work that would need to be addressed before publication.
1. 1. Positive tTG alone is not diagnostic of celiac disease. Therefore, positive tTG should be referred to as antibody positivity. Patients with positive tTG and EMA may be referred to as having celiac disease autoimmunity or serologic evidence of celiac disease.
Author`s reply:
Letter
We agree with the reviewer's comments, tTG alone is not a serological test for celiac disease. In our study we use anti-EMA and anti-tTG serological test for diagnosing celiac disease. As per reviwers suggestion we also change the terms positive tTG to "tTG antibody positivity", positive EMA to "EMA antibody positivity" and positive tTG and EMA to "serological evidence of celiac disease" in figure 1, table 3 and in the main text.

2. Previous publications report that tTG fluctuates in the first year after diagnosis with T1D. How many patients here, if any, were tested for tTG within 1 year of T1D diagnosis
Author`s reply:
We agree with reviewers' comments. In our study, all the patients had prolonged duration of diabetes with mean 7.4±4.2 years and we did not test for celiac disease in first year after diagnosis of T1D.

3. Previous work suggests false positive tTG in patients with T1D. This should be discussed in the paper and this suggests
caution regarding the conclusions should be made
Author`s reply:
In our study we use anti-anti EMA and anti tTG serological test for diagnosing CD. Type 1 diabetes children may have false positive anti tTG low values. So, determination of lower positive cut-off value of anti-TTG may help in differentiating unusual variant [8]. Prospective follow of this cohort in children is needed for endoscopic evaluation and histopathological examination of intestinal biopsy to confirm CD.

Other

Title: Would change to : Celiac autoantibody positivity in relation to clinical characteristics in children with type 1 diabetes
Author`s reply:
Thank you for your valuable comment. As per reviewers suggestion we corrected the title of the study as "Celiac autoantibody positivity in relation to clinical characteristics in children with type 1 diabetes.

Abstract:
Aim: This study is aimed to determine the celiac autoantibody status and the clinical characteristics of children with type 1 diabetes and autoantibody positivity for celiac disease compared to whose without
serologic evidence of celiac disease?.
Author`s reply:

Yes, the aim of our study was to determine the celiac autoantibody status and the clinical characteristics of children with type1 diabetes and autoantibody positivity for celiac disease compared to those without serological evidence of celiac disease.

Materials and methods: Were subjects tested for total IgA? This should be mentioned in the paper.
Author`s reply:
The participants were tested for IgA (Catalog No. KA2110, Abnova, Taiwan). The values of Immunoglobulin A are mention in table 1.

Results: Here it is reported that 66 patients were diagnosed with celiac disease. This is not appropriate as only 35 had serologic
evidence of celiac disease and the other patients only had one positive test which is not diagnostic of celiac disease
Author`s reply:
Thank you for your valuable comment. The sentence is modified and change to “Sixty-six (27.5%) children were seropositive for either EMA, tTG-IgA or both antibody positivity present at type 1 diabetes onset. The incident of multiple autoantibodies differs between the groups. Anti-endomysial positivity was rare appearing only in eight (3.3%) children. Conversely, antitransglutaminase positivity was detected in 23 (9.6%) children. Only 35 (14.6%) children had serological evidence of celiac disease and tested positive for both types of autoantibodies (Figure 1)”

Relevance for patients" most of the patients are detected by serological screening only." This statement should be removed as patients should not be diagnosed by serological screening. Patients should undergo an endoscopy to confirm a diagnosis of celiac disease.
Author`s reply:
Thank you for your valuable suggestion. The statement is removed and change to “Patients should undergo an endoscopy to confirm a diagnosis of CD”.

Page 6 line 23 does not make sense- some words must be missing
Author`s reply:
Thank you for your valuable comment we corrected the sentence “Sixty-six children who are seropositive for CD were divided in to 3 groups anti-endomysial positive group, anti-transglutaminase positive group, and serological evidence of celiac disease group”.

Discussion : Page 8 lines 24-29 discusses that children positive for these blood tests should undergo referral to GI and endoscopy however there is no mention that any of this occurred in this study. There is no mention of any follow-up in this case.
Author`s reply:
Type 1 diabetes children may have false positive anti TTG low values, so determination of lower positive cut-off value of antitTG
may help in differentiating unusual variant [8]. Prospective follow of this cohort in children is needed for endoscopic evaluation and histopathological examination of intestinal biopsy to confirm CD. We are designing a follow-up studies in these patients.

Page 8- after line 29 is a very general discussion about celiac disease and does not feel related at all to the study. I would remove this as it is not appropriate to include this general background in the discussion.
Author`s reply:
Thank you for your valuable comment. As per the reviewer suggestion we removed the sentence in the discussion and revised
the manuscript.

The discussion should include current recommendation for screening for celiac disease in patients with T1D.
Author`s reply:

We already include the current recommendation for screening for celiac disease in introduction section “European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), American Diabetes Association (ADA) and American College of Gastroenterology (ACG) clinical guidelines recommend the use of celiac-specific autoantibodies serology as markers to identify enteropathy in type 1 patients with CD”.

2nd editorial decision

30-Jan-2020

Ref.: Ms. No. JCTRes-D-19-00030
Celiac Autoantibody Frequency and Their Relationship with Clinical Characteristics in the Children with Type 1 Diabetes.
Journal of Clinical and Translational Research

Ref.: Ms. No. JCTRes-D-19-00030R1
Celiac Autoantibody Frequency and Their Relationship with Clinical Characteristics in the Children with Type 1 Diabetes.
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Feb 29, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: I appreciate the authors attention to my initial comments which have been satisfactorily addressed.

In order to support publication I would suggest the discussion address the large discrepancy among the antibody tests and that a statement be added to the conclusion (like that in the relevance to patients section) that states that an endoscopy is of particular important to confirm celiac disease in this population. If 66 patients have autoantibody positivity and only 35 have both tTG and EMA positive nearly half of the identified patients have discrepant findings. This should be emphasized in the discussion as a reason and need to perform an endoscopy.

Author's response

Dear Prof Heger,

On behalf of my co-authors, we thank you very much for giving us an opportunity to re-revise our manuscript, we appreciate editors and reviewers very much for their positive and constructive minor comments and suggestions on our manuscript Ref.:JCTRes-D-19-00030 R1 "Celiac Autoantibody Frequency and Their Relationship with Clinical Characteristics in the Children with Type 1 Diabetes". We have studied comments carefully and have made a correction which we hope to meet approval. Revised portions are marked in yellow in the paper.

Reviewers' comments:

Reviewer #1: I appreciate the authors attention to my initial comments which have been satisfactorily addressed.

In order to support publication I would suggest the discussion address the large discrepancy among the antibody tests and that a statement be added to the conclusion (like that in the relevance to patients section) that states that an endoscopy is of particular important to confirm celiac disease in this population. If 66 patients have autoantibody positivity and only 35 have both tTG and EMA positive nearly half of the identified patients have discrepant findings. This should be emphasized in the discussion as a reason and need to perform an endoscopy.

Author`s reply:

Thank you for your valuable comment and we have modified the abstract and, in the discussion, “There is a large discrepancy…. in this population” is highlighted and added to conclusion section and statement “There is a large discrepancy observed between the serological tests performed…. to confirm CD” is highlighted added to discussion section in the manuscript.(Page 1, 8 and 11)

Yours Sincerely
Dr. Khalid Siddiqui

3rd Editorial response

10-Feb-2020

Ref.: Ms. No. JCTRes-D-19-00030R2
Celiac autoantibody positivity in relation to clinical characteristics in children with type 1 diabetes
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Mar 11, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Thank you for modifying your manuscript in line with the reviewers' comments. In terms of substance your paper is now deemed suitable for publication. However, there is still an issue with the use of the English language in that there are too many grammar and spelling mistakes. Please have a native speaker correct your manuscript and resubmit a third revision to the editorial office via editorial manager. Your linguistically corrected manuscript will be evaluated by the editor-in-chief only and not resent to peer reviewers. This, however, does not mean that your manuscript will not be thoroughly examined before a final decision is made, so please do not take this final assignment lightly.

Thank you

Author's response

Dear Prof, Heger,

On behalf of my co-authors, we thank you very much for giving us an opportunity to re-revise our manuscript, we appreciate editors and reviewers very much for their positive and constructive minor comments and suggestions on our manuscript Ref.:JCTRes-D-19-00030 R2 "Celiac Autoantibody Frequency and Their Relationship with Clinical Characteristics in the Children with Type 1 Diabetes". We have studied comments carefully and have made a correction which we hope to meet approval. Revised portions are marked in yellow in the paper.

Reviewers' comments:
Thank you for modifying your manuscript in line with the reviewers' comments. In terms of substance your paper is now deemed suitable for publication. However, there is still an issue with the use of the English language in that there are too many grammar and spelling mistakes. Please have a native speaker correct your manuscript and resubmit a third revision to the editorial office via editorial manager. Your linguistically corrected manuscript will be evaluated by the editor-inchief only and not resent to peer reviewers. This, however, does not mean that your manuscript will not be thoroughly examined before a final decision is made, so please do not take this final assignment lightly

Author`s reply:

Thank you for your valuable comment and checked English grammar and spelling mistake with our language center at instigator support unit. Hope it meet your requirement.

Yours Sincerely
Dr. Khalid Siddiqui

4th editorial response

17-Feb-2020

Ref.: Ms. No. JCTRes-D-19-00030R3
Celiac autoantibody positivity in relation to clinical characteristics in children with type 1 diabetes

Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: