Author’s response to reviews

Title: Does the inflammatory potential of diet affect disease activity in patients with inflammatory bowel disease?

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Author’s response to reviews:

Point-by-point responses

Reviewer #1: Overview and general recommendation:

The study "The effects of the inflammatory potential of diet on disease activity in patients with inflammatory bowel disease: a cross-sectional study" has evaluated the association between two dietary indexes (Dietary Inflammatory Index -DII- and Empirical Dietary Inflammatory Pattern -EDIP) and disease activity in 143 patients with inflammatory bowel disease (IBD). The authors explicitly stated what the novelty of this study was. To the best of their knowledge, this is the first study examining the links between foods with inflammatory potential in habitual diet and disease activity in patients with IBD. The topic is one of interest; however, I believe that there are few points that need to be addressed before considering this manuscript:

Response: Thank you for reviewing the manuscript and the positive comment.

Major comments:

Abstract: The abstract clearly introduces and motivates the topic of this research. It contains adequate summary of the important findings of the study however it is missing a description of
the statistical tests used in the methods section of the abstract (Please refer to the Nutrition Journal guidelines).

Response: I have added the statistical tests in the methods section of the abstract; page 2, lines 39-42.

Background: This section adequately provided the background to the study and stated its aim.

Response: Much appreciated.

Methods: I found that the description of some important points is missing or inadequate such as:

1. The authors mentioned that they derived the DII score from a food frequency questionnaire (FFQ) previously validated on 132 adults in Tehran Lipid and Glucose Study. I suggest that the authors consider describing the dietary assessment section in more details.

Response: Thank you for the comment. Validity and reliability information of the FFQ have been added on page 7, lines 129-135.

2. The authors state they calculated DII score based on 39 food parameters instead of 45. However, they have mentioned the following food parameters twice: magnesium, zinc, niacin, and thiamin. Hence, the actual number of the parameters in the methods section is 34. In the strengths and limitations of the study, the authors say they have unavailable data on ginger, saffron, turmeric, thyme/oregano, and rosemary. So, I assume that the dietary intakes of the following food parameters were included in the study even though they did not mention them: alcohol, vitamin B6, eugenol, fibre, and pepper. Please confirm the number of food parameters used.

Response: Thank you for highlighting this point. DII were calculated based on 38 food parameters, and we have confirmed the food parameters used on page 7, line 137.

3. The above section would benefit from an explanation on how the omission of 6 (or 11) parameters was accounted for with more details.

4. Any data on the frequency of consumption of the omitted foods in the Iranian population? I believe that the answer to this question is important to discuss after you mention this point in the limitations of the study (page 9, line 205).

Response: You are right but unfortunately we do not have any published data regarding intakes of the items not included. However, Iranian people rarely do not consume eugenol, thyme/oregano, and rosemary. Drinking alcohol is also not common because of religious beliefs.
The consumption of turmeric, saffron, and ginger seems to be not high enough that can change the results.

5. I highly recommend the authors to include more details on calculation of DII and EDIP scores.

Response: We have tried to explain calculation of DII and EDIP in more detail on page 8, lines 151-155. In addition, to clarify the food items used to calculate EDIP, a table has been added; table 1.

Results: the results section, there was a need for a more appropriate approach to reporting the findings. I suggest adding a detailed description of the analysis of the two scores with a table explaining the results.

Response: We have added a table, table 3, reporting participants characteristics based on tertiles of the dietary inflammatory indices.

Table 1:

1. For consistency, space should be added before and after this symbol (±) and others like it throughout.

Response: Space has been added as suggested.

2. Please consider replacing "or otherwise stated" by "unless otherwise stated".

Response: It has been changed as mentioned.

3. Table 2: According to the journal guidelines, "table titles (max 15 words) should be included above the table". The word count of this table's title is 20. Please consider revising the table's title.

Response: table's title has been changed; table 4.

Discussion: I think that the manuscript should include further discussion of the results.

Response: We have tried to include further discussion; page 10, lines 205-215 and page 11, lines 222-226.

Conclusion: The conclusion included the summary of important findings and clinical implication and mentions the scope for further research.
Response: Thank you for the positive assessment.

References: Reference #5 is incomplete; please confirm all references are accurate and complete and follow journal requirements.

Response: we have corrected the reference. In addition, we have updated our references, generally. We have revised our references as suggested.

Minor comments:

Response: Much appreciated for you minor comments. All below comments have been implemented as suggested.

1. Page 2, line 43. For consistency, space should be removed after this symbol (±) in -1.20± 1.24.

Response: Page 2, line 45.

2. Page 2, line 50. Please add an "s" to deserve.

Response: Page 3, line 52.

3. Page 3, line 57. I suggest rephrasing this sentence: "The incidence and prevalence of IBD have been shown a significant rise…".

Response: we have rephrased the sentences, on Page 4, line 60-61.

4. Page 4, line 83. Please remove "of" from the following sentence: to predict inflammatory markers of CRP, IL-6,…

Response: it has been removed.

5. Page 4, line 84. "Has" been shown instead of "have" been shown.

Response: Page 5, line 88.

6. Page 4, line 87. Please remove "the" form the following sentence: An increased risk of UC with higher "the" DII scores.

Response: it has been corrected.

7. Page 4, line 97. Please remove word "ulcerative" from: …..CD and ulcerative UC.

Response: it has been corrected.
8. Page 5, line 99. In formal writing, sentences should not begin with shorthand (abbreviations, acronyms, etc); the shorthand should either be written out or the sentence should be rearranged so that the shorthand is not at the beginning. Please consider changing: "IBD patients….." to "Inflammatory bowel disease (IBD) patients ….. ".

Response: it has been corrected, page 6, line 102.

9. Page 5, line 115. Please mention the company and country of Seca scales.

Response: page 6, line 119.

10. Page 6, line 127. Please remove the extra comma.

Response: it has been corrected.

11. Page 6, line 129 and 132. Please remove "s" from parameters in "…each food parameters…".

Response: it has been corrected, page 7, line 140 and 143.

12. Page 6, Line 133. Same comment as above (#8); please consider revising the sentence that starts with DII per 1000kcal….

Response: it has been corrected, page 7, line 144-145.

13. Page 8, line 172. Please remove "ly" statistically: None of these findings reached "statistical" significance not "statistically" significance.

Response: it has been corrected, page 9, line 189.

14. Page 8, line 184. Please remove "s" from patterns.

Response: it has been corrected, page 10, line 202.

15. Page 8, line 184. Please define "US".

Response: it has been corrected, page 10, line 202.


Response: it has been corrected, page 13, line 261.

17. Page 10, line 224. Please remove "s" from employees: …. Is an employee of CHI.

Response: it has been corrected, page 15, line 297.
18. Please use a serial comma (Oxford comma) when listing more than two items. The absence of a serial comma can alter the meaning of the sentence:

Page 2, line 43. After adjusting for energy intake, drug use and IBD type: should add a comma after drug use, and…

Page 3, line 67. Innate immune cells including antigen-presenting cells (APC), T helper cells (Th cells), T regulatory cells and macrophages: should add a comma after regulatory cells, and macrophages.

Same for Page 3, line 68. Please add a comma after IL-1β.

And throughout the whole manuscript.

Response: we have tried to correct the use of comma throughout the whole manuscript.

Reviewer #2: This article illustrates the potential effects of inflammatory properties of diets on disease activity in patients with IBD. Despite the small sample size, the non-significant effect trends in the expected direction and could build on existing literature with incorporation of clarifications/adjustments listed below:

Response: Thank you for the valuable comments

BACKGROUND:

1. It is not clear what has been done in previous research in this area and why there is a need for the current study.

Response: We have added the previous findings on page 4, lines 68-75.

2. Some citations required in background that are missing.

Response: We have corrected our background citations.

3. Provide rates as appropriate when discussing this topic in the background.

Response: we have correct the rates for IBD on page 4, line 58-60.
- "...links between foods with inflammatory potential in habitual diet and disease activity in patients with IBD have not been previously investigated" - this sentence is not true as there is literature on this area. Please include summary of existing literature in this area to Background.

Response: Few studies investigated the association between diet component and disease activity in IBD patients [1-4]. One study investigated association between the DII and risk of UC but to date[5], no studies have been investigated the association between overall properties of dietary inflammation using the dietary inflammatory indices and disease activity in IBD. We have added previous studies on page 4, pages 68-75 and re-written the sentence on page5, lines 91-93 to clarify this point.

METHODS:

4. Why were the EDIP and DII used if they were not validated for use in the study population?

Response: Previous study using different inflammatory markers showed validity of the scores on predicting the inflammatory markers [6-8]. In Iran, a case-control study on gastric cancer, also showed the validity of the DII using 4 inflammatory markers [9] but their validity in the general population of Iran have not been investigated. However, the DII and EDIP have been suggested, and can be adapted for use in different populations[10, 11]; they are useful to study the association between inflammatory potential of diet and risk of inflammatory disease when no data on inflammatory markers available, discuss our study. We have added this point on pages 11 and 12, lines 236-240.

5. Why were only newly diagnosed IBD patients (less than 6 months following diagnosis) recruited?

Response: IBD patients usually change their dietary intakes to avoid or reduce their symptoms. Therefore, only newly diagnosed IBD patients were included in our study to reduce the possibility of changes in dietary intakes due to IBD disease. We have added this point on page 5, line 98.

6. What questionnaire was used to obtain data on education, drug consumption, etc?

Response: A pre-specified questionnaire was designed to collect data on demographic variables, past medical history, smoking, drug consumption; page 6, line 112.

7. It is not clear the tertile category make up. Please clarify.

Response: We have clarified on page 8, lines161-162 that inflammatory indexes were analyzed as categorical variables using both median cut-point and tertile cut-points.
8. Discuss validity of FFQ use in this population.

Response: Validity and reliability information of the FFQ have been added on page 7, lines 129-135.

9. Summary of Talbung study is too vague. "Other" fish, "other" vegetables, etc.

Response: Thank you for highlighting this point. To clarify the food groups used in EDIP, table 1 has been added.

10. Analysis plan does not state model will be adjusted for the education categories, please clarify.

Response: We have considered age, sex, smoking, BMI, education, drug consumption, type of IBD (UC/CD), and energy intakes as potential covariates, and those with significant univariate association with the risk of active disease (P<0.1) were included in the adjusted model. According to above mentioned criteria, total energy intake, type of disease, and drug consumption were included in the adjusted model. We did not adjust our model based on education; this point have been explained on page 8, lines 164-168.

RESULTS:

11. It is not clear if the 67.2% with UC are of the total population of just those with active disease. Please clarify.

Response: Thank you for highlighting this point. Among of those with active disease, 43 individuals (67.2%) had UC. We have clarified this point on page 9, lines 171 and 172.

12. Please explain decision to categorize groups on active versus inactive disease rather than CD and UC, especially given the difficulty to determine disease states in IBD.

Response: In this cross-sectional study, we hypothesized that inflammatory potential of diet may affect activity of disease in IBD patients. According to the objective of our study, we divided our participants into two groups of active and inactive, and odds of having active disease were estimated based on inflammatory indexes. Because of low sample size for CD, we decided not to stratify the participants based on IBD disease type.

DISCUSSION:
13. "To our knowledge, this is the first investigation of association between potential of diet-induced inflammation and disease activity in IBD patients" - not true, discuss existing literature on this topic.

Response: Few studies investigated the association between diet component and disease activity in IBD patients [1-4]. One study investigated association between the DII and risk of UC but to date [5], no studies have been investigated the association between overall properties of dietary inflammation using the dietary inflammatory indices and disease activity in IBD. We have added previous studies on page 4, pages 68-75 and re-written the sentence on page 5, lines 91-93 to clarify this point.

14. "FFQs are well known to be biased by a number of factors" - requires more information and how this could affect study results.

Response: This cohort of patients usually receive dietary advice on the possibility of this knowledge of the diet-disease relationship increasing changes in dietary intakes and reporting of bias. We have added this point on page 12, lines 247-249.

15. Again, why use tools that are not validated in your population? You must provide a reason for this.

Response: Previous study using different inflammatory markers showed validity of the scores on predicting the inflammatory markers [6-8]. In Iran, a case-control study on gastric cancer, also showed the validity of the DII using 4 inflammatory markers [9] but their validity in the general population of Iran have not been investigated. However, the DII and EDIP have been suggested, and can be adapted for use in different populations[10, 11]; they are useful to study the association between inflammatory potential of diet and risk of inflammatory disease when no data on inflammatory markers available, discuss our study. We have added this point on pages 11 and 12, lines 236-240.

16. Discuss why Mayo and CDAI scores may not accurately evaluate intestinal inflammatory activity.

Response: We have discussed this point on page 12, lines 252-255, as “CDAI and Mayo scores are the most frequently used tools to assess disease activity indirectly in patients with IBD but they may not be as accurate as direct methods of assessing intestinal inflammatory activity. Although direct methods, including histopathological and endoscopical examinations provide accurate evidence of intestinal inflammatory activity, they are time consuming, invasive, and expensive, which limit their applicability in routine use in clinical settings”.

17. Overall: Some spelling/grammar errors throughout. Some citations required in background that are missing. Clarification on above points required.
Response: English grammar and syntax of the manuscript have been edited and citations have been revised.

References


