

Dear Editor:

I am pleased to submit our revised version. We would like to thank the reviewers for their time, effort, invaluable input and clear directions into making our manuscript a better reading experience as a whole.

We will be addressing each remark in this document and the appropriate changes will be highlighted with track changes in the revised manuscript where that is applicable.

REVIEWER COMMENTS:

Reviewer 1: It was my pleasure to review your manuscript. Here are my comments: The manuscript does review effects of exercise on gut microbiome in animal models as well as humans. It also briefly reviews role of gut dysbiosis in the pathogenesis inflammatory bowel disease (IBD). There are no clinical studies on effect of exercise on the microbiome in patients with IBD. But there is mention of one study in mouse model of chemically induced colitis that reported reduced inflammation associated with voluntary exercise while increased mortality with forced exercise. Another study on similar mouse model reported effect of exercise on the microbiome with changes that would facilitate less inflammation. Lastly, there is review of effects of exercise in patients with IBD citing anti-inflammatory effects of exercise. There is an attempt to relate the gut microbiome changes seen in exercise as being restorative of the alterations in microbiome seen in patient with IBD. Based on indirect evidence from the above-mentioned studies, you suggest that the beneficial effects of exercise in the patients with IBD may be mediated through changes in the gut microbiome. You very well conclude that the effect of exercise on microbiome in patients with IBD needs further research to explore if the changes in microbiome cause decrease in inflammation as a result of exercise. Further type and intensity of exercise as well as specific IBD patient population that will benefit from such intervention needs to be determined. There is paucity of clinical data on role of exercise in restoring gut dysbiosis in IBD. However, the manuscript very well summarizes available data on the topic and suggests direction for future research. I would suggest to rephrase the last sentence in the abstract as it suggests that actual data on effects of exercise on the microbiome of patients with IBD were studied.

Changes were made in the revised manuscript according to your suggestions.

Reviewer 2: The authors wrote a generally good review on microbiome and IBD. This is, overall, of very high interest. Microbiome is increasingly important. Following things should be addressed and the authors should improve the paper. There are many environmental, dietary, and lifestyle factors that influence the microbiome (in both intestinal lumen and tissue), immune system, pathogenic mechanisms. The authors should discuss these factors, eg, smoking, alcohol, diet, obesity, microbiome, immunity. There are also influences of germline genetic variations on both immune system and microbiota. Gene-by-environment interactions should be discussed. In such contexts, research on dietary / lifestyle factors, microbiome, immunity, and personalized molecular

biomarkers in these diseases is needed. The authors should discuss molecular pathological epidemiology, which can investigate those factors in relation to microbiome, molecular pathologies, immunity, and clinical outcomes. Molecular pathological epidemiology research can be a promising direction and improve prediction of response to pharmacological, dietary, and lifestyle intervention. Strengths and challenges of molecular pathological epidemiology (in Epidemiology 2016, J Pathol 2019, etc.) should be discussed.

The factors were discussed as suggested.

For any further clarification, please do not hesitate to contact me.

Sincerely

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