

Dear Editor in Chief, Prof. Wailea Ma,

Thank you very much for giving me the opportunity to revise my manuscript (World Journal of Gastroenterology, manuscript NO: 91582). The changes in the manuscript could be identified in track change mode.

Reviewer #1 (code: 05262195):

1. The editorial page of the current manuscript covers the issue of gastric problems, including the incidence of bowel syndrome, and its pathogenetic aspects. This article adheres to the journal style and includes current references.

1) Thank you for the appreciation of my study.

2. It would be great if the author includes major genes involved in the initiation and progression of the disease to highlight the relevance of the genome.

2) I have included the references [25] and [36] detailing the implication of genes. I also added the following sentence in the paper (Relevance of the Genome): "...confirms the relevance of the genome, for genetic syndromes such as idiopathic chronic intestinal pseudo-obstruction (mutation in ACTG2, ERBB2-3, etc) and for diseases in which immune and oxidative stress is a determining factor [25]."

3. It would be helpful to identify the up and downregulatory signaling molecules involved in the Vit D signaling pathway.

3) I have included the references "30" and "31" which details the up and down regulatory signaling molecules involved in the VitD signaling pathway. I also added the following sentence in the paper (Centrality of microbiota, motility and nutrients): "...induces the differentiation and function of tolerogenic rather than pro-inflammatory T cells (increases the production of anti-inflammatory cytokines IL-4/IL-10 and decreases IL-17/IL-6/IL-2/IFN γ /TNF α [30]."

Reviewer #2 (code: 03307766):

1. The title could be more informative about the central topic of editorial. Accordingly, the authors should clearly state the aim of this editorial.

1) Thank you for pointing out this. I have done what you suggested.

2. One figure schematically summarizing the picture that the author tried to provide to describe the multiple factors modulating bowel inflammation, should be drafted.

2) Thank you for pointing out this. I have done what you suggested by introducing Figure 1.

3. I think the authors should re-organize the manuscript in subsections specific to each domain (host genetics, microbiome, immunological factors, environmental triggers, others). Basically, this editorial should be more structured.

3) I have revised the paper considering your suggestions, also enriching it with references. A future systemic review could be planned.

4. The author focuses on the immunomodulatory role of vitamin D. However, several other factors should be discussed, including IgA role (which is in turn related to the host genome: The Role of HLA in the Association between IgA Deficiency and Celiac Disease. *Dis Markers*. 2021 Dec 13;2021:8632861. doi: 10.1155/2021/8632861) or innate molecules/cells (e.g. Gut Microbiota, Inflammatory Bowel Disease, and Cancer: The Role of Guardians of Innate Immunity. *Cells*. 2023 Nov 19;12(22):2654. doi: 10.3390/cells12222654), for instance, which may play a different role in different diseases.

4) I have revised the paragraphs considering your suggestions and including the two references.

5. The role of gut microbiome should be discussed in specific gut diseases, wherein the evidence for a disease signature is variable, but where the effect on the gut inflammation is plausible (refer to: *Front Pediatr*. 2021 Apr 22;9:652208. doi: 10.3389/fped.2021.652208; *immunology*. 2024 Jan 4. doi: 10.1111/imm.13749. Epub ahead of print; *Mini Rev Med Chem*. 2023;23(13):1376-1389. doi: 10.2174/1389557522666220914093331)

5) I have enriched the references.

6. The conclusion should highlight the novel message and/or hypothesis that the author would like to communicate.

6) I have modified the conclusion as suggested.