Author’s response to reviews

Title: Partially Responsive Celiac Disease Resulting from Small Intestinal Bacterial Overgrowth and Lactose Intolerance

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PDF covering letter
Point-by-point response to reviewers’ comments

Article title: Partially Responsive Celiac Disease Resulting from Small Intestinal Bacterial Overgrowth and Lactose Intolerance

Dear Sir,

Thanks for reviewing our manuscript so promptly. We have revised our manuscript according to the useful comments given by the reviewers. We hope that now the article will fulfill the standard of your journal. Please note that the sentences marked red in the original manuscript are the portions that are revised or added.

In the point-by-point response to the reviewers’ comments, the sentences marked blue are the original comments from the reviewers and the black portion below that are the responses on those comments. The references marked within second-bracket are those in the original manuscript.

Reviewer 1

1. “Concern about the concept that celiac disease may considered unresponsive after 40 days of gluten free diet (GFD)”
Though normalization of duodenal histology may take long time up to one to two years, clinical response such as reduction in diarrhea and weight gain occurs within weeks [14]. Normalization of duodenal histology has been proposed for the diagnosis of refractory sprue [14]. Persistent symptoms despite normalization of duodenal histology may suggest causes other than refractory sprue such as SIBO and lactose intolerance.
2. “SIBO can be consequence of malabsorption as undigested food is a great pabulum for colon bacteria that may colonize ileum”
We fully agree to it. Therefore, we have added this sentence in the discussion.

3. “It is unclear to me why tetracycline had no effect in first instance and full effect after 40 days when malabsorption was still present.”
We beg to differ. In fact, it was clearly shown in Fig. 1 that tetracycline had marked effect in reducing diarrhea. However, once it was stopped after 2 mo, diarrhea recurred, though with lesser severity. Subsequently, though GFD reduced symptoms, but not completely. Addition of tetracycline to GFD at this stage resulted in complete recovery of symptoms.

4. “It is good practice to limit milk intake during first weeks/months of GFD…..”
We fully agree. In fact, this report is re-enforcing the same, more so in patients whose symptomatic response to GFD is inadequate. Since, adhering to lifelong GFD is a major undertaking for anybody, complete withdrawal of milk and milk product in addition to GFD should be taken so lightly as compliance to it is difficult. Therefore, test and treat strategy regarding complete lactose withdrawal may be better as lactose hydrogen breath test and lactose tolerance test are cheap and non-invasive. However, it is an open question and more studies are needed on this issue.

5. “Authors should better describe the number of celiac disease patients they have seen………..”
We have done that. However, this does not include children below 12 y age as they are seen separately by our pediatric gastroenterology unit.

Reviewer 2

1. “We should not forget the risk of refractory celiac disease before to look for other causes of unresponsiveness to GFD”
We agree. We have discussed that in the discussion section as follows: “Refractory celiac sprue is defined as an initial (primary) or subsequent (secondary) failure of a strict GFD to restore normal intestinal structure and
function and may result from several mechanisms [14]. It is important to keep all these causes of refractory celiac sprue in mind and to investigate and treat for all these factors [14].”

2. Use Marsh classification
We have done that. Since we did not have access to Eur J Gastroenterol Hepatol, we used another paper from Gastroenterology as the reference.

3. How many months the first patient was on GFD before to define duodenal histology “normal”?
Please refer to Fig. 2. Duodenal biopsy normalization was there in the second patient and not the first patient. We have mentioned the duration of GFD before second duodenal biopsy and it was 18 months.

4. “Antigliadin or anti-tissue transglutaminase antibodies? Methods used to evaluate anti-endomysium evaluation?”
We did not test for either antigliadin or anti-tissue transglutaminase antibodies. We performed anti-endomysial antibody test which as good as anti-tissue transglutaminase antibodies and both are superior to antigliadin antibody. Anti-endomysial antibody was tested using indirect immunofluorescence assay (Binding Site, UK).

5. “Whether this is primary or secondary lactose intolerance is matter of conjecture. But what is the authors’ opinion about this matter?”
We have described this in the discussion section as follows:
“Lactase deficiency causing intolerance to lactose is known to be either primary or secondary; though in our patient, whether it was primary or secondary is matter of conjecture, the latter is more likely as degenerated intestinal epithelial cells in patients with celiac disease are often found to have sparse endoplasmic reticulum, reflecting low level of digestive enzymes including lactase [9] and primary lactase deficiency is somewhat uncommon [10].”

6. “None of the reference is described about refractory celiac disease………”
Now it is discussed in the discussion section.

7. “Authors should explain better why SIBO or lactose intolerance may perpetuate the symptoms in these patients?”
We have described this in the discussion section as follows:
Small bowel bacterial overgrowth in patients with celiac disease may lead to persistent diarrhea due to disturbances of luminal digestion and alteration of mucosal function, albeit minor [13]. Bacteria in small intestine in patients with SIBO causes deconjugation of bile acids, which causes watery diarrhea due to stimulation of colonic secretion and steatorrhea due depletion of bile acid pool [13]. Lactose intolerance causes persistent diarrhea mainly due to osmotic effects of unabsorbed lactose and flatulence due to production of gas from fermentation of unabsorbed lactose.

**Reviewer 3**

1. “D-xylose tests are now rarely performed in most developed countries. I would be interested in why the authors use this test as often as they appear to?”

   We are aware that D-xylose test is rarely done in developed countries currently. In most developed countries celiac disease is the commonest cause for chronic small bowel diarrhea and malabsorption syndrome. Since several sensitive serological tests are available for celiac disease, one would do such non-invasive test first, and if positive would do a duodenal biopsy. Situation in India is different. Tropical sprue (TS) is still the commonest cause of sporadic malabsorption syndrome in adults. There is no non-invasive test available for TS. Further, even if duodenal biopsy is performed in all patients with chronic small diarrhea in India, still a normal biopsy may not always exclude TS as changes in this disease may be patchy and a mild abnormality may be present even in subject suffering from other causes of chronic diarrhea like IBS as a part of tropical enteropathy. Therefore, D-xylose test is useful as it gives an idea about the functional status of intestinal mucosa. Therefore, D-xylose test is used in almost all patients with suspected malabsorption syndrome.

8. **Ref 2 and 5 are same.**

   Sorry. This has been corrected.
9. Normal ranges for both total protein and albumin should be provided.
   Done.