June 27, 2016

Dear Sir,

Thank you for the decision on our manuscript (ESPS Manuscript NO: 26815; Original Title: Logical hypothesis: Low FODMAP diet for diverticulitis) together with the comments from the two reviewers. We are happy to oblige with the suggestion of changing our submission from the World Journal of Gastroenterology to the World Journal of Gastrointestinal Pharmacology (WJGPT) and Therapeutics. I herewith submit our revised manuscript for consideration in the WJGPT, in which we have incorporated all of the reviewers' suggestions and addressed all of the comments that arose from our first peer review. In addition, please find below our point-by-point responses to the reviewers' comments.

We believe the manuscript has been improved satisfactorily and we hope that it will be deemed acceptable for publication in the WJGPT.

Sincerely,

_____

Dr. Yoshiharu Uno

yoshiharu333@hotmail.com

First, we would like to thank both of our reviewers for their interest in our topic and positive comments regarding our manuscript. We believe the changes made according to their advice have strengthened our review substantially.

Reviewer A (03475689, Review Time:2016-05-15 21:38)

Thank you for the opportunity to revise the manuscript. In their review the authors suggest that adoption of a low FODMAP diet (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) may help prevent recurrence of diverticulitis, differently from what is suggested from the actual guidelines. The manuscript is well organized and has its rationale. However, some of the references cited by authors are also reviews and the lack of high-quality clinical studies prevent from withdrawn strong conclusions. My main concern regards the lack of proof of causality and this should be acknowledged by the authors. In particular, it is unclear if there is a causative event among small intestine bacterial overgrowth syndrome, right diverticular disease, or maybe gut dysbiosis, or if it is a continuum of a unique disease. Moreover, the lack of literature prevent from discuss the role of gut microbiota in the pathogenesis of diverticular disease and its complications. Minor comments: - Page 1: Since the study hypothesis is that low FODMAP diet may help prevent recurrence of diverticulitis and not treat patients with diverticulitis, I would suggest to edit the title as "Logical hypothesis: Low FODMAP diet for diverticular disease patients" or "Logical hypothesis: Low FODMAP diet to prevent diverticulitis" - Page 5: "The proximal colon, consisting of the transverse colon and rectum…". The proximal colon do not include the rectum but the ascendant colon. - Page 6: "Moreover, these clefts may contain blood vessels [34][33]3]include the rectum but the ascendant colon. - Page 6: "Moreover, these clefts may contain blood vessels [34 gut microbiota in the pathogenesis of diverticulaces. - Page 15: "Abstruct"bstructlude the rectum but the ascendant colon. - Pact.

Major comments

My main concern regards the lack of proof of causality and this should be acknowledged by the authors. In particular, it is unclear if there is a causative event among small intestine bacterial overgrowth syndrome, right diverticular disease, or maybe gut dysbiosis, or if it is a continuum of a unique disease.

Moreover, the lack of literature prevent from discuss the role of gut microbiota in the pathogenesis of diverticular disease and its complications.

Response: Thank you for this insight. After careful consideration, we see that this topic was inappropriate for inclusion in the manuscript and we have removed the text (i.e. two paragraphs introducing the inappropriate ideas of small intestine bacterial overgrowth (SIBO) and microbiota).

Minor comments

1. Page 1: Since the study hypothesis is that low FODMAP diet may help prevent recurrence of diverticulitis and not treat patients with diverticulitis, I would suggest to edit the title as "Logical hypothesis: Low FODMAP diet for diverticular disease patients"or "Logical hypothesis: Low FODMAP diet to prevent diverticulitis"

   Response: Thank you for helping us to provide a title that is more informative and relevant to the precise topic of our manuscript. The title has been changed as "Logical hypothesis: Low FODMAP diet to prevent diverticulitis."

2. Page 5: "The proximal colon, consisting of the transverse colon and rectum…". The proximal colon does not include the rectum but the ascendant colon. –

   Response: We apologize for this mistake. The text has been corrected.

3. Page 6: “Moreover, these clefts may contain blood vessels [34][33]”. Please, either delete or include reference 34. –

   Response: Reference [34] was deleted. Please note, because additional references were added in the preceding text, reference [33] is now numbered as [36].

4. Page 11: “Several reports have addressed the potential correlation between IBS and DD”. Please, add references. –

   Response: We apologize for this oversight. The appropriate references ([100-103]) have been added.

5. Page 15: “Abstruct” (reference 39 in the reference list). Please, correct.

   Response: We apologize for the typo. The mistake has been corrected.

Change other than the review comments

Figure 4 was insufficient in eight of the country relationship. New figure 5 was compared to the nine countries.

Figure 4 has become Figure 5 in the revised version of our manuscript, as a result of adding an additional earlier figure as requested by another reviewer. In addition, the information for the figure has been clarified to show the correct data correlation (i.e. r2 = 0.9524).

Reviewer B (03475780, Review Time: 2016-05-24 16:41)

Dear author16:41 advice, our paper has been upgraded.cond However, it should be thoroughly revised since at this point in time it is not pleasant to read. .Please constrict yourself to facts and leave stories such as about a female patient out of the manuscript. Furthermore try and keep a clear line in your writing and do not elaborate on every little detail. Finally it is my believe that some conclusion's are a bit premature; a few examples; 1. Subsequent studies found that intake of a higher fiber diet led to increased volume and less viscous feces accompanied by a shorter transit time [4-6], thereby preventing the rise of internal pressure in the large intestine. Advocates of the fiber diet suggested that it would help to spread the lumen of the large intestine, thereby suppressing the excessive contraction that would otherwise be caused by large amounts of compacted feces. These findings have led to the widely accepted theory that DD is strongly related to constipation [7]. 2. Please explain and highlight in your piece the difference between right sided and left sided diverticula. They can not be compared as they are in this piece. 3. Finally, prevalence of colonic DD has been correlated with advancing age [19], In recent times the correlation between age and diverticula has become less and less strict. Please comment on this. I would be very interested in reading a revised version. Kind regards.

0. Please constrict yourself to facts and leave stories such as about a female patient out of the manuscript.

Response: As suggested, the case report in reference [39] has been removed from the manuscript.

1. *"Finally it is my believe that some conclusion's are a bit premature."*

Response: Thank you for expressing this concern. Our intent was only to describe the high-fiber diet theory [4-7] and its potential, but not to absolutely affirm it. Considering this and the most recent research reports from 2016 regarding methane gas [8-10], we do not feel that the theory itself is premature; however, we apologize for any confusion our initial text may have caused. In order to clarify our intended objective with this review, we have now added the following information:

"The most important data published so far in support of the fiber hypothesis is that showing a correlation between amount of feces and transit time. In particular, the relationship between stool volume and transit time is not inverse, but is exponential [i.e. log(time) = 2.81633-0.56057log(weight)] [4]. It is not feasible to shorten transit time for stools over 300 g; therefore, theoretically, the effectiveness of high-fiber diet is limited. Methanogenesis has been linked to the presence of diverticulosis [8], and cellulose, which is contained in dietary fibers, is fermented by methane-producing bacteria [9]. A very recent study used a gas-sensing capsule to measure gas produced by diets of various fiber content found that the high-fiber diet produced more gas in the large intestine than the low-fiber diet [10]. Therefore, ingestion of excess dietary fiber may exacerbate the conditions that support accumulation of feces and gas in the intestine."

2. Please explain and highlight in your piece the difference between right sided and left sided diverticula.

Response: We apologize for not having clarified this in the original manuscript. The difference between right-sided and left-sided diverticula has been added to the manuscript (see below), accompanied by a pictorial description in Figure 4.

New text in the manuscript:

"There are seven sphincters located along the length of the colon [53]. The hydrodynamics of each sphincter and influence of its contraction (including the Haustral type) may be explained by Bernoulli's principle (Figure 4). Thus, the difference in frequency of right DD and left DD may be related to differences in pressure at each site."

3. In recent times the correlation between age and diverticula has become less and less strict. Please comment on this.

Response: Indeed, as more studies on diverticula have been completed additional contributing and risk factors have been identified, including ethnicity and geographic locale; this more comprehensive understanding of the disease and its etiology have also revealed distinct correlations between age of onset in different populations afflicted with the disease. For example, it has been found that left-side DD in Japanese and Korean populations is related to increasing age [REF]. This finding, in particular, also serves to highlight a previously unrecognized relationship between aging and diverticulosis as influenced by the site of onset (i.e. right vs left). This information has been added to the manuscript.
