

Author's response to reviews

Title: An Anti-Inflammatory Diet as Treatment for Inflammatory Bowel Disease: A Case Series

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Author's response to reviews: see over

Reviewer 1:

1. Small number of patients, especially those with eligible complete health records for detailed analysis (only 3 with UC), heterogeneity of their medical therapies and absence of comparable control group of patients without dietetic intervention unable us to drive any firm conclusions about real efficacy of described diet.

We agree. However, this is simply an observational case series, meant to stimulate further study and lead to a randomized, controlled trial to evaluate efficacy of the intervention.

2. As concluded by the authors themselves, a prospective controlled randomized clinical trial should be advocated to assess the efficacy of this specific dietary approach. Moreover, even the name of the diet, anti-inflammatory diet, can be misleading until its real effect on mucosal inflammation and healing would be proven by pre- and post- treatment endoscopic and histologic evaluation.

It is believed that a diet containing healthy fats, fiber-rich fruits and vegetables, and limited amounts of animal protein—except when it comes to oily fish has anti-inflammatory properties. Our diet contains several of these foods. We agree, though symptomology (less bleeding, medication changes and chemistries that include CRP and ESR) are indicative but not definitive indicators of decreased inflammation. However, we feel this evidence is compelling enough to report, and these results may lead to further investigation.

3. The observed symptomatic relief during the diet is not necessarily the result of its anti-inflammatory effect but can also be the result of its influence on the symptoms of irritable bowel syndrome, a functional disorder accompanying IBD in up to 70% of IBD patients. It has been described that fiber-rich diet may aggravate symptoms in number of IBS patients due to bacterial fermentation of non-digestible carbohydrates with consequential production of intestinal gases and organic acids. On the other hand, non-digestible but fermentable carbohydrates usually do not act as chemical irritants or substrates for fermentation by potentially pathogenic bacteria. More often they serve as prebiotic substances that stimulate growth and metabolism of health-promoting bacterial genera such as Bifidobacterium and Lactobacillus. Products of their metabolisms, especially short-chain fatty acids, have numerous beneficial effect including enhancement of gut epithelium repair and barrier function and down-regulation of intestinal inflammation.

In fact, even in phase one of the IBD-AID, soluble or fermentable fiber (pureed or ground) is encouraged to help regulate bowels. It's quite possible that these substrates help growth and metabolism, as this reviewer states, and could be helpful not only with irritable bowel, but also with inflammatory bowel disease. However, as this reviewer correctly pointed out, since we have

no control group, the effect of the diet cannot be assessed. Further clinical trials can elucidate histologic differences between IBD and IBS and evaluate any effect due to the diet.

4. Page 4: “Despite histological differences... - recommendation: Despite clinical and immunological differences...”

Done.

5. Page 4: “dietary therapy has been similar for both” – that is not true. As mentioned later in the text, nutritional therapy with enteral nutrition is an efficient therapeutic option in patients with mild and moderate Crohn’s disease, especially pediatric ones. Several studies and meta-analyses revealed that the efficacy of such therapy is comparable to standard anti-inflammatory drugs (corticosteroids) and can result in mucosal healing. However, such therapy has no effect in ulcerative colitis.

This is true for enteral nutrition, and for other dietary changes to an extent. The text has been changed to reflect this comment. An additional reference has been added to support this reviewer’s concern. As we only had 3 cases of ulcerative colitis, and most of our results reflected Crohn’s disease, we noted this in the Discussion.

Patients with UC and Crohn’s both make dietary changes based on their disease, to avoid foods that are thought to cause symptoms. Physicians often support their patients in such changes, since distinctions between UC, Crohn’s, and dietary guidelines are lacking. Further studies of diet in each category of disease are needed.

6. Page 4: “Others have investigated nothing by mouth for a period of time, and used tube feeding with elemental diets.” – That is over-simplification of exclusive enteral feeding approach. The first, meta-analyses revealed that the use of polymeric formulas is as efficient as the use of elemental ones. And the second, the use of more palatable polymeric formulas for enteral nutrition enable us to take them by mouth and not by tube.

We agree. We do not disparage using enteral and parenteral methods, however, the scope of this article is on using whole foods in various forms (liquid or pureed among them), not commercially prepared enteral and parenteral nutrition. The words “whole foods” has been added to this paragraph to define the scope of the article more clearly.

7. Page 5: Paragraph Materials and methods. Do not need Table 1, it goes to Results

We rely upon the editor to decide this. Since this is a case-series study with limited cases, we think that a table providing a summary of the range of patients,

medications, and demographics in visual form is necessary. Since our patients were varied, this would take a lot of text to describe in results. Please advise.

8. Page 5: “The goal of IBD-AID is to... - ... and to provide adequate nutrition for patients needs for energy, macro- and micronutrients

This has been changed as suggested.

9. Page 7: “and diet was reviewed for foods of intolerance”- Question: Which criteria were used for the diagnosis of food intolerance? Only patients’ observations? For, example, in functional GI disorders food intolerances are reported by up to 70% of patients, however, when blind placebo-controlled provocation are performed, they are objectively proven in only minority of them. Moreover, how can changes in texture/form of food influence real intolerances?

. We define intolerances as a subjective description, not as an allergy. This can also be quite tedious, as often the patient is not aware of which foods are truly causing sensitivity, confusing acute reactions with those incurred over time. Definition as per Allergy and Immunology is:

Food Intolerance

A food intolerance, or a food sensitivity occurs when a person has difficulty digesting a particular food. This can lead to symptoms such as intestinal gas, abdominal pain or diarrhea.

A food intolerance is sometimes confused with or mislabeled as a [food allergy](#). Food intolerances involve the digestive system. Food allergies involve the immune system. With a food allergy, even a microscopic amount of the food has the potential to lead to a serious or life-threatening reaction called [anaphylaxis](#).

Since this was not clear to this reviewer, we have reworded the paragraph (in italics) as follows:... the fourth encourages a review of the overall dietary pattern, *detection of missing nutrients, and identification of intolerances.* The last component modifies the textures of the foods (e.g.; blenderized, ground, or cooked) as needed (per patient symptomology, see Table 2) to improve absorption of nutrients and minimize intact fiber. The phases indicated in Table 2 are examples of the modification of texture complexity, so that dietitian and patient can expand the diet as the patient’s tolerance and absorption improves. *Some sensitivities are common to many patients (not just those with IBD), and are eased through supplementation of digestive enzymes or avoidance.*

10. Page 8, Discussion: “Presently there is no way of examining the impact of the IBD-AID on the intestinal microbiome” – That is not true. The authors themselves explain the possibilities. They only did not do this in their cases, but can be done in further prospective studies.

This sentence has been reworded as follows: *In the current study, we were unable to confirm our hypothesized mechanisms of action by examining the impact of the IBD-AID on the intestinal microbiome.*

11. Page 9: The paragraph addressing gluten-free diet may be misleading. It is crucial for celiac patients but has no scientifically proven effect in IBD.

We apologize for any confusion. The sentence was modified so that readers may understand that while it is (by coincidence) predominantly gluten free, we have not designed the diet around gluten. In addition, we have modified the previous paragraph to include, “While a gluten free/grain free diet may be beneficial, this diet is not designed around gluten, and strives to address other micro- and macronutrients. “

12. Page 9: “since oats (and possible other pre-biotic grains)...” – We should not use a term prebiotic grain as prebiotics are specific substances and not foods (such as grains or vegetables)

We agree that this may be confusing. Prebiotics are new to research. We find the reference by Marcel Roberfroid (J. Nutr. 137: 830S–837S, 2007)³ quite informative, as follows:

The original definition of a prebiotic only considered microbial changes in the colonic ecosystem of humans. However, it may be timely to extrapolate this into other areas that may benefit from a selective targeting of particular microorganisms. As such it has been proposed to refine the original definition to “a prebiotic is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora, that confer benefits upon host well-being and health” (*Gibson GR, Probert HM, Van Loo JAE, Roberfroid MB. Dietary Modulation of the human colonic microbiota: Updating the concept of prebiotics. Nutr Res Rev. 2004;17:257–9.*)⁴

We have changed that sentence, and added this additional reference, as follows:

The IBD-AID is not a gluten-free diet per se, since oats (**and possibly other fermentable grains that provide a substrate for probiotics**) can be well tolerated and indeed are useful in regulation of bowel frequency and consistency. We do group all oats as tolerated in the IBD-AID, but acknowledge some oats cultivars are gluten free, while others contain gluten. (*Gut*. 2011 July; 60(7): 915–922. Published online 2011 February 12. doi: 10.1136/gut.2010.225268).

13. Page 9: “Poorly digested complex carbohydrates may lead to bacterial overgrowth...” – Please, specify! Some of them have defined prebiotic properties.

This sentence has been changed to: Poorly digested complex carbohydrates (even those with defined pre-biotic properties) may lead to dyspepsia, or worse, adverse bacterial overgrowth and bowel injury with increased intestinal permeability.

14. Page 10: “This irritation causes inflammation, leading to further tissue injury” – I

disagree with this! Please, have a look to major comments at the beginning of this review.

This sentence has been deleted. We hope we've addressed other concerns of this reviewer.

Reviewer 2.

1. Did any patients who showed "mixed results" qualify for the medical record review?

The 11 patients were chosen for medical record reviews were selected because they had IBD and went through our IBD-AID diet program. Potentially ALL of the patients would have qualified who saw the nutritionist, but not all shared the IRB-approved gastroenterologist. This sentence has been clarified to reflect this.

In the abstract, the paper categorizes the 40 patients who were consecutively offered the IBD-AID as follows:

- (a) 13 patients chose not to attempt the diet
- (b) 24 had "good or very good response" after reaching compliance
- (c) 3 showed mixed results.

Based on record completeness/data availability, the authors reviewed medical records for 11 patients who used the IBD-AID. It appears from the positive results in Table 1 that all 11 medical record reviews were from group (b)? Did any group (c) patients meet the criteria for medical record review?

No. All group C patients (mixed results) saw only the nutritionist and a non-IRB approved GI doc.

2. Numerical error/typo (either in abstract or results)

Page 7. First paragraph of "Results" section.

In the Results section, the patient "breakdown" lists 21 patients (page 7) having a Positive response to the diet. However, the abstract (page 3) lists 24 patients as having a "good or very good response. One of these numbers is incorrect.

Thank you~! The results section has been corrected.

3. Ambivalent/Negative responses to the diet.

Page 7. First paragraph of "Results" section. For the 3 patients who had ambivalent or negative responses, please provide examples of symptoms as well as whether the patients had UC or Crohn's disease. If the records permit, were these results related to compliance? Other factors? Co-morbid conditions?

The following has been added:

Of the 3 patients (2 with UC, 1 with CD) with ambivalent or negative response, 2 were diagnosed with Clostridium Difficile (C-diff), and the other (UC) patient's response is attributable.

4. What is the definition of compliance?

Page 7. First paragraph of results section. Last sentence.

The researchers write: " Of the patients reporting improvement, they were able to Reach greater than 70% compliance to the diet." [Boldface added] Please specify, or give an example, of "70% compliance." Does compliance indicate following the IBD-AID for 70% of the day? For 70% of the week? For 100% of the 1st three weeks of the IBD-AID and then dropping off? Please expand on the definition of compliance.

. For the purposes of this study, compliance was determined by food records (patient self-report), and included all food components for the duration of the study. This has been added to the text.

5. How does the "Specific Carbohydrate Diet" (SCD) play a role in the context of The paper?

Page 9. 2nd paragraph

The transition into the description of the SCD is abrupt. An earlier pilot study Poster (2011) describes the IBD-AID as "derived and augmented from The Specific Carbohydrate Diet (SCD)." The language from the poster, or similar language, should be used to provide a transition/context for why the SCD is mentioned/discussed in this paper.

This has been added to the beginning of that paragraph.

6. Components of the original SCD

Page 9. 2nd paragraph

This paragraph describes the SCD as a "gluten-free/grain free" diet. While this is true, the SCD was notably more restrictive, focusing on reducing polysaccharide content. The following paragraph, from a Haas publication, describes the SCD as also eliminating rice, potato, sugar (as a sweetener), and whole milk: In prescribing this diet, it is almost more important to stress what is not fed than what is fed. Any cereal grain is strictly and absolutely forbidden, including corn, wheat, rye, or rice in any form, whether as bread, cake, toast, zwieback, crackers, cookies, or breakfast cereals. Potato is prohibited. Sugar is forbidden as sweetening or in the form of candy, pastries, breads, etc., as well as dextrins such as are found in corn syrups and lollipops. Whole milk, per se, is not allowed. [Boldface added]

HAAS, S. V, & HAAS, M. P. (1955). The treatment of celiac disease with the Specific carbohydrate diet; report on 191 additional cases. The American journal of gastroenterology, 23(4), 344–60. Page 348. To put this in context, the SCD was originally used for celiac disease. After World War II, Willem-Karel Dicke is credited with simplifying celiac disease dietary treatment to only be gluten-free--and not as onerous as the Haas diet. (In at least one medical journal article, Sidney Haas publicly criticized this transition of celiac disease treatment to only gluten-free.) In short, the SCD was

more comprehensive/restrictive than "gluten/grain free" and Haas specifically reduced the polysaccharide content of the diet. "Gluten free" diet treatment is credited to Dicke. (The Haas article above is included in the reference list for this IBD-AID study.)

We agree. The paragraph, and the one following, have been modified to clarify this point.

7. What is the "original diet"?

Page 10, paragraph 1, 3rd complete sentence. It is unclear what "original diet" refers to. Presumably, it refers to the SCD. This ties into the transition in comment "5" above.

. We have inserted SCD instead of "original diet".

8. Role of supplements

The last row of Table 2, the food chart, includes "Vitamins/Minerals/supplements As directed". In the discussion, please comment on the role of supplements. Are the Patients routinely advised to take supplements in the course of using the IBD-AID? If so, which ones? Etc.

The following information has been added to the methods section:

"Patients taking supplements (probiotics, vitamin/minerals, omega-3 fatty acids) included this information for the dietitian and were advised to continue or discontinue, depending on the needs of the individual and the dietary intake."

Discretionary Revisions

1. Texture phase / Symptomology

Page 6. Last sentence of middle paragraph.

Table 2 Chart

On page 6, the authors write, "the patient is advised to begin at a texture phase of the diet matching with symptomology, starting with phase one if in an active flare." It would be helpful to have more detail, or even a brief chart, describing the Relationship between texture phase and symptomology. Specifically, describing symptoms in more detail than Table 2's headings of "flare", "improving", or "most symptoms improved" may provide more guidance.

This becomes quite detailed. Each patient has a varied number and severity of symptoms. We leave this to the editor's discretion, as it would require more space. We have, however, modified table 2 to provide more detail.

2. Table 2. IBD-AID Food and Phase Chart

It may be instructive to include a paragraph or two summarizing the rationale of The "Phase Types" in regards to food. For example, describe the differences in vegetables and fruits from phase to phase. (Why are apples a Phase III food and pears a Phase II food? Or what makes spinach more tolerable than tomatoes?) This comment is asking for a general rationale, not a food-by-food listing. E.g., in the researchers' experience, does higher sugar content or fiber appear to make a fruit more/less tolerable?

Table 2 has been modified. These are excellent questions, but take much more space to describe the characterization and metabolism of each food and food group.

3. Updates to the Haas diet since the 1950s Page 9. 2nd paragraph
It may be noted that Elaine Gottschall, who popularized the SCD diet in the mid-1990s/2000s, had augmented Sidney Haas' original SCD as well as bringing the research in step with information available up to (approximately) the year 2000. One example of Gottschall's dietary augmentation was the inclusion of nut flours.

The SCD is the basis for our further development into the IBD-AID, but is quite complex in its own right. We leave this to the editor's discretion, as we are happy to devote more space to the details of the SCD.

Reviewer 3.

1. The study needs to be extended with increasing the number of subjects. Currently, only 8 CD (Crohn's disease) patients and 3UC (ulcerative colitis) patients are studied. This lack in number of subjects makes the data statistically non-significant.

We agree. The data is not significant, but remains important for further study, and provides a forum for exploration into diet and IBD. We do hope this leads to a larger study, which specifically determines how the diet works best for either CD, or UC.

2. Furthermore, the subjects should be age-matched for the study. For example: There is a significant variation in the ages of subjects in UC group. While, two subjects are #70 yrs old, one subject is 19 yrs. It is not advisable to take mean age in such cases.

We agree. Only range is now listed.

3. Authors have repeatedly made statements about the role of nutrition in maintenance of gut microbiota and its significant in IBD. However, there is no data in this study that supports such statements. To increase the impact of study, data pertaining to changes in microbiome before and after IBD-AID diet consumption should be included and correlated to clinical outcomes.

We agree that such a study is necessary. The microbiota and other physiological changes are postulated as hypothetical mechanisms behind the diet. We would certainly plan to prove this in a prospective study.

4. The diet schedules and durations should be clearly indicated. As indicated the patients used the diet for at least 4 weeks to see symptomatic relief. The authors are

suggested to provide the data related to recurrence of the symptoms once the diets were stopped. Alternatively, if the patients are still on these diets how well the diet is tolerated and correlate it to clinical symptoms of IBD.

We did not stop the diets, nor ask the patients to do so. Once the review was completed, IRB does not allow us to re-contact the patients, or review medical records without additional approvals. Of those patients seen in clinic by IRB-approved authors, anecdotally, most of them continued the diet and continued to show overall improvement, however, this was not rigorously studied and documented and is therefore not included in the manuscript.

Minor Comments:

1. Details regarding the clinical assessment criteria and parameters should be included in the text. The result should be represented in a consolidated table.

We admit some confusion regarding this comment, as the HBI and MTLWSI are described in methods. Table 1 outlines the medications, demographics and summary results.

2. Finally, there is extensive redundancy in the text. The manuscript needs to be clearly edited for such mistakes.

We have been through the paper, and have removed or reworded redundancies.

Discretionary Comments

1. It should be clarified if the patients were still on medication while consuming these foods? If so, how long they were on these treatments? Furthermore, it would be interesting to carry on this study in patients under remission. This will help in evaluating the efficacy of IBD-AID diet in maintaining remission as mentioned for Phase III.

Yes, the patients were all under the care of and following the advice of their GI docs. We agree that future studies need to look at maintenance of both the diet and of any remission. We bring this sentence to the reviewer's attention, in hopes this clarifies the questions (boldface added):

“After using the IBD-AID, which was the **only additional** intervention added, all (100%) of the patients **worked with their gastroenterologists to downscale their medication regimen** and all (100%) of the patients had their IBD symptoms reduced.”

Overall, there are some serious drawbacks in the experimental design of the study and it needs major revisions to be considered for publication.

We sincerely hope we have addressed several serious drawbacks of our manuscript, however, as this is a case-series study, not a RCT, we could not address drawbacks of the study design, and hope further RCT study will be stimulated.

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3. Marcel Roberfroid. *J. Nutr.* 137: 830S–837S, 2007.
4. Gibson GR, Probert HM, Van Loo JAE, Roberfroid MB. Dietary Modulation of the human colonic microbiota: Updating the concept of prebiotics. *Nutr Res Rev.* 2004;17:257–9.
5. Isabel Comino,¹ Ana Real,¹ Laura de Lorenzo,^{1,2} Hugh Cornell,³ Miguel Ángel López-Casado,⁴ Francisco Barro,⁵ Pedro Lorite,⁶ Ma Isabel Torres,⁶ Ángel Cebolla,⁷ and Carolina Sousa. Diversity in oat potential immunogenicity: basis for the selection of oat varieties with no toxicity in coeliac disease. *Gut.* 2011 July; 60(7): 915–922. Published online 2011 February 12. doi: 10.1136/gut.2010.225268.