Peer Review File

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Reviewer A

Comments:
Given the body of evidence you have presented it would be more accurate to include the words 'in Japan' (or something along those lines) in the title.
Reply The content of our paper is not restricted to Japan/Japanese. It applies to patients with inflammatory bowel disease worldwide.

Figure 5, 7 and 8 are unnecessary given that the data in these plots could easily be described in text.
Reply Readers will more easily understand the outcomes of our therapy incorporating a plant-based diet compared to those in the literature if bar graphs rather than text are used.

Table 2: Given that most of these studies contained in this Table were also conducted in patient cohorts prior to availability of biologics, I don't think much can be concluded from this.
Reply Relapse-free rates in the biologic era (after year 2000) have not been reported except for our article. In Table 2, five and three references show surgical rates after and before the biologic era, respectively.

Plant based diet score seems too specific to the Japanese diet to be broadly applicable to other cultures, this should be acknowledged by the authors.
Reply Plant-based diet score reflects adherence to a plant-based diet. I have added the following sentence at the end of the second paragraph (Line 530).
Our PBD can be modified among nations, races, and individuals based on their culture and tradition.

Line 108: simpler to just state Western diet.
Reply I have deleted "current".

Line 110: Need to explain further what you mean by 'Pro-inflammatory state'.
Reply 'Pro-inflammatory state' is briefly mentioned in Introduction. "Pro-inflammatory state" and the process leading to pro-inflammatory state/subclinical inflammation as a result of a westernized diet is described in Characteristics of PBDs in Lines 221-253.

Line 128-135: This argument is confusing. There are lots of other factors that could also be considered such as stress and exercise. I would suggest re-phrasing this.
Reply I have added stress and exercise to the list of representative environmental factors as follows.
Representative environmental factors are as follows: smoking, breastfeeding, non-steroidal anti-inflammatory drugs, antibiotic use in childhood, oral contraceptives, appendectomy, air pollution, stress, exercise, and diet (3).

Line 150: The incidence rate of UC appears to be increasing faster than Crohn's disease particularly after 1990 according to Figure 3.
Reply There would be a period of different increasing rates of incidence in ulcerative colitis and Crohn's disease: faster increasing rate in ulcerative colitis than Crohn's disease and vice versa.

Line 200: Reference 35 doesn't support this statement.
Reply I have deleted Line 200. I have inserted the following sentence in Line 200.
Because our PBD is lenient in terms of animal food exclusion, supplementary vitamins B12 and D needed in vegan diets (35) were not provided.

Line 217-228: Need references for these statements.
Reply The description of Line 217-228 is a summary of references (11-16). I have added the references (11-16) at the end of the sentence (Line 228).

Line 264: Need to define if these outcomes were self-reported or as assessed by a clinician, given the open nature of these studies this does potentially compromise the validity of the data.
Reply I have added assessed by a clinician at the end of the sentence at Line 265.

Line 283-286: Information describing the study cohorts would be better suited to a Table.
Reply All demographics of study patients are presented in tables in the original published articles cited.

Line 289-290: Given the broad lifestyle advice provided to patients it seems difficult to directly attribute the PBD to subsequent disease outcomes.
Reply Outcomes of our studies are thought to be largely due to replacement of a westernized diet with a plant-based diet. Comprehensive health care is fundamental in medicine. As you mentioned, healthy lifestyle education is thought to contribute to some extent to our outcomes.

Line 429: How much dietary fibre is provided in the PBD and have you measured butyrate/SCFA levels in patients on PBD? This data is important to support the argument made in this paragraph.
Reply The amount of dietary fiber is described at Line 194-195. We did not measure butyrate/SCFA levels.

Line 507: Unclear.
Reply I have added several words at the end of Line 507.
There will be a limitation to mere reduction of potentially untoward foodstuffs, red and processed meat, on suppression of relapse in Crohn's disease (105).

Line 523-524: I do not understand this argument, a placebo diet may still have some clinical benefit in this patient group.
Reply I take your point and I have deleted Lines 523-524.

Line 526: Tolerability of diet is an important factor that must be considered. Particularly as some patients may struggle with increased fibre intake from a PBD.
Reply I did not have such an experience in a few hundreds of patients with IBD.

Line 535-537: There are a number of studies in this area that have been done that should be acknowledged! See: DOI: 10.1080/17474124.2020.1733413
Reply Grosse CSJ et al. The role of plant-based diet in the pathogenesis, etiology and management of the inflammatory bowel diseases. Expert Rev Gastroenterol Hepatol 2020 Mar;14:137-145. DOI: 10.1080/17474124.2020.1733413. This is a review article introducing our four original articles published as of 2019. There was no original interventional study of plant-based diet in inflammatory bowel disease except for our studies.
Diets in inflammatory bowel disease are acknowledged, citing recent representative references. Reference (103) in Line 492 was published in 2021, and reference (105) in Line 508 was published in 2019.

Reviewer B

The authors utilize a PBD scoring system that allows assignment of each patient to following low, medium or high degree of PBD in their life, or when there is follow-up assessment.

There is no explanation, however, why certain foods lower the score, and certain foods raise the score. For example, why is red meat, eggs and fish lower the risk, when some fish can provide anti-inflammatory fats. It would be advantageous to explain the potential mechanisms why certain foods are considered IBD inducing. In that regard, it would be highly advantageous to separate fatty fish consumption from non-fatty fish consumption to better separate the individuals eating pattern and risk of IBD. Similarly, red meat that is highly processed could be assessed and score differently (negatively) compared to grass-fed organic meat which is not processed (potential positive attribute).
Reply The reason for risky foods or preventive foods for Japanese IBD patients are described in the reference cited (62).

Two references, one from Japan and one from France, reported fish was a risky food for IBD.
1) Sakamoto N et al. Epidemiology Group of the Research Committee on Inflammatory Bowel Disease in Japan. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis 2005 Feb;11(2):154-163.
2) Jantchou P et al. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. Am J Gastroenterol 2010 Oct;105(10):2195-2201.

Eggs are permitted in our plant-based diet (lacto-obo-vegetarian diet).
Grass-fed organic meat is new to me.

The authors make a good assessment of macronutrient characteristics of their dietary intervention, including a good indication of fiber intake, soluble fiber and insoluble fiber. This information can be used to model and develop personalized dietary patterns that produce similar macronutrient patterns but better fit an individual's preference through different ingredient selections that still produce the same macronutrient pattern.

There is still some concern about active, narrowing disease Crohn's patients who may not tolerate such high insoluble fiber intake early in their dietary therapy and whether a more animal-sourced pattern or elemental pattern would benefit these patients until they can tolerate increase fiber intake through resolution of localized inflammation.
Reply From my experience with a plant-based diet in patients with IBD who have diarrhea/loose stool and patients with constipation, it seems that a plant-based diet restores gut microbiota toward symbiosis, followed by suppression of symptoms. Therefore, both diarrhea and constipation become normalize with a plant-based diet. Chiba M et al. Efficacy of a plant-based diet (semi-lacto-ovo-vegetarian diet) for treating constipation. Recent Progress in Nutrition 2022;22(2) doi: 10.21926/rpn.2202012. We provide the diet from the beginning of treatment and patients achieve remission during the diet. This patient experience seems to enhance self-management skills. A plant-based diet works well even in severe active IBD, which convinced me that it is the right diet for IBD.

This information is missing in the current literature where there is a large body of clinical studies assessing the short term (up to 2 years) efficacy of targeted pharmaceuticals which generally have a limited efficacy ceiling of 50% or less, even with the use of immunomodulators, treat to target strategies and lately, dual biologic use.
Reply In this review, I want to point out the biggest problem with current IBD treatment in this review. For this purpose, the long-term efficacy of the therapeutic modality is of paramount importance rather than the short-term one.
I have added the following sentence to the text. Figure 7 shows remission rates, including the highest one in the literature in CD, of three biologics (infliximab, adalimumab, and ustekinumab) with/without azathioprine (71,78-82).

Clearly, the IBD field badly needs alternative approaches to break through this ceiling and this manuscript offers an excellent clinical narrative of patients over a decade or longer. It will certainly spawn new interest in researching diet as a modality for IBD and expand our understanding of an actual underlying mechanisms behind IBD etiology.

Reviewer C

The article is interesting and is an interesting supplement to the knowledge in the field of diet in IBD. However, it requires redrafting, systematization of sections and supplementation of some information.

1. The main concern is that the current knowledge in the introduction on dietary research in IBD of treatment-promoting substances in plant products has not been exhausted.
Kikut, J., Konecka, N., Ziętek, M. et al. Diet supporting therapy for inflammatory bowel diseases. Eur J Nutr 60, 2275–2291 (2021). https://doi.org/10.1007/s00394-021-02489-0
Diet Advice for Crohn's Disease: FODMAPs and Beyond.

Popa SL, Pop C, Dumitrascu DL.
Nutrients. 2020 Dec 6;12(12):3751. doi: 10.3390/nu12123751.

1B-anti-inflammatory diet
Food and Food Groups in Inflammatory Bowel Disease (IBD): The Design of the Groningen Anti-Inflammatory Diet (GrAID).
Campmans-Kuijpers MJE, Dijkstra G.
Nutrients. 2021 Mar 25;13(4):1067. doi: 10.3390/nu13041067.
Reply In this review, my goal is to point out the biggest problem with current IBD treatment. For this purpose, induction of remission and the long-term efficacy of the therapeutic modality are of paramount importance. It seems unnecessary to cite references which do not report on induction rates or long-term efficacy of dietary intervention.

2. Western diet is too general a statement covering a number of modifications related to animal husbandry, plant cultivation, food production, food additives that are worth briefly describing to avoid the simplification that it is only about fast food
https://www.degruyter.com/document/doi/10.1515/pteridines-2018-0020/html
Reply The dietary change with economic transition in Figure 4 is called westernized diet. Westernized diets are generally described as high in fat, animal protein, and sugar, and low in dietary fiber, as described in Line 221.

3. There is no section materials and methods which should include:
- description of the study group (number, sex, age, race, number in remission and exacerbation phase).
- dietary intervention - characteristics, average duration of the intervention.
Reply This paper is not an Original Research Study. It is a Clinical Practice Review. Materials and methods are described in detail in the references cited.

4. A paragraph on food interactions of the drugs in question may be added.
Reply The relation between food and drugs is a new area to be investigated. It is discussed in Lines 419-431.

5. In the discussion, it is worth considering and referring to similar assumptions of the Israeli diet popular in other regions and in Europe.
Yanai H, Levine A, Hirsch A, Boneh RS, Kopylov U, Eran HB, Cohen NA, Ron Y, Goren I, Leibovitzh H, Wardi J, Zittan E, Ziv-Baran T, Abramas L, Fliss-Isakov N, Raykhel B, Gik TP, Dotan I, Maharshak N. The Crohn's disease exclusion diet for induction and maintenance of remission in adults with mild-to-moderate Crohn's disease (CDED-AD): an open-label, pilot, randomized trial. Lancet Gastroenterol Hepatol. 2022 Jan;7(1):49-59. doi: 10.1016/S2468-1253(21)00299-5.
Reply Yanai et al. assessed the effect of the Crohn’s disease exclusion diet (CDED) for mild-to-moderate Crohn’s disease. The study was not designed for all patients with Crohn’s disease. Moreover, their follow-up period was only 24 weeks. The remission rates at week 6 and 24 were 57.1% (12/21) and 38.1% (8/21), respectively. Average C-reactive proteins were above the reference range at both 6 and 24 weeks. It seems unnecessary to refer to this reference. References (103) and (105) in our text focus on dietary treatment in IBD.

6. Line 515-516 is redundant.
Reply The outcomes of our modality in IBD are the best in the world. A new modality has to surpasses our induction rate in CD (96%) and relapse-free rate at 10 years (52%) before its widespread uptake. If use of our modality becomes widespread in the future, historians will want to know how and when a plant-based diet was incorporated. I do not think Line 515-516 is not redundant. It will encourage researchers whose new observation was previously rejected for publication.

7. The article should be adapted to the editorial guidelines of the journal.
Reply To the best of our knowledge, we have followed the guidelines for Clinical Practice Review. If the editorial office points out a violation, we will amend it.