

July 21, 2015

Dear Editor,

First of all, I would like to thank the Editor and the Reviewers for the very valuable comments which help us revise and improve the quality of our manuscript.

Please find enclosed the revised manuscript in Word format (file name: 18608-revised manuscript.doc).

Title: Advances in nutritional therapy in inflammatory bowel diseases: review

Author: Andrzej Wędrychowicz, Andrzej Zając, Przemysław Tomasik

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 18608

The manuscript has been improved according to the suggestions of reviewers: The individual response is provided below each comment. We indicated the individual responses for the reviewers in yellow hi-liter color in the text of the manuscript and also cited in the answering reviewers letter.

1 Manuscript format has been updated according to the format for Topic Highlight.

2 Revision has been made according to the suggestions of the reviewer 00483653:

This is a comprehensive, extensively referenced and thought provoking review, only a few issues

1) Clarify whether the title of your article should be “Nutrition as cause and treatment of Crohn’s disease”! not IBD, both UC and Crohn’s. Is enteral or IV nutrition effective for UC patients?

Answer: We modified the title of our article, but we decided to keep the “IBD” term in the title. We definitely agree with the reviewer that nutritional therapy is evidently more effective in CD than UC patients and we discussed it in our review, but we also showed and discussed the latest research data regarding etiopathogenesis of UC and compared them with CD. That why, in our opinion the term

“IBD” in the title better reflect the content of the article than term “CD”.

2) Tell the reader in detail the difference between an elemental, semi-elemental and polymeric diet. There are three components to an enteral formula, what are the precise differences in the lipid, protein and carbohydrates between an elemental formula, a semi-elemental formula and a polymeric formula?

Answer: We described the differences between an elemental, semi-elemental and polymeric formula in protein, carbohydrates and lipid composition.

“Three main types of enteral formulas are used in EEN depending on the degree of protein hydrolysis. Polymeric formulas are planned to mimic the general diet with non-hydrolyzed proteins, carbohydrates and fat. The source of protein is usually casein, carbohydrates are provided as corn maltodextrin while the source of fat is canola or soybean. Semi-elemental and elemental formulas are planned for use in patients with malabsorption, so the nutrients are partially (semi elemental formulas) or fully hydrolyzed (elemental formulas). Protein is usually in form of dipeptides or tripeptides in semi elemental formulas and free amino acids in elemental ones. Carbohydrates are supplied as hydrolyzed cornstarch, maltodextrin or fructose, and lipids as fatty acids esters or medium-chain triglycerides ^[180]. Additionally, diet may be of standard concentration (1kcal/ml) or high concentration (2 kcal/ml). Depending on the fat concentration, very low fat diets (< 3g/1000 kcal), low fat diets (< 20g/1000 kcal) and high fat diets (>20g/1000 kcal) may be distinguished ^[3].”

3) If possible, decide which component, carbohydrate, fat or protein, that you the authors think is inducing and maintaining remission in patients with Crohn’s disease needs to be discussed. I personally think that it is the carbohydrate component. There is a decent literature on the role specifically of carbohydrates other than monosaccharides on Crohn’s disease and other so called autoimmune diseases, the carbohydrates feeding either specific microbes such as *Klebsiella pneumoniae* or generally “bad microbes.” Rashid T, Ebringer A, Tiwana H, Fielder M. Role of *Klebsiella* and collagens in Crohn's disease: a new prospect in the use of low-starch diet. *Eur J Gastroenterol Hepatol*. 2009 Aug;21(8):843-9. doi: 10.1097/MEG.0b013e328318ecde. Review. PubMed PMID: 19352192. Ebringer A, Wilson C. The use of a low starch diet in the treatment of patients suffering from ankylosing spondylitis. *Clin Rheumatol*. 1996 Jan;15 Suppl 1:62-66. Review. PubMed PMID: 8835506. Ebringer A, Rashid T, Tiwana H, Wilson C. A possible link between Crohn's disease and ankylosing spondylitis via *Klebsiella* infections. *Clin Rheumatol*. 2007 Mar;26(3):289-97. Epub 2006 Aug 29. Review. PubMed PMID: 16941202.

Answer: We described and discussed the role of *Klebsiella pneumonia* and low-starch diet in the etiopathogenesis of IBD. We also cited the references suggested by the reviewer.

“Starch, one of the most important carbohydrates present in the human diet has strong influence on the microbiome as well. It is a necessary substrate for intestinal

bacteria, especially promoting the development of *Klebsiella* microbes [29]. Because in CD patients high levels of anti-*Klebsiella* antibodies were detected, there is a theory indicating *Klebsiella* species are an important factor, inducing autoimmunological reactions through the mechanism of molecular mimicry. Furthermore, strong positive correlation and cross-reactive antibodies were observed between *Klebsiella* and collagen in CD and ankylosing spondylitis patients [30]. Additionally, the “low starch diet” used in ankylosing spondylitis patients decreased the level of inflammatory mediators and reduced the clinical symptoms of disease [31].

4) Along this vein, reference and discuss what in English literature is called the specific carbohydrate diet, ie a monosaccharide/low carbohydrate diet, which now has a small literature discussing it: Cohen SA, Gold BD, Oliva S, Lewis J, Stallworth A, Koch B, Eshee L, Mason D. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2014 Oct;59(4):516-21. PMID: 24897165. Suskind DL, Wahbeh G, Gregory N, Vendettuoli H, Christie D. Nutritional therapy in pediatric Crohn disease: the specific carbohydrate diet. J Pediatr Gastroenterol Nutr. 2014 Jan;58(1):87-91. PubMed PMID: 24048168.

Answer: We described the content and discussed the latest references regarding specific carbohydrate diet in the treatment of IBD.

“Recently, interesting studies regarding the use of the “specific carbohydrate diet” (SCD) in CD children were published. SCD, initially used in celiac disease treatment almost 70 years ago, contains almond, nut and coconut flours, and excludes grains (wheat, rice, corn). Additionally, the majority of dairy products are restricted, except fermented yogurt and the only sugar allowed is fructose (honey). Two small, independent US retrospective studies, assessing the SCD as the sole method of treatment in CD children showed that the use of SCD for 5 to 30 (or 12 to 52, respectively) months, had positive effects on laboratory inflammatory markers and clinical presentation of the disease, including mucosal healing [32, 33]. The direct reason for the improvement was not known, but modification of the intestinal microbiome was the most probable cause. Nevertheless, prospective studies are necessary to confirm these preliminary results.”

5) Consider including a discussion of a specific “bad bacteria” associated with Crohn’s disease and UC, *Mycobacterium avium* subspecies paratuberculosis (MAP), that ties together your discussion of meat and dairy products (both containing MAP) and in most studies high sugar diets (via increasing the invasiveness of MAP?) increasing the risk of both UC and Crohn’s: Patel D, Danelishvili L, Yamazaki Y, Alonso M, Paustian ML, Bannantine JP, Meunier-Goddik L, Bermudez LE. The ability of *Mycobacterium avium* subsp. paratuberculosis to enter bovine epithelial cells is influenced by

preexposure to a hyperosmolar environment and intracellular passage in bovine mammary epithelial cells. Infect Immun. 2006 May;74(5):2849-55. PubMed PMID: 16622223 Does the efficacy of elemental/semi-elemental/polymeric diets support or refute the idea of bad microbes in general or MAP in particular causing Crohn's or UC?

Answer: We cited and discussed the role of *Mycobacterium avium* subspecies *paratuberculosis* (MAP) and adherent-invasive *Escherichia coli* (AIEC) in the pathogenesis of CD and UC.

"On the other hand, an alternative explanation may be connected with *Mycobacterium avium* subspecies *paratuberculosis* (MAP) infection, which is strongly suspected in the pathogenesis of multiple diseases, including IBD [46, 47]. MAP is broadly distributed in the environment, water and food. Some nutrients, such as milk, meat and sugar may fortify its invasiveness [48, 49]."

and

"The role of invasive bacterial species as triggers and coinfection factors in IBD has not been fully identified. Recent studies reported an increased prevalence of MAP and adherent-invasive *Escherichia coli* (AIEC) in intestinal tissues, stool cultures and blood of CD and UC patients, especially in the active stage of disease [49]. EEN may influence invasive bacterial species and decrease their prevalence through modification of bacterial diversity and modulation of predominant intestinal bacterial microflora. This may also be a potential mode of action of nutritional therapy in IBD [199, 200]."

6) You are very clear that enteral feeding is superior to parenteral nutrition for multiple reasons. Consider changing your last sentence to ...while parenteral or intravenous nutrition should only be considered in those with enteral nutrition intolerance or during perioperative periods of treatment.

Answer: We modified the last sentence of the article according to the suggestion of the reviewer.

"EEN is the first-line therapy option in active CD in children and to a lesser degree in adult patients while PN should only be considered as an alternative method of nutrition for those with EN intolerance or during perioperative periods of treatment."

And according to the suggestions of reviewer 00033372:

Comments To Authors: This is an article reviewing about the role of nutrition in the management of inflammatory bowel disease (IBD), including ulcerative colitis and Crohn disease. Only a few points should be further clarified:

(1) Please clearly indicate the composition of "exclusive enteral nutrition", which has important role in inducing and/or maintaining the remission of Crohn disease in pediatric patients.

(2) Furthermore, the suggested kinds and percentages of carbohydrate, protein and lipid in the elemental, semi-elemental and polymeric formulas should be disclosed and compared to one another.

Answer: We combined answer for suggestions no 1 and 2. We described the composition of formulas used in exclusive enteral nutrition in CD patients.

“Generally, EEN is the provision of 100% of a person’s nutritional requirements from a liquid nutritional formula either orally or via a feeding tube. EEN is usually provided for 6–8 weeks and then a normal diet is gradually reintroduced [179].

Protocols of EEN may be different regarding composition of the enteral formula and route of administration. Three main types of enteral formulas are used in EEN depending on the degree of protein hydrolysis. Polymeric formulas are planned to mimic the general diet with non-hydrolyzed proteins, carbohydrates and fat. The source of protein is usually casein, carbohydrates are provided as corn maltodextrin while the source of fat is canola or soybean. Semi-elemental and elemental formulas are planned for use in patients with malabsorption, so the nutrients are partially (semi elemental formulas) or fully hydrolyzed (elemental formulas). Protein is usually in form of dipeptides or tripeptides in semi elemental formulas and free amino acids in elemental ones. Carbohydrates are supplied as hydrolyzed cornstarch, maltodextrin or fructose, and lipids as fatty acids esters or medium-chain triglycerides [180]. Additionally, diet may be of standard concentration (1kcal/ml) or high concentration (2 kcal/ml). Depending on the fat concentration, very low fat diets (< 3g/1000 kcal), low fat diets (< 20g/1000 kcal) and high fat diets (>20g/1000 kcal) may be distinguished [3].

(3) Please tell the readers how to conquer the odor of digested nutrients, mainly amino acid in the elemental formula, which is poorly tolerant to patients. Even the use of NG tube feeding, the belching or hiccup by patient himself would decrease the compliance.

Answer: We cited and discussed the problem with the bitter taste of the elemental formula.

“Bitterness, offensive smell, and belching and hiccup may considerably impair patients’ quality of life and compliance during EN with the use of elemental formula. Modification of the formula by changing the particle size of branched-chain amino acids reduced these symptoms and increased patient compliance [223]. Moreover, some additive flavors such as apple, pineapple, and fruit flavors increased sweetness and sourness and masked the bitterness of the formula [223].”

(4) The role of immunonutrients, such as glutamine and arginine, which were considered to modulate human’s immunity and hence influence the disease activity of IBD, should be reviewed in

[this article](#).

Answer: We reviewed and discussed the role of immunonutrients such as glutamine and arginine in EN in IBD patients. We also cited the actual guidelines and recommendations about immunonutrients in EN.

“Nevertheless, some components of EN such as glutamine, **arginine** and polyunsaturated fatty acids were shown to have beneficial properties in IBD patients [190].

Despite the fact that some experimental and clinical studies showed a positive effect of arginine and glutamine on clinical symptoms and inflammatory mediators in different inflammatory diseases, including CD, their role in IBD is poorly documented up to now [191, 192]. Although early studies showed an improvement in the clinical course of diseases after arginine-enriched formulas used in EN, the latest meta-analyses did not confirm these findings [193, 194]. Additionally, a glutamine-enriched enteral diet was not confirmed to be superior to a standard polymeric diet in active CD patient treatment [195]. Moreover, data from clinical studies on EN in critically ill patients showed conflicting results. In some groups of patients increased mortality was observed after glutamine-enriched EN [180]. Based on these results, the latest ESPEN guidelines did not recommend the use of immune mediating nutrients in EN [196].”

(5) The English-editing should be done before publication.

Answer: We used professional English editing service for language editing of our manuscript before the resubmission.

3 References and typesetting were corrected

We performed CrossCheck analysis using AntyPlagiat.net software. Because the article was too big for one analysis, the software divided it for two parts. We enclosed the screenshots and certificates of both parts of the manuscript.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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