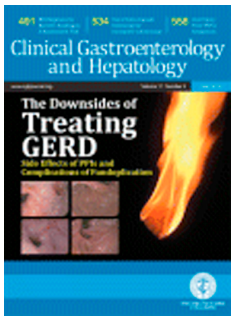
Journal Pre-proof



Dietary Guidance for Patients with Inflammatory Bowel Disease from the International Organization for the Study of Inflammatory Bowel Disease

A. Levine, MD, J.M. Rhodes, MD, J.O. Lindsay, MD, M.T. Abreu, MD, M.A. Kamm, MD PhD, P.R. Gibson, MD, C. Gasche, MD, M.S. Silverberg, MD, U. Mahadevan, MD, R. Sigall Boneh, RD, E. Wine, MD, O.M. Damas, MD, G. Syme, RD, G.L. Trakman, BSc RD, C.K. Yao, RD, S.I. Stockhamer, MD, M.B. Hammami, MD, L.C. Garces, RD, G. Rogler, MD, I.E. Koutroubakis, MD, PhD, A. Ananthakrishnan, MD, MPH, McKeever Liam, PhD, RDN, J.D. Lewis, MD MSCE

PII: S1542-3565(20)30185-3
DOI: https://doi.org/10.1016/j.cgh.2020.01.046
Reference: YJCGH 57007

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 24 January 2020

Please cite this article as: Levine A, Rhodes J, Lindsay J, Abreu M, Kamm M, Gibson P, Gasche C, Silverberg M, Mahadevan U, Sigall Boneh R, Wine E, Damas O, Syme G, Trakman G, Yao C, Stockhamer S, Hammami M, Garces L, Rogler G, Koutroubakis I, Ananthakrishnan A, Liam M, Lewis J, Dietary Guidance for Patients with Inflammatory Bowel Disease from the International Organization for the Study of Inflammatory Bowel Disease, *Clinical Gastroenterology and Hepatology* (2020), doi: https://doi.org/10.1016/j.cgh.2020.01.046.

Dietary Guidance for Patients with Inflammatory Bowel Disease from the International Organization for the Study of Inflammatory Bowel Disease

Levine A MD[1*], Rhodes JM MD [2*], Lindsay JO MD [3*], Abreu MT MD [4*], Kamm MA MD PhD[5*], Gibson PR MD [6*], Gasche C MD [7*], Silverberg MS MD [8*], Mahadevan U MD [9*], Sigall Boneh R RD[1], Wine E MD[10], Damas OM MD[4], Syme G RD[11], Trakman GL BSc RD [5], Yao CK RD [6], Stockhamer SI MD[8], Hammami MB MD[9], Garces LC RD [4], Rogler G MD [12*], Koutroubakis IE MD, PhD [13*], Ananthakrishnan A, MD, MPH[14], Liam McKeever, PhD, RDN[15], Lewis JD MD MSCE[15*],

Pediatric IBD Center, Wolfson Medical Center Holon, Tel Aviv University, Israel[1] , Institute of Translational Medicine, University of Liverpool, UK[2], Centre for Immunobiology, Blizard Institute, Barts and the London School of Medicine, Queen Mary University of London,UK[3] , Division of Gastroenterology, Department of Medicine, University of Miami Miller School of Medicine, USA[4], St Vincent's Hospital and University of Melbourne, Australia[5], Monash University and Alfred Health, Melbourne, Austarlia[6], Medical University Vienna, Austria [7], Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, University of Toronto, Toronto, Canada[8], University of California, San Francisco, USA[9], Departments of Pediatrics & Physiology, University of Alberta, Canada [10], The Royal London Hospital, Barts Health NHS Trust, London, UK [11], University Hospital, Zurich, Switzerland[12] ,University Hospital of Heraklion, Heraklion Greece [13], Massachusetts General Hospital, Boston, USA [14] Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA [15]

* IOIBD Nutrition Cluster members contributed equally to this manuscript

Address for Correspondence: James D. Lewis, MD, MSCE, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Authors' Contributions: Conception and design of the study (JL, AL, JR, JL). Generation, collection, assembly, analysis and/or interpretation of data (all authors).Drafting or revision of the manuscript (all authors). Approval of the final version of the manuscript (all authors). Conflicts of Interest: Dr. Lewis reports having received honorarium from Nestle Health Sciences, Pfizer, Gilead, UCB, Arena Pharmaceuticals, Samsung Bioepis, Bridge Biotherapeutics, and Bristol-Myers Squib. He has received grant funding from Nestle Health Science, Takeda and Janssen. He has received honorarium for participation in CME programs from Nestle Health Science. Dr. Levine received honorarium, IP, consulting or grants from: Nestle Health Science, Jannsen, Abvie, Takeda, Megapharm. Dr. Gibson has served as consultant or advisory board member for Allergan, Janssen, MSD, Pfizer, Anatara, Atmo Biosciences, Immunic Therapeutics and Takeda. His institution has received speaking honoraria from Janssen, Shire, Bristol-Meyers Squibb and Pfizer. He has received research grants for investigator-driven studies from MSD and A2 Milk Company. His Department financially benefits from the sales of a digital application and booklets on the low FODMAP diet. He has

published an educational/recipe book on diet. Ms. Boneh has received Speaker Honorariums from Nestle Health Science, Takeda and Manuscript Click here to download Manuscript CGH IOIBD diet 20190716 Clean.docx Megapharm. Dr. Koutroubakis has served as advisory board member for Abbvie, Astelas, Genesis, Janssen, MSD, Pharmacosmos, Pfizer, Shire and Takeda; Speaker for AbbVie, Astelas, Genesis, Janssen, MSD and Takeda; research support Abbvie and Ferring. Dr. Wine has received honoraria from AbbVie (advisory board; speaker fee), Janssen (speaker fee), and Nestle (speaker fee). Dr. Rhodes with the University of Liverpool and Provexis UK, holds a patent for use of a soluble fibre preparation as maintenance therapy for Crohn's disease plus a patent for its use in antibiotic-associated diarrhea. Dr. Abreu has served as a consultant to Prometheus Laboratories, Takeda, UCB Inc., Pfizer, Janssen, Focus Medical Communications and Eli Lilly Pharmaceuticals; is a trainer or lecturer for CME Outfitters and Imedex, Inc. and serves on the scientific advisory board of AbbVie Laboratories, Celgene Corporation, Shire Pharmaceuticals, Roche Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals, AMGEN, Allergan, SERES, Nestle Health Science, and GILEAD, as well as on the board of directors for the GI Health Foundation. Dr. Yao CKY has received research support for investigator-driven studies for Ferring Pharmaceuticals Pty Ltd, Danone and Yakult Australia. Drs./Mrs./Ms. Ananthakrishnan, Lindsay, Gasche, Rogler, Silverberg, Mahadevan, Kamm, Trakman, Hammami, Stockhamer, Damas, Garces, Syme and McKeever have no relevant conflicts of interest to report.

Abstract:

Recent evidence points to a plausible role of diet and the microbiome in the pathogenesis of both Crohn's disease (CD) and Ulcerative Colitis (UC). Dietary therapies based on exclusion of table foods and replacement with nutritional formulas and/or a combination of nutritional formulas and specific table foods may induce remission in CD. In UC, specific dietary components have also been associated with flare of disease. While evidence of varying quality has identified potential harmful or beneficial dietary components, physicians and patients at the present time do not have guidance as to which foods are safe, may be protective or deleterious for these diseases. The current document has been compiled by the nutrition cluster of the International Organization of IBD (IOIBD) based on the best current evidence to provide expert opinion regarding specific dietary components, food groups and food additives that may be prudent to increase or decrease in the diet of patients with IBD to control and prevent relapse of IBD.

Keywords: Crohn's disease; ulcerative colitis; meat; fruit; vegetables; food additives

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), have long been thought to arise from inappropriate and maladaptive stimulation of the immune system. Emerging evidence demonstrates that environmental factors, including diet, may play an important role in the pathogenesis and inflammation. This highlights the need to provide guidance to physicians and patients regarding which foods may be harmful, beneficial, or safe to consume.

To address this gap in patient care and education, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) formed a working group to formulate recommendations for physicians, dietitians, and patients based upon best available evidence. These recommendations focus on dietary patterns to control and prevent relapse of IBD.

Methods:

The IOIBD Nutrition Cluster is composed of 12 members from three continents (https://www.ioibd.org/clusters/). Following an organizational meeting in March 2018, 7 food groups, dietary components and 5 food additives were selected as the most important to address for patient dietary guidance. These included dairy, red meat, processed meat, poultry, eggs , fruits and vegetables, fat, refined sugar, wheat and gluten, alcohol, emulsifiers, maltodextrins and artificial sweeteners, gums and thickening agents, and nanoparticles. The group assigned members to review the published literature for each of the chosen foods or additives. The reviewer was to summarize the published data separately for studies involving humans and animal models. Animal data received more attention when human data was absent or the animal models were considered reproducible and of clinical importance. Given the broad scope of the topic and the quality of the existing data, no attempt was made to produce summary risk estimates.

The members prepared a concise document that included overall recommendations and a narrative summary. Where there were fewer data from studies in humans, more data were presented from animal models. Although it would be ideal to know the exact amount of each food that patients with IBD should consume, this could vary by age, sex, weight, etc. Additionally, there generally were insufficient published data for such specific recommendations. Therefore, recommendations were provided separately for CD and UC, and were chosen from 4 categories (prudent to increase consumption, to

decrease or avoid consumption, safe to consume or insufficient evidence to make a claim). During group discussion, some items were modified to state that it "may be prudent to increase or decrease consumption."

The Cluster chairs (AL and JDL), in collaboration with the workgroup co-leads (JOL and JR) edited the first drafts to create a common format. The IOIBD cluster members reviewed the data and the recommendations at a face-to-face meeting in March 2019 and voted upon the recommendations and wording, with consensus defined as >75% agreement. Following the meeting, the chairs slightly revised the wording of a few of the recommendations during the manuscript drafting in response to comments by the authors. Subsequently, a final vote was taken via a REDCap survey in July 2019, using the same definition of consensus. The evidence level (EL) supporting the recommendation was categorized loosely based on the following scale: randomized controlled trials (RCTs) provide high level evidence, observational studies in humans provide low level evidence and everything else is very low level evidence. Level of evidence could be increased or decreased based on the strength of association and reproducibility of findings, or quality of studies. Because the objective of the guidance document is to help patients with established diagnosis of IBD, studies examining the role of diet in the etiology of IBD were categorized as EL very low. When possible, the review focused on the effect of diet on inflammation and symptoms; although, in some cases, data were only available for symptom control. Exclusive enteral nutrition, a known effective therapy for Crohn's disease, was not addressed. All recommendations were made without consideration of other comorbid conditions that may influence choice of dietary patterns.

Recommendations

Consensus was achieved for all food types except pasteurized dairy consumption (Table 1).

Fruit & vegetables

In CD it is prudent to recommend moderate to high consumption of fruits and vegetables (EL low). In patients with symptomatic or significant fibrostricturing disease, insoluble fiber intake should be restricted (EL very low)

In UC, there is insufficient evidence to recommend any specific change or restriction in intake of fruit and vegetables. (EL very low)

Fruits and vegetables are a diverse group of foods that generally have in common high fiber content. Fibers are undigested in the human small intestine, but the majority are fermented by bacterial enzymes within the colon, soluble fiber usually more rapidly than insoluble. Fermentation produces short chain fatty acids (SCFA), such as butyrate, that act as carbon and energy sources for the colonic epithelium. Decreased production of SCFA may occur in patients with active IBD.[1]

Significant dietary restriction of fiber leads to greater bacterial consumption of colonic mucus which might contribute to inflammation.[2] Specific soluble fibers, including plantain (banana) and broccoli pectins, reduce bacterial adherence and translocation by the epithelium;[3] fiber may also serve as growth substrates for important SCFA-producing commensal bacteria.

Epidemiological studies suggested that IBD patients consume less fruit and vegetables before disease onset, particularly for CD.[4-6] In the prospective Nurses' Health Study, women in the highest quintile for fruit fibre had approximately half the risk for subsequent Crohn's disease development.[6] However, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, no association between fiber intake and subsequent risk for CD or UC was found.[7] Higher intake of fruits and vegetables has been associated with lower endoscopic activity of UC.[8] An internet-based prospective study found that, among people with CD in remission, those in the highest quartile for fiber consumption were nearly half as likely to flare during 6 months follow-up, but there was no such association in UC.[9] Patients with stricturing CD tend to avoid high fiber foods.

A RCT of 2-years high fiber/low sugar diet showed no significant benefit or harm in adults with inactive or mildly active CD.[10] In another trial among patients with CD, symptoms were worse with supplementation of inulin than placebo.[11]

Data from additional studies are presented in Supplemental Table 1.

Refined Sugar and Carbohydrates

Recommendation

In CD, there is insufficient evidence to recommend any specific change of intake of complex carbohydrates or refined sugars and fructose (EL low). It may be prudent to use a low FODMAP diet when for patients with persistent symptoms despite resolution of inflammation and absence of strictures (EL low).

In UC, there is insufficient evidence to recommend any specific change of intake of complex carbohydrates or refined sugars and fructose (EL very low). It may be prudent to use a low FODMAP diet for patients with persistent symptoms despite resolution of inflammation (EL low).

Several cross-sectional and case-control studies have observed increased sugar consumption in CD patients[6, 12-20], although others suggest that this reflects a 'modern lifestyle' and is not necessarily causal. Evidence is lacking for UC.

A randomized, controlled, multicenter study, including 352 patients with CD compared diets rich either in carbohydrate in its refined form or carbohydrate in its natural unrefined form without finding a significant difference in worsening clinical disease activity.[10] Another randomized, controlled, multicenter dietary study, including 134 patients with CD in remission[21] who were instructed either to adhere to a low carbohydrate diet (of less than 84 g per day), mainly in a fiber-rich form or diet as usual. The intention-to-treat analysis showed no significant difference relative to the control group for prevention of relapse after one year; though patients appeared to have a symptomatic benefit during time that they adhered to the diet. A small uncontrolled study of the specific carbohydrate diet which excludes sucrose, fructose and other refined sugars demonstrated reductions in symptoms and mucosal inflammation as assessed by capsule endoscopy among children with CD.[22]

There is no evidence of a role for altering the intake of slowly absorbed and non-digestible short-chain carbohydrates (collectively known as FODMAPs) in modulating inflammatory activity of IBD. A placebo-controlled trials involving 15 g/day fructo-oligosaccharides in patients with CD[11] and challenge for 3 days with specific FODMAPs in patients with quiescent IBD did not significantly change inflammatory activity[23], although fructans in both induced symptoms. Lowering of FODMAP intake in patients

with symptomatic but quiescent IBD was associated with amelioration of functional gastrointestinal symptoms in comparison with those on a placebo diet without change in inflammatory status[26], suggesting that these patients suffered from concomitant irritable bowel syndrome. Similar findings were noted in a feeding cross-over study[27].

Wheat and Gluten

Recommendations

In CD there is insufficient evidence to recommend restriction of wheat and gluten (EL Low)

In UC there is insufficient evidence to recommend restriction of wheat and gluten (EL Low)

Current evidence for restriction is based largely from 3 cross-sectional surveys where the prevalence of presumed gluten-associated symptoms was 5-28% in patients with IBD[28-30] (Supplemental Table 2). Presumed gluten-associated symptoms were more common among those with stricturing or more severe CD and active disease.[28, 30] In one study of gluten restriction, a high prevalence (65%) of patients observed improvements in one or more IBD symptoms, 38% described reduced frequency and severity of disease flares and strict dietary adherence was associated with marked improvement in fatigue.[29] There are no data to indicate whether mucosal healing can be achieved via this dietary approach. Since gluten co-exists in cereals with FODMAPs, improved symptoms might be related to reduced FODMAP intake.

Gluten is hypothesized to modulate immune pathways in the small intestine,[31] but the only supportive evidence comes from TNF knockout-mice.[32] Other wheat-protein components, such as amylase trypsin inhibitors (ATIs), may drive intestinal inflammation.[33]

Red Meat, Processed Meat, Poultry & Eggs

Recommendations

In CD, there is evidence that it is unnecessary to restrict moderate consumption of unprocessed red meat, lean chicken meat (breast of chicken) and eggs (EL high).

In UC, it is prudent to reduce intake of red and processed meat (EL low).

In a systematic review, 6 of 8 studies demonstrated an association between red meat intake and incidence or worsening of UC, two of which were statistically significant. In a prospective French inception cohort of 67,581 people,[34] high animal protein intake was associated with a significantly increased risk of IBD, CD and UC for the highest versus the lowest tertile of consumption (IBD overall HR 3.03, 95% CI 1.45 – 6.34, P_{trend} = 0.005 corrected for energy intake). Red meat intake was also associated with a greater than 5-fold increase in the odds of a UC relapse in one prospective study[35], but not in a recent smaller study that combined patients with CD and UC.[36] A cross-sectional study in 103 adults in remission[37] also demonstrated a higher risk of relapse with an OR of 3.6 for the highest quartile of red meat consumption. However, a more recent study[38] in 412 adults with UC in remission and followed until relapse demonstrated that the intake of fats and specifically myristic acid was associated with flares, while processed meats were not. Myristic acid is a saturated fatty acid enriched in coconut oils, dairy fats but also in beef from grain fed cattle.[39] Red meat was not assessed independently in this study.

One prospective clinical trial comparing high versus low levels of consumption of red meat or processed meat has been conducted in adults with CD.[40] Relapse rates did not differ between the two treatment groups. Recently published clinical trials involving a diet that required daily consumption of chicken breast and two eggs/day for 12 weeks was associated with high rates of remission in active CD[41-43] suggesting that these products are safe to consume in moderation as a source of protein in CD. A summary of studies of meat consumption is included in **Supplemental Table 3**.

Dairy

Recommendations

Consensus was not obtained for CD or UC for pasteurized dairy products. Consensus was obtained that unpasteurized dairy products should not be consumed.

Dairy products include a wide variety of natural and processed foods which may vary greatly from one product to another due to differences in processing, fat content and food additives. Most contain lactose, but some do not. In the developed world, dairy

products often contain significant amounts of emulsifiers, carrageenans and other thickening agents which are subsequently reviewed. This complicated the discussion and led to lack of consensus.

Exposure to casein in a DSS mouse model of UC led to increased severity of colitis. However human data are lacking to confirm this experiment.[44] In the prospective EPIC study, there were no statistically significant trends between the intake of dairy products and the development of CD or UC.[45] (**Supplemental Table 4**).

Prospective cohort studies report a prevalence of lactase deficiency of 40-50% in CD and 27-40% in UC, both higher than in healthy controls.[46, 47] A recent systematic review and meta-analysis of 17 studies reported an odds ratio compared to controls for lactose malabsorption in CD patients of 2.29 (1.09–4.80; p=0.03) and in UC of 1.14 (0.69–1.86; p = 0.62).[48] Therefore, it appears that lactose malabsorption is more common in patients with CD than healthy controls.

Baseline dairy intake was not associated with risk of disease flare in adults with quiescent UC and eliminating dairy in a small randomized trial had no apparent benefit on pediatric UC patients.[35, 49]

Unpasteurized milk should be avoided by all patients with inflammatory bowel disease given the potential risk of infections.

Fat

Recommendations

In CD, it is prudent to reduce exposure to saturated fats (EL low) and avoid trans fat (EL very low).

In UC, it is prudent to reduce consumption of myristic acid (palm oil, coconut oil, dairy fats) (EL low). It is prudent to increase dietary consumption of omega-3-fatty acids (DHA and EPA) from marine fish (EL low), but not from supplements (EL high). It is prudent to avoid trans fat (EL very low).

Total fat

In a prospective cohort of adult patients with UC, increased meat consumption, especially processed meats, and sulfur were associated with a higher risk of relapse.[35] The highest tertile of consumption of fat also had a higher risk for flare than the medium

tertile of fat consumption (OR 2.52 (1.06‑5.97)).Total fat intake is associated with active CD in some, but not all studies.[50, 51] Studies of enteral nutrition formulas show no consistent variation in efficacy for CD based on total fat content.[52]

Saturated Fats

Among 412 UC patients in clinical remission on mesalamine, only higher intake of myristic acid, a saturated fatty acid found in coconut oil, palm oil and dairy products, was independently associated with an increased odds of flare within 1 year (OR 3.01, CI 1.17-7.74), with a dose-response effect.[38]

Unsaturated Fats

Monounsaturated Fatty Acids (MUFAs)

Monounsaturated fat, including palmitoleic acid and oleic acid, is found in plant-based oils including olive oil, as well as in macadamia nuts, beef tallow and lard. Enteral nutrition supplemented with either oleic acid (a MUFA) or linoleic acid (an n6 PUFA) found that linoleic acid had higher remission rates in CD although neither was as efficacious as steroids for clinical remission.[53] However this was only one study. Studies with the Crohn's Disease Exclusion Diet allow unlimited olive oil rich in MUFA and this diet was associated with clinical remission and reduction in inflammation.[39] UC patients treated with olive oil derivatives had reduction in peripheral and intestinal T cell activation and interferon-γ production.[54]

Polyunsaturated Fatty Acids (PUFAs)

Foods rich in n-3 PUFA include marine fish like salmon, mackerel and herring, as well as certain nuts and seeds (such as walnuts, flax, hemp and chia seeds). A small study found a non-significant decrease in disease activity in UC patients who consumed 600 mg of Atlantic salmon weekly for 8 weeks.[55] In one study, patients whose diet approximated a ratio of n-3:n-6 closer to 1, were more likely to be in remission than those with a higher ratio of n-6 foods[56]. Higher dietary intake of α-linolenic acid (a precursor of long-chain n-3 PUFA) was associated with increased risk of UC relapse whereas total n-3 PUFA without supplementation was protective.

In a meta-analysis of three trials looking at maintenance of remission in UC with n-3 PUFA supplementation, there was no added benefit to supplementation (RR for relapse=1.02 (CI 0.51-2.03).[57] Similarly, a systematic review looking at n-3 PUFA supplementation for treatment of any IBD found no consistent benefit for prevention of UC relapse among 4 available studies.[58]

In CD, two large placebo-controlled multicenter RCTs using 4g/day of supplemental n-3 PUFA found no efficacy for the prevention of relapse.[59] However, a meta-analysis of six heterogeneous trials with 1039 patients showed a small benefit of supplementation for reduction of relapse (RR of relapse of 0.77, CI 0.61-0.98) (I2=58.4%, *p*=0.03).[57] Therefore, current evidence is inconclusive for n-3 PUFAs (like fish oil) in IBD. By contrast, foods naturally high in n-3 PUFAs and low in n-6 PUFAs may be beneficial although evidence is weak.

Trans-Fats (unsaturated fat)

A case-control study comparing 62 newly diagnosed UC patients to 124 healthy controls found higher consumption of total fats and trans-fats to be significantly associated with increased risk of UC.[60] In a prospective cohort, higher long-term intake of trans fats demonstrated a trend towards increased incidence of UC.[61] Moreover, trans-fats are believed to have other deleterious health effects. Though data in humans regarding the effect of trans- fat upon inflammation is lacking, due the deleterious nature we recommend avoiding trans- fat.

Alcohol

Recommendations

In CD, there is insufficient evidence to recommend changes in low level alcohol consumption (EL low).

In UC, there is insufficient evidence to recommend changes in low level alcohol consumption (EL low).

Alcohol use prior to a diagnosis of IBD

A meta-analysis of 9 UC studies did not find a significant association (RR=0.95 (95% CI, 0.65-1.39) with risk for UC comparing the highest to the lowest alcohol intake.[62] In CD, one study reported that alcohol (≥one drink/week) was not associated with new onset disease,[63] while another reported increased alcohol consumption (P=0.009) in recently diagnosed CD patients compared to healthy controls.[64] The EPIC study found no association between alcohol consumption prior to recruitment and subsequent UC or CD development.[65]

Triggering flares

In a small prospective cohort study, UC patients in the top tertile for alcohol consumption had a 2.7-fold higher odds of flare compared to the bottom tertile (**Supplemental Table 5**).[35] In contrast, a daily glass of red wine was associated with a reduction in fecal calprotectin in inactive IBD patients.[66]

In an internet-based survey of 2329 patients with IBD, alcohol consumption was identified as a potential trigger of worsening gastrointestinal symptoms.[67] However, inactive IBD patients consume alcohol at rates similar to that of the general US population, though 75% reported its impact on gastrointestinal symptoms.[68] Of CD patients who consumed alcohol, 40% reported symptom worsening while 41% did not; there was no association with a particular type of alcoholic beverage.

Maltodextrin and Artificial Sweeteners

Recommendations

In CD, it may be prudent to limit intake of maltodextrin-containing foods and artificial sweeteners (EL very low).

In UC, it may be prudent to limit intake of maltodextrin-containing foods and artificial sweeteners (EL very low).

In vitro and in vivo studies have linked food additives, artificial sweeteners and their components to IBD.[69-71] Maltodextrin is a hydrolyzed starch and a common dietary

polysaccharide used as a thickener for foods and confections.[72] Splenda®, an artificial sweetener, is comprised of 1% sucralose and ~99% maltodextrin as a filler.

Increased consumption of artificial sweeteners over the past few decades parallels the increased incidence of IBD cases.[73] This trend is similar for rising maltodextrin availability within the American diet.[74] Several epidemiologic studies correlated consumption of added sweeteners and sugar in soft drinks with an increased IBD risk (**Supplemental Table 6**).[75-77]

In animal models, consumption of artificial sweeteners has been shown to increase inflammatory markers in the gastrointestinal system (**Supplemental Table 7**). In vitro studies of GI tissue exposed to maltodextrin observed enhanced cellular biofilm formation of CD-associated E. coli strains (AIEC), which adhered to intestinal epithelial cells and mimicked dense biofilm formations found in the gut of CD patients.[70] MalX (maltose/maltodextrin binding protein gene) is a gene central to maltodextrin metabolism. Both studies of Splenda® supplementation in SAMP mice and in vitro culturing of GI tissue with maltodextrin observed an increase in bacterial malX gene expression in the ileal mucosa obtained from CD patients and murine model of CD relative to healthy controls ($p<0.0175$, $p<0.03$).[69, 70] This association links maltodextrin to CD pathogenesis by suggesting that its metabolism promotes the colonization and translocation of these CD-associated bacteria. Finally, common artificial sweeteners and maltodextrin induced alterations in the mouse gut microbiota that are similar to those observed in IBD.[69, 78-81]

It is notable that maltodextrin is found in many nutritional supplements, including some used for exclusive enteral nutrition which has been demonstrated to be an effective therapy. Thus, while there is theoretical and animal model data to support avoidance of maltodextrin among patients consuming a whole food diet, these data or recommendations should not dissuade the use of exclusive enteral nutrition in appropriate situations.

Emulsifiers and Thickeners

Recommendations

In CD, may be prudent to reduce intake of processed foods that contain carrageenan, carboxymethylcellulouse and polysorbate-80 (EL very low).

In UC, may be prudent to reduce intake of processed foods that contain carrageenan, carboxymethylcellulouse and polysorbate-80 (EL very low).

Manufacturers add emulsifiers to processed foods to improve food texture and quality.[82, 83] The most extensively used emulsifier, lecithin, is derived from egg or soya, and consists of varying proportions of phosphatidyl choline, ethanolamine or inositol.[84] Other emulsifiers and thickeners include carboxymethylcellulose (CMC), carrageenan, and polysorbate-80 (P80). Epidemiological data supports an association between some emulsifier exposures and IBD incidence[84-86]

A carrageenan-free diet supplemented with food-grade carrageenan (n=5) or placebo capsules (n=7) was administered to subjects with quiescent UC.[87] Three carrageenan-exposed but no control subjects relapsed. .

Tobacman [88] reviewed 45 studies on the health effects of degraded and un-degraded carrageenan in rats, mice, guinea pigs, rhesus monkeys, and rabbits. Study durations and carrageenan doses ranged from 1 day to 1 year and 0.1% to 10%, respectively. Carrageenan exposure led to intestinal lesions, neoplasia, ulceration, carrageenan accumulation in intestinal lymph nodes, stricture and UC-like inflammatory changes. Ulceration correlated with dose, duration of carrageenan exposure. Whether the doses used are relevant in humans is questionable.

Effects of carrageenan exposure also include increased occult blood in stool,[89] mucosal ulcerations,[90, 91] serum inflammatory makers,[91, 92] small bowel and colonic lesions,[93] reduction in crypts number and length,[94, 95] inflammatory cell infiltrate[90, 91] and epithelial damage [94, 96] (**Supplemental Table 8**).

Two emulsifiers or thickeners (Polysorbate 80 and carboxymethylcellulose) have been evaluated in animal models. P80 was been shown to increase intestinal permeability in mice[97]. Chassaing et al. demonstrated that addition of CMC and P80 to drinking water can reduce mucus thickness, elevate levels of fecal lipocalin2 and can induce colitis in IL-10 knockout (KO) mice.[98]

Hydrolysed carrageenan induced IBD in piglets, with associated increases in Proteobacteria and decreases in Firmicutes, Actinobacteria and Bacteroidetes.[99] In wild type and colitis-susceptible mice exposed to CMC and P80, microbial diversity decreased and *Akkermansia muciniphila* and Proteobacteria increased.[100] Transplanting

cecal content from emulsifier-treated to germ free mice caused microbial epithelium encroachment and low-grade inflammation, mediated by altered bacterial composition and elevated fecal lipopolysaccharide (LPS) and flagellin.

Recent studies in animal models of IBD also indicated that various EDTA compounds (Ca-EDTA, Na-EDTA, Fe-EDTA) as used for food preservation or iron fortification have proinflammatory and proneoplastic effects.[101]

Nanoparticles and Sulfites

Recommendations

In CD, it may be prudent to reduce exposure to processed foods containing titanium dioxide and sulfites (EL low).

In UC, it may be prudent to reduce exposure to processed foods containing titanium dioxide and sulfites (EL very low).

Sulfites are used to preserve wine and beer, commercial lemon juice and vinegars, dried or canned fruits and processed meats. When used as preservatives, they generally are not nanoparticles, but can be when used in other formulations such as iron sulfite. In IL-10 KO mice, dairy fat induced dysbiosis and colitis via a bloom of sulfite-reducing bacteria *Bilophila Wadsworthia*.[24] Bacteria such as *Bilophila* are potential intestinal pathobionts that may grow with a high fat diet or high dairy fat diet .An exogenous source of sulphites from food could theoretically have the same effect; whether exogenous sulfites would exert the same effect was not tested.

Nanoparticles such as titanium dioxide (Ti02) and aluminum silicates (AlSi) are used as food additives to color, coat or preserve food. Nanoparticles are highly stable and resistant to degradation. TiO2 is a white, crystalline powder, used as a pigment in confectionery, white sauces, dressings, nondairy creamers, and toothpaste.[102] AlSi is added to salt and other powdered foods to prevent clumping.

In mice, oral administration results in Ti02 accumulation in intestinal epithelial and immune cells with activation of the NLRP3 inflammasome.[103] Oral administration of TiO2 nanoparticles also enhances intestinal inflammation in a murine model of colitis.[103] Similar findings have been reported for dietary aluminum intake, which also impairs intestinal barrier function.[104]

Ti02 is normally trapped in the intestinal mucus layer,[105] although systemic absorption has been reported after supra-physiological intake in volunteers with normal intestinal permeability.[106] Nanoparticles (mostly TiO2 and AlSi) have been identified within phagocytes located in intestinal lymphoid aggregates in IBD patients. In addition, patients with active UC have higher serum titanium levels than UC patients in remission and controls.[103]

Two dietary intervention studies have assessed the impact of TiO2 on CD (**Supplemental Table 9**). A pilot study randomized 20 patients with active ileal or ileo-colonic disease (CDAI > 150) off immunosuppressive therapy to a TiO2/AlSi-restricted diet or a control diet for 4 months.[107] A significant reduction in mean CDAI was seen in the intervention group only, with seven patients on the intervention diet (70%) compared to 0 on the control diet (0%) achieving clinical remission (CDAI < 150).[107] A subsequent 16-week multicenter study randomized 83 patents with active CD to a low or normal nanoparticle diet, indicated no differences in remission or clinical response between groups.[108] Of note, patients in the pilot study followed a more restrictive diet, avoiding all processed foods. Given the first positive study combined with the animal models, the level of evidence for CD was rated as low.

Discussion

This dietary guidance consensus document from the IOIBD is based on the best available evidence to date. For patients with CD, we recommend regular intake of fruits and vegetables (in the absence of symptomatic strictures) and reduced intake of saturated-, trans-, and dairy-fat, additives such as polysorbate 80 and carboxymethylcellulose, processed dairy or foods rich in maltodextrins, artificial sweeteners containing sucralose or saccharine, and processed food containing nanoparticles. For patients with UC, we recommend increased consumption of natural sources of omega-3 fatty acids (e.g. from wild salmon and other natural sources, not from supplements). The foods that patients with UC should avoid are similar to CD with the possible addition of red and processed meat (Figure). There was insufficient evidence to recommend changes in the consumption of fruits, or vegetables for patients with UC. For patients with either CD or UC, there was insufficient evidence to recommend changes in consumption of wheat or gluten, poultry, alcoholic beverages

other than binge drinking (in the absence of other liver disease), and refined sugars. The committee was unable to come to a consensus on pasteurized dairy products. None of these recommendations are meant to exclude the role of nutritional assessment for malnutrition and correction of deficiencies when needed. Our main recommendations are aimed at reducing both symptoms and inflammation. For patients with persistent symptoms despite resolution of inflammation and absence of strictures, a low FODMAP or lactose-free diet may improve symptoms.

We acknowledge several limitations of this consensus document from the nutrition cluster of IOIBD. The recommendations were the consensus opinion of a relatively small group of IBD clinicians and scientists with expertise in the field. Dietary studies are particularly challenging to implement and therefore may be subject to various forms of bias.[109] For example, blinding study participants to treatment arm is difficult. When a food is eliminated, it is necessary to replace the calories usually obtained from this food with a different food. Sample sizes have historically been small, and therefore the studies were often under powered. Additionally, several of the recommendations are based largely on the results of experiments in animals, such as the effect of thickeners, emulsifiers, and maltodextrin. Moreover, some of these are in contrast to the known efficacy of exclusive enteral nutrition. For some of the members, the vote to reduce intake may be in part because these food additives are not believed to have nutritional value. However, we did not quantify this in the process of voting. Finally, these recommendations may require change as new information becomes available.

There are several dietary patterns that are commonly recommended for patients with IBD (e.g. Mediterranean diet, Specific Carbohydrate Diet, Crohn's Disease Exclusion Diet). At the outset, we hoped to make recommendations regarding specific dietary patterns. However, the lack of RCTs testing these dietary patterns precluded coming to strong recommendations. As such, we limited our recommendations to components of the diet. Nonetheless, several trials have just completed or are ongoing and may allow for stronger recommendations in the near future.

References

1. Gill PA, van Zelm MC, Muir JG, et al. Review article: short chain fatty acids as potential therapeutic agents in human gastrointestinal and inflammatory disorders. Aliment Pharmacol Ther 2018;48:15-34.

2. Desai MS, Seekatz AM, Koropatkin NM, et al. A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility. Cell 2016;167:1339-1353 e21.
3. Roberts CL, Keita AV, Duncan SH, et al. Translocation of Crohn's disease Escherichia coli across M-cells: contrasting effects of soluble plant fibres and emulsifiers. Gut 2010;59:1331-9.
4. D'Souza S, Levy E, Mack D, et al. Dietary patterns and risk for Crohn's disease in children. Inflamm Bowel Dis 2008;14:367-73.
5. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. Gastroenterology 2013;145:970-7.
6. Thornton JR, Emmett PM, Heaton KW. Diet and Crohn's disease: characteristics of the pre-illness diet. Br Med J 1979;2:762-4.
7. Andersen V, Chan S, Luben R, et al. Fibre intake and the development of inflammatory bowel disease: A European prospective multi-centre cohort study (EPIC-IBD). J Crohns Colitis 2018;12:129-136.
8. Magee EA, Edmond LM, Tasker SM, et al. Associations between diet and disease activity in ulcerative colitis patients using a novel method of data analysis. Nutr J 2005;4:7.
9. Brotherton CS, Martin CA, Long MD, et al. Avoidance of Fiber Is Associated With Greater Risk of Crohn's Disease Flare in a 6-Month Period. Clin Gastroenterol Hepatol 2016;14:1130-6.
10. Ritchie JK, Wadsworth J, Lennard-Jones JE, et al. Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in Crohn's disease. Br Med J (Clin Res Ed) 1987;295:517-20.
11. Benjamin JL, Hedin CR, Koutsoumpas A, et al. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. Gut 2011;60:923-9.
12. Martini GA, Brandes JW. Increased consumption of refined carbohydrates in patients with Crohn's disease. Klin Wochenschr 1976;54:367-71.
13. Miller B, Fervers F, Rohbeck R, et al. [Sugar consumption in patients with Crohn's disease]. Verh Dtsch Ges Inn Med 1976;82 Pt 1:922-4.
14. Kasper H, Sommer H. Dietary fiber and nutrient intake in Crohn's disease. Am J Clin Nutr 1979;32:1898-901.
15. Katschinski B, Logan RF, Edmond M, et al. Smoking and sugar intake are separate but interactive risk factors in Crohn's disease. Gut 1988;29:1202-6.
16. Mayberry JF, Rhodes J, Newcombe RG. Breakfast and dietary aspects of Crohn's disease. Br Med J 1978;2:1401.
17. Mayberry JF, Rhodes J, Newcombe RG. Increased sugar consumption in Crohn's disease. Digestion 1980;20:323-6.
18. Rawcliffe PM, Truelove SC. Breakfast and Crohn's disease--I. Br Med J 1978;2:539-40.
19. Reif S, Klein I, Lubin F, et al. Pre-illness dietary factors in inflammatory bowel disease. Gut 1997;40:754-60.
20. Tragnone A, Valpiani D, Miglio F, et al. Dietary habits as risk factors for inflammatory bowel disease. Eur J Gastroenterol Hepatol 1995;7:47-51.
21. Lorenz-Meyer H, Bauer P, Nicolay C, et al. Omega-3 fatty acids and low carbohydrate diet for maintenance of remission in Crohn's disease. A randomized controlled multicenter trial. Study Group Members (German Crohn's Disease Study Group). Scand J Gastroenterol 1996;31:778-85.

22. Cohen SA, Gold BD, Oliva S, et al. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. J Pediatr Gastroenterol Nutr 2014;59:516-21.
23. Cox SR, Prince AC, Myers CE, et al. Fermentable Carbohydrates [FODMAPs] Exacerbate Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: A Randomised, Double-blind, Placebo-controlled, Cross-over, Re-challenge Trial. J Crohns Colitis 2017;11:1420-1429.
24. Prince AC, Myers CE, Joyce T, et al. Fermentable Carbohydrate Restriction (Low FODMAP Diet) in Clinical Practice Improves Functional Gastrointestinal Symptoms in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2016;22:1129-36.
25. Gibson PR. Use of the low-FODMAP diet in inflammatory bowel disease. J Gastroenterol Hepatol 2017;32 Suppl 1:40-42.
26. Cox SR, Lindsay JO, Fromentin S, et al. Effects of Low FODMAP Diet on Symptoms, Fecal Microbiome, and Markers of Inflammation in Patients With Quiescent Inflammatory Bowel Disease in a Randomized Trial. Gastroenterology 2019.
27. Halmos EP, Christophersen CT, Bird AR, et al. Consistent Prebiotic Effect on Gut Microbiota With Altered FODMAP Intake in Patients with Crohn's Disease: A Randomised, Controlled Cross-Over Trial of Well-Defined Diets. Clin Transl Gastroenterol 2016;7:e164.
28. Aziz I, Branchi F, Pearson K, et al. A study evaluating the bidirectional relationship between inflammatory bowel disease and self-reported non-celiac gluten sensitivity. Inflamm Bowel Dis 2015;21:847-53.
29. Herfarth HH, Martin CF, Sandler RS, et al. Prevalence of a gluten-free diet and improvement of clinical symptoms in patients with inflammatory bowel diseases. Inflamm Bowel Dis 2014;20:1194-7.
30. Limketkai BN, Sepulveda R, Hing T, et al. Prevalence and factors associated with gluten sensitivity in inflammatory bowel disease. Scand J Gastroenterol 2018;53:147-151.
31. Levine A, Sigall Boneh R, Wine E. Evolving role of diet in the pathogenesis and treatment of inflammatory bowel diseases. Gut 2018;67:1726-1738.
32. Wagner SJ, Schmidt A, Effenberger MJ, et al. Semisynthetic diet ameliorates Crohn's disease-like ileitis in TNFDeltaARE/WT mice through antigen-independent mechanisms of gluten. Inflamm Bowel Dis 2013;19:1285-94.
33. Junker Y, Zeissig S, Kim SJ, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. J Exp Med 2012;209:2395-408.
34. Jantchou P, Morois S, Clavel-Chapelon F, et al. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. Am J Gastroenterol 2010;105:2195-201.
35. Jowett SL, Seal CJ, Pearce MS, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut 2004;53:1479-84.
36. Opstelten JL, de Vries JHM, Wools A, et al. Dietary intake of patients with inflammatory bowel disease: A comparison with individuals from a general population and associations with relapse. Clin Nutr 2018.
37. Tasson L, Canova C, Vettorato MG, et al. Influence of Diet on the Course of Inflammatory Bowel Disease. Dig Dis Sci 2017;62:2087-2094.
38. Barnes EL, Nestor M, Onyewadume L, et al. High Dietary Intake of Specific Fatty Acids Increases Risk of Flares in Patients With Ulcerative Colitis in Remission During Treatment With Aminosalicylates. Clin Gastroenterol Hepatol 2017;15:1390-1396 e1.

39. Daley CA, Abbott A, Doyle PS, et al. A review of fatty acid profiles and antioxidant content in grass-fed and grain-fed beef. Nutr J 2010;9:10.
40. Albenberg LG, Wu GD. Diet and the intestinal microbiome: associations, functions, and implications for health and disease. Gastroenterology 2014;146:1564-72.
41. Sigall-Boneh R, Pfeffer-Gik T, Segal I, et al. Partial enteral nutrition with a Crohn's disease exclusion diet is effective for induction of remission in children and young adults with Crohn's disease. Inflamm Bowel Dis 2014;20:1353-60.
42. Sigall Boneh R, Sarbagili Shabat C, Yanai H, et al. Dietary Therapy With the Crohn's Disease Exclusion Diet is a Successful Strategy for Induction of Remission in Children and Adults Failing Biological Therapy. J Crohns Colitis 2017;11:1205-1212.
43. Levine A, Wine E, Assa A, et al. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. Gastroenterology 2019;157:440-450 e8.
44. Llewellyn SR, Britton GJ, Contijoch EJ, et al. Interactions Between Diet and the Intestinal Microbiota Alter Intestinal Permeability and Colitis Severity in Mice. Gastroenterology 2018;154:1037-1046 e2.
45. Opstelten JL, Leenders M, Dik VK, et al. Dairy Products, Dietary Calcium, and Risk of Inflammatory Bowel Disease: Results From a European Prospective Cohort Investigation. Inflamm Bowel Dis 2016;22:1403-11.
46. Barrett JS, Irving PM, Shepherd SJ, et al. Comparison of the prevalence of fructose and lactose malabsorption across chronic intestinal disorders. Aliment Pharmacol Ther 2009;30:165-74.
47. Eadala P, Matthews SB, Waud JP, et al. Association of lactose sensitivity with inflammatory bowel disease--demonstrated by analysis of genetic polymorphism, breath gases and symptoms. Aliment Pharmacol Ther 2011;34:735-46.
48. Szilagyi A, Galiatsatos P, Xue X. Systematic review and meta-analysis of lactose digestion, its impact on intolerance and nutritional effects of dairy food restriction in inflammatory bowel diseases. Nutr J 2016;15:67.
49. Strisciuglio C, Giannetti E, Martinelli M, et al. Does cow's milk protein elimination diet have a role on induction and maintenance of remission in children with ulcerative colitis? Acta Paediatr 2013;102:e273-8.
50. Guerreiro CS, Ferreira P, Tavares L, et al. Fatty acids, IL6, and TNFalpha polymorphisms: an example of nutrigenetics in Crohn's disease. Am J Gastroenterol 2009;104:2241-9.
51. Tanaka M, Iwao Y, Sasaki S, et al. Moderate dietary temperance effectively prevents relapse of Crohn disease: a prospective study of patients in remission. Gastroenterol Nurs 2007;30:202-10.
52. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for inducing remission of Crohn's disease. Cochrane Database Syst Rev 2001:CD000542.
53. Gassull MA, Fernandez-Banares F, Cabre E, et al. Fat composition may be a clue to explain the primary therapeutic effect of enteral nutrition in Crohn's disease: results of a double blind randomised multicentre European trial. Gut 2002;51:164-8.
54. Cardeno A, Magnusson MK, Strid H, et al. The unsaponifiable fraction of extra virgin olive oil promotes apoptosis and attenuates activation and homing properties of T cells from patients with inflammatory bowel disease. Food Chem 2014;161:353-60.
55. Grimstad T, Berge RK, Bohov P, et al. Salmon diet in patients with active ulcerative colitis reduced the simple clinical colitis activity index and increased the anti-inflammatory fatty acid index--a pilot study. Scand J Clin Lab Invest 2011;71:68-73.

56. Uchiyama K, Nakamura M, Odahara S, et al. N-3 polyunsaturated fatty acid diet therapy for patients with inflammatory bowel disease. Inflamm Bowel Dis 2010;16:1696-707.
57. Turner D, Shah PS, Steinhart AH, et al. Maintenance of remission in inflammatory bowel disease using omega-3 fatty acids (fish oil): a systematic review and meta-analyses. Inflamm Bowel Dis 2011;17:336-45.
58. Cabre E, Manosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases - a systematic review. Br J Nutr 2012;107 Suppl 2:S240-52.
59. Feagan BG, Sandborn WJ, Mittmann U, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. JAMA 2008;299:1690-7.
60. Rashvand S, Somi MH, Rashidkhani B, et al. Dietary fatty acid intakes are related to the risk of ulcerative colitis: a case-control study. Int J Colorectal Dis 2015;30:1255-60.
61. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. Gut 2014;63:776-84.
62. Nie JY, Zhao Q. Beverage consumption and risk of ulcerative colitis: Systematic review and meta-analysis of epidemiological studies. Medicine (Baltimore) 2017;96:e9070.
63. Han DY, Fraser AG, Dryland P, et al. Environmental factors in the development of chronic inflammation: a case-control study on risk factors for Crohn's disease within New Zealand. Mutat Res 2010;690:116-22.
64. Octoratou M, Merikas E, Malgarinos G, et al. A prospective study of pre-illness diet in newly diagnosed patients with Crohn's disease. Rev Med Chir Soc Med Nat Iasi 2012;116:40-9.
65. Bergmann MM, Hernandez V, Bernigau W, et al. No association of alcohol use and the risk of ulcerative colitis or Crohn's disease: data from a European Prospective cohort study (EPIC). Eur J Clin Nutr 2017;71:566.
66. Hey H, Schmedes A, Nielsen AA, et al. Effects of five different alcoholic drinks on patients with Crohn's disease. Scand J Gastroenterol 2007;42:968-72.
67. Cohen AB, Lee D, Long MD, et al. Dietary patterns and self-reported associations of diet with symptoms of inflammatory bowel disease. Dig Dis Sci 2013;58:1322-8.
68. Swanson GR, Sedghi S, Farhadi A, et al. Pattern of alcohol consumption and its effect on gastrointestinal symptoms in inflammatory bowel disease. Alcohol 2010;44:223-8.
69. Rodriguez-Palacios A, Harding A, Menghini P, et al. The Artificial Sweetener Splenda Promotes Gut Proteobacteria, Dysbiosis, and Myeloperoxidase Reactivity in Crohn's Disease-Like Ileitis. Inflamm Bowel Dis 2018;24:1005-1020.
70. Nickerson KP, McDonald C. Crohn's disease-associated adherent-invasive Escherichia coli adhesion is enhanced by exposure to the ubiquitous dietary polysaccharide maltodextrin. PLoS One 2012;7:e52132.
71. Nickerson KP, Homer CR, Kessler SP, et al. The dietary polysaccharide maltodextrin promotes Salmonella survival and mucosal colonization in mice. PLoS One 2014;9:e101789.
72. Food and Drug Administration US. Additional Information about High-Intensity Sweeteners Permitted for Use in Food in the United States, 2018.
73. Qin X. Etiology of inflammatory bowel disease: a unified hypothesis. World J Gastroenterol 2012;18:1708-22.
74. Nickerson KP, Chanin R, McDonald C. Deregulation of intestinal anti-microbial defense by the dietary additive, maltodextrin. Gut Microbes 2015;6:78-83.
75. Racine A, Carbonnel F, Chan SS, et al. Dietary Patterns and Risk of Inflammatory Bowel Disease in Europe: Results from the EPIC Study. Inflamm Bowel Dis 2016;22:345-54.

76. Sakamoto N, Kono S, Wakai K, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis 2005;11:154-63.
77. Hansen TS, Jess T, Vind I, et al. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. J Crohns Colitis 2011;5:577-84.
78. Bian X, Tu P, Chi L, et al. Saccharin induced liver inflammation in mice by altering the gut microbiota and its metabolic functions. Food Chem Toxicol 2017;107:530-539.
79. Chi L, Bian X, Gao B, et al. Effects of the Artificial Sweetener Neotame on the Gut Microbiome and Fecal Metabolites in Mice. Molecules 2018;23.
80. Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 2014;514:181-6.
81. Forbes JD, Van Domselaar G, Bernstein CN. The Gut Microbiota in Immune-Mediated Inflammatory Diseases. Front Microbiol 2016;7:1081.
82. Halmos EP, Mack A, Gibson PR. Review article: emulsifiers in the food supply and implications for gastrointestinal disease. Aliment Pharmacol Ther 2019;49:41-50.
83. additives. JFWEcof. Compendium of food additive specifications. FAO/JECFA Monographs. Volume 4, 2007.
84. Roberts CL, Rushworth SL, Richman E, et al. Hypothesis: Increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease. J Crohns Colitis 2013;7:338-41.
85. Pfeffer-Gik T, Levine A. Dietary clues to the pathogenesis of Crohn's disease. Dig Dis 2014;32:389-94.
86. Shah R, Kolanos R, DiNovi MJ, et al. Dietary exposures for the safety assessment of seven emulsifiers commonly added to foods in the United States and implications for safety. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2017;34:905-917.
87. Bhattacharyya S, Shumard T, Xie H, et al. A randomized trial of the effects of the no-carrageenan diet on ulcerative colitis disease activity. Nutr Healthy Aging 2017;4:181-192.
88. Tobacman JK. Review of harmful gastrointestinal effects of carrageenan in animal experiments. Environmental health perspectives 2001;109:983.
89. Watt J, Marcus R. Carrageenan-induced ulceration of the large intestine in the guinea pig. Gut 1971;12:164-71.
90. Al-Suhail AA, Reid PE, Culling CF, et al. Studies of the degraded carrageenan-induced colitis of rabbits. I. Changes in the epithelial glycoprotein O-acylated sialic acids associated with ulceration. Histochem J 1984;16:543-53.
91. Wu W, Zhen Z, Niu T, et al. kappa-Carrageenan Enhances Lipopolysaccharide-Induced Interleukin-8 Secretion by Stimulating the Bcl10-NF-kappaB Pathway in HT-29 Cells and Aggravates C. freundii-Induced Inflammation in Mice. Mediators Inflamm 2017;2017:8634865.
92. Shang Q, Sun W, Shan X, et al. Carrageenan-induced colitis is associated with decreased population of anti-inflammatory bacterium, Akkermansia muciniphila, in the gut microbiota of C57BL/6J mice. Toxicol Lett 2017;279:87-95.
93. Swidsinski A, Ung V, Sydora BC, et al. Bacterial overgrowth and inflammation of small intestine after carboxymethylcellulose ingestion in genetically susceptible mice. Inflamm Bowel Dis 2009;15:359-64.
94. Wu W, Zhen Z, Niu T, et al. kappa-Carrageenan Enhances Lipopolysaccharide-Induced Interleukin-8 Secretion by Stimulating the Bcl10-NF-kappaB Pathway in HT-29 Cells and Aggravates C. freundii-Induced Inflammation in Mice. Mediators of Inflammation 2017;2017:8634865.

95. Al-Suhail A, Reid P, Culling C, et al. Studies of the degraded carrageenan-induced colitis of rabbits. I. Changes in the epithelial glycoproteinO-acylated sialic acids associated with ulceration. The Histochemical Journal 1984;16:543-553.
96. Shang Q, Sun W, Shan X, et al. Carrageenan-induced colitis is associated with decreased population of anti-inflammatory bacterium, Akkermansia muciniphila, in the gut microbiota of C57BL/6J mice. Toxicology Letters 2017;279:87-95.
97. Tagesson C, Edling C. Influence of surface-active food additives on the integrity and permeability of rat intestinal mucosa. Food Chem Toxicol 1984;22:861-4.
98. Chassaing B, Koren O, Goodrich JK, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature 2015;519:92-6.
99. Munyaka PM, Sepehri S, Ghia JE, et al. Carrageenan Gum and Adherent Invasive Escherichia coli in a Piglet Model of Inflammatory Bowel Disease: Impact on Intestinal Mucosa-associated Microbiota. Front Microbiol 2016;7:462.
100. Chassaing B, Koren O, Goodrich JK, et al. Corrigendum: Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature 2016;536:238.
101. Evstatiev R, Cervenka A, Lang M, et al. EDTA Compounds, as Used in Food Additives, Aggravate Intestinal Inflammation and Drive Tumorigenesis in a Mouse Model of Colitis-Associated Cancer. Gastroenterology 2017;152:S735.
102. Lomer MC, Thompson RP, Powell JJ. Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. Proc Nutr Soc 2002;61:123-30.
103. Ruiz PA, Moron B, Becker HM, et al. Titanium dioxide nanoparticles exacerbate DSS-induced colitis: role of the NLRP3 inflammasome. Gut 2017;66:1216-1224.
104. Pineton de Chambrun G, Body-Malapel M, Frey-Wagner I, et al. Aluminum enhances inflammation and decreases mucosal healing in experimental colitis in mice. Mucosal Immunol 2014;7:589-601.
105. Talbot P, Radziwill-Bienkowska JM, Kamphuis JBJ, et al. Food-grade TiO2 is trapped by intestinal mucus in vitro but does not impair mucin O-glycosylation and short-chain fatty acid synthesis in vivo: implications for gut barrier protection. J Nanobiotechnology 2018;16:53.
106. Pele LC, Thoree V, Bruggraber SF, et al. Pharmaceutical/food grade titanium dioxide particles are absorbed into the bloodstream of human volunteers. Part Fibre Toxicol 2015;12:26.
107. Lomer MC, Harvey RS, Evans SM, et al. Efficacy and tolerability of a low microparticle diet in a double blind, randomized, pilot study in Crohn's disease. Eur J Gastroenterol Hepatol 2001;13:101-6.
108. Lomer MC, Grainger SL, Ede R, et al. Lack of efficacy of a reduced microparticle diet in a multi-centred trial of patients with active Crohn's disease. Eur J Gastroenterol Hepatol 2005;17:377-84.
109. Lewis JD, Albenberg L, Lee D, et al. The Importance and Challenges of Dietary Intervention Trials for Inflammatory Bowel Disease. Inflamm Bowel Dis 2017;23:181-191.

Table 1. IOIBD Dietary Recommendations for patients with inflammatory bowel diseases

Dietary Component	Recommendation UC (evidence level, % agreement)	Recommendation CD (evidence level, % agreement)	Source of Evidence	Clarifications
Fruits	Insufficient evidence to recommend specific dietary changes (very low, 100%)	**Prudent to increase exposure (low, 84.6%)**	Epidemiology Clinical studies	Reduce insoluble fiber if stricture present (Evidence level very low)
Vegetables	Insufficient evidence to recommend any specific changes (very low, 100%)	**Prudent to Increase exposure (low, 84.6%)**	Epidemiology Clinical studies	Reduce insoluble fiber if stricture present (Evidence level very low)
Refined sugars and carbohydrates	Insufficient evidence to recommend any specific changes in refined sugar or complex carbohydrate intake (low, 92.3%)	Insufficient evidence to recommend specific changes in refined sugar or complex carbohydrates (low, 100%)	Epidemiology	
Wheat/Gluten	Insufficient evidence to recommend restriction of wheat and gluten (low, 100%)	Insufficient evidence to recommend restriction of wheat and gluten (low, 100%)	Epidemiology Animal models	Gluten has been associated with ileitis in a mouse model of CD
Red /processed meat	**Prudent to reduce intake of red and processed meat (low, 100%)**	Insufficient evidence to recommend restriction of intake (high, 100%)	Epidemiology Animal Models	

Poultry	Insufficient evidence to recommend dietary changes (low, 100%)	Insufficient evidence to recommend restriction of intake (high, 100%)	Epidemiology	Lean chicken breast is a low animal fat & low taurine source of protein and is allowed in the CD exclusion diet
Pasteurized dairy products	Unable to reach consensus (92.3%)	Unable to reach consensus (92.3%)	Epidemiology Animal models	Dairy products encompass a wide range of products. Lactase deficiency and lactose intolerance is common among patients with IBD. Prudent to reduce dairy fat and processed dairy rich in maltodextrins and emulsifiers
Unpasteurized dairy products	Prudent to avoid in all patients (100%)	Prudent to avoid in all patients (100%)	Expert opinion, Case reports	Avoid infections that can result from consumption of unpasteurized dairy products
Dietary Fats	**Prudent to reduce consumption of myristic acid (palm oil, coconut oil, dairy fats (low, 100%)** **Prudent to avoid trans-fat (very low, 100%)** **Prudent to increase dietary consumption of omega-3-fatty acids (DHA and EPA) from marine fish (low) but not from dietary supplements (high, 100%)**	**Prudent to reduce exposure to saturated fats (GRADE low, 100%) and avoid trans-fat (very low, 100%)**	Prospective, observational studies	Myristic acid linked to UC is found in palm and coconut oil, dairy fat and meat from grain fed as opposed to grass fed animals Natural omega-3 fatty acids are found mainly in wild marine fish

Alcoholic Beverages	Insufficient evidence to recommend changes in low level alcohol consumption (low, 100%)	Insufficient evidence to recommend changes in low level alcohol consumption (low, 100%)	Epidemiology	A trial of avoidance alcohols containing high levels of sulfites (i.e. beer and wine) is reasonable (EL 3b)

Food additives

Dietary Component	Recommendation UC	Recommendation CD	Source of Evidence	Clarification
Maltodextrins/artificial sweeteners	**It may be prudent to limit intake of maltodextrin-containing foods and artificial sweeteners (very low, 92.3%)**	**It may be prudent to limit intake of maltodextrin-containing foods and artificial sweeteners (very low, 92.3%)**	Epidemiology Animal models	
Emulsifiers and thickeners	**It may be prudent to limit intake of carboxymethylcellulos and polysorbate-80 (very low, 92.3%)**	**It may be prudent to limit intake of carboxymethylcellulos and polysorbate-80 (very low, 92.3%)**	Animal models, epidemiology,	E433 – polysorbate 80 E466 - corboxymethylcellulose
Carrageenans	**It may prudent to reduce intake of processed foods containing carageenans (very low, 92.3%)**	**It may prudent to reduce intake of processed foods containing carageenans (very low, 92.3%)**	Epidemiology Animal models One very small RCT	Found in dairy-based desserts, frozen meals, and processed meats
Titanium Dioxide and other nanoparticles	**It may prudent to reduce intake of processed foods which contain titanium**	**It may prudent to reduce intake of processed foods which contain titanium**	Clinical trial in CD Animal models and translational	The inconsistent results of the two clinical trials of low nanoparticle diets led to a

	dioxide and sulphites (very low, 92.3%)	**dioxide and sulphites (low, 92.3%)**	studies in UC	downgrading of the evidence

CD – Crohn's disease; UC – ulcerative colitis

BLUE= a recommendation to increase consumption

RED= a recommendation to reduce consumption

Supplemental Table 1: Interventional studies of fiber, inulin, and low FODMAP diets

Author (year)	Study design	Sample size	Patient characteristics	Key outcome measures	Key findings
Ritchie (1987)	Randomized single blind	352	Inactive or mildly active CD	Relapse over 2 years defined by need for alternative treatment	No difference between high fiber, low sugar diet and unrestricted diet
Benjamin (2011)	Randomized double blind placebo-controlled	103	Active CD (CDAI>/=220)	Response (CDAI fall of >/=70) by week 4	Supplementation with 15g/day fructo-oligosaccharides (including inulin) caused non-significant worsening of response rate and increased withdrawal with more flatulence (p= 0.004) and abdominal pain (p= 0.048)
Prince (2016)	Case series of consecutive cases referred for low FODMAP diet, uncontrolled	88	39 CD, 38 UC, 11 IBD-U	Satisfactory relief of functional gut symptoms (FGS) by follow-up (mean 2.6months)	78% satisfactory relief of symptoms by follow-up compared with 16% at baseline
Cox (2017)	Randomized double-blinded, placebo-controlled re-challenge with FODMAP components	32	18 UC, 14 CD	IBD in remission, previous functional symptoms that had responded to low-FODMAP diet	Challenge with 12g/day of fructans for 3 days but not 6g/day of galacto-oligosaccharides, or 6g/day of sorbitol or 12 g/day of glucose (placebo) reduced proportion of patients free from functional symptoms (62% vs 90%, p = 0.033)

CD – Crohn's disease

Supplemental Table 2. Cross-sectional surveys of patients regarding use of gluten free diets and patient reported outcomes

Author (year)	Study design	Sample size	Patient characteristics	Key outcome measures	Key findings
Aziz (2015)	Cross-sectional survey	145	Combination of CD (68% with active disease, 32% quiescent) and UC (% active vs quiescent not reported)	Prevalence of self-reported non-celiac gluten sensitivity (NCGS) Use of gluten-free diets (GFD)	Prevalence of self-reported NCGS was 28% in IBD patients (29% Crohns, 27% UC) None had diagnosed celiac disease 19% IBD patients had tried GFD but only 9% were still adhering to the diet Abdominal pain, discomfort, bloating, diarrhea, fatigue and headaches were symptoms associated with gluten ingestion in IBD Patients with Crohn's and NCGS tended to have stricturing and more severe disease, and associated gluten ingestion with joint pain
Herfarth (2014)	Cross-sectional survey	1647	63% Crohn's and 37% UC/indeterminate colitis	Prevalence of self-reported NCGS Use and adherence to GFD Symptomatic improvement on GFD	5% patients with IBD had reported NCGS whereas 0.6% had concurrent coeliac diagnosis 19% had tried GFD and 8% were still following the diet 66% reported improvement of gastrointestinal symptoms 38% also reported a decrease in frequency and severity of flares Strict adherence to a GFD was associated with improved fatigue
Limketkai (2018)	Cross-sectional survey	102	54% Crohn's, 45% UC, 3% unclassified IBD	Prevalence of self-reported NCGS	20% had self-reported gluten sensitivity (Excluding those with concurrent celiac disease) Of these, 64% were following a GFD

					No differences in reported GI or extra-intestinal symptoms in those with or without gluten sensitivity Presence of stenosis in Crohn's, recent flare and dermatological symptoms were associated with gluten sensitivity	CD – Crohn's disease

Supplemental Table 3. Clinical studies of meat consumption in IBD

Author (year)	Study design	Sample size	Patient characteristics	Kind of meat	Methods	Key findings
Albenberg (Gastroenterology 2019)	Prospective randomized controlled trial.	214 CD patients (n=118 in arm A and n=96 in Arm B).	Adult patients in remission on a biannual survey and who reported consumption of red meat at least once weekly	Red or processed meat	Arm A- a minimum of 2 servings/week or Arm B- not more than 1 serving per month of red or processed meat for 48 weeks.	Adherence to the high meat diet, determined by % weeks consuming 2+ servings of red or processed meat, was 98.5% compared to 57% adherence to the low meat diet. At least a mild relapse occurred in 59% of patients during the study. There were no significant differences in time to overall (Fig 1, p=0.61) or moderate/severe (Fig 2, p=0.50) relapse.
Prévost Jantchou (Am J Gastroenterol 2010)	National cohort study	67,581 participants	Women living in France, aged 40 – 65 years	Meat (red and white meat)	Women aged 40 – 65 years, free of major diseases were followed for 10.4years. FFQ questionnaire and Questionnaires on disease occurrence were completed every 2 years.	77/67,581 cases of IBD High total protein intake, specifically animal protein was associated with a significantly increased risk of IBD, (HR 3rd Vs 1st tertile 3.31 (1.41 – 7.77), P = 0.007), and 3.03 (1.45 – 6.34) (P = 0.005) for total and animal protein, respectively). High consumption of meat or fish but not of eggs or dairy products was associated with IBD risk

Jowett (Gut 2004)	Prospective cohort study	191 patients	UC patients in remission	Red and processed meat	Determine the effect of habitual diet on Relapse. Relapse was defined using SCCAI, . Nutrient intake was assessed using a FFQ follow up of 1 year	52% of patients relapsed. Consumption of meat (OR) 3.2 95% (CI) 1.3‑7.8)), particularly red and processed meat (OR 5.19 (95% CI 2.1‑12.9)), in the top tertile of intake increased the likelihood of relapse compared with the bottom tertile of intake.
Tasson (Dig Dis Sci 2017)	cross-sectional study	103 adult patients	50 with active disease and 53 in remission, divided by their calprotectin level	Meat	Cross sectional study, evaluating food intake using FFQ and disease activity by calprotectin	meat intake showed a positive effect on disease relapse, the highest quartile for meat consumption coinciding with a higher risk of active disease (OR 3.61, 95% CI 1.15–11.38)
Barnes (Clinical Gastroenterology and Hepatology 2017)	prospective, multicenter, observational study	412 patients, from 25 sites,	UC in remission during monotherapy with an aminosalicylate	Processed meat	Patients completed a validated food frequency questionnaire at enrollment and were followed for 12 months	Forty-five patients (11%) had a UC relapse within 1 year of study enrollment. Processed meat, was not associated with an increased risk of flare.
Hou (Am J Gastroenterol 2011)	Systematic review					
Giovanni (World J Gastroenterol 2010)	case-control study	83 patients	new cases of IBD (41 ulcerative colitis, 42 CD) and 160 healthy controls	red meat	Portions per week of 34 foods and beverages before onset of symptoms were recorded using a validated questionnaire	Changes in dietary habits, due to the presence of symptoms, were reported by 38.6%. high consumption of red meat (OR = 7.8) (95%CI: 1.61‑37.9) was associated with

						CD.
Amarapurkar (Indian J Gastroenterol 2018)	Case Control	1054 patients IBD 1580 Controls	765 UC 289 CD	Vegetarian versus non-vegetarian		Vegetarian diet protective for UC OR 0.329, 95% CI 0.27–0.39 not for CD
Le Leu (Dig Dis Sci 2013)		DSS-animal model				Consumption of a diet high in red meat increased DSS-induced colitis as evidenced by higher disease activity and histopathological scores. Addition of resistant starch to the red meat diet abolished the effect in acute DSS-induced colitis.
Opstelten JL et al Clin Nutr 2018	Cross sectional with prospective follow up	165 IBD 1469 controls adults	Patients in cancer surveillance program	Animal protein	FFQ at enrolment and follow up for relapse	Higher intake of animal protein and carbohydrates among patients. No increased risk of relapse by animal protein intake
Levine (Gastroenterology 2019)	Randomized Controlled Trial 12 weeks	78 children with CD	Mild to Moderate Disease treated with Exclusive enteral nutrition (EEN) or CD exclusion diet	Chicken breast +eggs	CDED arm received 150-200 gram chicken breast and 2 eggs every for 12 weeks EEN arm received free diet	CDED arm superior remission and reduction in inflammation by week 12

			(CDED)			

CD – Crohn's disease

Supplemental Table 4. Clinical studies of dairy consumption in IBD

Author (year)	Study design	Sample size	Patient characteristics	Key outcome measures	Key findings
Opstelten (2016)	EPIC Prospective cohort study	401,326	Habitual diet of healthy men and women (20-80 yrs) self-completed food frequency questionnaires. 110 incident cases CD and 244 UC each matched to 4 controls.	Consumption of dairy products against development of IBD	Validated food frequency questionnaires completed within healthy individuals over 12 European centers suggest no relationship between quartiles of dairy consumption and development of IBD. Comapred to non-consumers, those that consumed mild had a reduced risk of CD (OR 0.30, 95% CI, 0.13-0.65)
Barrett (2009)	Prospective cohort study	484	Comparisons of hydrogen breath testing in Caucasian adults with various GI disorders Including: Crohns disease (91), UC (56), Functional GI disorders (201), Coeliac disease (136), Healthy control group (71)	Raised hydrogen breath testing of >10ppm from baseline following 50g lactose ingestion between 2 x consecutive 15 minute intervals.	Lactose malabsorption was most common in CD (42%) and UC (40%). Lactose malabsorption was more frequent in patients with Ileal CD than those with Ileocolonic (39% P= 0.058).
Eadala (2011)	Prospective cohort study	165	Breath and genotype testing for prevalence of lactose intolerance between CD (*n*-70),	RT-PCR testing for genotype CC. Hydrogen and methane breath test following	Genotype CC is associated with low levels of lactase in duodenal biopsies, CT slightly greater and TT genotype represents higher lactase concentrations. None of the healthy volunteers had CC

			UC (*n*-95) and healthy control (*n*-30). Male and female Caucasian adults mean age 47years. Disease in remission.	consumption of 50g lactose. FGID questionnaire comparing IBD and genotype.	genome and none tested positive for hydrogen or methane breath testing. 7% of IBD patients had CC genome suggesting no absolute association IBD and lactose intolerance. The effects of hydrogen breath testing suggested 26% UC and 49% of CD versus 0% of the healthy control. 65% of UC and 76% CD patients with hydrogen levels >20ppm reported GI symptoms up to 48hrs post ingestion of 50g lactose.
Lopes (2014)	Cross sectional dietary questionnaire	65	IBD patients aged 20-75years. (Brazil)	Food frequency questionnaire and dietary analysis of dairy consumption. (DietWin-Porto) Vs patient reported symptoms	FFQ and photographs to demonstrate portion sized were used to estimate dairy intake. Bloating and bleeding were the main symptoms reported although disease activity was not discussed. 64.7% of patients restricted dairy produce following diagnosis, 45.5% due to exacerbation of symptoms, 36.4% advised by health professional. 80% of patients had seen a Nutritionist. Ethnicity had not been documented; greater prevalence of lactose intolerance in non-Caucasian population groups may be a factor contributing to high level of dairy avoidance.
Nolan-Clark (2011)	Secondary analysis	165	Caucasian adults with IBD in New Zealand. Male-49 Female-116	Self-reported disease activity, diary intake and symptom profile reassessed at 6 month intervals.	Dairy products had no effect on self-reported CD symptoms for most people. Dairy products with a high fat content were most frequently reported to worsen perceived CD symptoms

CD – Crohn's disease; UC – ulcerative colitis

Supplemental Table 5. Studies of alcohol in IBD

Author (year)	Study design (country)	Sample size	Patient characteristics	Key outcome measures	Key findings
Cohen (2013)	Cross sectional survey (USA)	6,768	Mix of CD and UC patients with or without ostomy or pouch.	Association between food and symptoms exacerbation or amelioration.	Alcohol was more frequently reported to worsen symptoms within most disease categories.
Swanson (2010)	Cross sectional survey (USA)	129	Mix of CD (52), UC (38), and IBS (39) patients.	Patterns of alcohol consumption and its association with GI symptoms.	Inactive IBD patients drink alcohol similar to general population. Inactive IBD drinkers more likely to report worsening GI symptoms than current IBS drinkers.
Swanson (2011)	Prospective cohort study (USA)	23 (21 analyzed)	Mix of inactive UC patients (8), inactive CD patients (6), and healthy controls (7).	Effect of daily moderate red wine consumption for 1 week on intestinal permeability and stool calprotectin.	Moderate alcohol did not change clinical disease activity scores (UCAI, CDAI) or CRP but decreased stool calprotectin and increased intestinal permeability in IBD patients.
Hey (2007)	Randomized, 5 intervention, cross over, open label study (Denmark)	32	Inactive CD patients (20) and healthy controls (12).	Effect of ethanol and sugar content in five different alcohol drinks on abdominal discomfort.	Higher plasma AUC for glucose and more pronounced abdominal discomfort in CD patients following intake of alcohol drinks with higher sugar concentration. No difference in AUC for ethanol between CD patients and controls.
Zutshi	Survey of registry	4,464 (1,220	CD patients seen in	What patients think	Alcohol increased symptoms

(2007)	(USA)	analyzed)	a digestive disease center between 2002 and 2007.	is relevant to their symptoms and helps them cope.	in 40%.while 41% did not have any change in their symptoms. There was no particular type of alcoholic beverage that affected symptoms.
Jowett (2004)	Prospective cohort study (England)	191 (96% completed follow up)	UC patients in remission.	Association between dietary factors and UC relapse risk.	Alcohol increased likelihood of relapse (OR 2.7, 95% CI 1.1-6.67).
Hsu (2016)	Retrospective population based cohort study (Taiwan)	288,055	57,611 inpatients with new onset alcohol intoxication (AI) and 230,444 randomly selected controls.	Association between AI and IBD development risk.	AI cohort had increased risk of IBD (HR 3.17, 95% CI 2.19-4.58). Mean (SD) between hospitalization for AI and IBD onset 6.08 (3.48) years.
Wang (2013)	Multicenter case-control study (China)	2616	1308 UC patients and 1308 matched controls.	Risk factors for UC development.	Alcoholic drinkers were at higher risk of developing UC (light drinkers: OR 1.264, 95% CI 1.073-1.490, heavy drinkers: OR 1.453, 95% CI 1.122-1.882).
Jiang (2007)	Case-control Study (China)	354	177 UC patients and 177 matched controls.	Association between environmental factors and UC development risk.	No association.
Samuelsson (1991)	Case-control study (Sweden)	334	167 UC patients and 167 matched controls.	Association between socioeconomic factors, dietary, personnel habits, and medical history	No association between UC development and alcohol.

				and UC development risk.	
Nie (2017)	Meta-analysis	16 studies	3,689 UC patients and 335,339 controls.	Association between beverage consumption and UC development risk.	No association between UC development and alcohol.
Nakamura (1994)	Case-control study (Japan)	93 public health centers	384 UC patients who received financial aid for treatment of their disease and 384 matched age and sex controls.	Association between current smoking and alcohol drinking with UC development risk.	Usual consumption of alcohol reduced the risk of UC compared with less frequent use (OR 0.57, 95% CI 0.37-0.86).
Porter (2017)	Prospective cohort study (The millennium cohort study) (USA)	108,129 (40,807 were analyzed)	Incident IBD was identified from medical encounters from 2001 to 2009 or by self-report. 58 and 49, new onset cases identified for CD and UC, respectively.	Incidence and risk factors of IBD in a US military population.	23.2 and 21.9 diagnoses per 100000 person-years, respectively, for CD and UC. Moderate alcohol consumption was associated with lower UC risk (aHR 0.4, 95% CI 0.2-0.6).
Boyko (1989)	Population based case- control study (USA)	304,000 members of a pre-paid health plan.	209 UC patients and 209 matched controls of a pre-paid health plan.	Association between coffee and alcohol consumption and UC development risk.	Current alcohol users had a lower risk of UC compared to non-users. Risk of disease decreased as number of alcoholic drinks consumed per day increased.
Han (2010)	Case-control (New Zeeland)	736,000 New Zealanders	315 CD patients and 536 matched controls.	Association of environmental factors and UC	Drinking alcohol once per week showed a slight protective effect.

		of European descent		development risk.	
Octoratou (2012)	Questionnaire (Greece)	96	28 newly diagnosed CD patients (2-4 weeks), 30 patients with established diagnoses of CD (2 - 11 years), and 38 matched controls.	Assess food consumption in CD patients exactly at the time of diagnosis and identify dietary constituents as risk factors for development of CD.	Increased consumption of alcoholic drinks (P = 0.009) in recently diagnosed CD patients in comparison with healthy controls.
Bergmann (2017)	Prospective cohort (10 European countries)	198 UC and 84 CD incident cases and 792 matched UC controls and 336 matched CD-controls.	Nested case-control study within the EPIC cohort study.	Assess the role of pre-disease alcohol consumption on the risk of developing UC or CD.	There was no evidence of associations between alcohol use and the odds of developing either UC or CD.
Cannon (2018)	Retrospective analysis (USA)	State In-patient Databases (SID) for New York and Florida from 2009–2013.	41,810 IBD patients, 18,695 UC patients, and 24,059 CD patients.	Assess alcohol's role in exacerbating UC flare and/or onset.	IBD patients with documented history of alcohol use may have an increased risk of infections as well as require more diagnostic and therapeutic procedures.

CD – Crohn's disease

Supplemental Table 6. Studies of artificial sweeteners in humans.

Author (year)	Study design	Sample size	Patient	Key outcome	Key findings

			characteristics	**measures**	
Racine (2016)	Prospective case-control study	256 with UC and 117 with CD (from sub-cohort of 366,351), matched 1:4 with controls	UC: median age 51.5 years at diagnosis (CD – 50.3 years), 61% female (CD – 73%), range: 20-80 years old, 3.8 years between entry into cohort and diagnosis (CD – 4.6)	Food/dietary pattern frequency pre-IBD diagnosis	Positive association between "high sugar and soft drink" dietary pattern and UC risk (IRR for fifth versus first quintile = 1.31 [0.85-2.02]; Ptrend = 0.05) only if also low vegetable intake, no association with CD
Sakamoto (2005)	Multi-centre retrospective case-control study	108 with UC, 126 with CD, 211 control	Ages 15-34, within 3 years of diagnosis, each case matched with control of same sex, age and hospital	Food/dietary pattern frequency pre-IBD diagnosis	Positive association between consumption of sugars and sweeteners and CD risk (OR 2.12; 95% CI, 1.08 to 4.17), UC risk not significant
Hansen (2011)	Case-control study	123 with CD, 144 with UC	Diagnosed during 2003-2004 in Copenhagen, median age of IBD patients 37.5 years, Caucasian	Food/dietary pattern frequency pre-IBD diagnosis	High sugar intake positively associated with IBD, more significant odds for CD (CD: OR 3.50; 95% CI, 1.73-7.07) (UC: OR 1.68; 95% CI, 0.96-2.97), confounding factor is low intake of fiber (adjusted OR, 2.46; 95% CI, 1.15–5.27)

CD – Crohn's disease

Supplemental Table 7. Animal studies of artificial sweeteners and maltodextrin

Author (year)	Animal models employed	Key outcome measures	Key findings
Rodriguez-Palacios (2018)	CD-like ileitis-prone SAMP mice Ileitis-free control AKR	Fecal microbiome, ileal MPO reactivity, histological and stereomicroscopy intestinal inflammation scores, *E. coli* infiltration of ileum mucosa, malX gene expression	Splenda did not alter ileal inflammatory scores, percent of SM-abnormal mucosa, 3D morphology of cobblestone lesions Supplementation of Splenda increased *Proteobacteria*, no significant impact on *Bacteroidetes* or *Firmicutes* abundances, increased Enterobacteria MPO activity in Splenda-supplemented SAMP mice 2.7 times higher compared to control SAMP Increased *E. coli* abundance and penetration into ileal mucosa Increased bacterial malX gene expression in treated SAMP mice compared to control SAMP (P=0.03), undetectable malX in all AKR
Bian (2017)	C57BL/6J male mice	TNF-α, iNOS, fecal microbiome	6 month supplementation of saccharin in drinking water increased iNOS and TNF-α ($p<0.05$) in liver, decreased *Dorea* and *Ruminococcus* (*Clostridiales*), increased *Roseburia* and *Turicibacter*
Chi (2018)	CD-1 mice	Fecal microbiome	4 week supplementation of neotame in drinking water decreased α-diversity, altered β-diversity, decreased genes responsible for butyrate synthesis (SCFA), decreased *Firmicutes* and increased *Bacteroidetes* phyla
Nickerson (2012)	Ileal and colonic human tissue culture	Epithelial biofilm formation and adhesion of LF82 AIEC strain, malX gene expression	MDX promotes biofilm formation of LF82 and its adhesion to epithelial cells of CD tissue but not invasiveness, malX gene more expressed in ileal mucosa of CD patients compared to controls (71% positive vs. 18% positive)
Nickerson (2014)	a) Cell culture (Human intestinal epithelial cells, human and murine macrophages)	a) *Salmonella enterica* clearance b)Mucosal *Salmonella*	a) MDX supplementation on healthy epithelial and macrophage cells infected with *Salmonella* increased viability of Salmonella b) MDX consumption in drinking water alone did not

	b) Animal model: C57BL/6 mice (*Salmonella* colitis model)	colonization, bacterial localization score	affect intestinal inflammation, though enhanced *Salmonella* colonization and increased bacterial localization score in colonic epithelial cells
Suez (2014)	a) Animal model: C57Bl/6 mice b) *In vitro*: Fecal culture (of C57BI/6 naïve mice) c) (Part of) prospective cohort study	a) Fecal microbiome b) Fecal microbiome c) Artificial sweetener consumption, fecal microbiome (172 from cohort of 381 non-diabetic individuals)	a) Mice consuming saccharin in drinking water compared to glucose had increased relative abundance of *Bacteroides* and *Enterobacteriaceae*, decreased *Lactobacilli* and some *Clostridiales* b) Fecal matter of mice grown on medium with saccharin, increased *Bacteroidetes* and reduction in *Firmicutes* phyla c) Increased relative abundance of *Enterobacteriaceae*, *Deltaproteobacteria* and *Actinobacteria* with higher AS consumption

CD – Crohn's disease

Supplemental Table 8. Studies in animals of emulsifiers and gums.

Author (year)	Animal models employed	Key outcome measures	Key findings
Watt J (1971)	Adult male albino guinea pig	Weight change, stools and FOBT, and histopathology	Exposure to carrageenan (5% w/v in drinking water consumed *ad libitum* for 20 to 45 days) led to weight loss (15 – 25% in exposed group *vs* none in control group),loose stools (100% in exposed group *vs* none in control group), positive fecal occult blood test (100% in exposed group *vs* none in controlled group) and ulcerations (86% in exposed group *vs* none in control group)
Al-Suhail A (1984)	Young adult New Zealand white rabbits	Weight change, stools and, histopathology	Exposure to carrageenan (1%w/v in drinking water consumed *ad libitum* for up to 63 days) led to (a) weight loss (-1.47g vs + 1.310g gain in control group), (b) loose stools, positive fecal occult blood test, (c) mucosal ulceration and increased inflammatory cell infiltrate
Swidsinski A (2008)	Il10-/- mice	Intestinal permeability	Exposure to Polysorbate-80 **(**100µl 2% solution via gavage orally for 3 weeks) led to an increase in intestinal permeability
Taggeson, 1984	Rat	Intestinal permeability, activities of N-acetyl-beta-glucosaminidase, alkaline phosphatase, 5'-nucleotidase and phospholipase A2	Exposure to Polysorbate-80 (deposited directly into lumen of cannulated rat intestinal mucosa) led to increased intestinal permeability andincreased levels of N-acetyl-beta-glucosamine and decreased levels of phospholipase A2. There were no changes in alkaline phosphatase and 5'nucleotidase
Chassaing B (2015)	WT C57B1/6 mice and IL10-/- mice and TLR5-/-	Weight, intestinal permeability, microbiota and its inflammatory potential	Exposure to CMC and P80 (1%w/v in drinking water and 0.1%, 0.5% in chow) led to modest weight gain, reduced mucus thickness and changes in microbiota composition (including increases in health associated and decreases in IBD-associated species). Transplanting the cecal contents of emulsifier-treated mice into germ free mice caused microbiota encroachments and low grade inflammation that correlated with altered microbiota species composition and elevated levels of fecal lipopolysaccharide (LPS) and flaggelin. Emulsifier treatment caused colitis in IL-10 deficient mice.
Wu W (2017)	NIH(s) mice +/- inflammation induced using DBS100 *Citrobacter freundii*	Weight, histological activity index and inflammation and	Mice with and without induced inflammation were treated with varying doses (None or 1.7mg/kg or 8.3mg/kg or 41.7mg/kg) of carrageenan, for one week via gavage. Carrageenan exposure led to weight loss in all mice with induced inflammation. Weight loss was dose dependent (5.1%+/-1.01 for none versus 15.7%+/-1.43 for 41.7mg/kg). In mice with induced inflammation, high-dose carrageenan exposure led to a 2.08-fold increase in histological activity index (HAI) . Amongst mice with induced inflammation, carrageenan exposure led to i a decreased T-regs ratio, increased serum levels of pro-

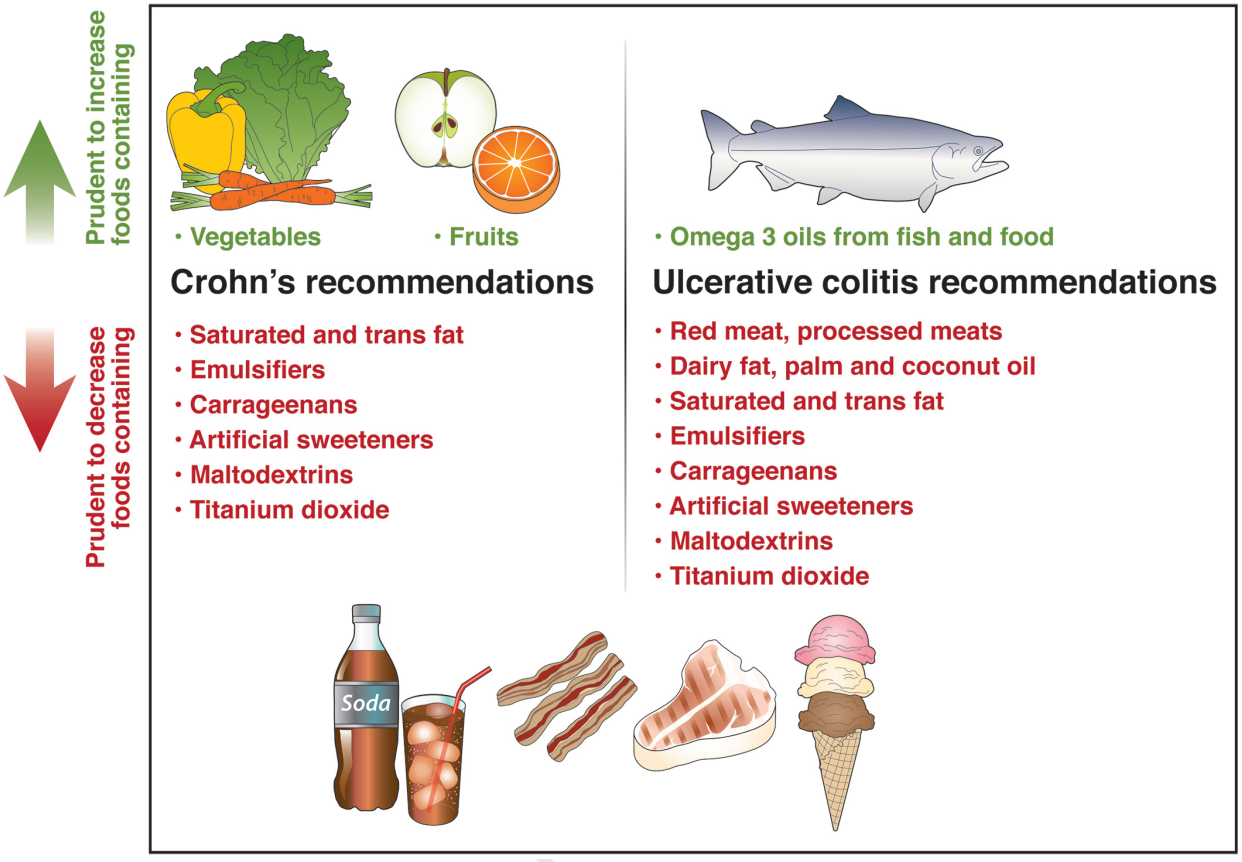
			inflammatory cytokines (e.g. TNF, IL-6, IL-4, INF-γ) and up-regulation of TLR, NFκB; compared to the group that was not exposed to carrageenan, the high-dose carrageenan group had a 1.29-fold, 1.32-fold up-regulation in TLR and NF-kB, respectively. Likewise, T-regs ratio was lowest, and cytokine levels were highest in the group exposed to the highest dose of carrageenan. .
Shang Q (2017)	C57BL/6 mice	Weight, colon length, inflammation and microbiome	Emulsifiers had no effect on weight or colon length. Exposure to three isomers of carrageenan (20mg/L in drinking water) led to an increase in histological score of inflammation and increased levels of serum TNF-α. ι-carrageenan increased bacterial richness and diversity but ƙ-carrageenan had the opposite effects. All isomers of carrageenan decreased the abundance of Bacteroidetes and Verrucomicrobia but increased Firmicutes. Proteobacteria increased in response to ι and λ-carrageenan but decreased in relation to κ-carrageenan. (c)
Chassaing B (2017)	M-SHIME (in vitro model of human microbiome) *placed into* C57BL/6 and RAG -/- mice	Microbiome and its inflammatory potential; gene expression	CMC and PS80 did not impact the microbiota of ASF mice. Exposure to PS80 (but not CMC) led to clear, direct changes in bacterial diversity (increased Proteobacteria, Enterobacteriacae and decreased Bacterioadaccea) in M-SHIME model inoculated with human faces. Exposure to CMC and PS80 in the M-SHIME model induced changes in genes related to flagella expression. Levels of bioactive flaggelin increased rapidly in response to CMC and more slowly in response to PS80, with PS80 also inducing increases in LPS. A clear dose-dependent relationship was not observed. Compared to water treated M-SHIME, CMC and PS80 treated M-SHIME samples inserted into RAG -/- mice significantly increased IL-6 levels. Certain M-SHIME perturbations induced by CMC and PS80 persisted when transferred into germ free mice.

CD – Crohn's disease

Supplemental Table 9. Clinical trials of low nanoparticle diets.

Author (year)	Study design	Sample size	Patient characteristics	Key outcome measures	Key findings
Lomer, MC. (2001)	Double blind study, randomized to a low microparticle diet	20	Active corticosteroid-treated ileal or ileo-colonic CD	Crohn's disease activity index (CDAI) and corticosteroid requirement	In the diet group there was a progressive decrease in CDAI from entry (392 +/- 25) to month 4 (145 +/- 47) (P = 0.002 vs control group) and seven patients were in remission (CDAI <150). In the control group there was no significant change to baseline levels (302 +/- 28 on entry and 295 +/- 25 at month 4), Corticosteroid intake was reduced more in the trial group although this did not reach significance.
Lomer, MC. (2005)	16 week 2x2 factorial design randomized trial. Patient allocated to sham diet or microparticle free diet and to low calcium or normal calcium intake diet.	83	active CD	Crohn's disease activity index, Van Hees index, quality of life and a series of objective measures of inflammation including erythrocyte sedimentation rate, C-reactive protein, intestinal permeability and faecal calprotectin	Dietary manipulation provided no added effect to corticosteroid treatment on any of the outcome measures during the dietary trial (16 weeks) or follow-up (to 1 year);

CD – Crohn's disease


Prudent to increase foods containing
Prudent to decrease foods containing
• Vegetables
• Fruits
Crohn's recommendations
• Saturated and trans fat
• Emulsifiers
• Carrageenans
• Artificial sweeteners
• Maltodextrins
• Titanium dioxide
• Omega 3 oils from fish and food
Ulcerative colitis recommendations
• Red meat, processed meats
• Dairy fat, palm and coconut oil
• Saturated and trans fat
• Emulsifiers
• Carrageenans
• Artificial sweeteners
• Maltodextrins
• Titanium dioxide
Soda