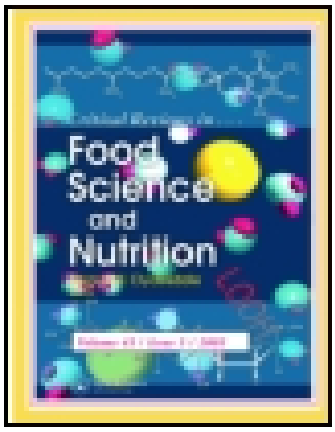

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The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: A Systematic Review

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The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: a Systematic Review

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Abstract

Diet may be a successful part of the treatment plan for improving outcome in patients with inflammatory bowel disease (IBD). This study aimed to systematically review all published clinical trials evaluating the effects of a regular diet on symptoms of IBD. Three medical databases were searched for clinical trials evaluating an intervention that involved dietary manipulation using a regular diet on adults with IBD whose symptoms were objectively measured before and after the intervention. The most common types of regular diet interventions that we observed in the literature fell into the following three categories: low residue/low fibre diets, exclusion diets, or other specific diets. Of all included studies, the few that were of higher quality and that observed a statistically significant improvement in symptoms in the diet group compared to the control group fell under the exclusion diet group or the other specific diet group. We were able to identify several high quality clinical trials evaluating dietary manipulations on symptoms of IBD. Exclusion diets and the low FODMAP diet are two areas identified in this review that show promise for having therapeutic benefits for patients with IBD.

Keywords: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, diet, exclusion diets, low FODMAP diet, nutrition

Introduction

Inflammatory bowel disease (IBD) is highly prevalent in western society, with a prevalence of 249 per 100, 000 persons with ulcerative colitis and 319 per 100, 000 with Crohn's disease in North America and the incidence rate continuing to rise around the globe (Molodecky et al. 2012). The goal of IBD treatment is to heal the inflammation and reduce the symptoms associated with the disease. Currently, the most commonly used treatment strategies include pharmacological therapy, and if unsuccessful, surgery to remove the affected areas of the gastrointestinal tract. Though medical therapy is usually effective, sustained response and potential drug toxicity limits its role in management; surgery has considerable upfront morbidity, is costly, and typically does not lead to long term remission (Cunliffe and Scott 2002), (Sands et al. 2003).

Over the past two decades, researchers have begun to assess the impact of diet in addition to pharmacological therapies and surgery as part of the treatment plan for patients with IBD worldwide. Earlier research demonstrates that elemental diets are somewhat effective in inducing remission in these patients, however once the transition to a regular diet occurs the maintenance of remission is mostly unsuccessful (C Axelsson and Jarnum 1977). In more recent years, investigators have begun to explore the manipulation of regular diets for a more sustainable treatment strategy in this population. The most common diets that have been investigated include low fibre or low residue diets, exclusion diets, and other specific diets that focus on eliminating or increasing a certain food or group of foods that is thought to worsen or improve symptoms or have impact on a patient's microbiome (Levenstein et al. 1985; Ritchie et al. 1987; V.Alun Jones et al. 1985; Riordan et al. 1993; Candy et al. 1985; Rajendran and Kumar 2011; Bentz et al.

2010; Lomer et al. 2005; Bartel et al. 2008; Chiba et al. 2010; Croagh et al. 2007; Grimstad et al. 2011). In practice, it is common for registered dietitians and medical doctors to prescribe a low fibre diet during a flare-up and a low residue diet in patients with known structuring disease. A decrease in the consumption of greasy foods, caffeine, alcohol, and sometimes dairy products depending on individual tolerance are commonly recommended diet alterations. However, it remains difficult to draw conclusions for one specific diet strategy to help manage IBD symptoms in a clinical setting.

There are a few contributing factors responsible for the lack of evidence involving dietary manipulations as a treatment strategy for patients with IBD. Firstly, it is difficult to design a randomized control trial and be able to control all dietary variables, unless all meals and snacks are provided and research subjects are closely monitored (a costly and challenging venture to undertake). Secondly the research in this area is poorly funded and few clinical trials exist that examine dietary manipulation to treat the symptoms of IBD. The majority of published studies look at the association of dietary exposures and the development or the course of inflammatory bowel disease.

The objective of this review was to examine the literature evaluating the effects of a regular diet without the use of supplements on the symptoms of inflammatory bowel disease. Furthermore, our focus was to evaluate clinical trials involving dietary manipulation instead of dietary exposures. Drawing conclusions from the existing evidence will allow registered dietitians and doctors to help their IBD patients manage symptoms, or highlight the need for more research to be done in the area.

Methods

Search strategy

MEDLINE (OvidSP) (http://ovidsp.ovid.com/), EMBASE (OvidSP) (www.embase.com), and CNIHL (http://www.ebscohost.com/biomedical-libraries/the-cinahl-database) databases were searched. The following search terms were used: inflammatory bowel diseases, Crohn's disease, ulcerative colitis, diet therapy, fish oils, dietary supplements, and enteral nutrition. The terms were used combined using the operator "AND" and using a standard method to exclude articles using the operator "OR" for the last three search terms. The search was further restricted to the English language and humans. For the MEDLINE and EMBASE searches, we used MeSH for all search terms, and exploded all search terms. These searches are shown in **Table 1.** The last literature search was completed in September 2012. Bibliographies of studies that matched our search criteria were also reviewed to identify additional relevant articles

Selection of articles

Each study was evaluated for inclusion using the following predetermined criteria: adults diagnosed with inflammatory bowel disease (either Crohn's disease or ulcerative colitis), clinical trial study design, an intervention that involved dietary manipulation using a regular diet (i.e. no formulas or supplements used), and symptoms of IBD objectively measured before and after the intervention. All studies were reviewed by a registered dietician (AC) and verified by a senior gastroenterology resident (GR).

Results

A total of 34 studies were evaluated for inclusion using search methods outlined in **Figure 1**. However, only 12 were eligible and included in this review. 21 trials were excluded after screening titles and abstracts – 12 because they did not involve a regular diet (most used an elemental diet) (Zorich et al. 1997; Takagi et al. 2009; O'Moráin, Segal, and Levi 1984; Messori et al. 1996; Malchow et al. 1990; Leiper et al. 2001; LARSEN et al. 1989; Gorard et al. 1993; Goode et al. 1976; Capristo et al. 2000; Borrelli et al. 2006; Björck et al. 2000), and 9 because they involved the use of dietary supplements (Mitsuyama et al. 1998; Kanauchi et al. 2002; Kanauchi et al. 2003; Imes et al. 1986; Hallert, Kaldma, and Petersson 1991; French et al. 1997; CASELLAS et al. 2007; Bostick et al. 1997; C Axelsson and Jarnum 1977). Among the remaining 13 trials that were assessed, 12 met all eligibility criteria and were included in our review (Levenstein et al. 1985; Ritchie et al. 1987; V.Alun Jones et al. 1985; Candy et al. 1985; Riordan et al. 1993; Bentz et al. 2010; Rajendran and Kumar 2011; Lomer et al. 2005; Bartel et al. 2008; Chiba et al. 2010; Croagh et al. 2007; Grimstad et al. 2011) The one trial that was excluded at this point did not objectively measure symptoms after the diet intervention (Heaton, Thornton, and Emmett 1979).

The 12 included studies fell in to one of three categories: low residue/low fibre diets, exclusion diets, or other specific diets (**Table 2**). These categories reflect what we observed to be the most common types of regular diet interventions in the literature available on this subject.

Low residue / low fibre diets

There were two studies that met our criteria which fell under the low residue or low fibre diet category (Levenstein et al. 1985; Ritchie et al. 1987). Neither study showed significant

differences in symptom management between the control and treatment group. Levenstein et al. randomly assigned patients with active CD who were following a low residue diet upon recruitment to either continue with a low residue diet or to gradually normalize their diet to an unrestricted Italian diet for an average of 29 weeks (Levenstein et al. 1985). Foods that were forbidden on the low residue diet included legumes, whole grains, nuts, and all vegetables and fruit except bananas and potatoes without skin. Fruit juice was not allowed, with the exception of solid free extracts of vegetables and fruits with the home use of a centrifuge. Handouts were given for both diets to reinforce verbal explanation by the research physician. This included a diet plan to gradually reintroduce fibre for patients previously following a low residue diet. Symptoms were assessed by two treating physicians who were blinded to the dietary intervention, and considered pain, severity of diarrhea, and a global clinical assessment to finally yield an 'overall physician assessment'. Compliance to diet guidelines was assessed using diet histories three to six months after randomization in 22 unselected patients with active disease in each group, and in seven of twelve disease-free after surgery. No difference was found between the low residue diet and normal diet for these symptoms.

In the second study, patients with mild or inactive CD were advised to eat an unrestricted sugar and refined carbohydrate diet or were advised to eat only unrefined carbohydrates with no sugar (Ritchie et al. 1987). At baseline and every 6 months patients met with a dietitian who assessed their diets and reinforced dietary advice. The proportion of patients in each group who had relapse of disease activity was the primary outcome. Over the 24 months of the trial, there was no difference in outcome between the groups.

Exclusion Diets

There were five trials which fell under the exclusion diet category that met our eligibility criteria – all of which showed significant improvements in symptoms post diet intervention. The exclusion diets in the first three trials involved introducing certain foods and eliminating those that caused symptoms (V.Alun Jones et al. 1985; Riordan et al. 1993; Candy et al. 1985). The last two trials used a more specific approach and assessed IgG-targeted exclusion diets (Rajendran and Kumar 2011; Bentz et al. 2010).These diets involve identifying and eliminating foods that trigger an IgG mediated antibody response. This is usually done by observings IgG levels in blood serum after exposure to specific food antigens and subsequently eliminating the foods that produce high levels.

Among the more general exclusion diets, the studies by Alun-Jones et al. and Riordan et al. were similar in that they first induced remission in patients with active CD with TPN and observed how long the patients stayed in remission to evaluate effectiveness (V.Alun Jones et al. 1985; Riordan et al. 1993). The controlled trial by Alun-Jones et al. involved randomizing patients to an unrefined carbohydrate and fibre-rich diet or an exclusion diet for 6 months (V.Alun Jones et al. 1985). The patients belonging to the exclusion diet group were instructed to introduce a single food each day. Any food which provoked symptoms was to be avoided. Once this food testing stage was completed, foods suspected of provoking symptoms were reintroduced to confirm this, and a dietary assessment made to ensure nutritional adequacy of the diet. All patients were followed up every 6 months and by the dietitian as often as necessary. At the 6-month mark, there was a significantly higher number of patients in the exclusion diet group that remained well without relapse compared to the unrefined carbohydrate and fibre-rich diet

group (7 of 10 in the exclusion diet group compared to none in the latter), and a longer time to relapse. Mean time to relapse was 1.38 +/- 1.74 (SD) months in the unrefined carbohydrate and fibre-rich diet group and 2.75 +/- 1.98 months in exclusion diet group. There was also non-significant improvement in patient's ESR (41.3 +/- 28.04 in exclusion diet group and 30.8 +/- 25.7 in the unrefined carbohydrate, fibre-rich diet group) and orosomucoid concentrations a marker of inflammation detected in serum (230 +/-124.89 in the exclusion diet group and 220 +/- 66.9% in the unrefined carbohydrate, fibre-rich diet group).

In the double blind trial by Riordan et al., participants were randomly assigned to receive corticosteroid treatment or to an exclusion diet (Riordan et al. 1993). The corticosteroid group started at 40 mg prednisolone daily and tapered off within 3 months. Patients in the diet group were instructed to reintroduce a single food each day and exclude any foods that provoked symptoms. The trial duration was 2 years, or patients left the trial when they developed a clinical relapse. Disease activity was monitored by the Harvey and Bradshaw index (HBI), and a score of >6 was considered a relapse. There was a significant improvement in the diet group compared to the corticosteroid group in terms of number of patients who completed the trial without experiencing clinical relapse (66% of patients had clinical relapse in corticosteroid group compared to 30% in diet group) and median time in remission (7.5 months in diet group compared to 3.8 months in steroid group). No p values were reported. There were significant improvements in albumin (36.5 +/- 2.0 on recruitment, 40.5 +/- 3.4 on last visit), ESR (37.9 +/- 6.6 on recruitment, 19.7 +/- 4.7 on last visit), and a serum measurement of inflammation (1.16 +/- 0.12 on recruitment, 0.74 +/- 0.07 on last visit) in patients in the diet group. In this group there was no statistically significant improvement in hemoglobin (12.2 +/- 0.4 on recruitment,

13.1 +/-0 0.5 on last visit) or C-reactive protein concentrations (61.8 +/- 19.0 on recruitment, 19.7 +/- 6.4 on last visit). Contrary to the other trials that fall under this category, Candy et al. looked at the effect of an exclusion diet on patients with mild to moderately active UC (Candy et al. 1985). Patients were randomized to an exclusion diet group or to a control group where they were asked to document daily food intake and record any symptoms. The exclusion diet group were given a very restricted diet in the first week with only one item of food allowed at breakfast and lunch, and two foods at supper. No foods were repeated more than once this week. The subjects in this group were interviewed individually and their symptoms were reviewed in relation to foods consumed. The menu was slowly expanded over the 6-week period to include foods that did not produce symptoms. After 6 weeks, there was a significant improvement in symptoms as measured by stool frequency, and presence of diarrheal stools and/or rectal bleeding (P=0.009).

The last two trials that examined exclusion diets did so with the use of IgG-guided elimination on CD patients with active disease (Rajendran and Kumar 2011; Bentz et al. 2010). Rajendran & Kumar performed a pilot study and tested the sera of their patients for IgG4 antibodies to 14 specific food antigens, and subsequently removed each patient's 4 most reactive foods from their diets for 4 weeks (Rajendran and Kumar 2011). This diet resulted in significant symptomatic improvement post-intervention compared to baseline using the modified CD activity index (mCDAI) (171 +/- 108 upon entry compared to 97.5 +/- 87 at 4 weeks, P=0.0001). The greatest improvements were seen in number of bowel movements per day (mean reduction from 4 to 2, P=0.0001), followed by mean pain rating (reduction from 0.71 to 0.43, P=0.030), and general well-being (improvement from 0.88 to 0.63, P=0.045). ESR , C-reactive protein and

albumin levels were also assessed before and after the intervention. There was a non-significant reduction in ESR (fell from 22.3 +/- 16.0 to 17.1 +/- 15.2, P=0.032), and no significant change in C-reactive protein or albumin levels. The study done by Bentz et al. used a randomized, double-blind, cross-over intervention trial to further examine an IgG-guided exclusion diet in patients with active CD (N=23) (Bentz et al. 2010). The exclusion diet was based on the presence of IgG antibodies to food on symptom outcome in CD patients. The first step of this study involved measuring the reactivity of T cells, CD4 and CD25 to patient-specific food antigens in vitro. Patients who were first randomized to this specific diet group received an elimination diet for 6 weeks based on these IgG results before crossing over to the sham diet, without a washout period. The control group received a sham diet during the same time, also being asked to eliminate certain foods that were different than their specified IgG results, and then crossed over to receive the exclusion diet. During the IgG diet, stool frequency was significantly lower in comparison to the sham diet (stool frequency reduced by 11% compared to sham diet group, P =0.004). However, there was a significant increase in stool frequency of 9% after crossing over to the other diet, regardless of type of diet (P=0.025). There was a non-significant improvement in the combined score to rate general well-being and abdominal pain for the IgG diet group compared to the sham group, with an average reduction of the total weekly score of 6.5 points in the IgG group (P=0.07).

Other Diets

There were five studies that met our criteria which did not fall under low fibre / low residue or exclusion diets, but that were instead very specific and different from one another (Lomer et al. 2005; Bartel et al. 2008; Chiba et al. 2010; Croagh et al. 2007; Grimstad et al.

2011). Among the five, three assessed symptom outcome of a diet intervention in CD patients (Lomer et al. 2005; Bartel et al. 2008; Chiba et al. 2010), and two assessed similar outcomes in patients with UC (Croagh et al. 2007; Grimstad et al. 2011).

Lomer et al. used a 2 x 2 factorial design to assess a diet low or normal in microparticles and/or calcium for 16 weeks on patients with active CD (Lomer et al. 2005). Low calcium was considered 400 mg/day, whereas high calcium was considered to be 800 mg/day. In the low microparticle group, foods that contained the dietary microparticles titanium dioxide and particulate silicates were excluded from the participants' diet. In the normal microparticle group, dietary advice to avoid a different group of food additives (sulphur dioxide and sulphites) was used as a sham diet. There were no significant differences found between groups for CDAI (P=0.3), Van Hees index (P=0.4), quality of life (P=0.7), or objective measures of inflammation (CRP P=0.6, ESR P=0.6, faecal calprotectin P=0.9, permeability P=0.5), demonstrating that there is no benefit from reducing dietary microparticles or manipulating dietary calcium for patients with active CD.

A more successful outcome was seen in the study by Bartel et al. which assessed a diet low in ingested matter from environmental factors (i.e. fertilizers, pesticides, preservatives, food additives) (Bartel et al. 2008). Patients with active stricturing CD in the dietary intervention group were instructed to follow a restricted diet composed of red meat, sourdough bread, rape oil, and fresh butter which all came from intensively monitored organic farming. The control group was instructed to eat a well-balanced, low-fat, high-carbohydrate diet while avoiding fruits and vegetables and red meat. Both groups followed their respective diets for 6 weeks. This study primarily assessed signs of improvement in intestinal inflammation based on MRI and

endoscopy scores, and secondarily examined transabdominal sonography scores, Crohn's Disease Activity Index (CDAI), IBD Questionnaire (IBDQ), and inflammatory parameters (C-reactive protein, α1-acid glycoprotein, and ESR). 3 of 4 patients in the intervention group and 1 of 9 patients in the control group showed significant improvement on either MRI or endoscopy evaluation (75% versus 11%, P = 0.027). Sonography scores also showed significant improvement in 4 of 5 patients in the intervention group compared to 1 of 8 patients in the control group (80% versus 12.5%, P=0.016). However, no statistically significant changes in CDAI (113 +/- 35 in intervention group versus 117 +/- 47 in controls), IBDQ (196 +/- 20 versus 192 +/- 20 in controls), or inflammatory parameters (C-reactive protein: 1.1 +/- 1.0 intervention versus 0.7 +/- 0.4 controls, α1-acid glycoprotein: 78 +/- 16 intervention versus 99 +/- 34 controls, ESR: 15 +/- 3 intervention versus 20 +/- 15 controls) were seen.

Chiba et al. also achieved success in prolonging remission in CD patients with the use of a semi-vegetarian diet (Chiba et al. 2010). CD patients achieved remission either surgically or medically, and were provided lacto-ovo-vegetarian diets while still recovering in the hospital (patient stay ranged from 43-82 days). At the end of hospitalization, a dietitian and doctor instructed the patients to continue following the semi-vegetarian diet and provided them with resources to do so. Patients were also discouraged to eat foods that were believed to be a risk factor for IBD including sweets, bread, cheese, margarine, fast foods, carbonated beverages, alcohol, and juice. Healthy eating habits such as regularity of meals and not eating between meals were encouraged. Patients were followed up for 2 years. They were categorized into two groups at the end of follow-up based on their compliance to the diet. If they met pre-established criteria they were considered to be in the semi-vegetarian diet group, if they didn't they were

grouped in the omnivorous diet group. The final results of the study demonstrated clinical remisson rates at 2 years to be significantly higher in the semi-vegetarian diet group compared to the omnivorous diet with 100% in remission at 1 year follow-up in the diet group vs. 67% in the control group, and 92% in the diet group at 2 years compared to 25% in the control group (p=0.0003).

One study assessed dietary interventions on symptom management in IBD patients who required a colectomy for treatment and had either an ileoanal pouch or a ilealrectal anastomosis (Croagh et al. 2007). This was a pilot study that looked at a diet low in short-chain carbohydrates – a low FODMAP diet (Fermentable Oligo-, Di-, and Mono-saccharides, And Polyols). There were two cohorts of patients studied. The first was a retrospective study investigating results from a low FODMAP diet intervention of patients who were referred to a dietitian for the management of a dysfunctional pouch or poor results following colectomy and ileorectal anastomosis. Five patients had UC, and two had CD. The second group was studied prospectively and consisted of patients with UC who had an ileolanal pouch. These patients were educated on the low FODMAP diet and asked to strictly follow the plan for 6 weeks with the assistance of a dietitian's guidance and follow-ups. In the retrospective arm, significant improvements in stool frequency and consistency (from median 8 to 4 per day, P=0.02) were reported and these benefits were sustained over 0.5-3 years of follow-up. There were 5 patients who completed the prospective arm. Three patients who did improve symptomatically did not have elevated inflammatory markers (fecal lactoferrin) upon initiation of the study, while the other 2 did improve both clinically had normal fecal lactoferrin levels. There was no change seen on stool frequency (median 6 to 5 per day, P=ns).

Finally, Grimstad et al. treated patients with active ulcerative colitis with a salmon-rich diet (Grimstad et al. 2011). The 8-week diet intervention assessed the effects of 600 g of weekly salmon consumption in the diets of UC patients. All participants' meals were prepared at the hospital, vacuum-packed, and ready for consumption at home. Simple Clinical Colitis Activity Index (SCCAI) – a symptom-based index, a dietary questionnaire, sigmoidoscopy, serum inflammatory markers, fecal calprotectin, and plasma and rectal biopsy fatty acid profiles were all assessed pre- and post-intervention. There were significantly increased levels of omega-3 in plasma and rectal biopsies, reflecting an elevated amount of DHA and EPA but not omega-6, resulting in an increased ratio of omega-3 to omega-6. There were significant improvements in SCCAI score from median (range) 3.0 (0-7) at visit one to 1.5 (0-6) at visit two (P=0.007), as well as non-significant reductions in CRP (P=0.066) and homocysteine levels.

Discussion

The current systematic literature review included 12 clinical trials that evaluated the effects of making dietary changes in either CD or UC patients, and its subsequent effects on disease outcome – most notably clinical response. Among the trials that met our specific eligibility criteria, we were able to group them into low residue/low fibre diets, exclusion diets, or other specific diets. Of all included studies, there were a few in particular that were of higher quality – three of which fell under the exclusion diet group (Riordan et al. 1993; Rajendran and Kumar 2011; Bentz et al. 2010), and two of which fell under the other specific diet group (Bartel et al. 2008; Croagh et al. 2007). All three high quality exclusion diet trials observed a statistically significant improvement in symptoms in the diet group compared to the control group, whether symptoms were measured by an objective scale (Rajendran and Kumar 2011), by

stool frequency (Bentz et al. 2010), or by sustaining remission times (Riordan et al. 1993). Of the two high quality included trials in the other specific diet group, one obtained success in decreasing inflammation as demonstrated by MRI and endoscopy scores but this was not coupled with an objective improvement in symptoms (Bartel et al. 2008). The other study in this category focused on an innovative diet involving the elimination of foods high in short chain carbohydrates, proving to be successful in decreasing the median number of stools per day in patients following colectomy and ileolanal pouch formation or ileorectal anastomosis without the presence of pouchitis (Croagh et al. 2007). An issue with all studies discussed is the low sample size which limits the generalizability one can draw from any of these interventions.

All of the five trials we assessed that used exclusion diets as the primary treatment strategy were beneficial, however, only three of these were well designed (Rajendran and Kumar 2011; Bentz et al. 2010). The Rajendran trial was particularly interesting as there was a significant reduction in stool frequency after 6 weeks for patients on the exclusion diet (Rajendran and Kumar 2011); however, the recurring problem for exclusion diets is compliance. These diets are very time-consuming and require a lot of effort, for both clinician and patients alike. This was reflected by the high number of dropouts due to noncompliance with diet (5 out of 40) in this trial, and in the study done by Riordan et al with (7 out of 40) (Riordan et al. 1993). Although IgG-guided exclusion diets are more specific and therefore, slightly easier to follow than regular exclusion diets that don't involve IgG-guidance, they may not be as feasible due to the increased cost and lack of accessibility to the materials needed. Furthermore, the accuracy of food-specific IgG testing for food intolerances remains questionable as there is currently no evidence to support its effectiveness (Teuber and Porch-Curren 2003).

The results of our systematic review is in line with a review written by Rajendran and Kumar which systematically reviewed the role of diet in the management of IBD, but focused on different inclusion criteria than ours as they included all types of diets (not just regular), as well as the use of supplements as a primary therapy (Rajendran and Kumar 2010). This review reported the effectiveness of exclusion diets for prolonging remission in IBD patients. Although there are limitations mostly as a results of small sample sizes, exclusion diets should be considered as a potential method for improving symptoms in IBD. Furthermore understanding why symptoms improve with this diet manipulation would be critical.

One way that compliance could be improved in exclusion diets would be if foods were grouped together based on similarities exhibited upon digestion and their impact upon symptoms in IBD patients. The low FODMAP diet is a good example of such strategy. A low FODMAP diet trial done by Croagh et al. demonstrating improvement in symptoms in those without evidence of pouchitis with this strategy seems quite promising (Croagh et al. 2007). This was only a pilot study and lacked a control group, limiting the generalizability of the results. However, this intervention merits further investigation in CD patients as well as surgery naïve UC patients. Another pilot study assessed the low FODMAP diet in both CD and UC patients using a retrospective telephone questionnaire for IBD patients with coexisting functional gut symptoms (Gearry et al. 2009). This study showed an improvement in symptoms of those who responded – particularly in abdominal pain, bloating, flatulence, and diarrhea. Furthermore, there has been much success with the low FODMAP diet in irritable bowel syndrome (IBS) patients over the past few years improving overall abdominal symptoms, flatulence, bloating, abdominal pain, and tiredness (Gibson and Shepherd 2010; Shepherd et al. 2008). IBD patients often

experience similar symptoms to that experienced by IBS patients. In fact, one study reported that 33% of UC patients and 57% of CD patients experienced IBS-like symptoms of at least moderate severity (Simren et al. 2002). It is this association which may explain the improvement seen in patients on this diet in those with UC requiring a colectomy. Although the success of the low FODMAP diet has been observed primarily in IBS patients, it would be interesting to see more clinical trials done to evaluate improvement of symptoms in IBD patients.

There are certain limitations of the present systematic review. Due to the highly specific criteria we defined for our literature search, it resulted in less restrictions placed on other important aspects of clinical trials such as study design. We did not restrict our search to RCTs – the gold standard of clinical trials. This resulted in certain studies being included that we decided to place less weight on due to a poor study design. Additionally, we could not focus on a specific IBD population. For example, we looked at the effects of dietary manipulation on symptom management in both CD and UC, and included trials that assessed diet changes in patients with both active and inactive forms of disease. This makes it difficult to draw specific conclusions for a particular IBD sub-group. However, the major purpose of our systematic review was to look at the use of a regular diet in symptom management of IBD to aid clinicians in treatment strategies with their patients and to assess what further research needs to be done in this area. Although it has its limitations, this review is unique from others done on IBD and diet in that we looked specifically at regular diets, excluding those with a primary focus on supplement use and those that use parenteral or enteral nutrition. Furthermore, we only included clinical trials that involved dietary manipulation instead of diet exposures to specific foods. These specifications restricted

other areas of our systematic review, but allowed us to draw some important conclusions about the effects of dietary therapy for IBD symptoms.

The impact diet has as part of the management of IBD patients is an extremely important but yet still a poorly understood area. Aside from the direct contact of ingested foods and its subsequent side effect on either improving or worsening IBD symptoms, there are also longer term health effects diet can have in this population. Due to lack of knowledge on what foods will not aggravate symptoms, patients often decrease their consumption of food, resulting in inadequate nutrient and caloric intake. Additionally, due to the disease state and inflammation, malabsorption and accelerated nutrient losses can further worsen health and symptoms. Patients are constantly concerned about what they can eat that will allow them to maintain a healthy weight and meet nutrient requirements, but that won't exacerbate symptoms. Even better, they want to know what foods might even improve symptoms. More research done in this area will enable clinicians to better advise their patients on what type of diet will allow them to not only meet nutritional requirements, but that can possibly improve symptom outcome for a better quality of life.

In conclusion, our systematic review evaluating dietary manipulations on symptoms of IBD found 12 studies, most of which were poorly controlled cohort studies. Nevertheless, we were able to identify several potential dietary manipulations which may prove beneficial for improving the symptoms of IBD. Further research using more precise methods of implementing exclusion diets, as well as, the low FODMAP diet are two areas identified in this review that show promise for having therapeutic benefits for patients with inflammatory bowel disease.

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TABLE 1: Search used for systematic review.

MeSH and Key Words
"inflammatory bowel diseases" AND "diet therapy", NOT "fish oils", NOT "dietary supplements", NOT "enteral nutrition".

TABLE 2: Summary of included studies.

Author and Year of Publication (reference)	Sample Size and Condition	Intervention	Results
Low Residue/Low Fibre			
Levenstein et al, 1985 (5)	N = 58, n (low residue) = 30, n (normal) = 28. Active CD[1].	Randomized to a low residue diet or an unrestricted italian diet.	No difference between low residue diet and unrestricted diet.
Ritchie et al, 1987 (6)	N = 352, n (unrestricted sugar, refined carbohydrate) = 162, n (little sugar, unrefined carbohydrate) = 190. Inactive or mildly active CD.	Randomized to either eat carbohydrates in refined form with unrestricted sugar intake, or to eat unrefined carbohydrates only.	No difference between groups.
Exclusion Diets			
Alun Jones et al, 1985 (7)	N = 20, n (UCFR[2]) = 10, n (exclusion) = 10. Active CD followed by induced remission.	Randomized to UCFR diet or exclusion diet that avoided foods to which a patient was intolerant.	Longer time to relapse in UCFR group compared to exclusion diet group. Mean time to relapse was 1.38 +/- 1.74 (SD) months in the UCFR diet group and 2.75 +/- 1.98 months in exclusion diet group. Non-significant improvement in patient's ESR[3] and orosomucoid concentrations.
Riordan et al, 1993 (8)	N = 78, n(diet) = 40, n(corticosteroids) = 38.	Patients all treated with elemental diet until achieved remission. They were randomly assigned to receive corticosteroid	Significant improvements in diet group in ESR, s. albumin, and CRP[4]. Greater percentage of patients withdrawn

		treatment or an exclusion diet.	from corticosteroid group due to relapse compared to diet group (66% versus 30% respectively).
Candy et al, 1995 (9)	N = 18, n(control) = 7, n(diet) = 11. Mild to moderately active UC[5].	Participants were assigned to receive an exclusion diet or act as controls where they kept a food and symptom journal without any dietary changes.	Significant improvement in symptoms in diet group from beginning to end of study (p=0.0009).
Rajendran N, and Kumar D, 2010 (10)	N = 40. Active CD.	Patients excluded 4 of most immunoreactive food types from their diet for 4 weeks according to IgG4 blood tests of 14 common foodstuffs.	Significant improvement in mCDAI[6] scores from beginning to end of study (171 +/- 108 upon entry compared to 97.5 +/- 87 at 4 weeks, p=0.0001). Non-significant reduction in ESR, no significant change in CRP or albumin levels.
Bentz et al, 2010 (11)	N = 23, n (IgG diet) = 12, n (sham diet) = 11. Active CD.	Nutrition intervention planned based on IgG antibodies - either received elimination diets based on true sensitivity results, or sham diet.	Stool frequency was significantly lower in elimination diet group compared to the sham diet group (reduced by 11% compared to sham diet, p=0.004). After crossing over to the other diet there was a significant increase in stool frequency (p=0.025).
Other Specific Diets			
Lomer et al, 2004 (12)	N = 83, n(LCLM[7]) = 22, n(LCNM[8]) = 21, n(NCLM[9]) = 20, n(NCNM[10]) = 20. Active CD of ileum	Patients were randomized to one of four groups: LCLM, LCNM, NCLM, or NCNM.	No significant differences found between groups for any measure.

	and/or colon.		
Croagh et al, 2007 (15)	N = 15 (13 pouch, 2 IRA[11]). Retrospective arm: n = 7, prospective arm: n = 8. Had UC and treated with collectomy and ileal pouch formation or ileorectal anastomosis.	Retrospective arm - symptoms and adherance to low FODMAP[12] diet analyzed retrospectively. Prospective arm - patients instructed to follow low FODMAP diet.	In the retrospective arm, there were significant improvements in stool frequency and consistency (from median 8 to 4 stools per day, p=0.02). In the prospective arm, only the three patients who began the study without elevated inflammatory markers improved symptomatically, not those with elevated inflammatory markers.
Bartel et al, 2008 (13)	N = 18. n(active) = 8, n(control) = 10. stricturing CD.	Randomized to receive a diet low in ingested matter from environmental factors, or a low-fat and high-carbohydrate control diet.	Significant improvement in MRI or endoscopy evaluation compared to controls (75% versus 11% respectively, p=0.027), and significant improvement in sonography scores in the intervention group compared to the control group (80% versus 12.5%, p=0.016). No statistically significant changes in CDAI[13], IBDQ[14], or inflammatory parameters.
Chiba et al, 2010 (14)	N = 22. Active CD, followed by medically-induced or surgically-induced	Patients instructed to follow lacto-ovo-vegetarian diet. After assessing diets,	Clinical remisson rates at 2 years were significantly higher in the semi-vegetarian

	remission.	patients were divided into 2 groups based on compliance: semi-vegetarian or omnivorous diet.	diet group compared to the omnivorous diet group (92% versus 25% respectively, p=0.0003).
Grimstad et al, 2011 (16)	N = 12. UC patients, SCCAI[15] of >/= to 4, fecal calprotectin of > 50 mg/kg.	Participants ate a salmon-rich diet containing 600 g of salmon per week.	Significant improvements in SCCAI score from pre- and post-intervention visitis (median score 3.0 pre-intervention versus 1.5 post-intervention, p=0.007), and non-significant reductions in CRP and homocysteine levels.

[1]Crohn's Disease

[2]Unrefined Carbohydrate Fibre-Rich Diet

[3]Erythrocyte Sedimentation Rate

[4]C-Reactive Protein

[5]Ulcerative Colitis

[6]Modified Crohn's Disease Activity Index

[7]Low Calcium, Low Microparticle

[8]Low Calcium, Normal Microparticle

[9]Normal Calcium, Low Microparticle

[10]Normal Calcium, Normal Microparticle

[11]Iloerectal Anastomosis

[12]Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

[13]Crohn's Disease Activity Index

[14]Inflammatory Bowel Disease Questionnaire

[15]Simple Crohn's and Colitis Activity Index

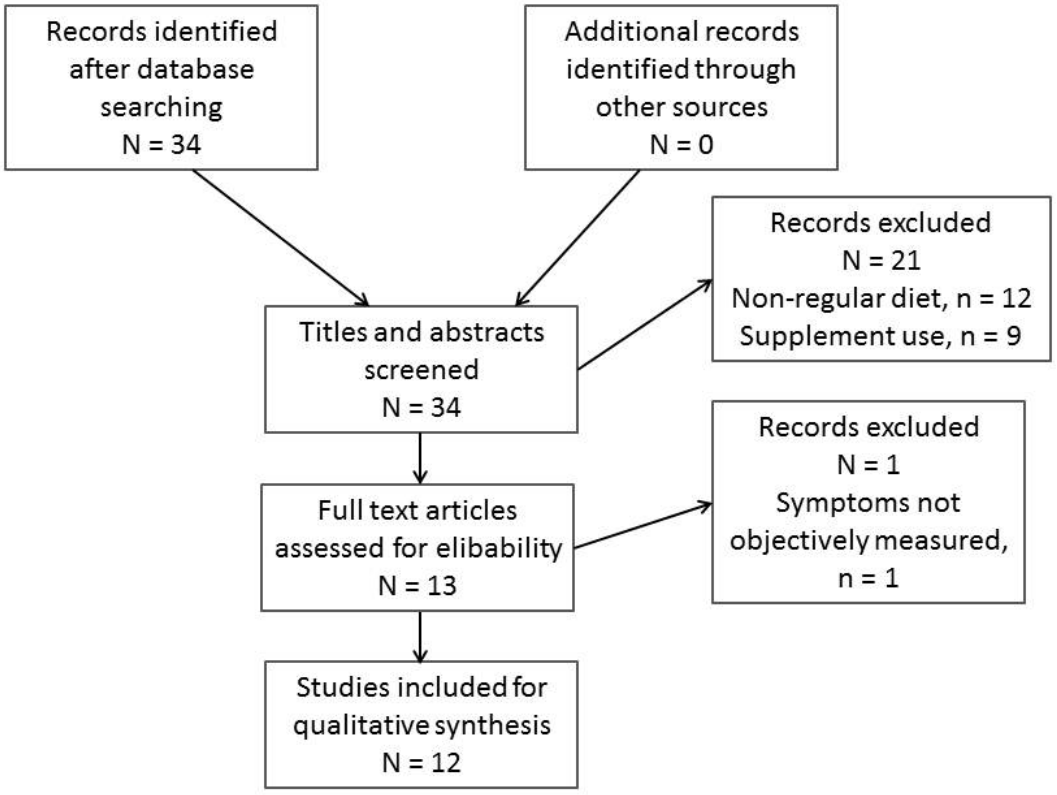

Figure 1: Studies evaluated for inclusion