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Nutritional implications of the dietary interventions for managing gastrointestinal disorders

Heidi M Staudacher
University of Queensland
Faculty of Medicine
Brisbane, Queensland, Australia

Matthew Kurien
University of Sheffield
Academic Unit of Gastroenterology
Department of Infection, Immunity & Cardiovascular Disease
Sheffield, United Kingdom

Kevin Whelan
King's College London,
Department of Nutritional Sciences
Faculty of Life Sciences and Medicine
London, United Kingdom

Corresponding author:
Professor Kevin Whelan
King's College London
Department of Nutritional Sciences
150 Stamford Street
London
SE1 9NH
United Kingdom
kevin.whelan@kcl.ac.uk
ph: +44 (0)207 848 3858

Abstract (200 words)

Purpose of review: The aim of this review is to summarise some of the key dietary interventions recommended for common GI disorders and discuss recent evidence regarding their nutritional implications.

Recent findings: Evidence from short-term randomised controlled trials of the low FODMAP diet in irritable bowel syndrome suggests intake of some nutrients such as fibre, iron and calcium may be compromised, although findings vary across studies, meanwhile long-term uncontrolled trials suggest dietary adequacy improves with reintroduction and personalisation. The gluten-free diet, which is the only treatment for coeliac disease although it is increasingly used for other perceived health benefits, has also been shown to negatively influence overall diet quality. Although high-fibre diets may be beneficial in diverticular disease and constipation, it may lead to reductions in energy intake and nutrient absorption in at-risk populations.

Summary: The role of therapeutic diets in the management of gastrointestinal disorders is increasingly recognised, but there are limited studies investigating the nutritional implications of these. The judicious use of expertise in nutrition and dietetics should minimise potential nutritional deficits, however further prospective trials are needed to identify subgroups of individuals most susceptible to these deficits and the nutrients most at risk.

Introduction

Dietary interventions play an integral role in the management of some gastrointestinal (GI) disorders. Whilst diet remains the mainstay of treatment for coeliac disease, there has been intensifying interest in the use of diet to manage GI disorders such as irritable bowel syndrome (IBS), constipation, diverticular disease and inflammatory bowel disease (IBD). There has not only been progressing momentum in the identification and/or evaluation of new dietary treatments for these disorders, but also much needed synthesis of findings in the form of systematic reviews and meta-analyses. Exclusion of one or more foods or dietary constituents for the purposes of managing GI disorders may increase the risk of inadequate nutrient intake and may have other other nutritional implications. This review will summarise some of the key dietary interventions recommended for common GI disorders and discuss recent evidence regarding their nutritional implications.

Low FODMAP diet

Multiple randomised controlled trials (RCT) report that the low FODMAP diet leads to improvement in symptoms of irritable bowel syndrome (IBS), such as bloating and abdominal pain, in 50-80% of individuals (1, 2)*, although the quality of these trials with respect to their choice of control groups and blinding has been questioned (3). The low FODMAP diet has also been investigated in quiescent inflammatory bowel disease (IBD), demonstrating efficacy for symptoms such as diarrhoea and bloating (4), although many trials are uncontrolled (Prince) and only one RCT has been published (Pedersen). The two major mechanisms by which FODMAP carbohydrates provoke GI symptoms are through increasing small intestinal water and colonic gas, which occur 60-120 minutes post ingestion (5)**. Other less studied mechanisms include the effect of FODMAP carbohdyrates on altering GI motility and modifying the microbiome (1)*1

The low FODMAP diet involves the restriction of oligosaccharides (inulin-type fructans, galacto-oligosaccharides) found in wheat and pulses, disaccharides (lactose) found in dairy products, monosaccharide (fructose in excess of glucose) found in honey, and polyols (e.g. sorbitol, mannitol) found in a variety of fruit and vegetables. Foods considered high in one or more FODMAPs are restricted for a short period of restriction period (4-6 weeks) (6). After this period, individuals are recommended to systematically reintroduce FODMAPs into their diet to determine the tolerable limits of intake. This aims to increase dietary diversity and the prebiotic content of the diet whilst maintaining symptom control (7).

The low FODMAP diet requires alteration of intake of a number of food groups including grains, fruits and vegetables, and dairy products. There is therefore a potential risk of reduced intake of certain nutrients if suitable replacements are not included. Specifically, restricted foods such as wheat products are an important source of carbohydrate, fibre, B vitamins and iron (from fortified breakfast cereals); pulses provide protein and fibre; milk provides calcium and fat-soluble vitamins; and fruit and vegetable provide a wide range of vitamins, minerals and fibre. A reduction in overall food intake could also lead to decreased energy intake resulting in bodyweight loss.

Three recent RCTs have examined the effect of a short-term low FODMAP diet on energy intake in IBS (Table 1). In one of the largest RCTs of the low FODMAP diet to date, energy intake was not different to those following placebo dietary advice and change in bodyweight was minimal (mean <0.5 kg) and not different between groups. (8). This contrasts with findings of two other large 4-week RCTs, where within-group reductions in energy intake were demonstrated in the low FODMAP group (9, 10). However, in these trials the patients in the control groups also reduced their energy intake whilst following standard dietary advice, suggesting this may not be unique to the low FODMAP diet, but a result of following any therapeutic diet for IBS. Bodyweight was not reported in either study.

The low FODMAP diet does not lead to significant changes in protein and fat intake, however a number of studies have reported reductions in fibre intake during the low FODMAP diet.For example, one RCT in IBS (11), a small uncontrolled trial in patients with radiation-induced GI symptoms (12) reported reductions in fibre intake during the low FODMAP diet compared with baseline, whereas a large randomised comparative trial reported reductions in fibre and carbohydrate intakes that were more substantial than that reported in the control group receiving standard dietary advice(9). Inadequate substitution of high FODMAP grains and fruit and vegetables with suitable low FODMAP/high fibre replacements could explain these findings. However, data from another large RCT suggests there is no difference in fibre or macronutrient intake in patients with IBS after a 4-week low FODMAP diet (8), and therefore it is unclear whether fibre intake is definitively at risk throughout a low FODMAP intervention.

There is some data to suggest that intakes of iron, calcium and other micronutrients may be compromised during the low FODMAP diet. One RCT in IBS has reported a within-group reduction in iron intake after low FODMAP diet compared with baseline according to 7-day food records of 47 patients, although no difference was found for the proportion meeting the dietary iron recommendation (8). Importantly, significantly fewer achieved the recommended calcium intakes during the low FODMAP diet compared with baseline. Similarly, a substantial reduction in calcium intake has been reported for 41 patients with IBS compared with their habitual diet at baseline (10). This was accompanied by a reduction in intake of other micronutrients including retinol, thiamin and riboflavin . Variability in the impacts of a low FODMAP diet could be due to true variation in the populations studied, differences in habitual diet in that population due to cultural, religious or socio-economic determinants, local availability of alternative food choices or the depth, detail and delivery method of the dietary advice given by the dietitian. Interestingly, the only two long term studies investigating dietary intake during a modified FODMAP diet (FODMAP personalisation, with

FODMAP reintroduction to patients' tolerance), suggest calcium (11, 13)*, iron and other micronutrients (13)* are not compromised at 6-18 months in patients with IBS.

In addition to the impact on nutrient intake, the low FODMAP diet may have psychosocial impacts relating to nutrition. Patients have been reported to find the diet 'demanding to follow' (12), and a questionnaire study reports eating out and travelling to be more difficult in those following a long term modified FODMAP diet compared with those following their usual diet (13)*. On the other hand, there are demonstrated beneficial effects of the low FODMAP diet on health-related quality of life (11, 14)*, and a range of food-related quality of life scores are no different to those following a habitual diet (13)*. Whether there are psychological ramifications in select patients as a result of following a long term modified FODMAP diet requires formal evaluation.

Gluten-free diet

A gluten-free diet (GFD) is the only established treatment for coeliac disease, which has been used since the 1950s to improve symptoms and intestinal mucosal healing (15). As the spectrum of gluten-related disorders has evolved and interest in using a GFD in IBS has emerged, there has been an increase in the numbers of people following this diet (16). This change is not confined to clinical practice, with increasing numbers of healthy people going "gluten free" for perceived health benefits (16). Although evidence consistently supports the role of a GFD in improving health in coeliac disease, dermatitis herpetiformis and gluten ataxia, the advantages of strict GFD adherence in other conditions or for lifestyle choices remains uncertain and in some cases untested (17).

Gluten describes a complex network of storage proteins found in grains such as wheat (gliadins and glutenins), rye (secalins) and barley (hordeins). It has a key role in determining rheological dough properties and baking qualities (18). Adherence to a GFD entails three components: 1) the avoidance of foods containing gluten, 2) eating naturally occurring GF foods and 3) using commercially

prepared gluten-free substitute foods (17). The labelling of gluten-free foods is defined in law in Europe and North America, with food mandated to contain less than 20 ppm gluten (20 mg gluten/kg food). Although foods are not completely GF, previous research has shown that this defined threshold is safe and tolerated in coeliac disease. This threshold is not universally adopted, with the Food Standards Australia New Zealand defining GF as <5 ppm gluten.

Historically, concerns have been raised regarding the safety of oats in coeliac disease, leading to variations in international guidelines. This issue has recently been addressed in a systematic review and meta-analysis of 433 studies (19)**. Findings support the safety of pure (uncontaminated) oats in coeliac disease, with no evidence that oats influences symptoms, histology, immunity, or serological markers.

As the use of the GFD grows and the number of available gluten-free foods rise, there has been increasing interest in the potential risks associated with a GFD. These risks relate to the inherent restrictive nature of the diet, the chemical modification of gluten-free foods as well as suboptimal dietary habits in those with coeliac disease (e.g. increased biscuit and cracker consumption (21)).

In a recent review of 281 articles evaluating the nutritional quality of a GFD, findings showed fibre intake was low in individuals following a GFD, alongside sub-optimal intakes of vitamins B12 and D , folate, iron, zinc, magnesium and calcium (20)*. Calcium and vitamin D are micronutrients that may warrant close monitoring in individuals following a GFD. Both micronutrients can be deficient at the time of CD diagnosis, with recent studies demonstrating deficiencies persisting during follow-up despite adherence to the GFD (22, 23). Heavy metal bioaccumulation may also be a consequence of a GFD, with higher urine levels of total arsenic and blood levels of mercury, lead, and cadmium seen in individuals avoiding gluten (24)*. These novel findings necessitate further exploration to determine what influence this has long-term health outcomes.

The role a GFD has on macronutrient intake is conflicting in the literature. A number of studies have shown lower carbohydrate consumption in favour of a higher fat and protein intake in people following a GFD, whilst other observational studies contradict this (16). A common finding to all studies is that the GFD is high in sugar and low in fibre. This may have implications for glycaemic control, as has been shown in a recent study showing higher postprandial glycaemia for gluten-free pasta compared with conventional wheat pasta in healthy individuals (25)*. Coronary heart disease risk may also be affected, with a recent cohort study examining more than 110,000 people showing risk to be highest in those with the lowest gluten consumption, with this risk attributed to a lower intake of wholegrains (26)*.

As understanding about GFDs evolve it is important to consider the psychosocial aspects associated with this diet. Previous research has shown that maintaining a GFD has cost implications, influences quality of life and can be socially isolating by restricting meals out (17, 27). Further work is now needed to address the long-term nutritional consequences of a GFD in individuals without coeliac disease, and determining whether gluten is really the culprit causal agent driving symptoms in these individuals.

Other dietary interventions in gastrointestinal disorders

Lactose restriction

Lactose intolerance is characterised by GI symptoms associated with lactose ingestion. The disorder is associated with the LCT-139103C>T gene variant, which has variable prevalence but is highly prevalent in Asian populations. Treatment with lactose restriction involves reduced intake of high lactose dairy foods, including milk, yoghurt and soft cheese and substitution with low lactose or lactose-free alternative plant-based products (e.g. soy, rice, nut-based), although this has variable efficacy. Concerns regarding exclusion of this entire food group centre around the adequacy of

protein, calcium and vitamin D intakes, although the nutritional adequacy of lactose restriction has not recently been explored. One study reported individuals with the *LCT*-13910c>T genotype consume a lower intake of dairy and have a lower plasma 25 (OH)D concentration (28), suggesting nutrient intake may be compromised in some individuals with lactose intolerance, although the limitation of a cross-sectional design in this context is acknowledged. Short- and long-term evaluation of nutrient intake in patients with confirmed lactose intolerance (lactose restriction with subsequent symptom improvement) is required.

High-fibre diet

Dietary fibre manipulation is a common approach to managing some GI disorders, mostly through increasing intakes of high-fibre foods or the use of fibre supplements (e.g. psyllium). Rich sources of fibre include whole grain cereals and some fruits and vegetables and therefore a high-fibre diet is often associated with healthful properties. However, a high-fibre diet may have potentially deleterious effects on nutrient intake and status. Firstly, many trials have shown that some dietary fibres, including gel-forming and fermentable fibres, increase satiety and reduce energy intake (29). Secondly, *in vitro* studies have shown that fibres such as cellulose and hemi-cellulose can bind calcium, iron and zinc and therefore interfere with mineral absorption, although *in vivo* studies show conflicting evidence (30). Taken together, this suggests that where a high-fibre diet is required in populations at risk of undernutrition and mineral deficiencies, these patients should be carefully monitored by a dietitian.

Despite the theoretical risk of deleterious effects, few studies investigating a high-fibre diet in GI disorders measure the consequential impact on nutrient intake. For example, a recent systematic review of 19 trials in diverticular disease described many studies where fibre led to beneficial effects in reducing or preventing symptoms of diverticulitis. The quality of studies was low, however, with

few included studies measuring compliance with the intervention or dietary intake, and many lacking randomization or suitable control groups (31). Furthermore, a recent meta-analysis of seven RCTs reported that fibre supplementation in chronic constipation increased response, increased stool frequency and softened stool consistency compared with placebo (32)*. However, again few of the trials reported the impact of fibre supplementation on background dietary fibre intake, let alone nutrient intake, diet quality or nutritional status.

The most recent major fibre intervention study in GI disorders was a RCT of both high-fibre diet and low-fibre diet, compared with habitual-fibre diet, in the prevention of acute and chronic GI toxicity in 166 patients receiving pelvic radiotherapy for lower GI or gynaecological cancer (33)*. This trial reported a smaller reduction in toxicity score in the high-fibre group both at the end of radiotherapy and 1-year following radiotherapy compared with the habitual-fibre group. Following detailed dietary counselling from a dietitian, fibre and protein intake was higher in the high-fibre diet group but with no significant impact on energy, fat and carbohydrate intake (33)*.

Specific-carbohydrate diet

The specific carbohydrate diet excludes all grains (e.g. wheat, barley, corn, rice), sugars (except for honey), processed foods and milk. The diet is gaining some traction for its use in inflammatory bowel disease (IBD), where a survey of patients showed great interest in the diet with some self-reported benefit (34). However, the SCD has not been subjected to a RCT in IBD and only data from case-series exist in the literature. For example, a retrospective review of 26 children who followed the SCD reported a reduction in disease score at four weeks and six months (35). Meanwhile the same centre reported GI symptom improvement in seven children following a modified SCD (allowing rice, oats, quinoa) but failed to show complete mucosal healing in any (36). However, a dietary analysis of eight children following the SCD reported adequate energy intakes in approximately two thirds of

patients and achievement of vitamin requirements in the majority (37)*. Intakes of calcium were low but were consistent with population norms.

Conclusion

The use of diet as a therapeutic intervention in GI disorders has been driven by growing evidence of clinical efficacy but also patient interest in use of diet as an alternative to drug therapy. Unfortunately a shortcoming of diet therapy in this context is the potential and established effects on nutrient intake and/or status. This, as well as the potential impact on psychosocial aspects, should be carefully weighed against the likely benefit of dietary intervention in each clinical case. Whether individuals with GI disorders that self-modify their diet rather than seek expert guidance from a dietitian face a significantly greater risk to nutritional adequacy is unknown. In order to clarify the long term impact of dietary interventions in GI disorders, future trials that carefully measure longitudinal dietary intake are necessary.

Key points: P*lease include 3 to 5 key bullet points that summarise your article after the main body of text. The aim of these is to encourage others to cite your article based on the stated key points. Please ensure each bullet is no longer than one sentence.*

- A short term low FODMAP diet has specific impacts on nutrient intake, however prospective follow up studies are required to confirm whether this continues in the long term

- The use of a GFD beyond coeliac disease needs to be made judiciously, as nutritional consequences are increasingly recognised, including reduced fibre intake and heavy metal bioaccumulation.

- A high fibre diet may be effective in diverticular disease and constipation but careful monitoring of the impact on energy intake and micronutrient status is required.

Bulleted references

* O'Keefe 2017 Long term impact of the low FODMPA diet…
This is the largest of a few studies that has evaluated long term nutrient intakes in patients following a modified FODMAP diet. Proportions of patients meeting nutrient requirements was similar to those following habitual diet at long term follow up (6-18 months).

* Staudacher et al 2017 the low FODMAP diet: recent advances…
This is a state of the art review of the mechanisms and effectiveness of the low FODMAP diet in irritable bowel syndrome

** Major et al 2017 Colon Hypersensitivity to Distension, Rather Than Excessive Gas Production…
A landmark mechanistic study showing that patients with IBS and healthy controls demonstrate increased small intestinal water and increased colonic gas in response to FODMAP challenge.

*Staudacher HM et al 2017A Diet Low in FODMAPs Reduces Symptoms in Patients With Irritable Bowel Syndrome and A Probiotic Restores Bifidobacterium Species
The first placebo-controlled dietary advice study of the low FODMAP diet. The totality of the symptom outcomes revealed clinical repsonse to the low FODMAP diet over and above placebo.

*Vici et al 2016 Gluten free diet and nutrient deficiences…
Contemporary review evaluating the nutritional quality of a gluten free diet and impact on specific micronutrients.

*Raehsler et al 2017 Accumulation of Heavy Metals in People on a Gluten-Free Diet…
Large population-based cross-sectional study showing that heavy metal bioaccumulation is increased in a gluten free diet, potentially relating to increased rice and fish consumption.

*Johnson et al 2017 Commercially available gluten-free pastas elevate postprandial glycemia in …
A double-blind randomized crossover trial showing how commercial gluten free pasta composed of rice and corn flours increases post-prandial peak glycemic response.

**Pinto-Sanchez MI, et al. 2017 Safety of Adding Oats to a Gluten-Free Diet for Patients With Celiac Disease…
Rigorous systematic review and meta-analysis assessing the role of pure oats within a gluten free diet.

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