Editorial: on "Fermentable carbohydrates (FODMAPs) exacerbate functional gastrointestinal symptoms in patients with inflammatory bowel disease: a double-blind, placebo-controlled, randomised, cross-over, re-challenge trial"

Title: Fermentable Carbohydrates in IBD – Trouble Brewing?

Author: Dr Giles Major, PhD MRCP, Clinical Assistant Professor in Gastroenterology, University of Nottingham

Address for Correspondence

NIHR Nottingham Biomedical Research Centre, NDDC, E Floor West Block, Queen's Medical Centre, Nottingham NG7 2UH, United Kingdom UK.

Tel: +44 (0) 115 8231090. Fax: +44 (0) 1158231409.

Email: giles.major@nottingham.ac.uk

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‘Fibre’ means different things to different people. World, European and national definitions variously emphasise carbohydrate chain length, digestibility, and the particular monosaccharide components included. The European Food Safety Authority defines fibre as non-digestible carbohydrates with chain length of three or more monomeric units, and associated components of plant walls that are not carbohydrates, especially lignin[1]. This broad definition includes oligosaccharides, such as oligofructose, that are artificially derived from larger molecules and commonly added to food during production.

Changes in definition should be considered when interpreting evidence of the health benefits of dietary fibre. In inflammatory bowel disease (IBD), dietary fibre has been of principal interest for its potential to reduce inflammation by modulating the microbiota. Prebiotics, a term coined by Glenn Gibson and Marcel Roberfroid, are non-digestible food ingredients that selectively stimulate a limited number of bacteria in the colon to improve health[2]. Where non-digestible carbohydrates can be fermented, the products of their metabolism include short-chain fatty acids which may stimulate regulatory T-cell proliferation[3], contribute to colonic epithelial nutrition and improve intestinal health.

The paper by Cox and co-workers[4] addresses another consequence of fermentable carbohydrate ingestion: worsening of ‘functional-like gastrointestinal symptoms’. The authors have used this term to maintain the perceived boundary between inflammatory and non-inflammatory bowel disease but put simply these are ‘symptoms’. The growing emphasis on patient reported outcomes (PROs) to

evaluate treatment means that more attention will be needed to issues that bother patients daily without ignoring important, but distant, outcomes such as a future need for surgery. The weight given to bowel frequency, abdominal pain and well-being in the Harvey Bradshaw Index or Crohn's Disease Activity Index would lead to high scores in patients with active diarrhoea-predominant irritable bowel syndrome (IBS-D). In IBD, there is increasing recognition that troubling symptoms can persist despite mucosal healing[5]. The link between dietary carbohydrates and symptoms is decades old but interest has resurged since the grouping of fermentable oligo-, di-, mono-saccharides and polyols under the term FODMAP by Peter Gibson and Sue Shepherd[6].

The patients recruited for this study were all in remission but continued to have symptoms consistent with functional bowel disorders according to Rome Foundation criteria. The investigators sought to tease out the role of different compounds within the FODMAP group: fructo-oligosaccharides (FOS, average monomeric chain length 4), galacto-oligosaccharides (GOS) and sorbitol. The methodology mirrored the approach of Shepherd et al. used to demonstrate symptom induction by FODMAPs in IBS: brief, blind challenges in a crossover design with appropriate washout. As in IBS, FOS induced pain, bloating and flatulence with faecal urgency while upper tract symptoms did not vary. The lack of symptom induction with GOS and sorbitol may reflect the lower challenge doses used. While the rationale to model common dietary intake is understandable, doses were still in excess of daily intake described previously: around 0.4g for sorbitol, 2 g for GOS and 4 g for FOS with a further 4 g from fructose-based polysaccharides such as inulin. As a proof of principle it would be interesting to know the effect of equal doses. This is particularly relevant for GOS

as one randomised controlled trial has shown relief of IBS symptoms when GOS was used as a prebiotic at a dose of 7 g/d[7].

Is an effect therefore specific to FOS, or can it be generalised to all FODMAPs? Does each carbohydrate need individual evaluation? The effect of 'input' (diet) on output 'health' is heavily dependent on the interwoven metabolic processes that occur in the colon microbiota; small adjustments may result in significant changes[8]. Inulin has been shown to induce colonic distension through gas generation, with consequent symptom severity relating to the sensitivity to distension of the individual[9]. There may be other reasons to suspect FOS. In the original FODMAP paper Gibson and Shepherd proposed mechanisms by which FODMAP fermentation might alter intestinal permeability[6]. A standard experimental model of horse laminitis feeds oligofructose 10 g/kg to the animals. Joint inflammation, accompanied by diarrhoea, occurs in 24 - 36 hours[10].

Before 'Gibson's Pendulum' swings too far from prebiotic to FODMAP, the application of these data to clinical practice needs careful consideration. Laminitis can also be induced by starch overload and the equivalent human dose required of 500g – 1kg reduces the likelihood of similarly gross observable effects in humans. Demonstration that dietary supplementation induces symptoms does not mean that dietary reduction will relieve them although evidence for such dietary advice in IBS continues to accrue. The gut lumen in IBD is a more dynamic environment; dietary interventions may have different effects at first induction of disease, during a flare and when in remission.

Cox et al. went to considerable lengths to ensure that their study was rigorous. Their CONSORT diagram shows the challenges of identifying suitable participants. All those included had previously reported benefit from a low FODMAP diet. Many patients in remission from IBD will not have symptoms and where patients have symptoms, many will respond to changes in immunomodulation rather than dietary adjustment. However, acknowledging that therapies used in functional bowel disorders may benefit patients with IBD can only widen the options available to clinicians. Priority setting partnerships with IBD patients in the United States and United Kingdom have both highlighted the need for evidence on the role of diet in symptom control.

Many questions relating to the FODMAP diet remain. Cox et al. intensively monitored dietary intake but determining the FODMAP content of food remains a challenge. Beyond the original work of the Monash group, little analytical work has been done to measure the non-digestible, fermentable component of foods. More complete dietary databases are needed to allow comparison between sites and studies. Fermentable carbohydrates are not ingested in isolation so the effect of co-ingested products and the food matrix on fermentation needs to be understood. Lastly, efficacy of dietary advice needs to be tested in clinical trials before committing patients to a restrictive approach such as the low FODMAP diet, using endpoints of relevance to patients. The proof of the pudding will be in the eating.

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