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Personal view: food for thought – western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis

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SUMMARY

Susceptibility to the development of Crohn's disease involves a combination of genetic and environmental factors. The association of Crohn's disease with westernization has implicated lifestyle factors in pathogenesis. While diet is a likely candidate, evidence for specific changes in dietary habits and/or intake has been lacking.

A new hypothesis is proposed, by which excessive delivery of highly fermentable but poorly absorbed short-chain carbohydrates and polyols (designated FODMAPs – Fermentable Oligo-, Di- and Mono-saccharides And Polyols) to the distal small intestinal and colonic lumen is a dietary factor underlying susceptibility to Crohn's disease. The subsequent rapid fermentation of FODMAPs in the distal small and proximal large intestine induces conditions in the bowel that lead to increased intestinal permeability, a predisposing factor to the development of Crohn's disease. Evidence supporting this hypothesis includes the increasing intake of FODMAPs in western societies, the association of increased intake of sugars in the development of Crohn's disease, and the previously documented effects of the ingestion of excessive FODMAPs on the bowel. This hypothesis provides potential for the design of preventive strategies and raises concern about current enthusiasm for putative health-promoting effects of FODMAPs.

One of the greatest challenges in defining the pathogenesis of Crohn's disease is to identify predisposing environmental factors. Such an achievement might lead to the development of preventive strategies for, and the definition of, possible target for changing the natural history of this serious disease. The present paper describes a new hypothesis for one such environmental factor.

BACKGROUND INFORMATION

Crohn's disease is associated with the western lifestyle

Since the mid-20th century, the incidence of Crohn's disease has steadily risen in western Europe and North America from a rare condition to one that affects up to 0.2% of the population.[1] Furthermore, the incidence may still be rising as shown by recent studies of children in northern Europe and Australia.[2, 3] Countries previously of very low incidence, such as Japan, are now observing the marked increase in incidence seen in western countries four decades earlier, an observation that has been linked, correctly or incorrectly, to the 'westernization' of the developing countries.[4] Migrants from countries of low prevalence are tending to take on the prevalence of their adopted country.[5–7] Hence, it is intuitive that environmental factors that predispose individuals to Crohn's disease are linked to the western lifestyle.

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Diet as a candidate

One of the candidate areas of western life that has changed considerably in concert with the emergence of

Crohn's disease is diet. Several case–control dietary surveys have been performed in an attempt to identify putative dietary factors. Accurately determining dietary intake retrospectively in a patient with established Crohn's disease is problematic. Recall of dietary intake prior to developing the illness is fraught with inaccuracies, particularly when the onset of the disease is not easily determined and current diet might be influenced by illness-induced changes. Despite these methodological limitations, such studies do offer potential insights into dietary factors of importance, particularly if the findings are reproducible and biologically plausible.

Several dietary factors have been documented to be associated with Crohn's disease. These include the quantity and quality of fat intake,[8–10] fast food ingestion,[11] and total protein and energy intake.[12] However, the validity of such findings is uncertain as they have not been reproduced or conflicting results have been reported. In marked contrast, a large number of case–control studies have examined the association of refined sugar intake with Crohn's disease, either by examining the intake of selected sugar-containing foods or of total dietary sugars. Eleven of fifteen studies [11, 13–26] have reported a significant increase in intake in patients with Crohn's disease when attempts have been made to examine diet pre-illness or pre-diagnosis. Likewise, 12 of 13 [13, 15, 17–21, 27–32] studies examining current intake of sugars have shown significantly greater intake in patients with Crohn's disease than in controls. This association seems to apply to populations of disparate geographical location and ethnicity.

While the remarkable consistency of this observation suggests that it represents a real relationship, a major difficulty has been experienced in identifying a biologically plausible mechanism for the relationship prior to the onset of Crohn's disease. The findings have generally been attributed to an associated dietary perturbation, such as deficient fresh fruit and vegetables,[17, 25] excess in the intake of fast food,[11] or food additives,[13] or to be related to disturbed perception of sweet taste in patients with Crohn's disease.[19] The evidence for these, however, is not good. The other approach to dealing with consistent observations that defy simple explanation is to dismiss them as artefacts due to methodological deficiencies and limitations.[33] A fresh look at the data is needed and a new explanation of the association of sugars with Crohn's disease is offered below.

Changing patterns of food intake and dietary behaviour

Changes have occurred in multiple aspects of dietary behaviour and some of the more relevant observations are presented in Table 1.

Biomarkers of susceptibility to Crohn's disease

Gaining direct support for an effect of a particular dietary component on susceptibility to Crohn's disease is difficult as the disease is likely to result from a complex interaction of environment and genes. A single environmental factor is unlikely to act alone. Furthermore, interventions based on a putative dietary factor cannot realistically be tested with the development of Crohn's disease as the end point. A biomarker of susceptibility – that is, a physiological abnormality that might mechanistically be involved in the increase of the likelihood of

Table 1. Changing patterns of food intake and dietary behaviour over the last 20 years

Changes observed	Details
Spectrum of sugars consumed	Sucrose less, lactose stable, fructose increased (fourfold in 10-year-old children,[34] nearly 20% in population[35])
Location of food intake	Increase in away-from-home food (fast food outlets or restaurants); >35% food consumed away from home[36]
Pattern of eating	Nearly 50% increase in proportion of energy from snacks compared with meals across all age groups[37]
Food selection	Increase in salty snacks, pizza, sweetened beverages doubled in 20 years;[36] increase in consumption of pasta, cakes, breads, cereals, high fruit products[37–39]
Use of caloric sweeteners	Increase, particularly in beverages[40, 41]

developing Crohn's disease, is needed. Then, the influence of the dietary factor on that biomarker of susceptibility can be directly examined.

To date, the only putative biomarker of susceptibility to Crohn's disease recognized is an elevated intestinal permeability.[42] The concept has biological plausibility in that inefficiencies in the intestinal barrier may lead to increased mucosal exposure to luminal pro-inflammatory molecules and micro-organisms, and to subsequent potential modulation of the mucosal immune responsiveness. Increased intestinal permeability has been demonstrated in 10–20% of first-degree relatives of patients with Crohn's disease. This has been consistently demonstrated using different techniques of assessment in patients from several centres from North America and Europe.[43–48] The hyper-responsiveness of intestinal permeability to aspirin or ibuprofen observed in patients with Crohn's disease is also found in a higher proportion of first-degree relatives than in controls.[49, 50] Elevated expression by peripheral blood B cells of CD45RO was reported in a proportion of relatives with increased intestinal permeability but not in those where permeability was normal,[51] supporting the notion that the permeability probes used are reflecting barrier competence and antigen exposure in the mucosa. The development of Crohn's disease in a first-degree relative many years after the demonstration of elevated intestinal permeability further supports the concept.[52]

A key question is whether this abnormality reflects genetic factors or the influence of environmental factors. Three studies from different investigating groups have shown that increased intestinal permeability is also found in 13–36% of spouses of patients with Crohn's disease.[46, 47, 53] By contrast, hyper-responsiveness to non-steroidal anti-inflammatory drugs (NSAIDs) appeared restricted to the first-degree relatives.[47] Thus, the evidence supports the involvement of environmental factors in the pathogenesis of general 'background' permeability abnormalities, while NSAID-induced abnormalities might have a stronger genetic basis.

Dietary factors and intestinal permeability

Unfortunately, few environmental factors that increase intestinal permeability have been identified. The most notable is the intake of NSAIDs including aspirin.[47, 54] While the intake of NSAIDs is not a viable candidate as a major environmental factor in the pathogenesis of Crohn's disease, understanding the mechanism by which they increase permeability might provide clues as to a mechanism by which diet might change in permeability (see below).

There is a paucity of studies linking dietary factors with alterations of intestinal permeability. When the epithelial barrier is impaired in non-physiological conditions, such as consuming a diet completely devoid of fibre, or following small intestinal injury from alcohol, dietary fibre corrects or ameliorates increased epithelial permeability.[54–57] Whether dietary fibre influences epithelial barrier function in more physiological situations has not been reported. However, high luminal concentrations of short-chain fatty acids can reversibly impair barrier function,[58, 59] presumably by inducing apoptosis of epithelial cells, as do NSAIDs. Short-chain, poorly absorbed carbohydrates increase the permeability of the colon in rats[60] (see below). Dietary fats may also potentially play a role. Rats on a high-fat diet have higher distal colonic paracellular permeability[61] and transcellular transport and efflux mechanisms are altered in the jejunum of rats fed different long-chain fatty acids.[62]

THE FODMAP HYPOTHESIS

Excessive delivery of highly fermentable but poorly absorbed short-chain carbohydrates and polyols (designated FODMAPs – Fermentable Oligo-, Di- and Monosaccharides And Polyols) to the distal small intestinal and proximal colonic lumen is a dietary factor underlying susceptibility to Crohn's disease. Such elevated delivery can occur as a consequence of excessive intake of FODMAPs and/or malabsorption of fructose by the small intestine. The passage of these substances and their subsequent rapid fermentation induces conditions in the bowel and systemically leads to increased intestinal permeability, a predisposing factor to the development of Crohn's disease in a genetically susceptible host. The hypothesis is illustrated in Figure 1.

The spectrum of FODMAPs

The characteristics and common dietary sources of FODMAPs are summarized in Table 2. They comprise five main dietary components.

Fructose. This is present in the diet as a free monosaccharide, as a constituent of the disaccharide, sucrose, or polymerized as fructans (see below). When fructose is

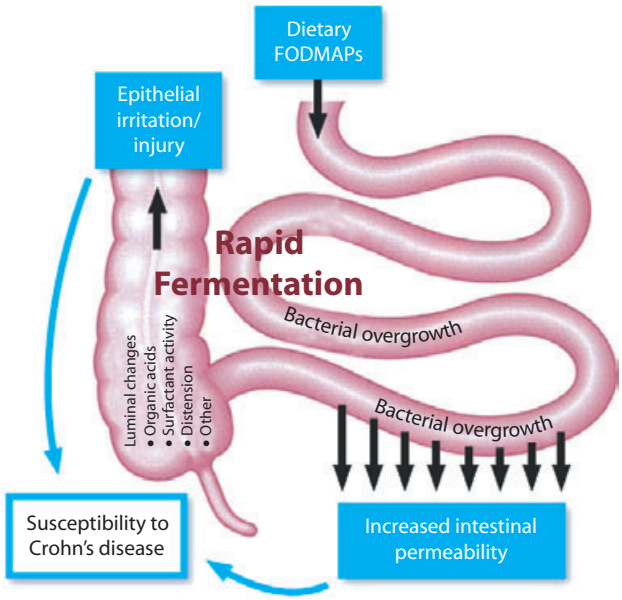

Figure 1. The FODMAP hypothesis of the link between diet and susceptibility to Crohn's disease. Dietary FODMAPs delivered to the distal small intestine and proximal colon are rapidly fermented. In the distal small intestine, this leads to an expansion of bacterial populations with secondary increase in intestinal permeability. In the proximal colon, changes in the luminal content and distension (not shown) have epithelial, neural and hormonal effects, one consequence of which is to irritate or injure the epithelium and impair its barrier function. In Crohn's disease, there is an increased delivery of FODMAPs to the colon because of excessive intake that might be compounded by fructose malabsorption. The response to the rapid fermentation of a greater load of FODMAPs in the distal small intestine and proximal colon may be exaggerated in patients susceptible to Crohn's disease because of genetic or other environmental factors.

ingested as sucrose, or in equimolar combination with glucose, it is absorbed with an efficiency estimated to be 85% that of glucose because it is of high capacity and glucose-facilitated.[63] Fructose in excess of glucose (free fructose) can also be absorbed by a low-capacity glucose-independent facilitated transport.[63] If the load of free fructose is sufficiently large, malabsorption of fructose is universal. However, about 30% of the population exhibits very limited ability to absorb free fructose[64, 65] and are considered to have 'fructose malabsorption'.

Fructans. These are oligo- and polysaccharides of fructose units with a glucose terminal end.[66] Fructans are classified according to the fructose–fructose bonds, being either inulins (β1-2 bond) or levans (β2-6 bond). Most dietary sources are of the former. Inulin termin-

Table 2. Dietary FODMAPs, their common sources in the diet and the physiology of their delivery to the large bowel lumen

Food component	Dietary form	Common sources/uses	Digestion &/or small intestinal absorption
Fructose		Fruits, honey, high fructose corn syrup (sweetener)	Absorptive capacity limited when in excess of glucose – low in 30% (considered to have fructose malabsorption)
Lactose		Milk, yoghurt, ice cream	No absorption if lactase deficient
Fructans	Fructooligosaccharide (oligofructose)	Wheat, onions, added for putative health benefit	No suitable small intestinal hydrolases – absorption <5%
Polyols	Sorbitol, xylotol, mannitol, maltilol	Apples, pears, plums, reduced caloric sweetener	Passive absorption only (<20%)
Galactooligosaccharides	Raffinose, stachyose	Legumes, beans, cabbage, Brussels sprouts, onions	No human α-galactosidase – minimal absorption
Other	Polydextrose, isomalt	Reduced caloric sweetener	Passive absorption only (<20%)

ology is confusing in that those with a chain length [degree of polymerisation (DP)] <10 are generally referred to as fructooligosaccharides (FOS or oligofructose), while molecules with DP of 10 or greater are generally called 'inulins'. Dietary fructans are mostly FOS, the major sources being wheat and onion (average DP 5), but FOS is increasingly being added to food for putative health benefits.[67] Average daily intake of fructans in USA has been estimated as 10 g per day.[68] As the human small intestine does not produce a hydrolase capable of breaking the β1-2 bond, more than 90% of dietary fructans are delivered to the large bowel, where they are readily fermented.[69]

Lactose. This is effectively digested and absorbed only if the disaccharide, lactase, has sufficient activity in the small intestine.[70] Lactase deficiency has a wide variation in prevalence across ethnic groups and countries, from 2% in Scandinavian countries to >90% in some Asian countries.

Polyols. These are sugar alcohols and include sorbitol, xylitol, mannitol and maltitol.[71, 72] While naturally occurring in foods such as apples, pears and stone fruits, they are often added to food as humectants and artificial sweeteners. Polyols are poorly absorbed in the small intestine and are readily fermented. Polydextrose and isomalt, used as food additives, behave in a similar way.

Galactooligosaccharides (GOS). These are oligosaccharides with a beta-fructosidic linkage and an alpha-galactosidic linkage.[73] The main dietary forms are raffinose, which comprises one fructose, one glucose and one galactose molecule, and stachyose, which is raffinose with one more galactose molecule. Humans lack α-galactosidase that hydrolyses the galactosidic linkages of stachyose and raffinose to their simple sugar constituents. GOS are rapidly fermented and induce gas formation.[74, 75] Significant dietary sources include legumes (such as soya beans, mung beans, chickpeas, lupin and split peas), common beans, cabbage, Brussels sprouts, onions, chicory and salsify. Cooking generally reduces the GOS content in legume foods.

Evidence to support the hypothesis

There are three main lines of evidence for the involvement of FODMAPs in the pathogenesis of Crohn's disease.

The intake of FODMAPs is increasing in western societies. As outlined above, urbanization has been associated with increased consumption of fructose as a proportion of sugars. This has been the result of changes in food selection and patterns of eating, and the use of caloric sweeteners, principally in beverages and fruit drinks, compounded by the widespread use of high fructose corn syrups as sweeteners in soft drinks and many other packaged snack food in the USA. While there are no direct studies of time trends in fructan ingestion, indirect evidence indicates changes in the patterns of fructan ingestion. As shown in Table 1, the intake of major sources of fructans, such as pasta and pizza, has increased.[35–40] The type of fructans in the diet is also changing. Fructans offer unique technological benefits in food manufacture and are being added to improve palatability and stability of foods,[76] while offering putative nutritional benefits as 'functional foods'.[67] There are no data available on trends in intake of polyols, but it is likely that exposure of the population to them as food additives has increased with the desire to have 'sugar-free' products to lower energy intakes and to protect dentition.[41]

The association of increased intake of sugars and the development of Crohn's disease. As outlined above, one of the few highly consistent associations between Crohn's disease and both current and pre-illness diet has been the intake of sugars. As most of the studies particularly addressed sucrose intake, they almost certainly indicate increased fructose intake as part of this disaccharide. As free fructose is increasing as a proportion of total sugars, at least in USA, it is likely that free fructose intake by patients with Crohn's disease is also elevated. However, the opposite was found in the only study (from UK) reporting fructose intake.[17] This was not surprising as assessment of free fructose intake appeared to be determined purely on the basis of fruit ingestion, which was low in those affected by Crohn's disease. Ingestion of other FODMAPs, especially fructans, has not been investigated and cannot be derived from published dietary data.

Excessive intake of FODMAPs creates conditions in the bowel that predispose it to Crohn's disease. FODMAPs may be associated with physiological effects in the distal small intestine and colon. First, by virtue of their small molecular size, they have a considerable osmotic effect and are associated with the delivery of increased

amounts of fluid to the colon.[77] Secondly, they are fermented by intestinal bacteria to short-chain fatty acids, including butyrate, and the gases, carbon dioxide and hydrogen.[78] Hydrogen is absorbed into the circulation and excreted in the breath, but varying amounts may also be further metabolized in the lumen to sulphides by sulphate-reducing bacteria, methane by methagens, or acetic acid via acetogens. As a substrate for bacterial metabolism, FODMAPs induce relatively selective bacterial proliferation, especially of bifidobacteria.[78, 79] This is the so-called prebiotic effect that conceptually carries health benefits.[67] The combination of the delivery to the large bowel of fluid that might flush the bowel, the luminal production of short-chain fatty acids such as butyrate, and the prebiotic effects would seemingly add up to a healthier colon. Considerable enthusiasm for these concepts has been expressed in numerous reviews.[67, 80, 81] Indeed, ingestion of FOS suppresses carcinogenesis in rats or mice exposed to the powerful carcinogens, dimethylhydrazine or azoxymethane,[82–86] and reduced the mortality of mice following the systemic or oral delivery of pathogens[86] compared with animals receiving no or non-fermentable fibre.

Paradoxically, FODMAPs may exert adverse effects on the distal small intestine, the colon and systemically, as outlined below.

Effect on the distal small intestine. FODMAPs might be considered the 'fast food' for bacteria. Experiments with faecal slurries *in vitro* have shown that FODMAPs of small molecular size are very rapidly fermented compared with those of long-chain carbohydrates.[78] Similar observations have been made *in vivo* utilizing the rapidity of increases in breath hydrogen after carbohydrates reach the colon as a marker of the rate of fermentation. Thus, the rate by which breath hydrogen rose was greatest for lactulose, less for inulin and least for resistant starch.[87] Delivery of fast food to the distal small intestinal lumen potentially can lead to expansion of bacterial populations. Such distal small intestinal bacterial overgrowth has been indirectly, but convincingly,[88] demonstrated to be common in patients with irritable bowel syndrome, coeliac disease and Crohn's disease.[89–92] Bacterial overgrowth in the small intestine has been associated with increased small intestinal permeability. An association between excessive delivery of FODMAPs and distal small intestinal bacterial overgrowth might reveal a mechanism for increased epithelial permeability.

Effects on the colon. When healthy rats were fed FOS or lactulose, evidence for injury to, or irritation of, the colonic epithelium was found, in addition to prebiotic effects.[60] Epithelial cell proliferation and mucin output increased in these rats. Of perhaps more relevance to Crohn's disease, intestinal permeability was also increased as shown by increased bacterial translocation[60] and permeation of the paracellular permeability probe, EDTA.[93] When the rats were experimentally infected with a salmonella species, the rats fed FODMAPs developed severe colitis in comparison with the mild colonic inflammation in the control animals.[60] Furthermore, the effect seemed to be a dose-dependent. A recent study in healthy human subjects (2-week exposure to FOS) led to a doubling of mucin output, although no change in permeability (using EDTA as the probe) was detected.[94] This was consistent with injury to, or irritation of, the colonic mucosa.

From a mechanistic point of view, rapid fermentation of carbohydrates in the proximal large bowel may lead to high concentrations of short-chain fatty acids and lactic acid in the lumen, which can disrupt the mucosal barrier,[58, 59] and increased surfactant activity in the faecal water, activity associated with increased epithelial turnover. Oral calcium reduced both the surfactant activity of faecal water and the severity of salmonella-induced colitis in FODMAP-fed rats.[95] FOS also increases the propensity for colonic epithelial cells to undergo apoptosis, demonstrated in an acute DNA injury model.[96] This is presumably the reason why FOS was able to suppress carcinogenesis in carcinogen-treated rats and mice. The balance between pro-apoptotic suppression of carcinogenesis on the one hand and loss of barrier function due to epithelial apoptosis on the other is well documented in association with NSAIDs.[97]

Support for a pathogenic role of the rapidity of fermentation comes from experiments in healthy rats where rapidly-fermentable fibres were delivered in the absence of other fibres.[98–101] Concurrent ingestion of rapidly fermentable with slowly and non-fermentable substrates contained within wheat bran slowed the rate of fermentation and shifted it more distally in rats,[99] pigs[100] and humans.[101] Following the ingestion of raw potato starch, guar gum and arabinoxylan in the absence of other fibres, the distal colonic epithelium shows evidence of injury/irritation, with striking increases in epithelial cell turnover and in the activities of brush border hydrolases and urokinase.[99, 102, 103]

Exposure to a colonic carcinogen under these conditions led to accelerated carcinogenesis. All these effects were abolished by the addition of wheat bran.[99] Thus, epithelial injury was associated with the site and rapidity of fermentation.

Systemic effects of FODMAPs. The ingestion of FOS induced greater gastro-oesophageal reflux and concomitant motility changes as well as increased heartburn than did placebo in human volunteers with gastro-oesophageal reflux disease.[104] This was associated with hormonal changes that potentially altered motility patterns.[104] There is also a reported association of mild depression with fructose malabsorption and lactose intolerance in women with irritable bowel syndrome.[105] The depression associated with fructose malabsorption appeared to improve when free fructose was eliminated from the diet.[106] Subjects with fructose malabsorption and an unrestricted diet have low circulating tryptophan levels,[107] suggesting secondary deficiency in serotonin synthesis.

Thus, rapid fermentation of FODMAPs might lead to changes in luminal ecology in the distal small intestine and injurious effects on the colonic epithelium with consequent increase in epithelial permeability in both the small and the large intestine, and has effects distant from the bowel on organs such as the oesophagus and the brain. These observations implicate excessive delivery of FODMAPs to the distal small intestine and proximal colonic lumen as potentially harmful and set up conditions that might predispose to Crohn's disease.

Implications of the hypothesis

This hypothesis provides a link between changes in western dietary intake and the incidence of Crohn's disease. It is novel in defining a biologically feasible mechanism underlying both the consistent observation that patients with Crohn's disease consume increased amounts of refined sugars and the biomarker of susceptibility, elevated intestinal permeability. Of importance is that the link between the excessive delivery of FODMAPs to the distal small intestine and proximal colon on the one hand, and increased epithelial permeability on the other can be directly tested in human interventional studies.

Several areas require clarification and/or further study. Information about the dietary intake of FODMAPs, including fructans, is required from the community in general and from Crohn's disease patients and their first-degree relatives specifically. Likewise, studies of the absorption of fructose are needed in patients with Crohn's disease and their first-degree relatives. Information on the effect of modifying FODMAP intake on the natural history of Crohn's disease might also be instructive. Even if FODMAPs do not prove to be aetiologically relevant as proposed in this hypothesis, they might provide a ready target for improving symptoms and for reducing the current reliance on drug therapy. Issues such as the effects of FODMAPs on small intestinal permeability and their postulated relationship with excessive growth of bacteria in the distal small intestine, and whether effects of FODMAPs observed in the colon of rats apply to humans also await clarification. Other issues of interacting dietary factors such as fat and calcium intake require evaluation.

If further evidence does support this hypothesis, there are critical public health implications. The development of Crohn's disease might potentially be prevented by modification of both eating behaviour and the nature of food eaten. FODMAPs are dietary components that are already being actively manipulated by the food industry. Issues in food production such as the amount of FODMAPs and the chain length of carbohydrates being added to foods, and the ongoing use of polyols might be addressed. Modification of eating behaviour, such as in the selection of foods and beverages, would also be important for any preventive approach. While this might seem an insurmountable challenge, success has been seen in the related challenge of reducing the intake of saturated fats across communities.[38–40]

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