



VIEWPOINT

Hypothesis: Increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease

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Abstract

Crohn's disease (CD) incidence has increased over the past fifty years but the explanation is unclear. CD can be brought into remission by liquid enteral feeding, but the mechanism for this response is unknown. We suggest that consumption of emulsifiers in processed foods may promote CD by increasing bacterial translocation. This is supported by evidence that (i) geographical variation in CD correlates with emulsifier consumption as does the increasing incidence of CD in Japan; (ii) although CD incidence also correlates with fat consumption, the response to enteral feeding is not affected by the fat content of the feed and (iii) very small concentrations of the emulsifier polysorbate 80 enhance bacterial translocation across intestinal epithelia. Undigested emulsifiers may increase bacterial translocation, particularly in the small intestine where the mucus layer is discontinuous. The hypothesis should be testable by trials of enteral feeding with/without emulsifiers.

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1. The relative importance of genetic and environmental factors in CD pathogenesis

One hundred and sixty-three gene loci associated with inflammatory bowel disease have now been identified¹ but much the strongest gene association is between CD and NOD2/CARD15, with three independently associated

mutations – arg702trp, gly908arg, and leu1007fsinsC. Together these confer a 15%–20% attributable population risk among cases of familial CD, yet individuals who are homozygotes for NOD2/CARD15 mutations still only have approximately 3% lifetime risk of developing the disease and only about 25% of CD patients have a family history, implying a strong role for environmental factors. Polymorphisms in the autophagy genes ATG16L1 and IRGM also associate with CD but have a much smaller attributable risk for pathogenesis. Each of these genes encode proteins that form part of the innate immune response to bacteria, indicating that a reduced ability to defend against intestinal microbiota, together with altered regulation of the immune response, are involved in CD pathogenesis.¹ A consequence seems to be invasion of the

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mucosa by bacteria, particularly by *E. coli* with an adherent and invasive phenotype.²

2. Increasing incidence of CD

CD incidence in many countries has increased markedly over the past 50 years,³ particularly in Asia with 3–5-fold increases in Japan and Singapore within the 10–14 years around the millennium.^{4,5} The incidence in the West has also increased and meta-analyses have shown about a 4-fold increase over the past 40 years with a particularly striking rise amongst juvenile-onset CD cases.⁶

3. Evidence for the role of specific environmental factors

Direct evidence from interventional studies exists only for smoking as a risk factor for CD but there is indirect evidence in support of hygiene in infancy, oral contraceptive use, and various dietary risk factors. There is also growing evidence for important associations with changes in the gut microbiota, particularly an increase in mucosa-associated *E. coli* and reduction in faecal *Faecalibacterium prauznitzii*, but there is no knowledge of how other environmental factors affect these components of the microbiota.

3.1. Smoking

There is a strong association between current smoking and CD and cessation of smoking reduces risk of relapse. However the proportion of the UK population that smokes has fallen over the last three decades, a pattern which is mirrored by much of western Europe. Smoking therefore does not account for the increasing incidence of CD.

3.2. Hygiene

Increased hygiene in infancy has been suggested as the explanation for several diseases with increasing incidence including asthma and CD. Increased risk of CD has been reported in individuals who grew up in households with hot running water as compared with those who had only a cold water supply. The hygiene hypothesis seems unlikely though to explain the very marked recent increased incidence of Crohn's disease in Japan.

3.3. Oral contraceptives

Use of oral contraceptives is a modest risk factor for CD that might account for some of the increase in women, but most studies have also shown a substantial increase in CD incidence in males.

3.4. Lack of sunlight

The increased prevalence of a range of immunologically-mediated disorders, including CD, in northern Europe has been attributed to lack of sunlight and its impact on the beneficial effects of vitamin D3.⁶ Vitamin D3 enhances dendritic cell

function, autophagy and expression of the CD associated gene NOD2 and supplementation with vitamin D3 has been shown to have promising therapeutic impact on the course of CD. This would however not explain the marked increase in incidence over time.

3.5. Diet

3.5.1. Associations between diet and Crohn's disease risk

The most consistent epidemiological association between diet and CD has been the high pre-illness intake of refined sugar.⁷ Exclusion trials have however been negative, whether this has been assessed as the sole intervention or as part of a high fibre, low sugar diet and it seems likely that the high sugar intake may be a correlate of some other harmful dietary factor. It has indeed proved frustratingly difficult to define an exclusion diet that will keep the majority of patients free from relapse after remission has been induced by a period of enteral feeding. Extensive rechallenge studies in a patient with CD showed that foods that are well tolerated during prolonged remission may not be tolerated in relapse, when the mucosa is presumably ulcerated.⁸

Fat consumption has been increasing worldwide over the past three decades, in both developed and undeveloped countries. The rapid recent rise in CD in Japan has paralleled the introduction and uptake of a western style diet and an increase in consumption of total fat, animal fat and n-6 polyunsaturated fatty acids (r for all these >0.8) with animal fat the strongest independent factor on multivariate analysis.^{9,10} However meta-analysis of trials comparing high fat and low fat enteral feeds has failed to show any difference in therapeutic response and has also failed to show difference in response according to n-3 versus n-6 fat content.¹¹

3.5.2. Induction of remission in Crohn's disease by use of liquid enteral feeding

There is good evidence supporting the benefits of enteral nutritional feeding with elemental or whole protein (polymeric) feed as either primary or adjuvant therapy for CD.¹¹ It has been suggested that enteral feeding directly affects intestinal inflammation by regulating gene expression in the gut epithelium as well as by modulating intestinal inflammatory and immune mediators production. Equally plausible is a quantitative effect of a very low residue intake on the intestinal microbiota.

3.5.3. Perhaps it is emulsifier intake rather than fat that increases risk for Crohn's disease? Geographical variation in Crohn's disease incidence and emulsifier consumption

We have looked at available country by country data for emulsifier consumption in food and beverages, including polysorbates and sorbate esters, and lecithin.¹² When this is compared with CD incidence, where known, on a matched year basis, a strong positive correlation is found ($P=0.017$ by Spearman Rank correlation; Fig. 1). In Japan where data for CD incidence and emulsifier consumption were available for the same years there was again a positive correlation (Fig. 2).

There is also evidence that frequent fastfood intake, likely to contain emulsifiers, confers a 3- to 4-fold greater risk for developing CD.¹³ Consumption of margarine, which contains both hydrogenated fats and emulsifiers, has been

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