

Inflammatory bowel disease: a focus on the involvement of dietary fats

Punyanganie S de Silva^{1,2}
Joshua R Korzenik^{1,2}

¹Department of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, ²Harvard Medical School, Boston, MA, USA

Abstract: Inflammatory bowel diseases (IBDs) are chronic immune-mediated diseases of the gastrointestinal tract well known to be associated with both genetic and environmental risk factors. Certain genotypes may develop clinical manifestations under particular environmental influences. There is increasing evidence to suggest that diet is a key environmental factor in IBD, and dietary fats in particular have been implicated in both pro- and anti-inflammatory roles. Previous epidemiological studies have highlighted variable results, most probably due to the complex pathways that may be mediated by fatty acid activity. We aim to review the available studies on dietary fats and IBD pathogenesis and explore mechanisms involved to identify potential opportunities for future research and therapies.

Keywords: inflammatory bowel disease, ulcerative colitis, Crohn's disease, lipids, n-3 polyunsaturated fatty acids, n-6 polyunsaturated fatty acids

Introduction

Inflammatory bowel diseases (IBDs) represent a spectrum of chronic inflammatory disorders of the intestine that is characterized by remitting and relapsing episodes. IBD is chiefly comprised of two main subtypes: ulcerative colitis (UC) and Crohn's disease (CD). While UC is characterized predominantly by inflammation limited to the mucosa, in CD the inflammation is transmural, often resulting in stricturing or penetrating phenotypes.

The diseases were traditionally believed to be limited to the Western industrialized world, with high incidence and prevalence recorded in Western Europe and North America.^{1,2} However, in the last decade, a dramatic increase has been noted in countries that have recently adapted a more Westernized lifestyle, which includes dietary changes.³⁻⁶ In addition, there is an increasing number of first- and second-generation immigrants to countries with a historically high incidence and prevalence of IBD who have been diagnosed.^{7,8} This changing epidemiology suggests that environment, and particularly diet, may have a role to play in the etiopathogenesis.

While both diseases are distinct in terms of presentation and often response to treatment, it is believed that they share a common underlying pathogenic mechanism in that IBD is a dysregulated immune response to single or multiple environmental risk factors in a genetically susceptible host.⁹⁻¹¹ It is also increasingly evident that the gut commensal microflora, genetic composition of the host, and the mucosal immune response may be altered through interaction with dietary components, thereby potentially increasing or reducing an individual's risk of developing inflammation.

Correspondence: Punyanganie S de Silva
Department of Gastroenterology,
Hepatology and Endoscopy, Brigham and
Women's Hospital, 75 Francis Street,
Boston, MA 02115, USA
Tel +1 617 838 5352
Fax +1 617 525 8740
Email pdesilva@partners.org

Overview of dietary fats

In the US, consumption of nutrient fat has increased by approximately 25% over the last 60 years.¹² These dietary fats consist of saturated, *trans*, polyunsaturated, monounsaturated, and cholesterol forms. Saturated fats are commonly found in high-fat cheeses and cuts of meat, whole-fat milk, cream, and butter. Naturally occurring *trans* fat is found in the fatty parts of meat and dairy products. Artificial *trans* fat comes from foods that contain partially hydrogenated oil, and is formed when hydrogen is added to liquid oil, turning it into solid fat. Cholesterol is also derived from animal-based foods, such as meats, poultry, egg yolks, and whole milks. Olive oil and nuts are the commonest dietary source of monounsaturated fatty acids, and ω -6 (n-6) polyunsaturated fatty acids (PUFAs) are commonly derived from soybean, corn, and safflower oils along with red meats and pork. Sources rich in n-3 PUFAs include canola oil, walnuts, flaxseed, and fish, such as trout, herring, and salmon.¹³

Epidemiology of dietary fats in inflammatory bowel disease

In the past, studies have attempted to assess food groups and their role in IBD activity. The vast majority of these studies have been retrospective, and have not specifically assessed individual fatty acid intakes, thereby possibly giving rise to recall bias and confounding potential associations. Prospective studies that have investigated the effects of dietary factors in predicting the likelihood of clinical relapse are also limited, and results have been variable. Of the studies that have been carried out, there is evidence to suggest that lipids, and in particular PUFAs, may have a role to play in intestinal inflammation.

A large prospective dietary study of 191 patients with UC identified red and processed meat as a predictor of clinical relapse.¹⁴ It is well established that both these food groups contain large amounts of n-6 PUFAs, giving rise to a potential proinflammatory association. This is further supported by two case-control studies, from Israel and the Netherlands, which demonstrated statistically significant odds ratios of 6.5¹⁵ and 5.1¹⁶ for higher intakes of total PUFAs and the development of new-onset UC. The study from the Netherlands reported that the two highest tertiles of linoleic acid approximately doubled the risk, although this were not statistically significant.¹⁶ A prospective cohort study involving seven regions across Europe in the EPIC (European Prospective Investigation into Cancer and Nutrition) study¹⁷ reported that participants with the higher dietary intakes of linoleic acid (an n-6 PUFA and precursor to arachidonic acid), as measured by

food-frequency questionnaires, had more than a doubling of the risk of developing UC (odds ratio 2.49, 95% confidence interval [CI] 1.23–5.07).¹⁷

Two subsequent prospective cohort studies of diet in the development of incident cases of UC also identified a positive association with total PUFA intake, and increased levels of the n-6 PUFAs linoleic acid and arachidonic acid with UC incidence increased by two- and fourfold, respectively.^{18,19} Furthermore, another study from this same European cohort revealed that an increased intake of dietary n-3 PUFAs, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was associated with a reduced incidence of UC.²⁰ A recent prospective cohort study by Chan et al also investigated the association between dietary fatty acid intake and CD in 229,702 participants recruited from nine European centers. Seventy-three incident cases of CD were identified during a 12-year follow-up period, and it was noted that there was a statistically significant reduced intake of DHA in cases compared to controls when adjusted for smoking, body mass index, oleic acid, EPA, linoleic acid, and total energy intake ($P=0.04$).²¹ However, these epidemiological studies were undertaken in older European populations with a male predominance, and did not specifically address disease activity after diagnosis or genetic susceptibility. Recent data from a large prospective cohort of younger North American women did not find cumulative energy-adjusted intake of total fat, saturated fats, unsaturated fats or n-6 and n-3 PUFAs to be associated with increased risk of CD or UC.²² However, within this same study, a greater intake of long-chain n-3 PUFAs was associated with a trend toward lower risk of UC (hazard ratio 0.72, 95% CI 0.51–1.01), and a high long-term intake of *trans* unsaturated fatty acids was associated with a trend toward an increased incidence of UC (hazard ratio 1.34, 95% CI 0.94–1.92).²² This variation in results may be explained by individual genetic variability, age, and other as-yet unidentified environmental factors leading to variable susceptibility to dietary risk factors. Case-control studies that included younger patients have also reported positive associations with PUFAs and linoleic acid, although these associations did not always reach statistical significance.^{15,16}

Another point of note is that the majority of these epidemiological studies focused on UC and not CD. This may be partially due to lower numbers of CD patients in the cohorts studied, but in those that did include CD patients, the lack of association may also be partially explained by the fact that inflammation in CD is transmural and not confined to the mucosa as in UC, thereby giving rise to the hypothesis that dietary agents may have a lesser role to play

in stimulating or suppressing nonmucosal inflammatory mechanisms.

Role of dietary fats in the pathophysiology of IBD

Dietary PUFAs and eicosanoids

There are many plausible biological mechanisms for how diet may be involved in the etiology of IBD. Dietary constituents are in direct contact with the intestinal wall of the colon. PUFAs are present in colonic cell membranes predominantly as arachidonic acid (AA, n-6 PUFA derived), EPA, and DHA (n-3 PUFA derived). Both n-3 and n-6 membrane phospholipids can be metabolized to eicosanoids, which include prostaglandins (PGs), thromboxanes, and leukotrienes (LTs). Those eicosanoids, derived from such n-6 PUFAs as PGE₂ and leukotriene B₄ (LTB₄), are more proinflammatory than the n-3 PUFA-derived eicosanoids PGE₃ and LTB₅,^{23,24} and may subsequently induce or exacerbate UC. Their proinflammatory effects include neutrophil aggregation, chemotaxis, and release of lysosomal enzymes.^{24–28} Therefore, hypothetically, a high dietary intake of n-6 PUFAs and their incorporation into colonic cell membranes would lead to a source of proinflammatory molecules that may induce UC relapses. This is supported by finding increased levels of PGE₂ and LTB₄ in the mucosa of patients with UC when compared to healthy controls.^{27,28} There is also a positive correlation between these eicosanoids and the histological level of inflammation ($r=0.89$, $P<0.05$).²⁹ Further supporting this hypothesis, first-line drugs used to treat UC, namely 5-aminosalicylic acid compounds, suppress PGE₂ levels in a dose-dependent manner.²⁶

Dietary fats and resolvins

In addition to modifying inflammatory responses and influencing the biochemical composition of colonocyte membranes, PUFAs may alter the balance of a wide range of lipid signaling molecules and their effects on nuclear receptors.³⁰ These molecules are involved in a complex network of pathways that regulate and resolve inflammation.³¹ Anti-inflammatory (“resolving”) molecules or resolvins include the lipoxins LXA₄ and LXB₄, which are formed from AA through multiple routes depending on tissue type, and aspirin-triggered lipoxin.³² It has been hypothesized that in IBD there is a decreased amount of lipoxins.³³ It is thought that while high intakes of n-6 PUFAs seem to be well tolerated and may have beneficial effects in most people, there may be a subgroup of individuals who are unable to convert AA to lipoxins in adequate quantities, and

as a result n-6 PUFA is directed toward proinflammatory PG synthesis.

Patients with UC are known to have reduced LXA₄ synthesis, and blockage of LXA synthesis in animal models has also been shown to induce UC.³⁴ This association between LXA₄ and UC was further demonstrated in a study by Vong et al,³⁵ where colonic mucosal biopsies were collected from 20 healthy volunteers with or without a prior history of UC, individuals with UC experiencing active disease (n=8), and UC patients in medically induced remission (n=16). It was noted that in individuals in remission, mucosal expression of LXA₄ was significantly elevated by nearly threefold compared to the other groups, further supporting LXA₄'s anti-inflammatory role.

Resolution of inflammation is also known to be mediated by the n-3-derived eicosanoids resolvin E and resolvin D, which are derived from EPA and DHA, respectively.^{30,36–39} A recent study of healthy volunteers demonstrated that following ingestion of 1 g of EPA, sera collected 3 hours later had elevated levels of 18-hydroxyeicosapentaenoate, which is a precursor to resolvins.³⁷ The n-3 PUFA-derived mediator resolvin E₁ has also shown important positive effects on dextran sulfate sodium and 2,4,6-trinitrobenzene sulfonic acid-induced colitis, reducing mortality and colon damage³⁸ in addition to reducing polymorphonuclear infiltration and production of the proinflammatory cytokines TNF α , IL-12p40, and IL-1 β in colonic tissue.³⁹

Animal models have also demonstrated that resolvin D₁ and D₂ are effective in preventing UC, mainly secondary to their ability to inhibit polymorphonuclear infiltration, down-regulating NF- κ B, and reducing proinflammatory cytokines, chemokines, and some adhesion molecules.⁴⁰ Mouse models have also demonstrated that n-3 PUFAs reduce cytokine- and adhesion-molecule production, enhance specialized pro-resolving mediator production, and decrease leukocyte-endothelial cell adhesive interactions.³⁷

Genetic regulation of fatty acid desaturases and dietary fat intake

The enzymes fatty acid desaturase (FADS)-1 and FADS2 are the rate-limiting enzymes in the synthesis of AA, EPA, and DHA from their dietary precursors linoleic acid and α -linolenic acid⁴¹ (Figure 1). The mammalian $\delta 6$ -desaturase coded by *FADS2* (HSA11q12–q13.1) catalyzes the first and rate-limiting step for the biosynthesis of long-chain PUFAs.^{42,43}

A recent large-scale study of 2,066 participants from the European Prospective Investigation into Cancer and

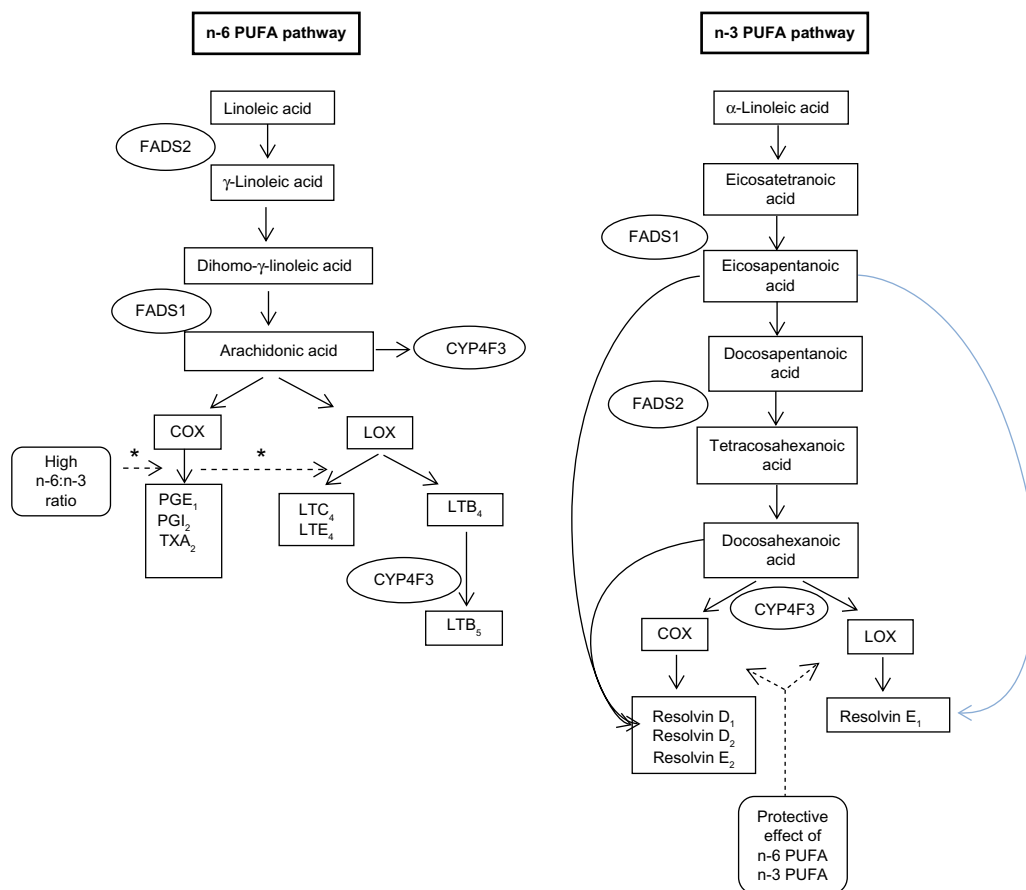


Figure 1 Schematic diagram of key n-3 and n-6 PUFA-metabolism pathways associated with inflammation in inflammatory bowel disease.

Notes: *Proinflammatory pathway. Some metabolites have been omitted to reduce complexity.

Abbreviations: PUFA, polyunsaturated fatty acid; FADS, fatty acid desaturase; CYP, cytochrome P450; COX, cyclooxygenase; LOX, lipoxygenase; PG, prostaglandin; LT, leukotriene; TX, thromboxane.

Nutrition – Potsdam study investigating the association between the rs174546 genotype single-nucleotide peptide block on chromosome 11 and dietary fatty acid intake, as measured through food-frequency questionnaires and serum, identified a strong correlation between this single-nucleotide peptide when coding for $\delta 6$ -desaturase and fatty acid intake.⁴⁴ $\delta 6$ -Desaturase is the key rate-limiting enzyme that converts EPA to DHA, which in turn is a precursor to resolvin D₁ and D₂. This association between *FADS* genes and IBD was explored in a cohort of pediatric CD patients.⁴⁵ It was noted in this study that there was an interaction between the *FADS2* single-nucleotide polymorphism rs11230815 and dietary n-3 PUFAs ($P=0.042$). When the dietary ratio of n-6 PUFA:n-3 PUFA was considered, significant interactions ($P<0.05$) were noted in the *CYP4F3* and *FADS2* genotypes rs1290617, rs1290620, rs11230815, rs17831757, rs968567, and rs174627. This suggests that there is an association between the dietary ratio of these fatty acids and CD according to the *CYP4F3* and *FADS2* genotypes.

Dietary fats and the PPAR receptors

Another potential mechanism for PUFAs in the etiology of IBD involves their effects on nuclear receptors, in particular peroxisome proliferator-activated receptors (PPARs). These act as transcription factors controlling the expression of genes related to a wide range of key functions, such as cell differentiation, lipid metabolism, and inflammation.⁴⁶ PUFAs and the arachidonic acid metabolite PGJ₂ act as ligands for PPAR α and PPAR γ ,^{47,48} and cyclooxygenase expression has been shown to be decreased through PPAR γ signaling.⁴⁹ This association is emphasized in studies highlighting the complex relationship between PUFAs and cyclooxygenase expression.^{50,51} These pathways are complex however, and studies have demonstrated that linoleic acid metabolites are ligands for PPAR δ , which in turn upregulates PPAR γ activity.⁵² The 5-aminosalicylic acid drugs are also known to bind PPAR γ .⁵³ The role of these PPARs in IBD is not fully elucidated, but these may transpire to be targets for future advanced therapies.^{51,52} NF- κ B expression is also

downregulated by PPAR γ activity, and has been shown to reduce experimentally induced UC.^{46,54} Furthermore, PPAR agonists can counteract the increased expression of proinflammatory cytokines induced through Toll-like receptor signaling.⁵⁵ Further studies are needed to better understand these complex associations.

Dietary fats, the microbiome, and IBD

The human gut contains a vast number of microorganisms known collectively as the “gut microbiota”. A further potential mechanism for dietary lipids in the pathogenesis of IBD may involve its alteration of the normal intestinal microbiota. Variations in the gut microbiota have been noted in IBD with increases in proinflammatory *Bacteroides* with long-term diets, particularly protein and animal fat.^{56,57} While there have been several studies that have demonstrated how alterations in dietary fiber can influence the microbiome,^{58,59} a high intake of PUFAs may also modify the gut microbiota, because approximately 2% of PUFAs consumed arrive intact in the colon, and thus can hypothetically alter the survival of bacteria.⁶⁰

Clinical significance and future prospects

As described, there are several potential mechanisms for how dietary lipids may be involved in the etiology of IBD, but further experimental investigation is required. Providing data in support of dietary fatty acid risk factors would strengthen the evidence for causality and provide a further basis for future potential dietary interventions as treatment in IBD. It would also help us to further understand the specific potential mechanisms by which diet may influence activity in UC and CD.

In the Western diet, there is a predominance of n-6 PUFAs. In a recent study conducted in the UK and the Netherlands, a ratio of n-6:n-3 PUFA intake of 8:1 was noted in patients treated in gastroenterology clinics,⁶¹ while a ratio of 2:1–4:1, which is closer to that of prehistoric diets, has been recommended.^{62,63}

The genetic loci associated with CD or UC can be broadly categorized into those involving abnormalities in innate immune response, mucosal barrier function, adaptive immunity, or immune regulatory response. These pathways are probably influenced by such environmental factors as dietary lipid agents. Therefore, it is likely that depending on the presence or absence of CD- or UC-risk alleles, response to dietary lipids may differ. Investigating the role of different polymorphisms in IBD may provide further insights; those

that have already been identified are only able to explain a small percentage of cases,⁶⁴ while there may be as-yet unidentified others that directly interact with dietary lipids.

Further evaluation of the role of lipid-mediated receptors in relation to dietary fatty acid intake would be useful in order to further understand the exact mechanisms by which these dietary agents affect IBD activity, which in turn could potentially lead to future dietary therapies for IBDs. Although interest in dietary therapies for IBD date back to the early stages of its management in the era of modern medicine,⁶⁵ progress to date has been poor. This is primarily due to the complexities surrounding diet and the variability of nutrient intake in humans, variations in dosage, treatment length, confounding medication, or translating evidence from the laboratory to the clinic. However, it is increasingly evident that the environment and particularly diet have a significant role to play in IBD pathogenesis.

The strongest evidence for associations between diet and IBD pathogenesis comes from interventional studies. Studies have shown that clinical remission and mucosal healing can be achieved in CD by a switch from a normal diet to a formula-defined enteral feed, but the mechanisms for this response are not well understood. Potential mechanisms include changes in gut-microbiota type or quantity, improved nutritional status, reduced allergenicity of gut contents, avoidance of food additives, or provision of an anti-inflammatory factor such as TGF β .^{66,67}

While initial results for supplementation of n-3 PUFA in CD were encouraging, this was not consistently reproduced. A further meta-analysis of six published trials shows a small benefit for maintenance supplementation (relative risk of relapse 0.77, 95% CI 0.61–0.98), but the studies were significantly heterogeneous (consistency index $I^2=58.4\%$, P for heterogeneity =0.03), and two large studies showed no benefit.⁶⁸ However, it is to be noted that some of the negative studies may have had variable bioactivity of n-3 PUFAs due to the different preparations used. The same meta-analysis also assessed dietary n-3 PUFA trials in UC. This was limited to three trials, and no significant benefit (relative risk of relapse 1.02, 95% CI 0.51–2.03) was noted.

More recently, an n-3 PUFA food-exchange table was used to assess changes in disease activity in individuals with IBD who underwent a dietary intervention to increase n-3:n-6 PUFA ratio levels. It was noted that the n-3:n-6 PUFA ratio was significantly higher in those patients who did not relapse during follow-up compared to those who did experience a flare.⁶⁹

Dietary interventions may be beneficial in IBD. However, there is now an opportunity to identify novel approaches to

preventing and reversing/resolving chronic inflammatory disease based upon the downstream metabolic products of EPA and DHA and their mechanisms of action or the interaction of these n-3 PUFAs with free fatty acid receptors.

Conclusion

In summary, current epidemiological and translational studies suggest that dietary lipids have a role in IBD pathogenesis. Further studies to understand these complex lipid-mediated mechanisms may open the window to effective therapeutic or complementary nutrition-modulation strategies for patients with UC or CD.

Disclosure

The authors report no conflicts of interest in this work.

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