Inflammatory bowel disease: can omega-3 fatty acids really help?

Sandra Maria Barbalho, Ricardo de Alvares Goulart, Karina Quesada, Marcelo Dib Bechara, Antoney de Cássio Alves de Carvalho

University of Marília and Food Technology School (FATEC); University Hospital, UNIMAR; Diagnostic Center in Gastroenterology, Brazil

Abstract

Adjuvants to the traditional therapy of inflammatory bowel disease (IBD) have been studied to enhance the efficacy of the treatment and improve patients’ quality of life. Omega-3 polyunsaturated fatty acids (ω3FA) have been associated with attenuation of the inflammatory responses in IBD, possibly acting as substrates for anti-inflammatory eicosanoid production, similar to prostaglandins and leukotrienes. ω3FA also act as substrates for the synthesis of resolvins, maresins and protectins, indispensable in resolving inflammation processes. These acids may influence the development or course of IBD by: reducing oxidative stress, production of tumor necrosis factor-α and proinflammatory cytokines; working as chemopreventive agents; and decreasing the expression of adhesion molecules. There are numerous controversies in the literature on the effects of ω3FA in the prevention or treatment of IBD, but their effects in reducing inflammation is incontestable. Therefore, more studies are warranted to elucidate the pathophysiological mechanisms and establish the recommended daily intake to prevent or induce remission in IBD patients.

Keywords Ulcerative colitis, Crohn’s disease, omega-3 polyunsaturated fatty acids

Introduction

The immune system prevents against infection involving inflammatory processes resulting in a response to trauma or microbial infections and it is related to the process completion in order to extinguish the stimulus or to remove the tissue damage. Many diseases such as cardiovascular disorders, Alzheimer’s disease, rheumatoid arthritis, cancer and inflammatory bowel disease (IBD) are caused by inflammatory processes and the course of the pathology continues because of the inappropriate or excessive responses that accompany them chronically [1,2].

Under homeostasis the gastrointestinal system represents a perfect balance between the host and the microbiota in a complex and dynamic process, with important role in the mucosal immunity. When this balance is lost the consequences can result in the increase in intestinal permeability and bacterial translocation across the intestinal mucosa, leading to a local and systemic immune activation implicated in many different diseases including IBD. The two main forms of IBD include Crohn’s disease (CD) and ulcerative colitis (UC) [3-7].

When a patient develops IBD, he acquires the disability of recognition of pattern recognition receptors (PRRs) as Toll-like receptors (TLR), on epithelial and immune cells in the intestine. This leads to the incapacity of differentiating between pathogenic and commensal bacteria (macrophages and dendritic cells on recognition of commensal microbiota modify their status to an activated phenotype) and consequently, extends the activation of nuclear factor kappa B (NFκB), a pro-inflammatory transcription factor which triggers overproduction of inflammatory cytokines, such as tumor necrosis factor (TNF) -α and interleukins (IL) -1β, -6, -12 and -23 (Fig. 1). Processed antigens are presented to naïve CD4 T-cells and the natural killer T cells produce IL-13, strongly associated with the epithelial cell barrier disruption. Circulating T cells bind to colonic endothelial cells through the mucosal vascular adhesion molecule 1, whose production increases in the inflamed intestine. This is accompanied by upregulation of inflammatory chemokines and consequent
recruitment of circulating leukocytes that leads to the perpetuation of the inflammation. The chronic inflammatory process involves modifications on the bowel habits, pain, bleeding, and increases the risk for bowel cancer [8-11].

UC and CD may affect adults and young population driving to a prolonged course and recurrence, affecting education, capacity for work and quality of life. The care IBD patient should have is a challenge due to the heterogeneous nature of the disease and the lack of consensus in many areas of practice. IBD management is usually conducted by pharmacotherapy but patients should be approached in different ways to have a follow up to match their needs and improve their quality of life. This should be done by a multidisciplinary team and the treatment should go beyond the use of conventional therapies.

Several substances as corticosteroids, thiopurines and biologic agents are available and antibiotics, probiotics, and nutritional supplements can be used as supportive therapy. Thus, the use of alternative therapies as omega-3 polyunsaturated fatty acids (PUFA) (n-3 or ω3 FA) could bring important benefits to the IBD patient [8,12-15].

**Methods**

This review was based on a survey of articles in order to bring relevant information about the use of ω3FA. We used the following databases: PubMed, Medline, Scielo, Scopus and Lilacs. A retrospective search was carried out to identify relevant clinical trials or epidemiological studies and reviews limited to indexed scientific articles involving humans and animals.

**Influence of diet on IBD patients**

There is a genetic predisposition to the development of IBD but its increasing incidence in developing countries suggests that environmental factors, such as diet, are also critical components of susceptibility to the occurrence of the disease. Authors have shown that highest consumption of red meat, saturated fat, refined carbohydrates, and food additives as well the low amount of dietetic fibers, fruits, vegetables and antioxidants had increased risk of developing IBD. Dietary compounds as protein, linoleic acid (ω6FA) and digestible carbohydrates may contribute to the pathogenesis because they cause intestinal microbiota modifications leading to an increase in intestinal permeability, and inflammation processes augment [16-25].

Several authors have shown that, in addition to modifications in the food choices, the use of ω3FA may bring benefits because may influence the development or course of IBD [16,26-30]. Normally, the recommended intake of ω3FA is 1.6 g/day for men and 1.1 g/day for women. This intake can come from the regular food consumption or from supplementation with fish or olive oil or use of emulsions consisting of coconut oil, soy, olive oil or fish. Literature shows converging opinions about a daily recommendation but authors agree that 500 mg/day of eicosapentaenoic acid/docosahexaenoic acid could bring health benefits. Di Nicolantonio et al [31] suggested 2 servings of fatty fish per week for the general population. There is no consensus on ω3FA dietary recommendations for IBD patients.

**ω3FA**

ω3FA belong to a lipid class called PUFA. This family includes lipids with two or more double bonds considered
to be essential nutrients because the body does not have the capacity to produce them endogenously. They can be found in significant proportions in different food sources, as in linseed, nuts and fish. Examples of these acids are α-linoleic acid with a chain with 18 carbon atoms and 3 double bonds (C18:3n-3), eicosapentaenoic acid (C20:5n-3), and docosahexaenoic acid (Fig. 2) (C22:6 n-3) [32-33].

While saturated fatty acids are related to insulin resistance, higher levels of triglycerides, weight gain, increase in the adipocyte size and increase in adipose tissue inflammation, ω3FA improve blood lipid levels, reduce weight and attenuate inflammation processes implicated in cardiovascular diseases and other inflammatory diseases. They can also improve neural function and sensitivity to acetylcholine, balance the membrane fluidity and decrease post-exercise inflammation leading to adaptations to exercises such as decreasing aspects of fatigue and improving peripheral neuromuscular function [32,34-36].

Pathophysiological data

The interest in the use of ω3 FA has grown tremendously in the last years. They are substrates for inflammatory and anti-inflammatory eicosanoid production, such as prostaglandins and leukotrienes, and so they have been used to the prevention of different inflammatory diseases in animals and humans (Fig. 3). One possibility to explain the beneficial effects of ω3FA is the competition that avoids conversion of arachidonic acid to pro-inflammatory eicosanoids such as prostaglandins, leukotrienes and lipoxins through the cyclooxygenase or lipoxygenase enzymes. Eicosapentaenoic acid and docosahexaenoic acid can replace arachidonic acid and inhibit pro-inflammatory mediator production. They may also inhibit inflammation acting in leukocyte chemotaxis, adhesion molecule expression and leukocyte-endothelial adhesive interactions, and suppressing the production of other inflammatory cytokines, and T-helper 1 lymphocyte reactivity. Furthermore, ω3FA are substrates to the synthesis of resolvins, maresins and protectins, indispensable in resolving inflammation processes [26,37-41].

The beginning of inflammation is important for the body to make the defense against trauma or microorganism infection, and so is the finalization of the process. If this does not occur, the organism will develop a disease. In this duet, i.e. the beginning and the end of inflammation process, the same lipid substances are involved. Thus, the use of eicosapentaenoic acid and docosahexaenoic acid may be promising in minimizing or preventing inflammatory diseases such as IBD [42-44]. Both animal and clinical studies show that these acids may have a potential role in the treatment of IBD. Besides, patients see them as both safe and natural [30]. IBD patients may exhibit a deficiency in essential fatty acids, and ω3FA supplements may benefit IBD patients by inhibiting natural cytotoxicity (by changing arachidonic acid metabolites) and/or improving oxidative stress. The anti-inflammatory actions of ω3FA may also be associated with their ability to change the composition of the cell membrane and the ability to activate the anti-inflammatory transcription peroxisome proliferator activated receptor (PPAR) γ [26,30,45-48].

There is evidence that the gastrointestinal mucosa is highly responsive to long-chain PUFA such as ω3. The intake of ω3FA can be helpful in the treatment of UC and CD as it can alleviate the symptoms and help the recovery of the mucosal due to its anti-inflammatory properties. Reasons probably are related to the reduction in the intestinal production of the precursor of pro-inflammatory cytokines (leukotrienes and prostaglandins) of odd series. Furthermore, there is evidence that these acids may reduce the protein expression of intestinal NFκB p65 related to apoptotic cells [28,41,48-52].

ω3FA may influence the membrane-cytoskeletal structure and function in CD4+ T cells leading to the reduction in

![Figure 2](https://example.com/figure2.png)

**Figure 2** Synthesis of eicosanoids from ω3 FA: 3 series prostanoids TXA3, PGE3 and PG13 and 5 series leukotrienes LT5, LTC5-LTE5. Modified from Barbalho et al [33] and Din et al [37]

ω3 FA, omega 3 fatty acid; TXA3, thromboxane A3; PGE3, prostaglandin E3; PG13 and 5, prostaglandin 13 and 5; LT5, leukotriene B5; LTC5-LTE5, leukotriene C5-leukotriene E5

![Figure 3](https://example.com/figure3.png)

**Figure 3** Structure of omega 3 fatty acids: first double bond at the third carbon molecule from the methyl end of the chain. There are three possibilities for names: C18:3n-3, C20:5n-3 and C22:6n-3omega, respectively linolenic acid, eicosapentaenoic acid and docosahexaenoic acid
the inflammation processes [22]. TLR and nucleotide-binding oligomerization domain proteins (NOD) have a critical role in the detection of microbial infection and induction of inflammatory and immune responses. When both TLR and NOD are activated, there is activation of NFκB which stimulates synthesis of pro-inflammatory cytokines. Studies are associating TLR4 and NOD signaling in multi-layered IBD, interfering in pathogen-associated molecular patterns leading to acute and chronic intestinal inflammation [10,49,53,54].

Results of clinical studies

Many authors have studied the role of omegas in the prevention, treatment and maintenance of remission of inflammatory diseases such as IBD. Pearl et al [55] studied colonic mucosa biopsies from 69 UC patients and found that inflamed mucosa had higher levels of arachidonic, docosapentaenoic and docosahexaenoic acids and lower levels of linoleic, α-linolenic and eicosapentaenoic acids compared with the control group. The severity of inflammation was positively associated with the levels of arachidonic, docosapentaenoic and docosahexaenoic acid and negatively associated with levels of linoleic, α-linolenic and eicosapentaenoic acids suggesting that there are modifications in fatty acid metabolism in the inflamed gut mucosa. These modifications can offer novel targets for intervention and nutritional strategies should also be considered. Table 1 summarizes the studies showing the effects of ω3FA in different types of participants; some show an important role of ω3FA in the course of CD, UC and reduction of colorectal cancer and polyp, while others provided inconclusive or negative results [56-62].

The controversial findings on the relationship between ω3FA and IBD (as seen in Table 1) may be due to a number of reasons: 1) different forms of ω3FA have different effects when compared to the native form found in fish; 2) genetic differences in ω3FA receptors may interfere with the responsiveness to fatty acid supplementation; 3) modifications in G-protein receptors and PPAR-α (considered to be a dietary lipid sensor); and 4) differences or problems in their methodology (insufficient number of patients, short period of study, heterogeneity of disease, lifestyle and other aspects of the studied population). These aspects may interfere in the efficacy of ω3FA in controlling symptoms, inflammation and remission in IBD patients [8,16,30,63,64].

ω3FA in animal models

Literature is also rich in studies using ω3FA in different types of animal models. Table 2 presents some studies showing that these acids may reduce weight loss and intestinal permeability, improve the intestinal morphology and barrier function and decrease the synthesis of inflammatory markers as TNF-α, IL-6, IL-1β, prostaglandin E2 and expression of TLR4 and NFκB [28,49,65-67].

ω3FA and pain

ω3FA are shown to regulate pain, depending on the amount of intake and subsequent cellular distribution. When a large amount of ω3FA was administered, reduced thermal hyperalgesia was observed compared with a group that received a large amount of linoleic acid, suggesting that there is a dose-dependent association between these acids and pain control. Pain relief was observed in several pathologies, including IBD, possibly because ω3FA reduce proinflammatory cytokine and eicosanoid production. The use of ω3FA can also block the activity of mitogen-activated protein kinase related to the modulation of central sensitization induced by inflammatory and neuropathic pain. Linolenic acid declines the production of lysophosphatidic acid that is strongly related to the development of neuropathic pain [68-73]. It has been hypothesized that the effects of docosahexaenoic acid in pain control are due to its anti-inflammatory effect via suppression of the arachidonic acid cascade; inhibition of voltage-gated sodium channels; and promotion of the agonistic action toward transient receptor potential vanilloid 1 (related to inflammation processes and calcium channels inhibition). They also found that docosahexaenoic acid reduces pain indirectly through the release of an endogenous opioid peptide β-endorphin and not only because it acts on the opioid receptor [74,75]. Other studies showed that increased consumption of ω3FA and decreased consumption of ω6FA can modify endocannabinoid production in humans thereby suggesting that their derivatives could have physical and/or psychological pain modulating properties [76,77].

| Table 1 Effects of the use of omega 3 fatty acids (ω3FA) in different type of participants |
|---------------------------------------------|-----------------------------|-----------------------------|
| **Type of participants** | **Effects of ω3FA** | **Reference** |
| Healthy subjects | Protection against development of UC | John et al [56] |
| UC | Protection against the effects of oxidative stress | Barbosa et al [57] |
| CD | Chemopreventive; protects against development | Chan et al [58]; Chan, Hart [59] |
| Colorectal cancer and polyp | Decrease in colorectal cancer risk and reduction of: 1) polyph formation and growth; 2) cell proliferation | Piazzi et al [60] |
| UC | Not as good as sulfasalazine | Dichi et al [61] |
| CD | No evidence for maintenance of remission | Lev-Tzion et al [62] |

CD, Crohn’s disease; UC, ulcerative colitis
Table 2 Effects of the use of omega-3 fatty acids (ω3FA) in animal models

| Type of model                                      | Effects of ω3FA                                                                 | Reference          |
|---------------------------------------------------|--------------------------------------------------------------------------------|--------------------|
| 5-fluorouracil induced mucositis in mice          | Reduction in weight loss and intestinal permeability with controlled bacterial translocation | Generoso et al [28]|
| Intestinal injury caused by Escherichia coli in pigs | Improvement in intestinal morphology and barrier function; reduction in TNF-α, prostaglandin E2 and expression of TLR4 and NFκB | Liu et al [49]     |
| Colitis in rats                                   | Reduction in the expression of adhesion molecules and vascular endothelial growth factor A receptor-2; down regulation of TNF-α and IL-1β | Ibrahimb et al [65]; Tyagi et al [66] |
| Colitis in mice                                   | Significant reduction in colonic pro-inflammatory eicosanoids                    | Bosco et al [67]   |

TNF-α, tumor necrosis factor α; TLR4, Toll-like receptor 4; NFκB, nuclear factor kappa B; IL-1β, interleukin-1β

Concluding remarks

IBD is considered a public health problem owing to the high cost it incurs for the Public Health System and the burden it has on the patients’ quality of life. Several studies show that ω3FA lead to the production of resolvins, protectins and maresins which attenuate the inflammatory processes possibly benefiting IBD patients. However, there are many controversies over the ω3FA effects on IBD, and results of the studies should be interpreted with caution due to the enormous variability in the size of the samples, the amount of ω3FA administered and the methodology employed. Studying the pharmacology of ω3FA will help establish their real effects, thus bringing new possibilities to the treatment of inflammatory diseases. More research is warranted to fully elucidate how these acids influence IBD and to define the daily amount recommended to help prevent or induce remission of IBD.

References

1. Stark AK, Sriskantharajah S, Hessel EM, Okkenhaug K. PI3K inhibitors in inflammation, autoimmunity and cancer. Curr Opin Pharmacol 2015;23:82-91.
2. Guerra I, Bermejo F. Biosimilars in inflammatory bowel disease: Management and care. Rev Esp Enferm Dig 2015;107:389.
3. Nee J, Feuerstein JD. Optimizing the care and health of women with inflammatory bowel disease. Gastroenterol Res Pract 2015;2015:435820.
4. Elia PP, Tolentino YF, Bernardazzi C, de Souza HS. The role of innate immunity receptors in the pathogenesis of inflammatory bowel disease. Mediators Inflamm 2013;2013:5936193.
5. Andrade ME, Araújo RS, de Barros PA, et al. The role of immunomodulators on intestinal barrier homeostasis in experimental models. Clin Nutr 2015;34:1080-1087.
6. Victoria CR, Sassaki YI, Nunes HRC. Incidence and prevalence rates of inflammatory bowel diseases, in midwestern of São Paulo State, Brazil. Arq Gastroenterol 2009;46:20-25.
7. Nguyena DL, Leea JG, Parekhka NK, Samarasenaa J, Betcholdb ML, Chang K. The current and future role of endomicroscopy in the management of inflammatory bowel disease. Ann Gastroenterol 2015;28:331-336.
8. Tabbaa M, Golubic M, Roizen ME, Bernstein AM. Docosahexaenoic acid, inflammation, and bacterial dysbiosis in relation to periodontal disease, inflammatory bowel disease, and the metabolic syndrome. Nutrients 2013;5:3299-3310.
9. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal world congress of gastroenterology. Can J Gastroenterol 2005;19(Suppl A):5-36.
10. Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet 2012;380:1606-1619.
11. Cheifetz AS. Management of active Crohn disease. J Am Med Association 2013;309:2150-2158.
12. Triantafyllidis JK, Merikas E, Georgopoulos E. Current and emerging drugs for the treatment of inflammatory bowel disease. Drug Des Devel Ther 2011;5:185-210.
13. Prüfer J, Schuchardt M, Tölle M, et al. Harmful effects of the azathioprine metabolite 6-mercaptopurine in vascular cells: induction of mineralization. PLoS One 2014;9:e101709.
14. Shores DR, Binion DG, Freeman BA, Baker PR. New insights into the role of fatty acids in the pathogenesis and resolution of inflammatory bowel disease. Inflamm Bowel Dis 2015;21:1922-2204.
15. Lichtenstein GR, Hanauer SB, Sandborn WJ. Management of Crohn’s disease in adults. Am J Gastroenterol 2009;104:465-483.
16. Dixon LJ, Kabi A, Nickerson KP, McDonald C. Combinatorial effects of diet and genetics on inflammatory bowel disease pathogenesis. Inflamm Bowel Dis 2015;21:912-922.
17. Reif S, Klein L, Lubin F, Farbstein A, Gilat T. Pre-illness dietary factors in inflammatory bowel disease. Gut 1997;40:754-760.
18. Russel MG, Engels LG, Muris JW, et al. Modern life in the epidemiology of inflammatory bowel disease: A case-control study with special emphasis on nutritional factors. Eur J Gastroenterol Hepatol 1998;10:243-249.
19. Frolkis A, Dieleman LA, Barkema HW, et al. Environment and the inflammatory bowel diseases. Rev Esp Enferm Dig 2015;107:2195-2201.
20. Sung MK, Park MY. Nutritional modulators of ulcerative colitis: clinical efficacies and mechanistic view. World J Gastroenterol 2013;19:994-1004.
21. Pfeffer-Gik T, Levine A. Dietary clues to the pathogenesis of Crohn’s disease. Dig Dis 2014;32:389-394.
22. Hou TY, McMurray DN, Chapkin RS. Omega-3 fatty acids, lipid rafts, and T cell signaling. Eur J Pharmacol 2015 [Epub ahead of print].
23. Farzaei MH, Rahimi R, Abdollahi M. The role of dietary polyphenols in the management of inflammatory bowel disease. Curr Pharm Biotechnol 2015;16:196-210.
24. Jantchou P, Morois S, Clavel-Chapelon F, Boutron-Ruault M-C, Carbonnel F. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. Am J Gastroenterol 2010;105:2195-2201.
25. Ananthakrishnan AN, Khalili H, De Silva PS. Higher dietary fiber intake is associated with lower risk of Crohn’s disease but not ulcerative colitis – a prospective study. Gastroenterology 2010;142(Suppl 1):S-148.
26. Calder PC. Marine omega-3 fatty acids and inflammatory processes.
effects, mechanisms and clinical relevance. Biochim Biophys Acta 2015;1851:469-484.

27. Lorente-Cebrián S, Costa AG, Navas-Carretero S, et al. An update on the role of omega-3 fatty acids on inflammatory and degenerative diseases. J Physiol Biochem 2015;71:341-349.

28. Generoso SV, Rodrigues NM, TrindadeLM, et al. Dietary supplementation with omega-3 fatty acid attenuates 5-fluorouracil induced mucositis in mice. Lipids Health Dis 2015;14:54.

29. Martin FP, Lichi P, Bosco N, et al. Metabolic phenotyping of an adoptive transfer mouse model of experimental colitis and impact of dietary fish oil intake. J Proteome Res 2015;14:1911-1919.

30. Farrukh A, Mayberry JF. Is there a role for fish oil in inflammatory bowel disease? World J Clin Cases 2014;2:250-252.

31. DiNicolantonio JJ, Niazi AK, McCarty MF, O’Keefe JH, Meier P, Lavie CJ. Omega-3s and cardiovascular health. Ochsner J 2014;14:399-412.

32. Lewis EJ, Radonic PW, Wolfe TM, Wells GD. 21 days of diet with menhaden oil or daily treatment with resolvin D1 on changes in glucose and lipid metabolism. Pflugers Arch 2015;467:1179-1193.

33. Barbalho SM, Bechara MD, Quesada K, Goulart RA. Omega 3 fatty acid and the resolution of inflammatory processes. Medicina 2011;44:234-240.

34. Duivenvoorde LP, van Schothorst EM, Swarts HM, et al. A difference in fatty acid composition of isocaloric high-fat diets alters metabolic flexibility in male C57BL/6JolaHsd mice. PLoS One 2015;10:e0128515.

35. Duivenvoorde LP, van Schothorst EM, Derouss EJ, et al. Oxygen restriction as challenge test reveals early high-fat-diet-induced changes in glucose and lipid metabolism. PloS One 2015;10:e0128515.

36. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. J Am Med Assoc 2012;308:1024-1033.

37. Din JN, Newby DE, Flapan AD. Omega 3 fatty acids and cardiovascular disease-fishing for a natural treatment. BMJ 2004;328:30-35.

38. Gdula-Arsagisfska J, Czepiel J, Wóźniakiewicz A, et al. n-3 Fatty acids as resolvents of inflammation in the A549 cells. Pharmacol Rep 2015;67:610-615.

39. White PJ, Mitchell PL, Schwab M, et al. Transgenic ω-3 PUFA alters endometrial morphology and gene expression profile in adipose tissue of obese mice: Potential role for protecints. Metabolism 2015;64:666-676.

40. Shevalye H, Yorek MS, Coppey LJ, et al. Effect of enriching the cellular ω-3 fatty acids only delay early relapse of ulcerative colitis in remission. Dig Dis Sci 1996;41:2087-2094.

41. Hawthorne AB, Daneshmend TK, Hawkey CJ, et al. Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. Gut 1992;33:922-928.

42. Parlat M, Yeretssian G. NOD-like receptors in intestinal homeostasis and epithelial tissue repair. Int J Mol Sci 2014;15:9594-9627.

43. Fukata M, Vanamdevan AS, Abreu MT. Toll-like receptors (TLRs) and Nod-like receptors (NLRs) in inflammatory disorders. Semin Immunol 2009;21:242-253.

44. Pearl DS, Masoodi M, Eiden M, et al. Altered colonic mucosal availability of n-3 and n-6 polyunsaturated fatty acids in ulcerative colitis and the relationship to disease activity. J Crohns Colitis 2014;8:70-79.

45. John S, Ruben L, Shrestha SS, Welch A, Khaw KT, Hart AR. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. Eur J Gastroenterol Hepatol 2010;22:602-606.

46. Barbosa DS, Cezchin R, El Kadri MZ, Rodríguez MA, Burini RC, Dichi I. Decreased oxidative stress in patients with ulcerative colitis supplemented with fishoil omega-3 fatty acids. Nutrition 2003;19:837-842.

47. Chan SS, Ruben L, Olsen A, et al. Association between high dietary intake of the n-3 polyunsaturated fatty acid docosahexaenoic acid and reduced risk of Crohn’s disease. Aliment Pharmacol Ther 2014;39:834-842.

48. Chan SS, Hart AR. Commentary: the association between high dietary intake of docosahexaenoic acid and reduced risk of Crohn’s disease-authors’ reply. Aliment Pharmacol Ther 2014;39:1322.

49. Piazzzzi G, D’Argenio G, Prossomariti A, et al. Eicosapentaenoic acid free fatty acid prevents and suppresses colonic neoplasia in colitis-associated colorectal cancer acting on Notch signaling and gut microbiota. Int J Cancer 2014;135:2004-2013.

50. Dichi I, Frenhane J, Dichi M et al. Omega-3 fatty acids and sulfasalazine in ulcerative colitis. Nutrition 2000;16:87-90.

51. Lev-Tzion R, Griffrin AM, Leder O, Turner D. Omega 3 fatty acids and sulfasalazine in ulcerative colitis. Crohns Colitis 2000;2:837-842.

52. Lev-Tzion R, Griffiths AM, Leder O, Turner D. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn’s disease. Cochrane Database Syst Rev 2014;2:CD006320.

53. Hoshi T, Wissuwa B, Tian Y, et al. Omega-3 fatty acids lower blood pressure by directly activating large-conductance Ca2+-dependent K+ channels. Proc Natl Acad Sci USA 2013;110:4816-4821.

54. Marion-Letellier R, Savoye G, Beck PL, Panaccione R, Ghosh S. Polynsaturated fatty acids in inflammatory bowel diseases: a reappraisal of effects and therapeutic approaches. Inflammm Bowel Dis 2013;19:650-661.

55. Ibrahim A, Aziz M, Hassan A, et al. Dietary α-linolenic acid-rich
formula reduces adhesion molecules in rats with experimental colitis. Nutrition 2012;28:799-802.

66. Tyagi A, Kumar U, Reddy S, et al. Attenuation of colonic inflammation by partial replacement of dietary linoleic acid with α-linolenic acid in a rat model of inflammatory bowel disease. Br J Nutr 2012;108:1612-1622.

67. Bosco N, Brahmbhatt V, Oliveira M, et al. Effects of increase in fish oil intake on intestinal eicosanoids and inflammation in a mouse model of colitis. Lipids Health Dis 2013;12:81.

68. Tokuyama S, Nakamoto K. Unsaturated fatty acids and pain. Biol Pharm Bull 2011;34:1174-1178.

69. Bagga D, Wang L, Farias-Eisner R, Glaspy JA, Reddy ST. Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. Proc Natl Acad Sci U S A 2003;100:1751-1756.

70. Wagner K, Vito S, Incrogliu B, Hammock BD. The role of long chain fatty acids and their epoxide metabolites in nociceptive signaling. Prostaglandins Other Lipid Mediat 2014;113-115:2-12.

71. Pérez J, Ware MA, Chevalier S, Gougeon R, Bennett GJ, Shir Y. Dietary fat and protein interact in suppressing neuropathic pain-related disorders following a partial sciatic ligation injury in rats. Pain 2004;111:297-305.

72. Mirnikjoo B, Brown SE, Kim HF, Marangell LB, Sweatt JD, Weeber EJ. Protein kinase inhibition by omega-3 fatty acids. J Biol Chem 2001;276:10888-10896.

73. Seung Kim HF, Weeber EJ, Sweatt JD, Stoll AL, Marangell LB. Inhibitory effects of omega-3 fatty acids on protein kinase C activity in vitro. Mol Psychiatry 2001;6:246-248.

74. Nakamoto K, Nishinaka T, Mankura M, Fujita-Hamabe W, Tokuyama S. Antinociceptive effects of docosahexaenoic acid against various pain stimuli in mice. Biol Pharm Bull 2010;33:1070-1072.

75. Nakamoto K, Nishinaka T, Ambo A, Mankura M, Kasuya F, Tokuyama S. Possible involvement of β-endorphin in docosahexaenoic acid-induced antinociception. Eur J Pharmacol 2011;666:100-104.

76. Ramsden CE, Zamora D, Makriyannis A, et al. Diet-induced changes in n-3- and n-6-derived endocannabinoids and reductions in headache pain and psychological distress. J Pain 2015;16:707-716.

77. Trépanier MO, Hopperton KE, Orr SK, Bazinet RP. N-3 polyunsaturated fatty acids in animal models with neuroinflammation: An update. Eur J Pharmacol 2015 [Epub ahead of print].

Annals of Gastroenterology 29