December 2007(II): S188–S193

Dietary Lipids in Early Development and Intestinal Inflammatory Disease

Sheila M. Innis, PhD, and Kevan Jacobson, MD

Inflammatory bowel diseases are life-long reoccurring inflammatory disorders of the gastrointestinal tract and have been increasing in incidence in recent decades, notably in the pediatric population. Although genetic predisposition remains an important factor, this increased incidence most likely reflects an environmental change. One potential contributor to this is the change in dietary fat intake, with dietary intake of n-6 polyunsaturated fatty acids (PUFAs) following a similar temporal pattern to the change in inflammatory bowel disease incidence. Dietary n-6 PUFAs comprise a major, modifiable, environmental factor known to promote a heightened inflammatory response through a number of pathways, including their role as precursors for synthesis of eicosanoids and their inhibitory effect on the synthesis of the n-3 PUFAs eicosapentanoic acid and docosahexanoic acid. The increase in n-6 PUFA intake affects individuals of all ages, with fetal PUFA accretion and infant dietary PUFA intake from breast milk reflecting maternal dietary intake. A high level of n-6 PUFA in milk results in increased n-6 PUFA in colonic phospholipids and an exaggerated inflammatory response to chemically induced colitis. Conversely, during development, a diet low in n-6 PUFAs and high in n-3 PUFAs increases colonic n-3 fatty acids, attenuates the inflammatory response, and lowers colonic damage. High dietary n-6 PUFA intake may be an important environmental modifier that contributes to inflammatory bowel diseases.

Key words: pediatric, maternal, ulcerative colitis, Crohn's disease, n-3 PUFA, n-6 PUFA, linoleic acid, arachidonic acid, interleukin, tumor necrosis factor, α-linoleic acid, eicosapentanoic acid, docosahexanoic acid

doi: 10.1301/nr.2007.dec.S188–S193

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic recurrent intestinal disorders of the intestinal tract that include ulcerative colitis (UC) and Crohn's disease (CD). Ulcerative colitis is characterized by a diffuse inflammation limited to the mucosa, extending from the rectum in a uniform manner to involve part of, or the entire colon.[1] In contrast, CD can affect any part of the gut, but it most commonly affects the terminal ileum and proximal colon, with localized regions of inflammation, which spreads beyond the mucosa into the deeper layers, resulting in inflammatory, structuring, or fistulizing disease.[1]

In geographical areas traditionally associated with IBD (i.e., North America, Northern Europe, and the United Kingdom), the rates of UC and CD incidence have increased dramatically since the 1960s, although they now appear to have stabilized.[2] As of 2004, as many as 1.4 million individuals in the United States and 2.2 million persons in Europe suffered from IBD.[2] While the mean age at diagnosis in North America is 33–45 years for CD and about 5–10 years later for UC,[3-5] the rising incidence of these conditions amongst children is of great concern. For example, epidemiological studies have revealed increases in the incidence of childhood CD in Scotland,[6] Wales,[7,8] and Western Canada,[9,10] while the incidence of pediatric UC rose between 1984 and 1995 in Sweden (Table 1).[11] These serious conditions, often require life-long medical intervention, or even major surgery. Therefore, identifying the causes of this recent increase in childhood IBD cases is an important quest.

NUTRITION AND INFLAMMATORY BOWEL DISEASE

Like many inflammatory disorders, the causes of IBD are legion, and both genetic predisposition and environmental factors are implicated. However, the rate of increase in incidence suggests environmental, rather than genetic, influences are to blame. Corroborating this are the changes seen in immigrant communities; Leicester, in the United Kingdom, has a large population of migrants from South Asia, a region with a low incidence of IBD. A prospective study of UC conducted between 1991 and 1994 found extensive colitis to be more common in second-generation South Asian migrants in Leicester than in the first generation, and the rates in second-generation migrants were comparable to those observed in the European community.[12] The results of

Drs. Innis and Jacobson are with the Department of Paediatrics, Nutrition Research Program, Child and Family Research Institute, University of British Columbia, Vancouver, British Columbia V5Z 4H4, Canada.

Please direct correspondence to: Dr. Sheila M. Innis, Department of Paediatrics, University of British Columbia, Child and Family Research Institute, 179A, 950 W 28th Avenue, Vancouver, BC V5Z 4H4, Canada. Phone: +1-604-875-2431, Fax: +1-604-875-3597, E-mail: sinnis@nutrition.ubc.ca

Table 1. Changes over time in the incidence of Crohn's disease (CD) and ulcerative colitis (UC) in populations with high rates of irritable bowel disease

Reference	Country	Population	Disease	Year	Incidence (per 100,000 population)
Armitage et al. (2001)[6]	Scotland	Hospital discharge data; patients <19 years	CD	1971–1975	1.0
				1991–1995	3.1
Cosgrove et al. (1996)[8]	South Glamorgan, Wales	Retrospective study; pediatric patients	CD	1983–1988	1.3
				1989–1993	3.11
Pinsk et al. (2005)[10]	British Columbia, Canada	Retrospective chart review; patients ≤16 years	CD	1990–1994	1.18
				2000–2004	5.06
Pinsk et al. (2005)[10]	British Columbia, Canada	Retrospective chart review; patients ≤16 years	UC	1990–1994	0.46
				2000–2004	1.14
Lindberg et al. (2000)[11]	Sweden	Prospective report; patients ≤15 years	UC	1984–1986	1.4
				1993–1995	3.2

this study also highlight the importance of genetic predisposition, since the incidence of UC in second-generation South Asians (17.2 per 100,000 population per year) was considerably higher than in the European population (6.0 per 100,000 per year); it was also considerably higher than the incidence in their country of origin.[12] Results from a study conducted in Western Canada support these findings, with the incidence of IBD among children of East Indian decent being almost three-fold that in the local pediatric community.[10] These results suggest that people from the Indian sub-continent have a higher genetic predisposition to IBD than Europeans, but this susceptibility does not manifest until they are exposed to a Western "pro-IBD" diet.

Thus, while genetic predisposition to IBD appears to be higher in some populations than in others, environmental factors are the primary suspect for its increased incidence over the past 50 years. Among the potentially important dietary factors, evidence from a number of sources points to dietary fat, specifically polyunsaturated fatty acid (PUFA) content, as a potential contributor.

POLYUNSATURATED FATTY ACIDS AND INFLAMMATION

Dietary PUFAs are a major modifiable environmental factor known to influence inflammation. The n-6 PUFA linoleic acid (LA) is the metabolic precursor for the synthesis of arachidonic acid (ARA), which is found in abundance in plasma membrane phospholipids.[13,14] Once the ARA is mobilized from the plasma membrane by phospholipase enzymes, it acts as a substrate for synthesis of a number of pro-inflammatory eicosanoids including the 2-series of prostaglandins (PGs) and the 4-series of leukotrienes. Prostaglandin E_2 has a number of pro-inflammatory effects including inducing fever, increasing vascular permeability and vasodilatation, enhancing pain and edema caused by other agents such as bradykinin and histamine, and inducing interleukin (IL)-6 production by macrophages. Leukotriene B_4 increases vascular permeability, is a potent chemotactic agent for leucocytes, induces the release of lysosomal enzymes, enhances the generation of reactive oxygen species and promotes production of pro-inflammatory cytokines such as tumor necrosis factor alpha, IL-1 and IL-6. Interestingly, ARA-derived eicosanoids are also responsible for the resolution of inflammation mediated via PGE_2, PGI_2, and lipoxins.[15,16]

An increased dietary intake of the n-6 PUFAs may also contribute to a pro-inflammatory environment by inhibiting the synthesis and incorporation of the n-3 PUFA eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) derived from α-linoleic acid (ALA) into membrane lipids.[17] The eicosanoids derived from EPA attenuate the inflammatory response through a number of mechanisms (Figure 1). They are substrates for the synthesis of the 3-PG and 5- leukotriene families of eicosanoids, they downregulate the expression of several genes involved in inflammation, including those encoding certain endothelial adhesion molecules, and decrease

production of tumor necrosis factor alpha, IL-1β, and IL-6 through several pathways including mitogen-activated protein kinases and the nuclear factor-kappa B signal transduction pathway.[13,14,18] In addition, DHA can be metabolized to bioactive docosanoids, which have potent anti-inflammatory actions that include attenuation of leukocyte entry into sites of inflammation.[19]

Increasing dietary n-6 PUFA intakes could therefore create a pro-inflammatory environment, while a diet low in n-6 PUFA with a favorable n-6 to n-3 PUFA balance should promote an environment more tolerant to immunological challenge. Some epidemiological evidence supports this. The major dietary source of n-3 PUFA, EPA, and DHA is fish. Inuit and Japanese societies with traditionally high EPA and DHA intakes from fish or marine mammals, and low intakes of n-6 PUFA, also tend to have low rates of IBD. Notably, the Japanese diet is becoming increasingly Westernized and IBD incidence is increasing.[20]

CHANGES IN DIETARY FAT INTAKE

In Western nations, increased understanding of elevated plasma LDL cholesterol as a risk factor for cardiovascular disease has led to the replacement of dietary sources of saturated animal fats with vegetable oils high in the n-6 PUFA LA in liquid oils, as well as in margarines and shortenings. As a result, the dietary intake of LA has increased from about 3% dietary energy in the 1930s to about 7% in the 1980s. Currently, n-6 PUFA intake represents approximately 7% of dietary energy in the United States and about 5% in Canada.[21–27] At the same time, the intake of n-3 PUFA ALA, EPA, and DHA has decreased; together with the increase in LA, this has resulted in a marked increase in the balance of n-6 to n-3 PUFA in the diet. This change in dietary PUFA intake coincides with the increased incidence of IBD[12] and may be contributing to the increase in childhood IBD mentioned above, since the increase in n-6 PUFA and decrease in n-3 PUFA intake has affected people of all ages, including infants—it even extends to before birth.

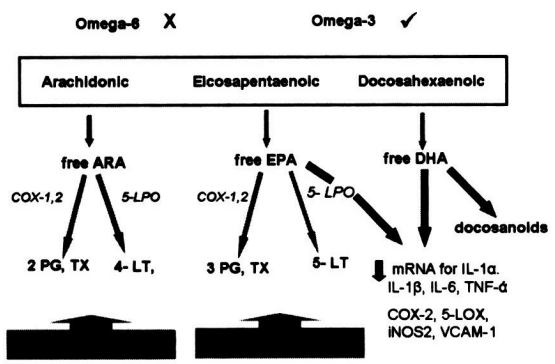

Figure 1. Schematic of the major pathways of n-6 and n-3 polyunsaturated fatty acid metabolism. Abbreviations: LPO, lipid peroxidation; PG, prostaglandin; TX, thromboxane; LT, leukotriene; HPETE, 5(s)-hydroperoxyeicosatetraenoic acid; HETE, 5(s)-hydroxyeicosatetraenoic acid; IL, interleukin; VCAM-1, vascular adhesion molecule-1; COX, cyclooxygenase; LOX, lipoxygenase; iNOS, inducible nitric oxide; TNF-α, tumor necrosis factor alpha.

INFLUENCE OF MATERNAL DIET ON FETAL AND NEWBORN EXPOSURE TO POLYUNSATURATED FATTY ACIDS

All n-6 and n-3 PUFAs accumulated by the fetus ultimately originate from the maternal diet, primarily through placental transfer, but also through swallowing of amniotic fluid. Although the relative proportions of ARA and DHA PUFAs are higher and LA and ALA PUFAs are lower in the plasma esterified lipids of the fetus than the mother,[27] there is extensive evidence indicating the maternal dietary intake of n-3 and n-6 PUFAs has a profound effect on n-6 and n-3 PUFA accumulation in the fetus. Concentrations of LA, ARA, and DHA in plasma phospholipids of fetal cord blood sampled at birth showed a significant correlation with the same fatty acid in maternal plasma.[28] Studies showing that supplementation of the maternal diet with DHA from fish or fish oils during gestation increases DHA in infant plasma and red blood cells at birth provide more specific evidence that maternal n-3 fatty acid nutrition is a critical determinant of fetal n-3 fatty acid accretion.[29–31]

Fetal exposure to PUFAs is not only a result of placental transfer; fetuses swallow amniotic fluid in utero, a process important for amniotic fluid homeostasis and for fetal somatic and gastrointestinal development.[31] Recently, it has been shown that maternal dietary fat intake also influences amniotic fluid PUFA composition. Pregnant rats who were fed an n-3 PUFA-deficient diet had significantly less DHA and higher amounts of the n-6 PUFA in their amniotic fluid when compared with rats fed a normal diet; differences were also observed in the fetal intestinal phospholipid composition.[33] These results, and those described above, suggest that both swallowing of amniotic fluid and placental transfer of fatty acid contribute to fetal PUFA accretion, and that a maternal diet high in n-6 and low in n-3 PUFAs can change fetal PUFA content to favor a more inflammatory gastrointestinal environment. Given the low n-3 PUFA intake identified in recent studies of pregnant women in Canada[25] and the United States,[34,35] this is a concern.

The influence of the maternal diet over the PUFA composition of plasma and cellular lipids in offspring continues in breast-fed infants after birth, as the composition of human milk fat also reflects the dietary intake of the mother. Numerous studies worldwide have shown that the n-6 PUFA LA and the n-3 PUFA ALA and DHA

contents in human milk depend on the mother's PUFA intake. It is not surprising, therefore, that the n-6 PUFA content of human breast milk has increased dramatically (about two-fold since the 1950s), echoing the changes in dietary fat consumption.[36–39] At the same time, the levels of DHA in human milk in Canada and the United States are some of the lowest worldwide, at about 0.2 to 0.3% compared to levels of 0.8% or higher in countries where fish is widely consumed (Table 1).[38–40] For many years the correlation between the n-6 and n-3 PUFA levels in human milk and the mother's dietary fat intake was poorly appreciated, and this led to the faulty extrapolation that the average fatty acid composition of milk in North America is the best model on which to base the PUFA composition of infant formula. Thus, modern infant formulas also contain 16–20% LA in the fat, representing 7–10% of dietary energy intake from LA in the formula-fed infant.[40] Human milk in the 1950s contained closer to 4% energy from LA.[36]

IMPACT OF FETAL AND PERINATAL POLYUNSATURATED FATTY ACID INTAKE ON COLON INFLAMMATORY RESPONSE

There is evidence that high n-6 PUFA intake early in life could result in a heightened response to gastrointestinal insult. Pregnant rats were fed a diet high in n-3 PUFA ALA and low in n-6 PUFA LA (i.e., low in both n-3 and n-6 PUFA) and with the n-9 monounsaturated oleic acid, or low in n-3 and high in n-6 LA.[47] Colitis was induced chemically in the pups on postpartum day 15; at this time the pups had received no food other than the mother's milk. The colon was then assessed for damage and inflammatory involvement. The PUFA content in the pups' milk, as well as in the jejunum and colon, differed significantly according to the mother's dietary PUFA intake.[47] The response to the chemical induction of colitis was also very different between the groups. Pups born to mothers fed the diet low in n-3 and high in n-6 PUFA LA showed an exaggerated inflammatory response associated with severe macroscopic and histologic damage. In contrast, the pups born to mothers fed the high n-3 PUFA diet showed protection from excessive colonic infiltration of neutrophils and inflammatory response.[47]

These results show that if the maternal diet is high in n-6 PUFAs, this results in increased transfer of n-6 PUFA across the placenta, increased swallowing of n-6 PUFA from amniotic fluid, and an increased level of n-6 PUFA in breast milk. This culminates in increased n-6 PUFA and decreased n-3 PUFA in developing infant tissue. In turn, when presented with an inflammatory insult, this leads to a heightened inflammatory response to a gastrointestinal challenge. Interestingly, transgenic mice capable of converting n-6 PUFA to n-3 PUFA exhibit increased EPA and DHA in colon phospholipids and reduced inflammation and tissue injury in response to chemically induced colitis; this shows it is possible to modulate the gastrointestinal inflammatory response altering intestinal n-6 and n-3 PUFA.[48] As such, it is entirely possible that the increased n-6 PUFA intake that has taken place over the past 50 years has resulted in a heightened gastrointestinal inflammatory response, so immune challenges that previously would have resolved naturally now become prolonged and develop into IBD.

CONCLUSION

Inflammatory bowel diseases are complex inflammatory conditions modulated by genetic and environmental factors. Since the 1950s the incidence of IBD has been increasing, notably in the pediatric population. Coincident with this, dietary fat intake has also changed, with increased consumption of n-6 PUFAs and a marked shift in the n-6 to n-3 PUFA balance. These changes in

Table 2. Comparison of major n-6 and n-3 polyunsaturated fatty acid content of human breast milk from different countries

	Country					
PUFA	USA[41] (N=81)	Canada[38] (N=103)	Germany[42] (N=15)	Japan[43] (N=20)	China[45]* (N=39)	Malaysia[44] (N=26)
n-6 PUFA						
18:2n-6	12.7	12.1	10.8	13.3	20.6	8.8
20:3n-6	NR	0.3	0.26	0.65	NR	0.27
20:4n-6	0.47	0.4	0.36	0.99	0.89	0.47
n-3 PUFA						
18:3n-3	0.95	1.4	0.81	1.1	3.0	0.30
20:5n-3	0.02	0.1	0.04	0.13	0.50	NR
22:6n-3	0.23	0.2	0.22	1.1	0.88	0.90

*Values are from urban Chinese subjects
Abbreviation: NR, not reported.

dietary PUFA intake promote a heightened gastrointestinal inflammatory response, and are present at all ages, starting at conception. Although further research is needed, plausible mechanisms exist to suggest that high intakes of n-6 PUFAs, such as LA, may be an important environmental modifier contributing to IBD.

ACKNOWLEDGMENT

Funding was received from the Canadian Institute for Health Research (CIHR) and the National Research and Engineering Council (NSERC)

REFERENCES

1. Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. Gastroenterology. 1998;115:182–205.
2. Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology. 2004;126:1504–1517.
3. Bjornsson S, Johannsson JH. Inflammatory bowel disease in Iceland, 1990–1994: a prospective, nationwide, epidemiological study. Eur J Gastroenterol Hepatol. 2000;12:31–38.
4. Loftus EV, Jr., Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. Aliment Pharmacol Ther. 2002;16:51–60.
5. Loftus EV, Jr., Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. Gut. 2000;46:336–343.
6. Armitage E, Drummond HE, Wilson DC, Ghosh S. Increasing incidence of both juvenile-onset Crohn's disease and ulcerative colitis in Scotland. Eur J Gastroenterol. Hepatol. 2001;13:1439–1447.
7. Hassan K, Cowan FJ, Jenkins HR. The incidence of childhood inflammatory bowel disease in Wales. Eur J Pediatr. 2000;159:261–263.
8. Cosgrove M, Al-Atia RF, Jenkins HR. The epidemiology of paediatric inflammatory bowel disease. Arch Dis Child. 1996;74:460–461.
9. Pinsk V, Lemberg D, Barker C, Schreiber R, Israel D, Jacobson K. The changing pattern of pediatric IBD at British Columbia Children's Hospital. J Pediatr Gastroenterol Nutr. 2005;41:545.
10. Pinsk V, Lemberg DA, Grewal K, Barker CC, Schreiber RA, Jacobson K. Inflammatory bowel disease in the South Asian pediatric population of British Columbia. Am J Gastroenterol. 2007;102:1077–1083.
11. Lindberg E, Lindquist B, Holmquist L, Hildebrand H. Inflammatory bowel disease in children and adolescents in Sweden, 1984–1995. J Pediatr Gastroenterol Nutr. 2000;30:259–264.
12. Carr I, Mayberry JF. The effects of migration on ulcerative colitis: a three-year prospective study among Europeans and first- and second-generation South Asians in Leicester (1991–1994). Am J Gastroenterol. 1999;94:2918–2922.
13. Innis S, Pinsk V, Jacobson K. Dietary lipids and intestinal inflammatory disease. J Pediatr. 2006;149:S89–S96.
14. Calder PC. Polyunsaturated fatty acids and inflammation. Biochem Soc Trans. 2005;33:423–427.
15. Gewirtz AT, Neish AS, Madara JL. Mechanisms of active intestinal inflammation and potential down-regulation via lipoxins. Adv Exp Med Biol. 2002;507:229–236.
16. Sartor RB. Pathogenesis and immune mechanisms of chronic inflammatory bowel diseases. Am J Gastroenterol. 1997;92(suppl):5–11.
17. Liou A, King DJ, Zibrik D, Innis SM. Decreasing linoleic acid with constant alpha linoleic acid in dietary fats increases (n-3) polyunsaturated fatty acids in plasma phospholipids in healthy men. J Nutr. 2007;137:1–8
18. Price PT, Nelson CM, Clarke SD. Omega-3 polyunsaturated fatty acid regulation of gene expression. Curr Opin Lipidol. 2000;11:3–7.
19. Marcheselli VL, Hong S, Lukiw WJ, et al. Novel doxosanoids inhibit brain ischemia-reperfusion-mediated leukocyte infiltration and pro-inflammatory gene expression. J Biol Chem. 2003;278:43807–43817.
20. Shoda R, Matsueda K, Yamato S, Umeda N. Epidemiologic analysis of Crohn disease in Japan: increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn disease in Japan. Am J Clin Nutr. 1996;63:741–745.
21. Cavadini C, Siega-Riz AM, Popkin BM. US adolescent food intake trends from 1965 to 1996. Arch Dis Child. 2000;83:18–24.
22. Popkin BM, Siega-Riz AM, Haines PS, Jahns L. Where's the fat? Trends in U.S. diets 1965–1996. Prev Med. 2001;32:245–254.
23. Raper NR, Cronin FJ, Exler J. Omega-3 fatty acid content of the US food supply. J Am Coll Nutr. 1992;11:304–308.
24. Stephen AM, Sieber GM. Trends in individual fat consumption in the UK 1900–1985. Br J Nutr. 1994;71:775–788.
25. Stephen AM, Wald NJ. Trends in individual consumption of dietary fat in the United States, 1920–1984. Am J Clin Nutr. 1990;52:457–469.
26. Innis SM, Elias SL. Intakes of essential n-6 and n-3 polyunsaturated fatty acids among pregnant Canadian women. Am J Clin Nutr. 2003;77:473–478.
27. Innis SM, Vaghri Z, King DJ. n-6 Docosapentaenoic acid is not a predictor of low docosahexaenoic acid status in Canadian preschool children. Am J Clin Nutr. 2004;80:768–773.
28. Innis SM. Essential fatty acid transfer and fetal development. Placenta. 2005;26(suppl A):70–75.
29. Elias SL, Innis SM. Infant plasma trans, n-6, and n-3 fatty acids and conjugated linoleic acids are related to maternal plasma fatty acids, length of gestation, and birth weight and length. Am J Clin Nutr. 2001;73:807–814.
30. Connor WE, Lowensohn R, Hatcher L. Increased docosahexaenoic acid levels in human newborn infants by administration of sardines and fish oil during pregnancy. Lipids. 1996;31(suppl):183–187.
31. Helland IB, Saugstad OD, Smith L, et al. Similar

effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. Pediatrics. 2001;108:E82.
32. van Houwelingen AC, Sorensen JD, Hornstra G, et al. Essential fatty acid status in neonates after fish-oil supplementation during late pregnancy. Br J Nutr. 1995;74:723–731.
33. Ross MG, Nijland MJ. Fetal swallowing: relation to amniotic fluid regulation. Clin Obstet Gynecol. 1997; 40:352–365.
34. Friesen R, Innis SM. Maternal dietary fat alters amniotic fluid and fetal intestinal membrane essential n-6 and n-3 fatty acids in the rat. Am J Physiol Gastrointest Liver Physiol. 2006;290:G505–510.
35. Stark KD, Beblo S, Murthy M, et al. Comparison of bloodstream fatty acid composition from African-American women at gestation, delivery, and postpartum. J Lipid Res. 2005;46:516–525.
36. Insull W, Jr, Ahrens EH, Jr. The fatty acids of human milk from mothers on diets taken ad libitum. Biochem J. 1959;72:27–33.
37. Tomarelli RM, Meyer BJ, Weaber JR, Bernhart FW. Effect of positional distribution on the absorption of the fatty acids of human milk and infant formulas. J Nutr. 1968;95:583–590.
38. Innis SM, King DJ. Trans fatty acids in human milk are inversely associated with concentrations of essential all-cis n-6 and n-3 fatty acids and determine trans, but not n-6 and n-3, fatty acids in plasma lipids of breast-fed infants. Am J Clin Nutr. 1999;70: 383–390.
39. Innis SM. Polyunsaturated fatty acids in human milk: an essential role in infant development. Adv Exp Med Biol. 2004;554:27–43.
40. Innis SM. Human milk and formula fatty acids. J Pediatr. 1992;120(Pt 2):56–61.
41. Mosley EE, Wright AL, McGuire MK, McGuire MA. trans fatty acids milk produced by women in the United States. Am J Clin Nutr. 2005;82:1292–1297.
42. Koletzko B, Mrotzek M, Bremer HJ. Fatty acid composition of mature human milk in Germany. Am J Clin Nutr. 1988;47:954–959.
43. Wang L, Shimizu Y, Kaneko S, et al. Comparison of the fatty acid composition of total lipids and phospholipids in breast milk from Japanese women. Pediatr Internat. 2000;42:14–20.
44. Kneebone GM, Kneebone R, Gibson RA. A fatty acid composition of breast milk from three racial groups from Penang, Malaysia. Am J Clin Nutr. 1985;41:765–769.
45. Ruan C, Liu X, Man H, et al. Milk composition in women from five different regions of China: the great diversity of milk fatty acids. J Nutr. 1955;125: 2993–2998.
46. Yuhas R, Pramuk K, Lien EL. Human milk fatty acid composition from nine countries varies most in DHA. Lipids. 2006;41:851–858.
47. Jacobson K, Mundra H, Innis SM. Intestinal responsiveness to experimental colitis in young rats is altered by maternal diet. Am J Physiol Gastrointest Liver Physiol. 2005;289:G13–20.
48. Hudert CA, Weylandt KH, Lu Y, et al. Transgenic mice rich in endogenous omega-3 fatty acids are protected from colitis. Proc Natl Acad Sci USA. 2006;103:11276–11281.