REVIEW ARTICLE

Long Chain Polyunsaturated Fatty Acids and Immunity in Infants

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An infant is usually born with a deficient immune system, and the long chain polyunsaturated fatty acids (LC-PUFA) in breast milk plays an important role in the development and maturation of infant's immune system. This article reviews the role of LC-PUFA in breast milk in the development of immunity and prevention of atopic manifestations in infants. The review also attempts to assess the correct proportion of these nutrients that needs to be present in infant formulae for babies in whom breast milk is unavailable and formula milk is unavoidable. It was concluded that LC-PUFA plays a vital role in overall development of immunity in the infant. Clinicians should ensure that LC-PUFA are supplied to the term and preterm infant in the form of breastmilk or provided in right proportions in formula, if breast milk is unavailable.

Keywords: *Immunity, Infants Nutrition, Polyunsaturated fatty acids.*

The immune system in human body is developed to protect the individual from pathogens. It has highly complex pathways for recognition of these "invaders" in order to eliminate them. Immunity of a person develops as he progresses from a neonate with an immature immune system to a mature immunocompetent adult and finally to a decline of host defenses with ageing. Breast milk offers many essential nutrients important for the development of the infant's immune system. There are four important components in infant diet that aid in development of immunity: nucleotides, glutamine, arginine and essential fatty acids. Omega-3 and omega-6 fatty acids are essential fatty acids *i.e.* those not synthesized by the body and need to be supplemented in diet. These form an important component of the human milk and have a significant role in the overall growth and development of the infant.

ESSENTIAL FATTY ACIDS, POLYUNSATURATED FATTY ACIDS AND LC-PUFA

Depending on their degree of saturation, fatty acids are classified as either saturated fatty acids, monounsaturated fatty acids, or polyunsaturated fatty acids (PUFA). PUFA are those that contain more than one double bond, and include omega-3, omega-6, omega-9, conjugate fatty acids and other polyunsaturates. The essential fatty acids (EFA) are all omega-3 (*n*-3) and omega-6 (*n*-6) methylene-interrupted fatty acids. Alpha Linolenic acid (ALA) is the principal Omega-3 fatty acid, which a healthy human can convert into eicosapentaenoic acid (EPA), and later into docosahexaenoic acid (DHA). Linoleic acid is the primary Omega-6 fatty acid. A healthy human with good nutrition will convert linoleic acid into gamma linolenic acid (GLA), which will later be synthesized, with EPA from the Omega-3 group, into eicosanoids. Arachidonic acid (AA) is an omega-6 PUFA and is a precursor in the production of eicosanoids. Linoleic acid is commonly found in plant oils (safflower, sunflower oil *etc.*) whereas alpha linolenic acid is found in flaxseed, soyabean *etc*. Long chain n-3 PUFA: EPA and DHA are either synthesized in human body from ALA or directly obtained in diet from marine fish oils. PUFA are found in high concentration (16.6%) in breast milk(1). The arachidonic acid content in breast milk is mostly constant, averaging about 0.45% of total fatty acid content. DHA level varies (0.1%–3.8%) with the diet

of the mother. Human milk also contains low amounts of some other PUFA, such as α-linolenic acid (18:3 *n*-6, GLA), dihomo-α-linolenic acid (20:3 *n*-6, DGLA) and docosapentaenoic acid (22:5 *n*-3 or 22:5 *n*-6 DPA)(2). Breast milk also contains lipases which aid in better fat absorption and utilization.

IMMUNITY IN NEWBORNS AND ROLE OF NUTRITION

A neonate is born with naïve and immature immune system, a state that is often termed as 'physiological immunodeficiency'. This encompasses all arms of the host immune system and is reflected in their increased susceptibility to infections, often with severe consequences. The infant has a gastrointestinal tract (GIT) lacking microflora, with undeveloped mucosal defenses. The innate immunity is mostly lacking in neonates and initially so is the humoral immunity, and the neonate is almost wholly dependent on the passively acquired maternal IgG and IgA antibodies. Maternal IgG is transported actively across the placenta to the fetus particularly in the last trimester, and IgA is passed on to the baby via breast milk(3). However, these passively acquired antibodies are incapable of mounting a cell mediated response rendering the neonate susceptible to various pathogens(4). Not just quantitative, there are also qualitative differences in the IgG and IgA produced by infants in response to pathogens(3).

T cells are important components of the cell mediated immunity with T-helper cells being important for the adaptive immunity. T cell function differs in neonates from adults in the respect that the former have fewer antigen-specific T-cell precursors than adults(5). It is also seen that neonates and children produce less of the T cell mediated interleukins like IL-2, IL-4, IL-6 and IL-10(6-8). There is a dominance of T helper cells and regulatory T cell effector responses in both mother and fetus during pregnancy. This helps in prevention of rejection of the immunologically different fetus by the maternal immune system(9). This T-helper dominance in neonates is usually down regulated soon after birth and inability to do so leads to development of allergic propensity.

During and soon after birth, the development of the neonatal immunity begins. The exposure to pathogens in the environment as well as the immunological factors provided in the breast milk make the foundations of development of an independent immune system in the infant. This immunity includes both systemic immunity like cell mediated and humoral, and gut associated immune systems from the gut associated lymphoid tissue (GALT) in the infant(10).

Nutrition in infants provides essential factors for development and growth in general, and also for development and maturation of the immune system. It helps develop the gastrointestinal microflora with subsequent benefits. On the other hand, introduction of nutrients in early life also provides the infant with food-derived antigens that his immune system must recognize so that these nutrients in turn may modify or modulate immune maturation and responses. These mechanisms have been cited as reasons why nutrition in infancy may affect strength and maturity of the immune system, tolerance to 'self' and benign environmental antigens, and development of immune mediated and autoimmune disorders(9).

Breast Milk and its Effect on Infant Immunity

Apart from various nutrients, the human milk also provides various protective agents to help boost the immunity of the feeding infant (***Box* I**)(10). Human neonates are able to synthesize small amounts of LC-PUFA (AA and DHA) from precursor fatty acids such as linolenic acid and alpha linolenic acid(11). However, the rate of synthesis may be insufficient to allow normal or optimal LC-PUFA accretion in body tissues. Thus it is important that the infant is provided these essential fatty acids in diet for optimum growth and development(2).

Box I IMMUNE-BOOSTING PROPERTIES OF BREASTMILK

1. For the acquired immune system
   - *a.* IgA and other immunoglobulins (Humoral)
   - *b.* Neutrophils and lymphocytes (Cell mediated)
2. For the innate immune system
   - *a.* Multifunctional milk components like fatty acids, lactoferrin and lactalbumin
   - *b.* Glycans
   - *c.* Immunomodulatory agents like cytokines, nucleic acids, soluble cytokine receptors, and antioxidants.

In comparison to human milk, cow's milk triglycerides contain a higher proportion of short chain fatty acids and a lower proportion of long chain and polyunsaturated fatty acids(12). In cases of adopted or abandoned infants or in cases where mother's milk is not available for the baby, cow's milk substitution does not provide the essential balance and quality of fatty acids. Thus the formula that is offered to babies in these cases should be fortified with the right quality and quantity of LA, ALA, AA, DHA and other LC-PUFA.

ROLE OF LC-PUFA IN THE INFANT

Long chain polyunsaturated fatty acids (LC-PUFA) are important for both structure and function in the neonate. Their structural role includes formation of the brain and the meninges since they form an important component of phospholipids(13). Phospholipids form an important component of cell membranes of the body and are also a part of the inflammatory precursor cells and mature cells. Thus, phospholipids form an important building block in the development of the infant's immune system. During neonatal life, there is a rapid accretion of AA and DHA in infant brain, DHA in retina, and of AA in the whole body. Essential fatty acids thus form an important part in the neurodevelopmental maturation and development of the visual functions(2). LC-PUFA also function as precursors of eicosanoids which play a role in the prostaglandin pathways. Prostaglandins, thromboxanes and leukotrienes play an important role in cellular functions, inflammation and regulation of cellular immunity(14).

Benefits to the immune system

There is compelling evidence that n-3 PUFA especially EPA and DHA have an impact on various functions of the immune system. LC-PUFA plays a role in host resistance to infection and other disorders of the immune system. Various mechanisms have been proposed to explain the role of these fatty acids as immunomodulators. LC-PUFA assists in lymphocyte proliferation and activation, macrophage function, natural killer cell function, and neutrophil function. These actions are mainly mediated by modulation of the eicosanoid pathways and lipid peroxidation pathways(15). The fatty acid composition of inflammatory and immune cells changes according to the dietary fatty acid composition(14).

The *n*-6 PUFA, especially arachidonic acid, play an important role in immunity as the precursors of prostaglandins and leukotrienes. However, an *n*-3 PUFA, EPA, is also a substrate for cycloxygenase and lipoxygenase and replaces other mediators of inflammation from the arachidonic acid pathways. This results in decreased monocyte and neutrophil chemotaxis and production of proinflammatory cytokines. Modulation of the prostaglandin synthesis pathways also affects the regional blood flow. An optimum ratio between plasma concentration of *n*-3 and *n*-6 PUFA thus needs to be maintained to ensure a normally functional immune system. Benefits have been noted in autoimmune disorders with supplementation of *n*-3 PUFA in diet. This is mainly due to their substitution in the arachidonic acid metabolism pathways that lead to inflammation(13). This shows that LC-PUFA has immunomodulatory as well as anti-inflammatory activity in humans.

Effects of maternal LC-PUFA administration during pregnancy and lactation on neonates

LC-PUFA is vital in development of the fetal nervous system and immune system during pregnancy. There is usually a decline in maternal plasma contents of n-3 PUFA especially in the early postpartum period. A DHA supplementation in diet may be helpful here. It has also been found that there is considerable placental transfer of LC-PUFA, enabling better growth in infants of pregnancies supplemented with LC-PUFA. Supplementation of pregnant mothers with LC-PUFA also improves birth size of the infant as well as reduces incidence of preterm birth(16). Such additions to diet during pregnancy and lactation have also proved to be beneficial in later cognitive development of the baby. Dietary supplementation of LC-PUFA, both to pregnant and lactating mothers and to neonates has shown evidence of improved immunity among infants(17).

Benefits to the low birth weight baby

About 80% of intrauterine DHA and AA accumulation occurs during the last 3 months of pregnancy, the period when the fetus develops

adipose tissue and extensive brain growth. Preterm birth interrupts this availability of DHA and AA for synthesis of structural lipids. Therefore, preterm infants are particularly disadvantaged with respect to access to AA and DHA needed for brain maturation and other developmental processes compared with term infants. During neonatal life, preterm infants also have a higher rate of growth; therefore, LC-PUFA needs are greater than in term infants(2). DHA deficiency in infants can lead to various complications like thrombocytopenia, dermatitis, lack of adequate growth, and most importantly makes the infant susceptible to various infections. DHA deficiency can manifest in preterm infants within 72 hours of birth(18).

Observational studies have shown that immune status among preterm and also in small for gestational age (SGA) full term neonates in India is poorer than full term babies making these special populations of infants more prone to infections(19). In low birth weight infant, breast milk is advocated after suitable supplementations since it provides essential nutritional benefits such as proteins, amino acids and fatty acids. Reduction in the rates of neonatal infection and necrotizing enterocolitis has also been noted with breastfeeding in such infants(20). However, when breast milk is unavailable, development of deficient immunity has been documented in preterm infants on artificial feeds(21). It has also been documented that such immune factor deficiency is correctable by LC-PUFA supplementation(21). There was a rise in levels of the immune markers among preterm neonates who were breastfed or who were fed with LC-PUFA supplemented formulas in comparison to those who were fed with formulas not having LC-PUFA. Another study in healthy infants (9-12 months) showed faster immune maturation when diet was supplemented with fish oils(22).

LC- PUFA Supplementation in Diet and Atopy

Infants of atopic mothers have a high risk of developing allergic phenotypes. Atopy in infants usually manifests as atopic dermatitis, allergic rhinitis or asthma. Cord blood estimation of $CD34^+$ cells is usually used as a marker to detect such propensity in neonates. Dietary LC-PUFA has been shown to reduce allergic tendencies besides significant immunomodulatory roles. In a double blind placebo controlled trial, it was found that mothers who were given LC-PUFA supplementation during pregnancy and lactation delivered babies with higher CD34+ cells and also when these infants were exposed to allergens, they did not show atopic tendencies. Levels and functions of various other immune mediators have also found to be altered favorably in such infants to decrease the risk of atopy(23).

Altered *n*-3 and *n*-6 ratio is noted in the mature milk of atopic mothers. They have an increased *n*-6 series of fatty acids and a lower level of *n*-3 PUFA that is sometimes linked to development of atopy among their breastfed babies. However, it is to be noted that colostrum of both atopic and non-atopic mothers is similar in fatty acid compositions. In mothers with mature breast milk having disturbed fatty acid ratios, it has been observed that infants are more prone to atopic sensitization later in life(24). This finding has been seen in both atopic and non-atopic mothers. Thus, there appears to be a link between low *n*-3 PUFA and disturbed fatty acid balance in breast milk and risk of atopy in infants. Dietary LC-PUFA might play an important role in protecting the infant from development of atopic diseases.

CONCERNS WITH LC-PUFA USAGE

LC-PUFA supplementation may cause the formula to become unstable because of ALA related lipid peroxidation and rancification. Appropriate balance of linoleic acid and ALA (linoleic to ALA 5-15 to 1) is recommended to improve stability of the formula as well as provide benefits to the infant. Addition of LC-PUFA in the right proportions to infant formula so that adequate availability to the infant is ensured also needs to be judged in terms of cost effectiveness. Most LC-PUFA containing formulas are more expensive in comparison to the usual formulas. However, increased demand and better techniques may take care of this problem in future.

RECOMMENDATIONS AND CONCLUSIONS

Supplementation with LC-PUFA in mothers beyond 22 weeks of gestation and during lactation is

beneficial in development of the immune system of the infant and reduction in risk of atopic sensitization. It is also beneficial for the cognitive and visual development of the infant. In infants supplemented with dietary fatty acids, similar benefits are noted. Preterm babies, especially, need these essential nutrients more than term babies. Breast milk is rich in the essential fatty acids, including LC-PUFA, needed for the optimum growth and development of the infant. However, when breast milk is not available due to maternal death or abandonment of infant, it is recommended that the formula offered to the baby is fortified with these fatty acids. LC-PUFA present in breast milk and formula that is supplemented with LC-PUFA prevents essential fatty acid deficiency and promotes protein accretion(25).

The IEG (International Expert Group) recommendations suggest that the addition of DHA should not exceed 0.5% of total fat intake, and AA concentration should be at least the same as DHA. The content of EPA in infant formula should not exceed the DHA content. As per these recommendations for ideal formula feed, the total fat content should be 4.4-6 g/100 kcal and linoleic acid 0.3-1.2 g/100 kcal, alpha linoleic acid 50 mg/100 kcal, and ratio of linoleic to alpha linoleic acid 5:1-15:1(26).

To conclude, it can be said that early nutrition in the infant plays an important role in the overall growth and development of the immune system, especially if it includes essential fatty acids. When a term or preterm infant is breast fed, she is provided with all the nutritional benefits as breast milk contains all the vital nutrients required for physical and mental development, and immunity of the child. All efforts, therefore, should be made to ensure breastfeeding in young infants, and mothers should be helped in the process by appropriate counseling. However, when breast milk is not available and formula is unavoidable, supplementation with LC-PUFA with right mix of fats, carbohydrates and proteins should be ensured.

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REFERENCES

1. Koletzko B, Mrotzek M, Eng B, Bremer HJ. Fatty acid composition of human milk in Germany. Am J Clin Nutr 1988; 47: 954-959.
2. Fleith M, Clandinin MT. Dietary PUFA for preterm and term infants: review of clinical studies. Crit Rev Food Sci Nutr 2005; 45: 205-229.
3. Janeway C Jr, Travers P, Walport M, Capra JD. Immunobiology: The Immune System in Health and Disease, 4th ed. London: Taylor & Francis Inc; 1999.
4. Wara DW, Barrett DJ. Cell-mediated immunity in the newborn: clinical aspects. Pediatrics 1979; 64: 822-828.
5. Hassan J, Reen DJ. Reduced primary antigen-specific T-cell precursor frequencies in neonates is associated with deficient interleukin-2 production. Immunology 1996; 87: 604-608.
6. Chheda S, Palkowetz KH, Garofalo R, Rassin DK, Goldman AS. Decreased interleukin-10 production by neonatal monocytes and T cells: Relationship to decreased production and expression of tumor necrosis factor-alpha and its receptors. Pediatr Res 1996; 40: 475-483.
7. Lewis DB, Prickett KS, Larsen A, Grabstein K, Weaver M, Wilson CB. Restricted production of interleukin 4 by activated human T cells. Proc Natl Acad Sci USA 2005; 85: 9743-9747.
8. Lilic D, Cant AJ, Abinun M, Calvert JE, Spickett GP. Cytokine production differs in children and adults. Pediatr Res 1997; 42: 237-240.
9. Calder PC, Krauss-Etschmann S, de Jong EC, Dupont C, Frick JS, Frokiaer H, *et al.* Early nutrition and immunity: progress and perspectives. Br J Nutr 2006; 96: 774-790.
10. Newburg DS. Innate immunity and human milk. J Nutr 2005; 135: 1308-1312.
11. Heird WC. The role of polyunsaturated fatty acids in term and preterm infants and breastfeeding mothers. Pediatr Clin North Am 2001; 48: 173-188.
12. Prentice A. Regional variations in the composition of human milk. *In:* Jensens RG, editor. Handbook of Milk Composition. New York: Academic Press; 1995. p. 115-221.
13. Calder PC. Polyunsaturated fatty acids, inflammation, and immunity. Lipids 2001; 36: 1007-1024.

14. Neonate and Infant Nutrition and Immunity. Available from: URL: http://www.arkinternational.co.uk/Infant%20nutrition.pdf. Accessed April 21, 2009.

15. Field CJ, Johnson IR, Schley PD. Nutrients and their role in host resistance to infection. J Leukoc Biol 2002; 71:16-32.

16. Koletzko B, Larqué E, Demmelmair H. Placental transfer of long-chain polyunsaturated fatty acids (LC-PUFA). J Perinat Med 2007; 35 (Suppl 1): S5-S11.

17. Helland IB, Saugstad OD, Smith L, Saarem K, Solvoll K, Ganes T, *et al*. Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. Pediatrics 2001; 108: 1-10.

18. Foote KD, Mckinnon MJ, Innis SM. Effect of early introduction of formula vs fat-free parenteral nutrition on essential fatty acid status of preterm infants. Am J Clin Nutr 1991; 54: 93-97.

19. Chatrath R, Saili A, Jain M, Dutta AK. Immune Status of full-term small-for-gestational age neonates in India. J Trop Pediatr 1997; 43: 345-348.

20. Schanler RJ. Suitability of human milk for the low birthweight infant. Clin Perinatol 1995; 22: 207-222.

21. Field CJ, Thomson CA, Aerde JEV, Parrott A, Euler A, Lien E, *et al.* Lower proportion of $CD45RO^+$ cell and deficient Interleukin-10 production by formula fed infants, compared with human-fed, is corrected with supplementation of long-chain polyunsaturated fatty acids. J Pediatr Gastroenterol Nutr 2000; 31: 291-299.

22. Damsgaard CT, Lauritzen L, Kjær TMR, Holm PMI, Fruekilde MB, Michaelsen KF, *et al.* Fish oil supplementation modulates immune function in healthy infants. J Nutr 2007; 137: 1031-1036.

23. Denburg JA, Hatfield HM, Cyr MM, Hayes L, Holt PG, Sehmi R, *et al.* Fish oil supplementation in pregnancy modifies neonatal progenitors at birth in infants at risk of atopy. Pediatr Res 2005; 57: 276-281.

24. Duchén K, Yu G, Björkstén B. Atopic sensitization during the first year of life in relation to long chain polyunsaturated fatty acid levels in human milk. Pediatr Res 1998: 44: 478-484.

25. Liet JM, Piloquet H, Marchini JS, Maugère P, Bobin C, Rozé JC, *et al.* Leucine metabolism in preterm infants receiving parenteral nutrition with medium-chain compared with long-chain triacylglycerol emulsions. Am J Clin Nutr 1999; 69: 539-543.

26. Koletzko B, Baker S, Cleghorn G, Neto UF, Gopalan S, Hernell O, *et al.* Global standard for the composition of infant formula: Recommendations of an ESPGHAN coordinated International Expert Group. J Pediatr Gastroenterol Nutr 2005; 41: 584-599.