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The Role of Nutritional Status in Immunity of Infants and Young Children

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Abstract: ***Widespread changes in dietary fat intake have occurred over the past 150 years in most industrialized nations, marked by a decrease in consumption of marine- and plant derived n-3 fatty acids and an increase in consumption of n-6 fatty acids. As intake of n-6 fatty acids has increased, the ratio of dietary n-6:n-3 fatty acids has shifted substantially. Inadequate levels of vitamins and minerals in the diet can have significant negative consequences for immune function. Key vitamins evaluated for their roles in immunity include the fat-soluble vitamins A and E and the water-soluble vitamins C, B6, B12, and folate. Of the many minerals with functions in immune cell response, iron, zinc, and selenium have been the primary focus of population-based supplementation studies. Although much insight has been gained in the past decade about how the immune system develops and how dietary factors affect that development, numerous questions remain.***

Keywords: Nutrition, Immunity, Infants, Children

1. Introduction

Breast milk intake is a key factor in the immune system development of newborns and infants, and breast milk contains numerous components that are thought to modulate immunological responses, such as cytokines, growth factors, lactoferrin, oligosaccharides, leukocytes, IgA, and polyunsaturated fatty acids. Clinical studies suggest that increased n-3 LCPUFA concentrations in breast milk are associated with increased breast milk levels of IgA and some cytokines. The effects of such alterations in breast milk content on immune development have not yet been determined. However, it has been speculated that maternally derived immune factors could have direct immunomodulatory effects and/or promote infant IgA production.(1)

Growing evidence suggests that long-chain polyunsaturated fatty acids (LCPUFA) have critical roles in the growth and development of infants and children and may have beneficial long-term effects on health throughout life.(2) Studies have shown that two LCPUFA in particular, docosahexaenoic acid (DHA; 22:6n-3) and arachidonic acid (ARA; 20:4n-6), have important roles in infant cognitive development, visual acuity, and growth. These two LCPUFA are naturally present in human milk and are permitted as supplemental ingredients in infant formulas available in many countries. The purpose of this monograph is to review published studies evaluating the roles of dietary LCPUFA in supporting immune system development and function.(3)

Widespread changes in dietary fat intake have occurred over the past 150 years in most industrialized nations, marked by a decrease in consumption of marine- and plant derived n-3 fatty acids and an increase in consumption of n-6 fatty acids. As intake of n-6 fatty acids has increased, the ratio of dietary n-6:n-3 fatty acids has shifted substantially.(4) Concomitant with changes in dietary LCPUFA intake have been significant increases in the prevalence of atopic disease in a number of populations. Some researchers have focused on dietary fatty acid intake as a potential factor in the increased prevalence of atopy.

Because atopic sensitization tends to occur in early life, clinical studies evaluating the relationship between LCPUFA intake and incidence of atopic disease in infants and children have focused in two areas:(5)

- The effects of maternal supplementation during pregnancy and lactation on breast milk LCPUFA content and neonatal blood LCPUFA levels, and correlations with atopic disease in infants, and
- The relationship between LCPUFA intake during infancy and childhood and subsequent development of atopy.

Some epidemiological studies and preliminary clinical studies have suggested that consumption of n-3 LCPUFA in pregnancy, lactation, and early childhood may have implications for immune development and the subsequent risk of asthma and atopic disease.

LCPUFA in Health: An Overview(6)

There is evidence from clinical studies that LCPUFA have key functions in maintaining health through their effects on the immune system and, in particular, through their modulation of the inflammatory response, which appear to be mediated through effects as precursors of inflammatory mediators, as well as through other complex cellular mechanisms. Epidemiological surveys support a protective role of oily fish, known to be naturally rich in n-3 LCPUFA, against atopic disease and reactive airways. A number of intervention studies using fish oil supplementation in early life are currently underway, as discussed later.

There is also accumulating evidence that supplementation of infant formula with preformed LCPUFA, particularly DHA, has positive effects on visual and mental development in preterm infants and term infants.

Sources of LCPUFA(7), (8)

LCPUFA can be supplied in the diet, from tissue stores, or by de novo synthesis from precursor fatty acids. Infants who are breastfed obtain LCPUFA postnatally from human milk.

LCPUFA concentrations in human milk vary widely. Pregnant women who consume diets containing little fish or meats may have inadequate LCPUFA intake to meet demands for infant LCPUFA accretion and replenishment of their own LCPUFA stores. Formula-fed infants who receive formula without preformed LCPUFA must rely on endogenous synthesis from essential fatty acid precursors to meet their LCPUFA needs. Many experts now agree that rates of DHA synthesis from alpha-linolenic acid typically provided in neonatal formula are variable from infant to infant and may not provide adequate tissue DHA availability required for optimal neural development. These unpredictable systemic DHA levels may further contribute to altered immune development at a critical time point during infancy and early childhood.

2. Effects of nutrition on immune function

Appropriate functioning of the immune system is dependent on nutritional status. Malnutrition, including protein-energy malnutrition and micronutrient deficiencies, is an important risk factor for illness and death, particularly among pregnant women, infants, and young children. Poor protein intake is associated with significantly impaired immunity.(9)

Inadequate levels of vitamins and minerals in the diet can have significant negative consequences for immune function. Key vitamins evaluated for their roles in immunity include the fat-soluble vitamins A and E and the water-soluble vitamins C, B6, B12, and folate. Of the many minerals with functions in immune cell response, iron, zinc, and selenium have been the primary focus of population-based supplementation studies.(10)

Overall nutritional status is closely linked to appropriate functioning of the immune system. In general, deficiency of several nutrients will lead to impaired immune responses, and replenishment of those specific components will typically restore the affected responses.(11) Consuming excessive amounts of some nutrients can also be detrimental to immune responses. Worldwide, malnutrition is closely linked to infectious diseases that are responsible for substantial morbidity and mortality among infants and children. Studies in both developing and developed countries have focused on the effects of dietary protein, dietary fat (including n-3 fatty acids), the fat-soluble vitamins A, D, and E, and minerals such as iron, selenium, and zinc. No single biomarker is available that accurately reflects the effect of nutritional interventions on the immune response; as a result, clinical outcomes are most important in determining nutrient effect.

3. Malnutrition

Scientists have observed the close relationship between infectious disease and malnutrition for more than 50 years. Malnutrition is an important risk factor for illness and death, particularly among pregnant women, infants, and young children.(12) Being malnourished increases susceptibility to infection and severity of infection through multiple interacting pathways, which can lead to further deterioration of an individual's nutritional status.(10) Proteinenergy malnutrition, including marasmus (starvation) and kwashiorkor (protein deficiency), is a major cause of immunodeficiency and is associated with significant morbidity and mortality from infectious diseases. A 2005 review of literature estimated that malnutrition is indirectly responsible for about half of all deaths in young children worldwide and that the risk of death is directly correlated with the degree of malnutrition. Deficiencies in iron, zinc, vitamin A, and iodine also impact immune function and susceptibility to infection among women and children in developing countries.(13)

Effects of LCPUFA on Immune Function(12)

Long-chain fatty acids, particularly DHA and ARA, are preferentially incorporated into cell membrane phospholipids. In cell membranes, LCPUFA contribute to membrane fluidity, have roles in signal transduction and gene expression, and provide substrate for production of chemical mediators. All three functions contribute to immune cell responses.

Early studies of LCPUFA effect on immune function(14)

Numerous studies in adults and children suggest relationships between intake of specific LCPUFA and alterations in markers of immune function. Results have shown that:

Persons with allergy may have altered levels and ratios of n-3 and n-6 fatty acids, including DHA and ARA, compared with non-allergic persons. Supplementing the diet with preformed LCPUFA alters the levels of those LCPUFA in plasma phospholipids and immune cells. Supplementing the diet with preformed LCPUFA results in discrete changes in immune cell and cytokine production; these changes differ with type of LCPUFA supplementation and are influenced by the ratio of n-6 to n-3 LCPUFA in the diet.

Protein intake

Inadequate protein intake leads to suboptimal tissue repair and reduced resistance to infection.(12) Poor protein intake is associated with significantly impaired immunity, as evidenced by altered immune responses and deficits in phagocyte function complement cascade, antibody concentrations, and cytokine production. The amino acids arginine and glutamine have been studied extensively for their roles in promoting immune response following surgery, trauma, and sepsis; studies suggest that in certain populations these amino acids may enhance wound healing, increase resistance to infection and tumorigenesis, and improve immune function.(15)

Nucleotides

The effect of preformed nucleotides on immune function has been evaluated in a limited number of studies, but clinical data are inconclusive. Infants fed a nucleotide-supplemented formula had higher serum concentrations of IgA throughout a 48-week study compared to infants fed a control formula. The supplemented infants had a lower risk of diarrhea between 8 and 28 weeks, but this difference was not statistically significant over the period of 48 weeks.(16),(17)

Vitamins and Minerals(18)

Inadequate levels of certain vitamins and minerals in the diet can have significant negative consequences for immune function. Much of what is known about the roles of vitamins and minerals in immune response has come from animal studies, where control of individual dietary components is easily accomplished. Population-based studies in countries where nutrient deficiencies are endemic have substantially increased our understanding of the effects of vitamins and minerals on the human immune response. Such studies have evaluated the impact of large-scale supplementation programs on morbidity and mortality in vulnerable populations—frequently infants and young children. While such studies do not directly show causation, they provide compelling evidence of nutrient effects on immune function.

Key vitamins evaluated for their roles in immunity include the fat-soluble vitamins A and E and the water-soluble vitamins C, B6, B12, and folate. Of the many minerals with functions in immune cell response, population-based studies have focused primarily on iron, zinc, and selenium, which are dietary deficiencies common among women, infants, and children in some developing countries. Iron deficiency is the most common nutrient deficiency in both developed and developing countries.

4. Conclusions

It has been suggested that fatty acids act as "gatekeepers" of immune cell regulation, with direct effects on the activities of cells and mediators involved in immune system response. Emerging data from clinical and animal studies suggest that dietary n-3 fatty acids provided in a(18)ppropriate ratios with n-6 LCPUFA and as part of a balanced diet in early life (beginning in utero) may influence immune system development, immune cell function, and incidence of atopic disease. These findings suggest that prenatal fatty acid supply is more important to infant immune development than previously understood. Because n-3 LCPUFA (eg, EPA and DHA) support anti-inflammatory and immune responses, dietary modification with these nutrients may have a potential role in influencing the development of allergic disease, including inflammation, in early life. Results of clinical studies in pregnant and lactating women, infants, and children suggest that interventions which increase intake of these fatty acids may have significant clinical effects on incidence and manifestations of atopy. Despite unanswered questions, clinical evidence to date suggests that relatively simple dietary interventions may influence the incidence and severity of allergic diseases among infants and children worldwide. The particular characteristics of the most effective interventions remain to be determined.

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