

Consumption of ω 3-fatty acids during perinatal life: role in immuno-modulation and allergy prevention

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Abstract

Epidemiological data suggest that dietary factors may have a role in recent increases of the prevalence of allergic diseases. One food-related component might be the reduced consumption of ω 3-polyunsaturated fatty acids observed especially in the Western societies; yet, clinical trials supplementing ω 3-fatty acids to adults with established allergies and bronchial asthma have generally been disappointing. However, it is known that the immature immune system is highly susceptible to immuno-modulatory environmental conditions particularly in the pre- and postnatal period. This review discusses the immuno-modulatory effects of ω 3-fatty acids supplementation in the perinatal life phase on the immune system of the child. Evidence exists that perinatal ω 3-fatty acid exposure affects T-cells and antigen presenting cells of the neonates likely due to altered eicosanoid metabolism. Although animal experiments strongly suggest a role of maternal ω 3-fatty acid intake on allergic immune responses in the offspring, the beneficial effect of ω 3-fatty acid supplementation has been studied in a small number of clinical trials. In these studies perinatal supplementation had some positive effects on distinct clinical phenotypes of the atopic syndrome. However, more studies are needed to fully explore the opportunity of perinatal immuno-modulation.

Keywords: Allergy; immuno-modulation; perinatal life phase; ω 3-fatty acids.

Introduction

Chronic inflammatory diseases, including allergies or autoimmune diseases are highly prevalent in Western and industrialized countries. Enormous increase, in incidence and prevalence of these disorders were observed

during the last 2–4 decades. Among these diseases, allergies represent an immunologic disorder strongly exemplifying the interaction between genetic and environmental conditions. Furthermore, especially the perinatal environment seems to play a decisive role for the initiation of allergic disorders. Epidemiological data indicate that several environmental changes could be associated with development of allergies [41]. However, no firm cause-and-effect relationship between environmental determinants and onset of chronic immunological disorders could be established. Therefore, there is increasing need to analyze in more detail the interplay between defined environmental changes and the development of allergic diseases with the aim to develop new and better preventive strategies.

One factor, among others, described to be associated with the increased prevalence of allergic disorders is the altered dietary behavior, especially that related to consumption of ω 3- and ω 6-polyunsaturated fatty acids (PUFAs). In many Western and industrialized societies the decreased consumption of ω 3-fatty acids paralleled an increased intake of ω 6-fatty acids. Therefore, the ratio of ω 6- to ω 3-fatty acids in Western diets is currently higher as compared to the past. It has been proposed that the high concentrations of ω 6-fatty acids in Western diets favor a TH2 differentiation of the immune system during critical early periods of ontogeny and development. The perinatal period represents an important window to initiate the development of allergic disorders. ω 3-fatty acids are described to act predominantly as anti-inflammatory components and have therefore generated great interest with regard to modulating inflammatory immune response such as allergy (Table 1).

It has been recently recognized that the very early life period is highly susceptible to immuno-modulation. Exposure to distinct environmental components during pregnancy and in the very early life period is considered to influence subsequent patterns of the neonatal immune systems, and this may contribute to the increase in allergic diseases. Therefore, a strong need exists to identify perinatal factors associated with this immuno-modulating capacity early in life. Accumulating evidence exists that maternal dietary PUFA consumption has effects on neonatal immune function and inflammatory reactions [5].

This review focuses on immuno-modulatory effects of ω 3-fatty acids on the developing neonatal immune system with special interest in allergic disorders, and its potential role in allergy protection. Secondly, it addresses

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Table 1 ω 3-fatty acids and allergic disorders.

Study/observation	Outcome	Author
Randomized, placebo controlled, prospective trial; Supplementation of pregnant women with fish oil (n=98)	Reduced sensitization to egg; less severe atopic dermatitis, but unchanged IgE levels at age of one year	Dunstan et al., 2003, Clin Exp Allergy Dunstan et al., 2003, J Allergy Clin Immunol
Randomized, placebo controlled, prospective trial; ω 3-supplementation of pregnant women and their children (n=616 women)	No effect on IgE levels and asthma, reduced prevalence to develop wheeze at age of 18 months; reduced risk to develop atopic cough at age of three years	Mihrshahi et al., 2004, Pediatr Allergy Immunol Peat et al., 2004, J Allergy Clin Immunol
Case control, retrospective study; ω 3-rich diet during pregnancy (n=85)	Development of autoimmune diseases (diabetes type 1) until age of 15 years	Stene et al., 2000, Diabetologia
Prospective cohort study; Supplementation of children with fish oil during the first year of life (n=2531)	Reduced risk to develop allergic rhinitis at age of four years	Nafstad et al., 2003, J Asthma

the question how ω 3-fatty acid effects are being transferred from the mother to the child, either during pregnancy or during lactation.

Effects of ω 3-fatty acids on immune functions

ω 3-fatty acids cannot be synthesized by man and are, therefore, essential components of the diet. They are found primarily in fatty fishes with high oil content. Two biologically very active fatty acids of the ω 3 family are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). These fatty acids seem to carry major immuno-modulatory functions. They might influence immune cell function for a variety of reasons: First, the fluidity of cell membranes is important in the function of all cell types, including immune cells. Membranes of most immune cells contain large amounts of the ω 6-fatty acid arachidonic acid (AA). High intake of ω 3-fatty acids decreases the proportion of AA in immune cell membranes and, consequently, the proportion of ω 3-fatty acids and, subsequently, cell responsiveness to exogenous stimuli.

Second, after mobilization of AA from cell membranes, this fatty acid acts as a substrate for the production of eicosanoids, namely the two-series of the prostaglandins (e.g., PGE_2) and the four-series of the leukotriens (e.g., LTB_4). These eicosanoids have different, partially opposing immuno-modulatory activities: PGE_2 is known to promote IgE production, whereas LTB_4 favors the expression of many pro-inflammatory cytokines including $\text{TNF-}\alpha$, IL-1, IL-6 and IL-2. Overall, these eicosanoids are predicted to be involved in maintenance of allergic inflammatory reactions, and to induce bronchoconstriction in asthmatic patients [42]. The ω 3-fatty acids EPA and DHA competitively inhibit the metabolism of AA, resulting in a reduced production of the “pro-allergic”

four-series of the leukotriens and the two-series of prostaglandins. Metabolism products of the ω 3-fatty acids are immunologically less active and are less potent in maintaining allergic reactions [27].

Third, ω 3-fatty acids are known to inhibit the activation of pro-inflammatory cell signals like the $\text{NF-}\kappa\text{B}$ signal transduction cascade [28, 29], the production of pro-inflammatory cytokines including IL-1 β , $\text{TNF-}\alpha$, IL-6 and IL-2 and the proliferation of lymphocytes as well as of NK cells [4].

The postulated anti-inflammatory role of ω 3-fatty acids on immune responses implies a relationship between the intake of fatty acids and the suppression of inflammatory diseases including allergy. Indeed, a reduced intake of ω 3-fatty acids, mainly DHA, has been observed during the period of increasing asthma prevalence [2]. Taken together, these observations resulted in the new concept of ω 3-fatty acids as “allergy preventing factors”. Whether ω 3-fatty acid exposure in the perinatal life phase modulates the neonatal immune response, and if so, by which mechanisms, is of major interest.

ω 3-fatty acids in cord blood and the development of immunological disorders

There are several studies associating cord blood fatty acid concentrations and the subsequent development of immunologic disorders such as allergic diseases. In this context, Yu et al. [49] observed that ω 3-fatty acid concentrations of maternal and fetal serum correlate only in children who did not develop allergic diseases within the first six years of life. They conclude that an abnormal metabolic relationship exists between mothers and children at risk of atopic disease. An impairment of cord blood ω 6-fatty acid composition was associated with the

development of allergic diseases [15]. In contrast, Yu et al. [49] detected increased levels of ω 6- and ω 3-fatty acids in cord blood and this was associated with the development of allergic diseases, whereas Beck et al. [1] found no differences in cord blood levels of ω 3-fatty acids between children who did or did not develop allergies. Thus, results concerning the associations between concentrations of ω 3-fatty acids in cord blood and allergies in later life seem to be controversial and require further investigation. Recently, Gold et al. [16] evaluated whether levels of ω 3- and ω 6-fatty acids in cord blood are related to neonatal immune response. They showed that higher ω 3-fatty acid levels in cord blood are associated with reduced lymphocyte proliferation and reduced IFN- γ production after antigen-specific (dust mite, cockroach) stimulation. Whether these observations have any clinical implications remains to be elucidated. However, several investigators found reduced neonatal IFN- γ levels to be associated with increased risks to develop allergic disorders later in life [36, 43].

Interventional studies

Because of the immuno-modulatory potential of ω 3-fatty acids and their metabolites, these fatty acids were often used for therapy aiming to ameliorate allergic diseases. Consequently, several clinical trials using ω 3-PUFA supplementation in adults or children with established bronchial asthma were performed [47]. The aim of these trials was to determine the effect of ω 3-fatty acid supplementation in asthma. A Cochrane review compared nine randomized controlled trials conducted between 1986 and 2001. In all of these studies the intervention period took at least four weeks. All study participants suffered from bronchial asthma. Seven of these studies were conducted in adults, whereas two were conducted in children. Eight studies compared fish oil with placebo and one compared high dose versus low dose of ω 3-fatty acid supplementation. In summary, there was no consistent effect on the analyzed outcomes such as lung function, asthma symptoms, asthma medication use, or bronchial hyperreactivity. Authors concluded that at least in adults, ω 3-fatty acid supplementation does not lead to an improvement of their asthmatic symptoms. Furthermore, there are no sufficient data to make a final judgment about supplementation on established asthma in young atopic children.

In the meantime, more studies have been conducted regarding the prevention of allergic disease by using ω 3-fatty acid supplementation in the perinatal life phase. In one randomized controlled trial in 98 atopic women who received either fish oil or placebo from 20 weeks' gestation until delivery [9], infants within the fish oil group had a reduced prevalence to develop sensitization against hen eggs at the age of one year. Furthermore,

these children developed less severe atopic dermatitis in comparison to children of the control group, although the prevalence of atopic dermatitis was not reduced. There was no difference in IgE-levels between study groups [10].

Mihrshahi and co-workers [32] have also used ω 3-fatty acids to prevent the development of allergic diseases. In this study, 616 pregnant women with a family history of atopic diseases were recruited and asked to prepare meals containing high levels of ω 3-fatty acids. After birth, children received a diet containing high levels of ω 3-fatty acids from the age of six months onwards, and were analyzed at 18 months and 3 years of age. The control families consumed food with a high content of ω 6-fatty acids and children received placebo supplements. The ω 3-intervention diet had no effect on neonatal serum IgE levels, atopy (assessed by skin prick testing) or bronchial asthma (diagnosed by the physician) at 18 months of age. However, the prevalence of wheezing was reduced significantly in the ω 3-supplemented study group. At the age of three years children had a clinical assessment for eczema, serum IgE levels and skin prick testing against ingested and inhaled allergens [35]. Children of the ω 3-supplementation group showed a reduced risk to develop atopic cough, whereas no changes were observed for IgE levels or skin prick testing. This suggests an immune modulating activity of ω 3-fatty acid supplementation in airway inflammation rather than allergic sensitization.

The study of Nafstad and colleagues [33], based on 2531 children, showed that fish oil supplementation during the first year of life was negatively associated with the risk to develop allergic rhinitis. A negative association with the development of allergic asthma was observed exclusively in children of non-atopic mothers.

A retrospective study underlined that supplementation with a diet rich in ω 3-fatty acids during pregnancy [38] and in the first year of life [39] seems to reduce the risk of TH1 mediated diseases like type-1 diabetes.

Although these studies are highly encouraging, an urgent need exists for more controlled studies examining the efficiency of fish oil supplementation in prevention of disease related to immunological disorders. This might lead to more safe and natural intervention strategies. Some published recommendations concerning the intake of ω 3-fatty acids during pregnancy and lactation are listed and summarized in Table 2.

Animal studies

Epidemiological studies provide the basis for the development of new hypotheses which then undergo testing in *in-vitro* and *in-vivo* systems. Until now only few animal studies were published analyzing the effect of maternal exposure to certain fatty acids on the developing neonatal immune system. One study was performed by

Table 2 Recommended dosage intake of ω 3-fatty acids.

References	Recommended daily dosage/type of ω 3 fatty acid	Population
Mele MC, Miggiano GAC, 2003	DHA: 100 mg/day (+50–60 mg/day in the third trimester)	Pregnant women
Dietary Reference Intakes, 2000	α -linolenic acid: 1.4 g/day pregnant women 1.3 g/day lactating women	Pregnant and lactating women
Makrides M, Gibson RA, 2000	ω 3 PUFA: 200–400 mg/day	Pregnant women
Simopoulos AP, 1999–2000	DHA: 300 mg/day	Pregnant and lactating women
European Food Safety Authority (EFSA)	DHA: 250 mg/day	Pregnant and lactating women
Scientific Advisory Committee on Nutrition (SACN)	EPA and DHA: 250 mg/day	Pregnant and lactating women

Korotkova and co-workers, examining whether maternal intake of dietary fatty acids influences the induction of oral tolerance to the food allergen ovalbumin (OVA) in neonatal rats [24, 25]. In addition, serum leptin levels in these neonates were assessed [23]. Leptin is known to be an immune-modulating hormone modifying T-cell responses in favor of a TH1 biased direction [30]. In this experiment rats were fed during late gestation and throughout lactation with the following diets: a PUFAs deficient diet, diet rich in ω 6-fatty acids, a diet rich in ω 3-fatty acids, or a specific combination of ω 6- to ω 3-fatty acids, respectively. Offspring of all groups were supplemented with OVA via breast milk and immunized either to OVA or to the heterologous antigen human serum albumin (HSA) at an age of three weeks. Breast milk analysis revealed a significantly different composition of fatty acids depending on maternal diet. Offspring of mothers treated with a diet deficient in PUFAs developed a suppressed antibody response against OVA, indicating an induction of tolerance against OVA. Maternal exposure to a diet rich in ω 3-fatty acid resulted in a suppressed immune response against OVA as well as against the unrelated antigen HSA, a mechanism known as bystander suppression. A maternal diet rich in ω 6-fatty acids led to OVA-specific tolerance induction in the offspring, but the immune response against the HSA-antigen was not inhibited. The underlying mechanism still remains to be elucidated, but antigen-specific T-cell unresponsiveness may be part of it. Maternal supplementation with a diet containing a specific ω 6/ ω 3-ratio did not lead to the development of oral tolerance in the offspring. These results suggest that the induction of the immunological mechanism of oral tolerance is dependent on the concentration of ω 6- and ω 3-fatty acids in the maternal diet.

Decreased serum leptin levels could be found in offspring of mice supplemented with ω 3-fatty acids. Leptin is believed to play an important role in the induction of inflammatory cell responses, suggesting a potential role in allergic reactions. Overall, the use of animal models

underlines the effects of ω 3-fatty acids on the developing neonatal immune system. However, further studies are needed in this field to fully appreciate the mechanisms of allergy prevention.

Potential immuno-regulatory mechanism of ω 3-fatty acids during pregnancy

In-vitro analysis, as well as animal and human *in-vivo* studies, indicate that ω 3-fatty acid supplementation somehow primes the development of the very young immune system, especially in the perinatal period. In order to develop effective prevention strategies it is important to uncover how these effects are transferred from mother to child.

Prior to birth, all of the ω 3-fatty acids accumulated by the fetus originate from the maternal circulation via placental transfer. After birth, transfer of the fatty acids occurs via breast milk. Several authors described that free fatty acids can pass the placenta selectively [13]. In addition, evidence now exists that cellular uptake of the free fatty acids occurs through a membrane translocation process involving a fatty acid binding protein. The preferentially transferred fatty acid in human is the ω 3-fatty acid DHA. Furthermore, fatty acids cross the placenta in the form of lipoproteins [18] via placental lipoprotein receptors. The levels of PUFAs in the fetus and in mothers are usually closely related [14]. Accordingly, ω 3-PUFA supplementation during pregnancy increases the neonatal composition of ω 3-PUFAs in cord blood detected in plasma and erythrocyte phospholipids [34]. Interestingly, Yu et al. [49] postulated that the correlation between the maternal fatty acid composition and those of the child was only found in non-allergic mothers, indicating a disturbed fatty acid metabolism in allergic mother. However, De Vriese and colleagues [7] observed that high fatty acid intake during the first and third tri-

mesters of pregnancy does not alter DHA concentration in cord plasma phospholipids.

Dunstan et al. [11] showed that fish oil supplementation during pregnancy enhances the DHA-composition of the phospholipid fractions of neonatal cell membranes, whereas levels of the ω 6-fatty acid AA were reduced. As described above, altered fatty acid composition of cell membranes might be causative for changes in immune responses. ω 3-fatty acid treatment during pregnancy is also described to effect cytokine expression patterns of neonatal cord blood cells. IL-13 levels in cord plasma were significantly reduced in prenatal fish oil supplemented children in comparison to those from placebo-supplemented mothers [10]. The predictive value of neonatal IL-13 levels concerning the risk to develop allergic diseases is controversial and, therefore, unclear [46]. However, lower IL-13 levels might shift immune responses in favor of a TH1 direction which is counterbalancing allergy-driven TH2 immune responses. Furthermore, Dunstan et al. [9] found a tendency of reduced expression levels of several neonatal cytokines as well as an inhibited lymphoproliferative immune response in children exposed to ω 3-fatty acids before birth.

Among other characteristic features, allergic diseases exhibit an accumulation of eosinophils paralleled by highly active differentiation process of these inflammatory cells. CD34 is a cell surface marker expressed by myeloid progenitor cells including eosinophilic progenitors. This marker is expressed differently in cord blood of neonates at risk to develop allergic diseases in comparison to healthy controls [44]. Denburg et al. [6] demonstrated that the percentage of CD34 positive cells in cord blood was higher in children from ω 3-fatty acid supplemented mothers. Furthermore, these cells showed an enhanced responsiveness to IL-5. Overall, this study shows that maternal dietary supplementation with ω 3-fatty acids significantly affects CD34⁺ progenitor populations in cord blood.

Other potential mechanisms explaining the immunologic activity of ω 3-supplementation during the perinatal phase are still being discussed. There is evidence that prostaglandin E₂ (PGE₂) synthesis in the neonate is suppressed by maternal ω 3-fatty acid supplementation [37]. PGE₂ is suggested to be involved in maintenance of allergic reactions, mainly bronchoconstriction and IgE synthesis [42]. It was also described that ω 3-fatty acids induce a state of tolerance at the materno-fetal interface by suppressing MHC class II expression [22].

Potential immuno-regulatory mechanisms of ω 3-fatty acids during lactation

ω 3-fatty acids affect the neonatal immune system not only via the placenta, but also via breast milk. Many com-

ponents present in breast milk have pro- or anti-inflammatory functions and, thus, the potential to affect the development of allergic diseases. ω 3-fatty acids participate in this regard. The PUFA composition of human milk is, at least partially, determined by the PUFA content of maternal diet [3, 31]. Concentrations of the ω 3-fatty acid DHA seem to be very tightly regulated by maternal intake [19]. Furthermore, breast milk concentrations of ω 3-fatty acids were related to infant plasma and erythrocyte phospholipid DHA concentrations [26]. There are opposing publications concerning the predictive value of ω 3- and ω 6-fatty acids in breast milk and the development of atopic diseases. Stoney et al. [40] reported that higher DHA contents of breast milk was associated with an increased risk to develop atopic disorders. In contrast, Duchon and co-workers [8] postulated that low ω 3-fatty acid concentrations in breast milk favor the development of atopic diseases.

The immuno-modulatory components of breast milk act at a first instance on the gastrointestinal tract of the neonate. Early events in the intestine are believed to play an important role in the development of immune tolerance mechanisms. Supplementation of pregnant mothers with ω 3-fatty acids enhances levels of IgA and soluble CD14 in breast milk [12]. There are studies showing that high levels of IgA in breast milk are associated with a reduced risk to develop cow's milk allergy in children [20]. IgA antibodies may bind antigens present in the neonatal intestine and, therefore, reduce antigen-presentation and development of pro-inflammatory reactions, contributing to tolerance inducing effects. Soluble CD14 (sCD14) is also known to affect immune responses in the infant's intestine. This factor has been shown to stimulate intestinal cells to release immuno-modulatory cytokines [45]. Accordingly, sCD14 in breast milk was identified as a protective factor for the development of allergies in the child [21].

In line with other studies, Hawkes et al. [17] reported that supplementation of lactating women with a ω 3-fatty acid diet rich in DHA increases DHA concentrations in maternal plasma as well as breast milk. Nevertheless, levels of the pro-inflammatory cytokines IL-6, IL-1 β and TNF- α as well as of the tolerance inducing cytokine TGF- β were not elevated in breast milk. This study suggests that immunologic effects of ω 3-fatty acid supplementation were probably not transmitted via cytokines of the breast milk from mother to child (potential immuno-regulatory mechanisms are summarized in Figure 1).

Conclusion

Animal as well as human studies indicate that supplementation with ω 3-polyunsaturated fatty acid in the very early life phase has the capacity to influence neonatal immune functions. Therefore, the concept to prevent or

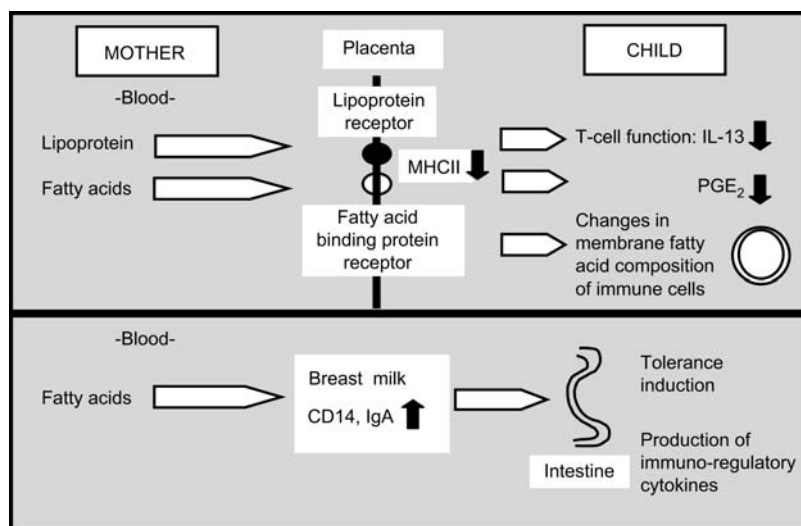


Figure 1 Summary of potential mechanisms of fatty acid action in the perinatal time phase.

at least to modify the development of allergic diseases by supplementing with ω 3-polyunsaturated fatty acids in a very early phase of life seems to be a promising approach. So far, only a limited number of studies deal with this allergy-preventing strategy. No clear observations indicate beneficial effects of a perinatal ω 3-fatty acid supplementation on the onset of bronchial asthma and IgE sensitization. Nevertheless, there is evidence that a perinatal ω 3-fatty acid supplementation has anti-allergic effects on disease-related symptoms like allergic rhinitis, wheeze or atopic cough. Therefore, ω 3-fatty acid supplementation during the very early life phase might be a promising strategy in the field of allergy prevention. There is a strong need for further research in this area to support this clinical approach.

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