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Invited review article

Role of omega-3 fatty acids and their metabolites in asthma and allergic diseases

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Abbreviations:
BALF, bronchial alveolar lavage fluid; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; HEPE, hydroxyeicosapentaenoic acid; IL, interleukin; LC, liquid chromatography; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; MS/MS, tandem mass spectrometry; PD1, protectin D1; PG, prostaglandin; Rv, resolvin; SPM, specialized pro-resolving mediator; SPT, skin prick test

ABSTRACT

Omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are found naturally in fish oil and are commonly thought to be anti-inflammatory nutrients, with protective effects in inflammatory diseases including asthma and allergies. The mechanisms of these effects remain mostly unknown but are of great interest for their potential therapeutic applications. Large numbers of epidemiological and observational studies investigating the effect of fish intake or omega-3 fatty acid supplementation during pregnancy, lactation, infancy, childhood, and adulthood on asthmatic and allergic outcomes have been conducted. They mostly indicate protective effects and suggest a causal relationship between decreased intake of fish oil in modernized diets and an increasing number of individuals with asthma or other allergic diseases. Specialized pro-resolving mediators (SPM: protectins, resolvins, and maresins) are generated from omega-3 fatty acids such as EPA and DHA via several enzymatic reactions. These mediators counter-regulate airway eosinophilic inflammation and promote the resolution of inflammation *in vivo*. Several reports have indicated that the biosynthesis of SPM is impaired, especially in severe asthma, which suggests that chronic inflammation in the lung might result from a resolution defect. This article focuses on the beneficial aspects of omega-3 fatty acids and offers recent insights into their bioactive metabolites including resolvins and protectins.

Introduction

Omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are polyunsaturated fatty acids found mainly in fish oil. Epidemiological studies have shown that these compounds play protective roles in cardiovascular diseases such as myocardial or cerebral infarction, hypertension, and hyperlipidemia.[1] Also, there is a growing evidence that omega-3 fatty acids have beneficial effects in chronic inflammatory diseases including chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis, and inflammatory bowel disease.[2,3] In addition, it is thought that atopic sensitization and allergic outcomes also can be prevented by fish intake during pregnancy, infancy, and childhood.[4,5] Contemporary changes in diet resulting in a lower omega-3:omega-6 fatty acid ratio might contribute to exacerbation and increased morbidity of asthma and allergic diseases.

Prostaglandins and leukotrienes are arachidonic acid-derived lipid mediators converted via cyclooxygenase and lipoxygenase, respectively. Prostaglandin D2 and cysteinyl leukotrienes, produced mainly by mast cells and eosinophils, function as potent bronchoconstrictors and pro-inflammatory molecules in allergic airway

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inflammation.[6,7] Recent biochemical studies showed that omega-3 fatty acids such as DHA and EPA function as precursors for bioactive molecules called resolvins, protectins, and maresins.[8,9] Currently, leukotriene and prostaglandin receptor antagonists are the newest drugs available for the treatment of asthma, but basic research findings now indicate that pro-resolving lipid mediators are potentially the next therapeutic targets for allergic diseases.

Asthma is a common respiratory disease affecting 300 million people worldwide.[10] Inhaled corticosteroids are an established treatment, but 5–10% of asthma patients are resistant to this therapy, leading to difficulties in managing the disease.[11] Leukotriene receptor antagonists are widely used as another first-line therapeutic agent in asthma, suggesting that abnormal lipid metabolism contributes to disease pathophysiology. Recently, several reports have indicated that biosynthesis of anti-inflammatory and pro-resolving lipid mediators, lipoxin A4 (LXA4) or protectin D1 (PD1), are dysregulated in severe asthma,[12–21] suggesting that an imbalance between pro- and anti-inflammatory molecules causes the exacerbation of inflammation observed in airways of asthmatic patients.

Epidemiological/clinical studies of omega-3 fatty acids in asthma and allergic diseases

A large epidemiological study in Greenland showed that intake of omega-3 fatty acids was inversely associated with asthma morbidity. Since then, many epidemiological and clinical studies focusing on omega-3 fatty acid intake or supplements have been conducted. For example, the concept underlying these studies is supported by the finding that the DHA content compared with arachidonic acid in nasal tissues from patients with asthma was lower than in healthy subjects,[22] which suggests a possible protective role of DHA in allergic diseases. Thus, it has been of great interest for some time whether long-chain omega-3 fatty acids or their natural sources, fish or fish oils, have beneficial effects on asthma or other allergic outcomes.

Many epidemiological studies of maternal fish intake during pregnancy have shown beneficial effects on allergic or atopic outcomes in infants or children of those pregnancies.[23–27] In addition, the majority of reports investigating fish intake during infancy or childhood have suggested a protective role in allergic outcomes.[28–36] These allergic or atopic outcomes included incidence of atopic diseases or symptoms (asthma, wheezing, eczema, and hay fever), food sensitization, and prevalence of positive skin prick test (SPT). One study of fish intake during lactation demonstrated that higher levels of EPA in breast milk correlated with a lower risk of atopic dermatitis.[37] On the other hand, observational studies in adults have been inconsistent in showing benefits in asthma of fish or fish oil intake.[38–45] However, several reports indicated that omega-3 fatty acid intake lower asthma incidence, prevalence of asthma-related symptoms, or exhaled nitric oxide (NO) levels and improve lung functions in adults.[38,40–43] An epidemiological survey of young adult Americans revealed that high intake of omega-3 fatty acids, especially DHA compared with EPA, prevented asthma onset.[43] These findings raise the possibility that omega-3 fatty acids are useful in the prevention of adult-onset asthma. Another study also demonstrated superiority of DHA compared to other fatty acids in terms of improved lung function.[42] A relationship between low omega-3 fatty acid intake and increased respiratory symptoms (chronic bronchitis, wheeze, and asthma) was shown in another study,[40] suggesting beneficial effects of omega-3 fatty acids in the lung.

Clinical trials using fish oil supplementation during pregnancy and lactation revealed that maternal intake of fish oil resulted in higher levels of omega-3 fatty acids in the offspring,[46–51] along with anti-inflammatory changes in immunological parameters (cytokine production, lipid mediator release, and cellular populations).[51–57] These studies also suggested that fish oil supplementation reduced the prevalence and severity of atopic dermatitis and food sensitization in the first year of life, and that these beneficial effects might persist until adolescence, with a reduced incidence of eczema, hay fever, and asthma.[53,58,59] Fish oil supplementation in infants and children increased the concentrations of those fatty acids in plasma[60–64] and blood cells[65] and had modulatory effects on the immune systems of infants[65] and children.[61,66] Clinical intervention with fish oil supplements in infants/children from 6 months old to 5 years old showed that there was a decreased prevalence of wheeze and lower bronchodilator use at 18 months of age,[63,67] and reduced allergic sensitization and prevalence of cough at 3 years of age, but without effects on asthma prevalence.[64] Two studies examined whether fish oil supplements have beneficial effects on asthmatic symptoms and lung function in patients with asthma in children,[61,68] but in only one study did intervention significantly reduce asthma severity and improve lung functions.[68] The data obtained from clinical trials of fish oil and omega-3 fatty acid supplements in adult asthma are inconsistent. However, several studies demonstrated protective effects of omega-3 fatty acid supplementation in adult asthmatic patients.[69–72] Mickleborough et al., showed that intake of omega-3 fatty acid supplements reduced bronchoconstriction after exercise accompanied by lower production of leukotrienes from polymorphonuclear cells in athletes[71] and adult patients with asthma.[70] Two other reports demonstrated the beneficial and suppressive effects of omega-3-rich supplementation on exhaled NO levels before and after allergen challenge, serum eosinophil counts, eosinophilic cationic protein levels, and *in vitro* cysteinyl leukotriene release,[72] or daytime wheeze, exhaled H_2O_2 levels, and morning PEF, respectively.[69] Various factors, e.g., types of oils, doses, duration, and quality or purity of fish oil or omega-3 fatty acid supplements were inconsistent among clinical studies. Characteristics of the subjects in these studies were also different (age, smoking history, country of origin, medication, etc.). There is clearly much room for improvement in study design and protocols to obtain more easily interpretable information.

Omega-3 fatty acids or their metabolites in murine asthma models

To investigate potential beneficial effects of omega-3 fatty acids in asthma, it is of interest to determine whether administration or elevated levels of omega-3 fatty acids can suppress eosinophilic inflammation *in vivo*. Several reports have indicated that omega-3 fatty acids function as protective molecules in murine models of asthma,[73–76] although those regulatory functions were not observed in other studies.[77,78] DHA inhalation during the allergen challenge phase in mice suppressed airway eosinophilic inflammation, and this was accompanied by reduced numbers of inflammatory cells in bronchoalveolar lavage fluid (BALF) and decreased airway hyperresponsiveness, and mucus production.[76] Morin et al., developed a new monoglyceride DHA derivative (CRBM-0244)[74] and EPA derivative (EPA-MAG)[75] and showed their preventive effects on airway eosinophilic inflammation, airway hyperresponsiveness and inflammatory cytokine production in OVA-induced asthmatic responses.

Fat-1 is a *C. elegans* enzyme that converts omega-6 fatty acids into omega-3 fatty acids. Fat-1 transgenic mice (Fat-1 mice) have been established and used as an experimental model to determine if higher ratios of omega-3 fatty acids to omega-6 fatty acids can contribute to anti-inflammatory responses in various conditions. In experiments using these mice, substantial amounts of omega-3