Omega-3 fatty acids: a potential future treatment for asthma?

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"A number of studies have shown that omega-3 fatty acids may have beneficial effects in a number of asthma phenotypes, by serving as effective inflammatory antagonists and/or pro-resolving agonists."

Asthma is a chronic disorder of the airways that is characterized by chronic airway inflammation, variable and recurring airflow obstruction, bronchial hyperresponsiveness and tissue remodelling. Approximately 300 million people suffer from asthma worldwide, and this global health issue has been estimated as attributing to over 250,000 deaths worldwide every year. Worryingly, asthma incidence has nearly doubled in the last three decades, which has resulted in higher rates of mortality, morbidity and healthcare costs. Bronchial asthma is one of the most common chronic lung diseases, which affects approximately 10% of school-age children; it is associated with exercise intolerance and a reduced quality of life, results in a loss of 10 million school days, and is a primary cause of hospitalizations in US children.

Currently available asthma treatments are not effective in preventing the airway remodeling processes and fail to prevent asthma exacerbations and hospitalizations even in well-controlled individuals. Regardless of the availability of a multitude of asthma medications, such as beta-agonists (short/long acting), leukotriene (LT) modifiers and corticosteroids, as many as 50% of asthma patients do not benefit from one, or a combination, of these drugs. Further it has been shown that bronchodilator tolerance occurs during normal dosing of beta-agonists, and the use of inhaled corticosteroids, especially at higher doses, has brought about concern relating to negative side effects. Therefore, the clinical responses to current asthma therapy are heterogeneous, and even with optimum treatment there appears to be considerable burden of unaddressed disease.

Since nearly a third of the estimated US$19.7 billion in 2007 for healthcare costs for asthma was attributed to prescription medications, there is a growing interest in non-pharmacological alternatives to treat this condition. Since asthma has been linked to societal changes in diet, a nutritional approach to managing this condition is appealing.

During the past four decades, there has been substantial interest in the beneficial effect of fish oil in treating a variety of inflammatory conditions, including asthma. Initially, Horrobin hypothesized that a low incidence of asthma in Inuit people was linked to consumption of large quantities of oily fish, rich in omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) [1], which led to reports that dietary supplementation with omega-3 fatty acids can reduce bronchial inflammation, arachidonic acid (AA) concentrations in neutrophils, LT generation and the late airway response to allergen exposure.

Omega-3 fatty acids are incorporated into cell membrane phospholipids and serve as precursors of inflammatory mediator synthesis. AA and EPA are converted through phospholipase A_2, cyclooxygenase and lipoxygenase to prostaglandins, thromboxanes, LTs, as well as various

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hydroxyl-fatty acids. The resulting metabolites are widely known as eicosanoids and have an important pro- and anti-inflammatory role. It is generally accepted that AA-derived eicosanoids are more physiologically potent and of a proinflammatory nature, whereas those derived from DHA and EPA show less proinflammatory activity. Moreover, it has been recently discovered that EPA and DHA are precursors of important pro-resolving autacoids, resolvins, protectins and maresins, which are powerful bioactive agents involved in the resolution of inflammation, and also have anti-inflammatory and immune regulatory activities, since they inhibit the production of inflammatory cytokines and decrease leukocyte recruitment and diapedesis [2]. Our laboratory has shown that a short-term (3 weeks) high dose of fish oil (3.2 g EPA and 2.2 g DHA) given daily reduces concentrations of proinflammatory mediators (LTC_4-LTE_4, prostaglandin [PG] D_2, IL-1β and TNF-α) in the sputum of asthmatics [3], and that EPA is more effective than DHA in suppressing proinflammatory mediator generation (LTB_4, PGD_2, TNF-α and IL-1β) from LPS-stimulated cultured human asthmatic alveolar macrophages [4]. In addition, similar high daily doses of fish oil have also been demonstrated to compare favorably with Montelukast (Singulair®), a LT receptor antagonist, in attenuating airway inflammation and hyperpnea-induced bronchoconstriction (HIB) in asthmatic patients [5].

Longer duration supplementation with lower doses of omega-3 fatty acids has also been shown to have pro-resolving effects upon airway inflammation. A small but significant improvement in forced expiratory volume in 1 s (FEV_1) was observed in asthmatic adults taking a low-dose of fish oil (1 g/day of EPA and DHA) for 12 months [6]. While an intake of 120 mg/day omega-3 fatty acids [7] taken over 10 months, as well as 6 weeks of dietary supplementation with 1 g of triglyceride oil containing 30% EPA/DHA taken daily by children with bronchial asthma resulted in a significant improvement in lung function [8].

> "It is quite possible that a gene–diet interaction exists within a subgroup of asthma patients; these particular asthmatic patients may have more than one polymorphism of specific genes in the 5-lipoxygenase pathway … Nutraceuticals such as marine oils may play an important role in the treatment of this condition by inhibiting 5-lipoxygenase, and the resulting proinflammatory mediators."

A high intake of omega-3 fatty acids (0.5:1 ratio of n-3/n-6) for 4 weeks [9] caused a positive change in the methacholine dose needed to evoke bronchoprovocation in more than 40% of adult asthmatics, in conjunction with increased urinary LTB_5 (derived from EPA) and a reduced LTB_4/LTB_5 ratio. Interestingly, a 3-week omega-3 fatty acid-enriched fat blend (0.7 g/day) given to allergic asthmatics attenuated exhaled breath nitric oxide levels (an indication of reduced airway inflammation), together with reduced serum eosinophils and *in vitro* cysteinyl-LT release before and after bronchial allergen challenge [10]. In children with asthma, 4 weeks of supplementation with fish oil (300 mg DHA + 700 mg EPA) suppressed NF-κB, and decreased IL-12 and IL-13 levels, and enhanced pulmonary function [11]. Further, approximately 184 mg of omega-3 fatty acids added to children's food once daily (from the age of 6 months) prevented the development of atopic cough, which is a symptom of allergic airway inflammation [12]. Seemingly better results are obtained when omega-3 fatty acid supplementation is given before symptoms of allergic disease manifest. Specifically, modification of the maternal diet to enhance the omega-3 fatty acid content of the fetal circulation appears to reduce the development of allergic respiratory diseases and other immune-mediated diseases in children [13]. Although we have briefly discussed selected examples of studies that have shown a positive effect of fish oil supplementation on asthma control, it should be emphasized that there are a number of studies that have not shown a positive effect [14].

> "Currently available asthma treatments are not effective in preventing the airway remodeling processes and fail to prevent asthma exacerbations and hospitalizations even in well-controlled individuals. Regardless of the availability of a multitude of asthma medications … as many as 50% of asthma patients do not benefit from one, or a combination, of these drugs."

Recently, our laboratory [15] examined the therapeutic potential of a different form of marine oil (PCSO-524®; Lyprinol™/Omega XL™), a patented extract of stabilized lipids from the New Zealand green lipped mussel, *Perna canaliculus*, in treating airway inflammation and HIB in asthmatic patients. PCSO-524™ given daily (400 mg n-3 PUFA; 72 mg EPA and 48 mg DHA) over 3 weeks significantly reduced airway inflammation and bronchoconstriction following a dry gas airway challenge, bronchodilator use and improved mean asthma symptom scores. Our study [15] supports a number of other studies that have shown PCSO-524™ is effective in treating human asthma [16] and allergic inflammation and lung function using a murine model of ovalbumin-induced allergic airway disease [17]. Since the levels of EPA and DHA in our study [15], and the Emelyanov *et al.* [16] study, using PCSO-524™ were very low, the physiological mechanism(s) behind the attenuation in airway inflammation and improvement in lung function are unclear. The potent anti-inflammatory action of PCSO-524™ may be due to the fact that this extract contains up to 91 fatty acid components, and contains furan acids, which have been shown to possess more potent anti-inflammatory activity than EPA [18].

Important to asthma research, a recent study [19] has shown that single-nucleotide polymorphisms (SNPs) within genes

involved in *de novo* lipogenesis may have an impact on the varied plasma TG response following an intake of fish oil, and that these SNPs may affect gene regulation by unknown mechanisms. This varied response to fish oil may possibly be ascribed to genotype determined differences between subjects, and it is quite possible that a gene–diet interaction exists within a subgroup of asthma patients [20]; these particular asthmatic patients may have more than one polymorphism of specific genes in the 5-lipoxygenase (ALOX5) pathway, resulting in an increased production of the AA-derived proinflammatory LTs [20]. Nutraceuticals such as marine oils may play an important role in the treatment of this condition by inhibiting ALOX5, and the resulting proinflammatory mediators.

While a low intake of omega-3 fatty acids does not appear to be a safety issue and pharmaceutical-grade supplements are essentially mercury free, a few side effects of omega-3 fatty acid supplementation can occur, such as a fishy aftertaste, flatulence, acid reflux, bloating, diarrhea, nausea and possibly an increased risk of bleeding and immunosuppression with a high intake of omega-3 fatty acids.

In summary, a number of studies have shown that omega-3 fatty acids may have beneficial effects in a number of asthma phenotypes, by serving as effective inflammatory antagonists and/or pro-resolving agonists. Further large-scale clinical studies in asthmatic patients are required, with the aim to determine the minimum effective dose and duration needed to observe the beneficial effect of omega-3 fatty acid supplementation in asthma, and to determine the prevalence of a number of genotypes in asthma patients which may potentially identify responders and non-responders to therapy, and the existence of a potential gene–diet (omega-3 fatty acids) interaction.

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