

Original Research Article

ASTHMA AND FATTY ACID IMBALANCE: IS THE OMEGA-3 SUPPLEMENT BENEFICIAL IN ASTHMA?

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ABSTRACT

Introduction. Asthma is a chronic airway inflammatory disease with the characteristic of eosinophilic infiltration, mucus hypersecretion, and airway hyper-responsiveness (AHR). Lipid mediators are one of mediators that were suggested to be involved in asthma pathophysiology. Then, the pro-inflammatory mediators initiate inflammation while pro-resolving mediators are produced at later stage in the resolution phase to bring back the cellular homeostasis. Pro-resolving mediators can be produced from omega-3 (n-3), one of the essential fatty acid needed from food. **Method.** This research is a literature review based on some sources like books and journals with the same topic. **Result & Analysis.** The relation between diet, especially fatty acid, and the risk of lung inflammatory process, such as asthma has long been suggested. The metabolites of fatty acids and the fatty acid itself become decisive factors in regulating the persistence and resolution of bronchopulmonary inflammation in asthma. The high concentration of n-3 in vitro decreases production of pro-inflammatory prostaglandins, cytokines, and ROS that play critical roles in inflammatory process. **Discussion.** Since asthma is known to be mainly caused by an inflammatory process, it has been hypothesized that high intake of n-3 fatty acid may be beneficial in prevention and management of asthma.

Keywords: Asthma, Fatty Acid Imbalance, Omega-3.

INTRODUCTION

Asthma is a chronic airway inflammatory disease with the characteristic of eosinophilic infiltration, mucus hypersecretion, and airway hyper-responsiveness (AHR) (Wendell, Baffi and Holguin, 2014; Mims, 2015; Monga *et al.*, 2020). The dominant diagnostic of asthma includes airway inflammation and airway remodeling (Kytikova *et al.*, 2019; Monga *et al.*, 2020). The studies on

asthmatic patients suggested that airway inflammation plays a central role in the pathophysiology of asthma (Luster and Tager, 2004). The inflammation causes reversible airway obstruction identified by intermittent wheezing and shortness of breath (Luster and Tager, 2004; Serhan, 2014) that related to bronchospasm in response to infection, allergen, or pollutant exposure (Serhan, 2014). The asthmatic inflammation causes airways to undergo remodeling that contributes to

impaired physiology (Yang *et al.*, 2021). There are some pathological changes found in asthmatic airway, including mucous cell metaplasia and regions of epithelial loss, subepithelial influx of myofibroblasts and collagen deposition resulting in basement membrane thickening, and angiogenesis (Vos *et al.*, 2012; Dharmage, Perret and Custovic, 2019).

Asthma is one of the most common non-communicable lung diseases in adult and children that caused by chronic lower respiratory tract inflammation. It causes problem of morbidity and even mortality in severe cases (Lochner, Berod and Sparwasser, 2015). Its incidence has been increased annually, an estimated of 262 million people had asthma in 2019 and 455,000 patients had died because of it (Kumar *et al.*, 2019). This disease is the most frequent chronic disease in children that causing mortality rate of 0 to 0.7 death in every 100,000 children (Voynow and Kummarapurugu, 2011; Szymańska *et al.*, 2012). It is known to be more frequent in people with atopy syndrome, like allergic rhinitis and atopic dermatitis (Bannenberg and Serhan, 2010).

Asthma can be triggered by several conditions, such as allergen, smoking, air pollution, infection of upper or lower respiratory tract, change in temperature, stress, and exercise (Lang *et al.*, 2019;

Rago *et al.*, 2019). The genetic and several environmental factors leads to body cellular inflammation that contributes to asthma. In allergic reaction, the well-known factors that triggers the asthma, the inflammation caused by type 2 of T helper cell lymphocyte that also associated with asthma. During the exacerbations of asthma, the inflammation is mainly driven by excessive cytokine profiles (IL-4, IL-5, IL-14), inflammatory cells (eosinophils, mast cells, basophils, type 2 T helper lymphocytes, IgE-producing plasma cells), adhesion molecules, inflammatory enzymes, and lipid mediators. This inflammatory process interacts with structural cells to trigger the airway hyperresponsiveness and remodeling (Yang, Xun and He, 2013).

Numerous mediators have been known to be involved in asthmatic airway inflammation, including cytokines, chemokine, growth factors, immunoglobulin, histamine, and lipid mediators (Monga *et al.*, 2020). Several studies on lipid mediators found that there are some specific points in inflammation process where these mediators are produced physiologically. Some lipid mediators initiate inflammation, and some others are produced in resolution phase to bring back the cellular homeostasis (Lang *et al.*, 2019). Meanwhile, when there are

problems in physiological process, specifically in the returning process to resolution phase from inflammatory phase of acute injury, there would be a negative physiologic consequence occurring. In asthma, the chronic airway inflammation causes consequences like bronchoconstriction and in later stage, airway remodeling (Serhan, Yacoubian and Yang, 2008; Adams *et al.*, 2018).

RESEARCH METHOD

This research is a literature review that conducted to evaluate the state of knowledge on a particular topic. It can be used to create research agendas, identify gaps in research, or simply discuss a particular matter. Literature reviews can also be useful if the aim is to engage in theory development (Snyder, 2019).

RESULTS

The results of the review from 31 journals are then compiled based on mapping the data to explain: 1) lipid mediators as pro-inflammatory and pro-resolving mediators in asthma, 2) fatty acid role in asthma pathophysiology, 3) omega-3 role in asthma.

DISCUSSION

1. Lipid mediators as pro-inflammatory and pro-resolving mediators in asthma

Through enzymatic or non-enzymatic process, the lipid transforms into lipid mediator that plays role in initial stage and resolution phase of acute inflammation, which divided into initiation and resolution phase. There are various lipid mediators that are involved in the regulation of inflammation. Pro-inflammatory mediators are involved in initiation phase and pro-resolving mediators are involved in resolution phase. Pro-resolving mediators could be biosynthesized from omega-3 (n-3) essential fatty acids (EFA). This phase was considered to be a passive process, but recent studies emerged that this phase might be an active, programmed response and not only a process of passive dilution of chemoattractants (Rago *et al.*, 2019).

Eicosanoids (Greek: “eicosa” means twenty that refers to the number of carbon atoms they contain) are biologically active lipids that are often generated rapidly at inflammation sites. The eicosanoids can be categorized into several groups, including prostanoid, LT and eoxin families. Prostanoid and leukotrienes (LT) are two classes of eicosanoid are involved in asthma pathogenesis. The prostanoid family consists of PG2, PGF2 α , PGD2, and 15d-PGJ2 that affect smooth muscle tone of the bronchi in asthma patient. People with asthma tend to have increased level of these eicosanoids in their airways

when compared to normal population (Mickleborough *et al.*, 2006).

Two classes of leukotrienes with different chemical characteristics are known as leukotriene B₄ (LTB₄) and its metabolites and cysteinyl leukotrienes (CysLTs), such as leukotriene C₄ (LTC₄), leukotriene D₄ (LTD₄), and leukotriene E₄ (LTE₄). LTB₄ recruits and activates inflammatory cells, such as neutrophils and promotes edema. On the other hand, CysLTs are known to increase the bronchial reactivity and mucus production. LT family is generated through 5-LO pathway that following the oxidation of AA which is released from phospholipid membranes by phospholipase A₂. The process of forming leukotriene A₄ (LTA₄) is induced by 5-LO and co-partnered by 5-LO-activating protein. LTA₄ is an unstable form that will be transformed into leukotriene B₄ or any of CysLTs subtypes by immune cells containing LTA₄ hydrolase and leukotriene C₄ (LTC₄) synthase that is confined to leukocytes. CysLTs that are known to have potent broncho-active and proinflammatory properties are mainly synthesized by activated effector cells, such as mast cells, eosinophils, basophils, and innate lymphoid cells (ILCs) to induce chemotaxis of inflammatory cells, bronchoconstriction, mucus hypersecretion, and vascular leakage with

edema of the airway (Mickleborough, Ionescu and Rundell, 2004).

2. Fatty acid role in asthma pathophysiology

The relation between diet, especially fatty acid and the risk of lung inflammatory process, such as asthma has long been suggested. The metabolites of fatty acids and the fatty acid itself become decisive factors in regulating the persistence and resolution of bronchopulmonary inflammation in asthma. The metabolites derived from omega-6 (n-6) or omega-3 (n-3) fatty acids is the most common lipid mediators regulating this inflammatory response. They include in arachidonic acid (AA; 20:4n-6), linoleic acid (LA; 18:2n-6), eicosatetraenoic acid (EPA; 20:5n-3), and docosahexaenoic acid (DHA; 22:6n-3). Omega-6 have been widely correlated with the proinflammatory activity while omega-3 is mainly correlated with anti-inflammatory one (Serhan, Yacoubian and Yang, 2008; Adams *et al.*, 2018). N-3 PUFA possesses the most potent immunomodulatory activities among all fatty acids from fish oil, EPA and DHA are known to be more biologically potent than ALA. The eicosanoids derived from n-3 fatty acid; EPA is known to have down-regulating effect to the production of PGE₂. In contrary, n-6, especially

linoleic acid that contributes in the biggest fraction of polyunsaturated fatty acids in typical diet is the precursor of AA which can be transformed into proinflammatory eicosanoids, leukotriene B₄ (LTB₄) and PGE₂. However, the latest studies found that when a fatty acid mediator is proinflammatory in a disease, it might be anti-inflammatory in other, one of those is AA-derived prostaglandin (PG) E₂ which plays a role in asthma pathophysiology through the arachidonate pathways (Yang, Xun and He, 2013; Lang *et al.*, 2019).

The exposure to allergen takes role in the release of AA from the cell membrane through phospholipase A₂ (PLA₂) secretion. The released AA then being oxidized into other lipid-based mediators, called eicosanoids (oxylipins) via enzymatic or non-enzymatic pathways. Cyclooxygenase/COX, lipoxygenase/LOX, and cytochrome P450 /CYP enzymes have roles in enzymatic pathway. COX helps in the synthesis of thromboxane (TX) and prostaglandins (PG) through the cyclooxygenase pathway, while LOX is responsible in lipoxygenase pathway to catalyze leukotriene (LT) biosynthesis, and CYP takes role in the peroxxygenase pathway to generate hydroxy eicosatetraenoic (HETE), epoxy eicosatrienoic (EETE), and hydroxy octadecanoic acids (HODE) that is known to have anti-inflammatory

effect and involved in resolution phase of inflammation. On the other hand, non-enzymatic pathway is mainly influenced by reactive oxygen species/ROS that is mainly generated by the interactions between environmental triggers, inflammatory cells, and structural cells in asthma (Lang *et al.*, 2019).

Under oxidative stress condition, AA reacts with ROS resulting in the abstraction of a bisallylic hydrogen atom and formation of lipid peroxide radical and endocyclization. An additional oxygen molecule than added to form an unstable bio cyclic endoperoxide intermediate. After reduction, the four potential of F_{2t}-isoP are formed, the 5-, 8-, 12-, or 15-series Regio isomers based on the location of the side chain hydroxyl residue. Among all different structure of isoprostanes, 15-F_{2t}-isoP have been mostly reported in detail (Adams *et al.*, 2018).

Several studies found that the exposure is following to environmental pollutants or during inflammatory disease exacerbations, the level of 15-F_{2t}-isoP is increased. It can be quantified in many different tissues and body fluids, like urine, bronchoalveolar lavage (BAL), exhaled breath condensate (EBC), and plasma. The elevated level of 15-F_{2t}-isoP has been detected in different inflammatory pulmonary diseases,

including ARDS, CF, pulmonary hypertension, chronic obstructive pulmonary disease, interstitial lung disease, and asthma (Rago *et al.*, 2019).

When it is compared with healthy controls, the level of 15-F_{2t}-isoP has been elevated consistently in exhaled breath condensate, plasma, and urine of patient with asthma. It has been reported that the use of inhaled corticosteroid (ICS) doesn't affect the elevation. The level of 15-F_{2t}-isoP is increased following the allergen exposure, eosinophilic inflammation, and exercise-induced bronchospasm. Its level may also vary on different asthma severity and increases during exacerbation and decreases when allergen exposure is avoided (Mickleborough, Ionescu and Rundell, 2004; Mickleborough *et al.*, 2006; Adams *et al.*, 2018). Therefore, the elevated level of 15-F_{2t}-isoP may reflect the inflammation due to infection, acute exposure to allergens or oxidants that trigger asthma such as pollutants or tobacco smoke (Adams *et al.*, 2018).

3. Omega-3 role in asthma

Omega-3 (n-3) has been a considerable as therapeutic potential interest for various inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, and asthma. N-3 such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are

categorized as the polyunsaturated fatty acids (PUFA) (Mickleborough, Ionescu and Rundell, 2004; Mickleborough *et al.*, 2006). N-3 fatty acids that mostly contained in fish oil have been known to have beneficial roles in health and organ function, it competes with AA as substrates for eicosanoids formation, such as LTs and PGs. The high concentration of n-3 in vitro decreases production of pro-inflammatory prostaglandins, cytokines, and ROS that plays the critical roles in inflammatory process. Besides that, n-3 has also appeared to have additional anti-inflammatory effects through direct action on neutrophil and monocyte production of inflammatory mediators and chemotactic responses (Serhan *et al.*, 2000; Hamid and Tulic, 2009).

Since asthma is known to be mainly caused by an inflammatory process, it has been hypothesized that high intake of n-3 fatty acid may be beneficial to prevent asthma. In recent years, several studies identified that EPA and DHA (major n-3 fatty acids) are precursors to the activation of novel enzymatic pathways during resolution phase. These newly identified pathways possess potent actions in controlling the resolution phase of inflammation (Villani *et al.*, 1998).

Accumulating reports have suggested that dietary modification has a

promising effect on reducing the prevalence and incidence of asthma (Diamant *et al.*, 2019). The typical regular diet consists of the imbalance of 20 folds more n-6 than n-3 fatty acids which lead to the excessive release of proinflammatory AA metabolites and contribute in the increasing cases of asthma. This fatty acid imbalance is caused by the excessive concentration of linoleic acid (LA) in the mostly consumed soy, corn, safflower, and sunflower oils cause the predominance of n-6 in typical diet. In contrast, food that are rich in α -linoleic acid (ALA), such as leafy green vegetables, flaxseed, and canola oil are less consumed. After ingested, LA and ALA (both are 18-carbon fatty acids) then being desaturated and elongated into 20-carbon PUFA. LA is converted into AA while ALA is converted into EPA. When compared to the intake of LA, AA and EPA are usually less consumed as they are mostly present in meat and fish respectively. LA and ALA cannot be synthesized in human body, therefore dietary LA and ALA is necessary to complete and they are classified as essential fatty acids (EFA) (Serhan *et al.*, 2000; Mickleborough, Ionescu and Rundell, 2004; Mickleborough *et al.*, 2006; Szymańska *et al.*, 2012).

It is believed that major lipid of fish oil, C20:5 acts on preventing the

conversion of AA to proinflammatory eicosanoids (PGs and LTs) and serving alternate substrate that produces 5-series LTs that are less potent (Brannan *et al.*, 2015; Diamant *et al.*, 2019). A cross sectional study of 642 subjects suggested that the consumption of n-3 fatty acids was significantly associated with the decreased risk of having bronchial hyperresponsiveness that was related with asthma symptoms (Kompauer *et al.*, 2008). Another study on the lung function and exercise testing found that the supplementation of fish oil on diet is improved pulmonary function with a concurrent reduction in bronchodilator use (Nagakura *et al.*, 2000). There is also a significant reduction of proinflammatory eicosanoid metabolite, including leukotriene C₄ (LTC₄)-leukotriene E₄ (LTE₄) prostaglandin D₂ (PGD₂), cytokine (interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , and leukotriene B₄ (LTB₄). A study by Nagakura (2000), found that dietary supplementation with EPA and DHA 17 – 26.8 and 7.3 – 11.5 mg/kg body weight respectively daily increased plasma EPA levels and decreased asthma symptoms significantly (Dry and Vincent, 1991). Another study by Dry suggested that low dose administered FA for 1 year brings positive effect when the patients were assessed in terms of FEV₁ (Kiecolt-Glaser *et al.*,

2011). Another study on the effect of n-6:n-3 ratio to inflammation process suggested that decreasing n-6:n-3 ratio is correlated with reductions in inflammatory cytokines (Arm *et al.*, 1988). Then, a study on patients with mild asthma suggested that supplementation of fish oil inhibits the production of eicosanoids, such as LTB₄ and LTB₅ but doesn't significantly change the severity of asthma.

CONCLUSION

There is accumulating evidence about the effect of diet and nutrition to the clinical manifestation of asthma. Since asthma is mainly caused by inflammation of the airway, the diet rich in precursor of anti-inflammatory mediator has been suggested to bring beneficial outcome. Several studies found that n-3, a fatty acid that is commonly contained in fish oil improve clinical manifestation in asthma by reducing the airway inflammation, and the supplementation of fish oil might be beneficial in asthma.

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