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## Review Article

# Dietary or Supplementary Intake Modulates Inflammatory Response in Asthma

### Summary

The importance of diet and supplement intake in the onset and development of asthma has been advocated recently, and it may be important in the prevention and management of bronchial asthma. Long-chain n-3 polyunsaturated fatty acids (LCn3PUFAs), vitamins (Vit), choline, and probiotics may be candidates to reduce medication use and provide some protection from risk. Experimental studies of diet in bronchial asthma have demonstrated modification of pulmonary function and the immune system through mechanisms involving antioxidant effect, T-helper (Th) 2 and Th17 inhibition, tolerogenic regulatory T cell (Treg) function promotion, nuclear transcription factors and epigenetic regulation. Although studies in animal models have provided evidence of supportive effects of diet in asthma, there have been few longitudinal studies of dietary or supplement intake and asthma, and the available epidemiological data remain controversial and inconclusive.

## Introduction

### Epidemiological study of asthma prevalence with diet

The diet has shifted towards one with less fruit and vegetables that is high in fat, salt and sugar and low in fiber and antioxidants. These changes are one possible explanation for the increase in bronchial asthma [1].

Frequent consumption of hamburgers showed a dose-dependent association with asthma symptoms [2]. Increased intake of saturated fatty acids (SFAs), myristic and palmitic acid, and butter were shown to be related to the risk of asthma in children [3]. Epidemiological studies have examined the association between the intake of fish or LCn3PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are abundant in fish, and the risk of asthma [4-7]. LCω3PUFA intake was significantly inversely associated with the incidence of asthma [8-10], but whether this benefit persists as other factors come into play remains to be determined.

A meta-analysis found a significant association between low dietary intake of Vit A and Vit C and asthma [11]. However, several studies indicated that supplementation of vitamins, such as Vit A [12] and Vit E [11] [13], was not associated with decreased risk of asthma. The potential benefits and risks of vitamin supplements might be considered in special situations, such as marked deficiency of dietary antioxidants, poor access to dietary antioxidants, or high exposure to environmental oxidants [14]. In pregnancy, consumption of antioxidant-rich food is a key modifier of clinical asthma status [15]. Maternal Vit E intake during pregnancy was inversely associated with wheeze in the first two years of life [16].

Low serum Vit D levels were observed in children with asthma [17-19]. Vit D deficiency in pregnant women resulted in a higher

prevalence of asthma and allergy in their offspring [20]. Cord serum 25-Hydroxyvitamin D level was inversely associated with the risk of transient early wheezing by the age of 5 years, but no association was found with asthma [21]. Recent published data demonstrated that Vit D3 did not reduce the rate of first treatment failure or exacerbation in adults with persistent asthma and Vit D insufficiency, suggesting that therapeutic Vit D3 supplementation in patients with symptomatic asthma was not useful [22].

Bacteria-host interactions may bring about beneficial changes in immune responses. Probiotics, defined as "live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host", may affect asthmatic condition in children [23]. However, there have been a limited number of clinical studies on the therapeutic potential of probiotics in asthmatics [24,25].

### Dietary effects on pulmonary function in asthma

A high-fat challenge increases airway inflammation and impairs bronchodilator recovery in asthma. The increase in circulating endotoxin concentration induced by a high-fat diet [26] may induce increased expression of toll-like receptor 4 (TLR4) in sputum cells, which results in airway inflammation [27]. Higher fat and lower fiber intake were associated with lower forced expiratory volume in one second (FEV1) and airway eosinophilia. Leptin levels were increased in asthmatics as compared with healthy controls [28].

Environmental oxidants and airway inflammatory cell-generated reactive oxygen influence asthma symptoms. Supplementation with antioxidants (Vit C and Vit E) ameliorated the decrease in lung function by ozone exposure in children with moderate to severe asthma [29].  $\alpha$ -tocopherol acts as a defense against oxidant-induced membrane injury in human tissue in that it disrupts the chain reaction of lipid peroxidation [30], suggesting anti-inflammatory properties. Maternal plasma  $\alpha$ -tocopherol level during pregnancy

was positively associated with post-bronchodilator FEV1 in the child at 5 years of age [31].  $\gamma$ -tocopherol has inflammatory properties [32]. High human plasma  $\gamma$ -tocopherol levels relate to intake of soybean oil, which is higher in  $\gamma$ -tocopherol than other oils such as sunflower, safflower and olive oil [33-35]. An increased serum concentration of  $\gamma$ -tocopherol is associated with lower FEV1 or forced vital capacity (FVC) [36], and high dietary intake of  $\gamma$ -tocopherol may be associated with the increase in asthma patients in the United States [37].

It has been reported that lower Vit D levels resulted in higher rates of asthma, associated with impaired lung function and increased airway hyperresponsiveness (AHR) [38,39]. However, the effect of vitamin D as sole therapy for airway hyper-reactivity and airway inflammation is still not clear [40].

### Effects on inflammatory cells and cytokines

Airway inflammation in asthma is heterogeneous and is characterized by activation of Th2 cells, Th17 cells, eosinophils and neutrophils. DHA reduced eosinophil infiltration into the lung and improved lung function in a methacholine challenge asthma model [41]. DHA affects several types of lung cells to reduce the airway inflammatory response to organic dust extract (ODE) challenge in bronchial epithelial cells via reduced interleukin (IL)-6 and IL-8 release [42] [43]. The *fat-1* transgenic mouse model has demonstrated that balancing the  $\omega$ -6/ $\omega$ -3 ratio can protect against chronic inflammatory diseases, and displayed increased endogenous LCn3PUFA. When allergen-sensitized and aerosol-challenged, these animals had decreased airway inflammation with decreased leukocyte accumulation in bronchoalveolar lavage fluid and lung parenchyma [44]. The n3PUFA-derived lipid mediators, protectin D1 and resolvin E1 (RvE1; 5S, 12R, 18R-trihydroxyeicosapentaenoic acid), may act as potent resolution agonists in airway inflammation. Intraperitoneal administration of RvE1 in mice was observed to decrease airway eosinophil and lymphocyte recruitment, a specific Th2 cytokine, IL-13, ovalbumin-specific IgE, and AHR to inhaled methacholine [45]. RvE1 promoted the resolution of inflammatory airway responses in part by directly suppressing the production of IL-23 and IL-6, which promote the survival and differentiation of IL-17-producing T helper cells in the lung [46].

Oxidative stress is involved in activation of various inflammatory cells, such as mast cells, lymphocytes, eosinophils, and neutrophils. Asthmatic subjects with AHR, uncontrolled asthma or a severe asthma pattern have impaired antioxidant defenses and are susceptible to the damaging effects of oxidative stress [47]. Fat-soluble vitamins have multiple modulatory effects on immune cells and exert their effects through their antioxidant and anti-inflammatory properties [48].

All-trans retinoic acid (ATRA), the most biologically active metabolite of Vit A, attenuated airway inflammation by inhibiting Th2 and Th17 differentiation and/or functions in a mouse model of allergic airway inflammation [49]. Vit A inhibits Th 17 cells [49] [50] and promotes differentiation of Treg cells [51,52]. The protective effect of fenretinide against ovalbumin-induced airway hyperresponsiveness and inflammation in the lungs was illustrated by complete block of infiltration of inflammatory cells to the airways and markedly diminished goblet cell proliferation, even though IgE

remained high [53]. High dietary Vit A can promote a Th2 bias, whereas Vit A deficiency (VAD) can produce a Th1 bias. High dietary Vit A enhanced and VAD diminished the development of experimental asthma in a mouse model, suggesting that excessive intake of Vit A may increase the risk or severity of asthma in industrialized countries [54].

The role of Vit D as an immunoregulatory agent has gained wide recognition in recent years. Vit D reduced human airway smooth muscle (ASM) expression of chemokines, including fractalkine and CX3C chemokine [55,56]. Vit D could affect epithelial growth and differentiation [57]. Vit D has effects on immune cells, including Th1 and Th2 responses, promotes Treg cells, inhibits the development of pathogenic effector Th17 cells, and regulates maturation of dendritic cells [58,59]. 1,25-dihydroxyvitamin D3 (1,25(OH)<sub>2</sub> D3) potentiates the efficacy of immunotherapy, and the regulatory cytokines IL-10 and TGF- $\beta$  play a crucial role in the effector phase of this mouse model [60]. Impaired induction of IL-10 by GC in T cells from GC-R asthmatics can be reversed by Vit D3 and IL-10 [61].

Respiratory effects of probiotics in animal models have included attenuating allergic airway responses and protecting against respiratory pathogens. Oral treatment with probiotics reduces allergic symptoms in ovalbumin-sensitized mice [62]. Perinatal *Lactobacillus rhamnosus* GG (LGG) supplementation has beneficial effects on the development of allergic asthma in offspring [63]. Oral treatment with LGG prior to sensitization attenuated airway inflammation and hyperreactivity in a mouse model of allergic airway inflammation [64]. Oral treatment with live *Lactobacillus reuteri* (L. reuteri) significantly attenuated influx of eosinophils into the airway lumen and parenchyma and reduced the levels of tumor necrosis factor, monocyte chemoattractant protein-1, IL-5, and IL-13 in bronchoalveolar lavage fluid of antigen-challenged animals [65]. Oral administration of L. gasseri attenuated allergen-induced airway inflammation and IL-17 pro-inflammatory immune response in a mouse model of allergic asthma [66]. LGG [67] [68], L. reuteri [69] and *Bifidobacterium longum* (B. longum) [70,71] have been reported to attenuate allergic airway response by induction of Treg cells. These protective effects may be associated with microbe-induced changes in dendritic cell phenotype and function [72]. Dietary fermentable fiber and short-chain fatty acids (SCFAs), which are metabolized by the gut microbiota, can shape the immunological environment in the lung and influence the severity of allergic inflammation [73].

### Effects on intracellular inflammatory pathways and nuclear factors

Excessive fat intake stimulates NF- $\kappa$ B and increases IL-6 and CRP, suggesting that a high-fat diet augments neutrophilic airway inflammation [27]. High dietary intake of saturated fat can activate the innate immune response, as saturated fatty acids can directly activate TLR4, which also leads to an NF- $\kappa$ B-driven inflammatory cascade [74]. LCn3PUFAs are known to decrease inflammation by inhibiting arachidonic acid (AA) metabolism to eicosanoids, decreasing the production of pro-inflammatory cytokines and reducing immune cell function. A recent study revealed that  $\omega$ -3 fatty acids are involved in altered pro- and anti-inflammatory transcription factor activation. EPA and DHA might suppress inflammatory signaling via NF- $\kappa$ B and

G-protein-coupled receptor 120 (GPR120), which initiates an anti-inflammatory signaling cascade that inhibits signaling leading to NF- $\kappa$ B activation [75].

Low antioxidant intake impairs the host's ability to scavenge reactive oxygen species (ROC), thereby promoting an NF- $\kappa$ B-mediated innate immune response, resulting in oxidative damage. Vit E has been shown to inhibit NF- $\kappa$ B pathways. Vit E blocks binding of transcription factors to two important IL-4 promoter binding sites for NF- $\kappa$ B and AP-1, and interferes with promoter activity upon T cell activation [76]. Vit E prevented the suppression of nuclear factor (erythroid-derived-2)-like 2 (NRF2), which has been found to be a critical regulator of antioxidant and defense genes with antioxidant response elements in their promoters [77].

Zinc is known to modulate the immune system via the NF- $\kappa$ B pathway [78]. Zinc supplementation alters NF- $\kappa$ B activity via the alteration of A20 activity [79].

### Effects of diet on epigenetic regulation in bronchial asthma

The influence of epigenetic variations on asthma pathophysiology has been discussed [80]. Epigenetic mechanisms, including DNA methylation [81,82], histone modifications, and noncoding RNAs, can affect gene transcription [83].

Recent evidence has shown that dynamic changes in DNA methylation can provide a possible mechanistic explanation for the link between exposure to allergens and airway hyperresponsiveness [84,85]. Changes in DNA methylation can affect asthma pathogenesis [86] by modulating the expression of disease-related genes [87]. Altered DNA methylation in the *STAT5A* gene, which might be intrinsic to asthma phenotypes, could have implications in allergic airway disease [81]. Methyl donors for DNA methylation are mostly derived from the diet, and a diet high in methyl donors, such as folic acid, Vit B12, and L-methionine, could contribute to asthma risk. Methyl donor exposure promoted the development of allergy in an animal model [88]. Excessive methylated Runt-related transcription factor 3 (*Runx3*), a gene known to negatively regulate allergic airway disease, has been advocated as one of the mechanisms [89].

Data on folic acid supplementation in humans and associated allergic disease have been mixed. While some studies found that prenatal folic acid supplementation was associated with more asthma, wheeze, and other respiratory problems in early childhood [90,91], others did not find an association [92-94]. Whether folate status affects disease severity or control in people who already suffer from asthma is also unclear [95]. Given its protective effects against neural tube and cardiac defects, there is no reason to alter current recommendations for folic acid supplementation during conception and pregnancy based on the findings on folate in asthma [96]. There is insufficient evidence to recommend the use of methyl donors for the prevention or treatment of asthma.

Choline can act as a methyl donor through its intermediate oxidation to betaine, which can subsequently convert homocysteine to methionine. A greater intake of choline and betaine from the diet was independently associated with a reduction in inflammation [97].

In a mouse model, choline might attenuate allergic inflammation in airway inflammation by reducing oxidative stress, possibly by modulating the redox status of the cell [98,99].

Differences in histone acetylation and methylation have been linked to either a difference in enzyme activity or chromatin binding in a disease state. 1,25(OH)<sub>2</sub> D3 upregulated histone H4 acetylation and participated in other chromatin remodeling events important to the expression of pro inflammatory genes [100]. *Acinetobacter lwoffii* F78 bacterium was able to prevent the development of an asthma phenotype via histone modification at the IFNG promoter [101]. Food allergens themselves have been found to be susceptible to epigenetic regulation. The promoter of the peanut allergen Ara h 3 underwent changes in histone acetylation, influencing its gene expression in early- and late-maturation embryos [102].

### Conclusion

In June 2015, the U.S. Food and Drug Administration (FDA) took steps to remove artificial trans fats in processed foods, which increase the risk of raised LDL-cholesterol level, which is involved in the development of heart disease. Considering that the shift in nutrition to higher intake of processed food and reduced intake of vegetables may associate with the prevalence and symptoms of asthma, similar intervention to that for SFAs or announcement that conventional foods that contain antioxidants, probiotics, choline, and  $\omega$ -3 fatty acids may reduce the risk of asthma could contribute to reduction of asthma prevalence and symptoms. To do so, further high quality research on asthma and diet is required.

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