Clinical reviews in allergy and immunology

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Effects of antioxidant supplements and nutrients on patients with asthma and allergies

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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Activity Objectives

1. To discuss the role of exogenous and endogenous antioxidants in asthmatic patients.
2. To discuss the nutrients and supplements involve in the antioxidant pathways.

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Asthma and allergic diseases have become a worldwide public health concern because of their increased prevalence. Despite decades of research on risk factors, the causes of these disorders are poorly understood. They are thought to develop through complex interactions between genetic and environmental factors. Because pulmonary and systemic oxidative stress increase inflammatory responses relevant to asthma and allergy, dietary or vitamin supplementation with antioxidants (a broad and varied category) has been proposed as an approach to reducing asthma incidence or morbidity. Meta-analyses of observational epidemiologic studies of variable methodological quality suggest associations of relatively low dietary intake of antioxidants and higher asthma and allergy prevalence. However, there have been few longitudinal studies of maternal or child dietary or vitamin/supplement antioxidant intake and asthma/allergy development. Moreover, there are no clinical trial data to support the use of dietary antioxidants or supplements to prevent asthma or allergy. A few small clinical trials suggest that specific antioxidants from diet or vitamin supplements might improve asthma control or lung function in asthmatic children or adults. Studies suggest that responses to antioxidants might be modified by life stage, genetic susceptibility, and environmental sources of oxidative stress. Large trials of antioxidant vitamin supplementation to prevent cancer suggest an increase in overall mortality with antioxidant vitamin supplementation, at least in populations with sufficient dietary antioxidant intake. This cautionary experience suggests that future trials to assess whether antioxidants reduce asthma incidence or improve asthma control should focus on supplementation of dietary sources of antioxidants. The potential benefits and risks of trials of vitamin supplements might be considered in special situations in which vulnerable populations have marked deficiency in dietary antioxidants, poor access to dietary antioxidants, and high exposure to environmental sources of oxidants. (J Allergy Clin Immunol 2014;133:1237-44.)

Key words: *Antioxidants, asthma, diet*

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Asthma, allergic rhinitis, atopic dermatitis, and food allergies are caused by excessive and inappropriate immune responses to environmental antigens, which lead to inflammation. Asthma and

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Abbreviations used
C-ACT: Childhood Asthma Control Test
CAT: Catalase
GST: Glutathione-S-transferase
GSTM1: Glutathione-S-transferase Mu1
GSTP1: Glutathione-S-transferase Pi1
GSTT1: Glutathione-S-transferase theta1
HMOX1: Heme oxygenase 1
Nrf2: Nuclear erythroid 2 p45-related factor 2
SOD: Superoxide dismutase

different allergic diseases often develop in the same person or in different persons within the same family.[1] The prevalence of asthma and allergic diseases has increased rapidly over recent decades in many countries, especially among young persons.[2,3] This increase most likely results from changes in lifestyle and environmental exposures.[3,4] Changes in exposure to antioxidants could play an important role. Some researchers have proposed that the increased prevalence of allergic diseases is a consequence of decreasing intake of antioxidants as people adopt Western diets characterized by a reduced amount of fresh fruits and vegetables. Others have suggested that it is linked to the increased antioxidant intake consumption of processed and antioxidant enriched foods.[5,6]

Epidemiologic studies have produced conflicting results. Low intake of antioxidants has been associated with the diagnosis of asthma and asthma-related disorders, such as wheezing, airway reactivity, and reduced ventilatory function.[2] However, some studies reported no association between antioxidants and allergy,[7,8] whereas others reported potential adverse effects.[9,10] We review the roles of antioxidant intake and supplementation on asthma and allergic diseases, discussing the mechanisms by which endogenous (produced by the body's enzymes) and exogenous (diet-derived) antioxidants might contribute to pathogenesis. We also review the epidemiologic evidence for associations between antioxidants and asthma and allergy from studies of diet alone, supplement intake, and genetic susceptibility, including interactions between genotype and diet. Epidemiologic studies were identified through a PubMed search from 2000 through 2013 on diet, antioxidants, asthma, and allergic disease. A complementary search was conducted on antioxidant genes and asthma. We report findings from recent systematic reviews and meta-analyses, as well as from most recent original research studies, covering different populations with various study designs.

MECHANISMS OF ACTION

Reactive species and antioxidants play an essential role in the immune system. An imbalance between pro-oxidant and antioxidant defenses is known as oxidative stress, which can cause dysfunction in cell signaling and arachidonic acid metabolism (Fig 1) and increase airway and systemic inflammation. Although oxidative stress might increase inflammation related to either T_H1 or T_H2 cytokine production, in some cases it might increase skewing toward a T_H2 phenotype,[11] which is associated with the development of allergic diseases.[10,12,13]

Oxidative stress

Oxidative stress occurs continually to kill some infecting microorganisms and prevent T cells from becoming overactivated.[14] Mitochondrial respiration, peroxisomes, and inflammatory cells are endogenous sources of reactive species. Enzymes associated with arachidonic acid metabolism, such as COX (which is responsible for the formation of prostaglandins and thromboxane) and cytochrome P450 (which catalyzes oxidation of organic substances), are another important source of reactive species.[15] Environmental exposures to ozone and xenobiotics provide sources of additional exogenous oxidants. Oxidative stress stimulates inflammatory responses that can lead to allergic disorders, such as asthma, allergic rhinitis, atopic dermatitis, and food allergies.[1] Asthmatic patients are exposed to additional endogenous oxidative stress[16]; their antioxidant system can be overwhelmed in comparison with that of healthy subjects.[17] Sources of increased oxidative stress in asthmatic patients include inhaled oxidants and reactive species generated by the inflammatory, immune, and structural cells of the airways. Despite the potential protective actions of antioxidants, Murr et al[10] have suggested that "too much" intake of antioxidants could increase susceptibility to allergic disease and asthma by downregulating the T_H1-type immune response, thereby increasing the T_H2-type cell response and immunoglobulin production.[10]

Antioxidants

Antioxidants are molecules that are stable enough to eliminate oxidants or prevent their conversion to more toxic compounds by neutralizing free radicals and thereby delaying or inhibiting cellular damage. They are the first line of defense against reactive species, acting at different levels in the oxidation process by scavenging initiating radicals, binding metal ions, or removing damaged molecules. At a low level of oxidative stress, healthy lung tissues have enough antioxidants to prevent accumulation of reactive species. Antioxidant enzymes, such as catalases (encoded by *CAT*), the glutathione-S-transferase (GST) enzymes (encoded by a supergene family located on at least 7 chromosomes), heme oxygenase 1 (encoded by *HMOX1*), and superoxide dismutase *(SOD)* are produced by cells in the human immune system. Vitamin C, vitamin E, flavonoids, and carotenoids are diet-derived antioxidants.

Antioxidant molecules are present to varying degrees in intracellular and extracellular spaces and are unevenly distributed in tissues. For example, concentrations of glutathione in the epithelial lining fluid of the respiratory tract exceed those of plasma levels by 100-fold,[16] whereas vitamins C and E are present in similar concentrations as those found in blood plasma.[5] Antioxidants can also interact with each other; for example, a group of SODs reduces O_2^- to H_2O_2, which is then converted to H_2O through oxidation of glutathione (Fig 2).[18] Fluid in the lining of the lungs contains a broad spectrum of antioxidants,[19] yet little is known about the mechanisms by which these enzymes or those from lung cells or tissues interact with exogenous and endogenous oxidants in this organ.[20]

Endogenous antioxidants. Most of the antioxidant capacity of cells comes from enzymes produced by the cells themselves.[21] In a hierarchic model a low level of oxidative stress leads to the activation of the transcription factor nuclear erythroid 2 p45-related factor 2 (Nrf2), which encodes more than 200 genes that control antioxidant, anti-inflammatory, cytoprotective, and detoxification activities. These include *SOD*, *CAT*, *HMOX1*, and GSTs, which encode the essential first-line enzymes with antioxidant activities in the lungs.[22] Briefly, *SOD* encodes a set of