Association of Antioxidant Vitamins with Asthma in Adults and its Therapeutic Efficacy - A Narrative Review

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ABSTRACT

Oxidant stress is well known in patients with bronchial asthma. The role of ROS and oxidant substances in the inflammatory and immunological cascades that are characteristic of asthma has much been studied. There are host of studies which point to the beneficial effects of vitamins A, C & E in the improvement of asthma outcome but the GINA 2022 guidelines have no mention of these. Probably this can be due to short term researches on the effect of antioxidant substances in asthma. Antioxidants vitamins A, C, and E and their beneficial effects in asthma management along with clinical trials have been discussed at length in this review. To know the effects of antioxidants on the inflammatory process in asthma long-term placebo-controlled studies of supplementation with vitamins A, C, and E are required.

The authors suggest that antioxidant agents like vitamins A, C, and E should be used as adjuncts to regular pharmacological treatment, in the future, viewing their efficacy in asthma management.

Keywords: Antioxidant vitamins; Adult asthma; Human Immunodeficiency Virus (HIV)

INTRODUCTION & BACKGROUND

Asthma is an allergic disease which manifest as airflow limitation, chronic inflammation and airway hyperreactivity. Reactive oxygen species have been proved to be involved in asthma. Oxidative stress in asthma is due to an imbalance between oxidant and antioxidant systems. This imbalance is caused by exogenous and endogenous reactive oxygen species emanating from inflammation cells or environment pollutants. Research evidences point to the efficacy of antioxidant treatments which include vitamins and food supplements in improving the symptoms and decreasing the severity of asthma. Different kinds of treatments showed...
antioxidative role, including diet, vitamins and food supplements; natural extracts; magnetic field and laser, etc. As of now, no antioxidants were applied as first-line therapy for asthma. To clarify the clinical value of antioxidant therapy more works are needed [1].

The prevalence of asthma varies widely among countries and also within countries with different geographies and socioeconomic strata [1,2]. The Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARCH) reported the national burden of asthma at 17.23 million with an overall prevalence of 2.05% [3]. The total burden of asthma in India as estimated by the recent Global Burden of Disease (GBD, 1990-2019) was 34.3 million, accounting for 13.09% of the global burden. The disability-adjusted life years (DALYs) in Indians was 27.9% due to asthma [4]. Compared to the global proportion of asthma burden India has three times higher mortality and more than two times higher DALYs [1].

Studies have shown that asthmatic adults on low-antioxidant diets had lower FEV1 scores, lower percentage predicted forced vital capacity, higher plasma C-reactive protein and more frequent exacerbation of asthma than those on a high-antioxidant diet [2]. Both symptoms and lung function improved notably on an exercise-induced asthma [3]. Vitamin A, vitamin E, and Se were found significantly lower in asthma cases than in controls. Vitamin E as estimated by FeNO level was found to be significantly decreased in a study involving dietary supplements. Also MDA level was negatively affected [4,5]. Vitamin E isoform γ-Tocotrienol inhibited oxidative damage by enhancing endogenous antioxidant production in the lung and also increasing the level of Nrf2 by blocking NF-κB. γ-Tocotrienol also up regulated acetylcholine- or methacholine-induced AHR, while down regulating lipopolysaccharides (LPS)-induced neutrophil infiltration [6-8]. In contrast, food supplements did not enhance glutathione or oxidized glutathione and had no clear role on the incidence of asthma [9,10].

The GINA 2022 guidelines do not mention the usage of antioxidant vitamins in the management of adult asthma. This is the rationale of our review. Oxidant stress is evident in patients with bronchial asthma. However, little is known about the role of ROS and oxidant substances in the inflammatory and immunological cascades that are characteristic of asthma. The pertinent question still unanswered is which antioxidant vitamins should be considered in management of adult asthma. Can it be used as a front line or supplementary line in the management of adult asthma, then what should be its dosage and other therapeutic options. This is the rationale of our review.

METHODS

In this narrative review, we have discussed the researches in English language till-date and further studies that are required have been suggested. To review a correlation between the antioxidant vitamins and adult asthma few studies were selected. On Google Scholar search, 65 out of 10,400 articles were relevant. On PubMed search 112 articles were found for the keywords Antioxidant vitamins, Adult Asthma, Role of vitamin C in adult asthma, Vitamin A and its association with adult asthma, Role of vitamin E in adult asthma in the abstract and title, out of which only 21 were selected for the review.
A total of 86 studies were selected out of which 5 were discarded as they reported the association on severe asthma in adults. The selected studies were analyzed to find out an association between the role of antioxidant vitamins and adult asthma.

The MESH terms used were antioxidant vitamins, etiopathogenesis, and asthma. In its inclusion criteria this review included studies on the epidemiology, environment, lifestyle, pathogenesis, clinical trials, recommended dosages of antioxidant vitamins in the management of adult asthma.

The exclusion criteria of this review were the studies not providing information regarding the correlation of epidemiology, environment, lifestyle and pathogenesis related to adult asthma. The studies which discussed the role of antioxidant vitamins in pediatric and old age group were excluded. Similarly, studies on the association between antioxidant vitamins and severe asthma were also excluded.

REVIEW AND DISCUSSION
Antioxidant Supplementation in Asthma- Vitamins
Vitamins C, E and A are all antioxidants, but the relationship between vitamin C (ascorbic acid) and asthma has received most attention.

A short-term study of supplementation with vitamin C showed decreased bronchial reactivity to methacholine in asthmatic subjects[11], but another study of 7 days of supplementation with vitamin C[12]. In street workers of Mexico City who were exposed to high ozone concentrations a combination of vitamins C, E and A therapy was given. Lung function showed significant protective effect[13,14]. Similarly, in a study on Dutch cyclists and in adults with asthma, vitamin C and E supplements provided partial protection against the acute effects of ozone on lung function[15,16]. In contrast, a randomized placebo-controlled trial of supplementation with 1 g/day of vitamin C in 95 subjects with chronic stable asthma for 16 weeks showed no additional improvement as compared to standard asthma therapy[17]. Another systematic review of the literature reported insufficient evidence at present but that further randomised, placebo-controlled trials are warranted to study the role for vitamin C supplementation in the management of asthma[18].

A randomised, placebo-controlled trial of 0.5 g/day of vitamin E for 6 weeks in patients with stable asthma showed no significant effect on bronchial responsiveness to methacholine or on secondary outcome measures including change in FEV1, symptom score and bronchodilator use[19]. These patients were asymptomatic; in order to obtain a better indication of the potential benefit of vitamin C or E supplementation asymptomatic patients were selected for this study. However the authors concluded that dietary supplementation with vitamin E has no effect on asthma control and suggested that combinations of antioxidants, as found in whole foods such as fruits, might be more beneficial. They also concluded that further trials are required in symptomatic and more
severe asthmatic patients in combination to other outcomes assessments like exacerbations and markers of airway inflammation\textsuperscript{[20,21]}. 

Many epidemiological studies and population surveys from the UK\textsuperscript{[22,23]}, US\textsuperscript{[24,25]}, the Netherlands\textsuperscript{[26]} and China\textsuperscript{[27]} have reported that a low dietary intake of vitamin C is coupled to reduced lung function. Insufficient dietary intakes of vitamin C has also been linked specifically with increased wheezing symptoms\textsuperscript{[28]} and bronchial sensitivity in adults\textsuperscript{[29]}. Plasma concentrations of vitamin C were found to be lower in asthmatic patients, particularly those with severe asthma\textsuperscript{[30,31]}. In mild asthmatic patients lung lining fluid and induced sputum concentrations of vitamin C were also found to be low\textsuperscript{[32,33]}. 

Some studies on low vitamin E intake has reported skin sensitization to allergens and total serum IgE\textsuperscript{[34]}, with the onset of wheeze, and with asthma exacerbations\textsuperscript{[27,31, 35,36]}. On the other hand some studies have shown no independent effect of vitamin E (α-tocopherol) on lung function in the general population\textsuperscript{[22,35]}, or on bronchial reactivity\textsuperscript{[27]}. 

Cross-sectional studies have pointed to the improved lung function and reduced respiratory symptoms in asthmatics with increased dietary consumption of carotene, the precursor of vitamin A (retinol)\textsuperscript{[25,37]}. There are also some studies that have reported low intakes of vitamin A in asthmatic Patients\textsuperscript{[31,35]}, but it has not been proved that the serum retinol levels vary in asthmatic and non-asthmatic subjects. 

**Vitamin A**

The 3 active forms of vitamin A are retinol, retinal, and retinoic acid, together called as retinoids. Vitamin A is a fat-soluble vitamin. There are also provitamin A compounds, defined as carotenoids. β-carotene is the major carotenoid, which prevents DNA damage secondary to lipid peroxidation\textsuperscript{[38]}. Researchers have shown beneficial effects of vitamin A and carotenoids in human diseases such as diarrhea, acute respiratory infections, ischemic heart disease, immunological disorders, and asthma\textsuperscript{[39-41]}. In asthmatic patients airway inflammation is associated with increased production of ROS (superoxide anion, hydrogen peroxide, and hydroxyl radicals) by alveolar macrophages, peripheral blood eosinophils, and neutrophils\textsuperscript{[42]}. β-Carotene exerts its antioxidant effect by quenching singlet oxygen and reduces airway inflammation in asthma\textsuperscript{[43]}. Few studies have shown that hypovitaminosis A can predispose to respiratory infections\textsuperscript{[44,45]} and cause respiratory epithelial changes, such as metaplasia\textsuperscript{[46]}. These findings suggest that vitamin A supplementation may be used as a supplement in the management of asthma.

**Vitamin C**

Vitamin C is present in 2 biologically active forms: ascorbic acid and its oxidized derivative, dehydroascorbic acid and is an water-soluble vitamin. Vitamin C acts as a hydrogen donor to reverse oxidation that reacts with free radicals (FRs) to deactivate them before they cause damage to proteins or lipids. This is how
vitamin C functions as an antioxidant\textsuperscript{[41]}. Oxygen metabolites have direct and indirect roles in affecting airway inflammation. Many studies show correlation between asthmatic severity and ROS products (FR scavengers in blood are significantly lower) in asthmatic subjects\textsuperscript{[47,48]}.

Epidemiological studies have shown that increased dietary intake of vitamin C is associated with a reduced risk of asthma\textsuperscript{[49-51]} and vitamin C levels are diminished in mild asthma\textsuperscript{[52]}. Similar findings were seen in a double-blind crossover study of adults with asthma, which examined the effects of dietary antioxidant vitamins (C and E) on ozone-induced bronchial hyper-responsiveness (BHR), concluding that such supplementation benefited asthmatic adults exposed to air pollutants\textsuperscript{[53]}. The Nutritional and Health Survey in Taiwan (NAHSIT) study in its report stated that a marginally significant association between vitamin C intake in the lowest quartile and an elevated risk for asthma existed. The study was on the relationships of nutrient intake, clinically-diagnosed asthma and allergic rhinitis in 1,166 adolescents (13-17 yr) (54). Another study by Kongerud et al\textsuperscript{[55]} found low levels of ascorbic acid in induced sputum which was collected from the respiratory tract of 16 mild-asthmatic subjects.

There are contradictory studies too that do not show any beneficial relation between asthma and vitamin C\textsuperscript{[56]}. 300 asthmatic patients (18-60 yr) in a randomized, placebo-controlled trial were tested for the association between vitamin C supplementation and clinical control of asthma. The study showed no added clinical benefit to the current standard therapy of asthma\textsuperscript{[57]}. The role of vitamin C as dietary supplementation in open-population samples has not been clearly reported though this vitamin has been maximally studied.

**Vitamin E**

In the airways the ROS cause bronchoconstriction, increases mucus secretion, microvascular leakage, and autonomic imbalance between muscarinic receptor-mediated contraction and β-adrenergic relaxation of the pulmonary smooth muscle. Vitamin E has regulatory roles in maintaining this balance\textsuperscript{[58]}. Vitamin E tocopherol isoforms have opposing regulatory functions on cell signaling. The γ-tocopherol is linked to lower lung function and increased allergic inflammation whereas α-tocopherol to the reverse. Normal plasma levels of tocopherol increases the lipoxygenation of arachidonic acid, but increased tocopherol levels causes a suppressive effect. In asthma there is receptor-mediated activation of neutrophils which results in the synthesis of leukotrienes. This activation is inhibited by tocopherol in a dose-dependent manner\textsuperscript{[59]}. A study of 2,633 adults reported that vitamin E intake was related to low serum IgE concentrations and low frequency of allergen sensitization suggesting a beneficial effect on asthma control\textsuperscript{[60]}. The beneficial effects of vitamin E supplementation in patients with bronchial asthma may be due to the enhanced functional activity of T-lymphocytes and phagocytic activity of peripheral granulocytes\textsuperscript{[61]}. 
In contrast a case-controlled study on 118 asthmatic patients, found no association between bronchial asthma and the intake of antioxidants. This study found a reduced level of platelet GSH-Px activity in severe asthma cases, pointing to a diminished capacity of restoration of their antioxidants[62].

Many studies have reported low plasma α-tocopherol levels in adults or children with asthma[63,64,65-68] and that there is a correlation between plasma and tissue tocopherol[69-71]. Hence as α-tocopherol levels are low in asthmatics and that α-tocopherol can reduce inflammation, then an increase in α-tocopherol and more so, a decrease in γ-tocopherol may be effective in addition to routine drug therapy in the control of asthma (Figure 1).

**Figure 1: Effects of Vitamins C, E & A**

**Pathophysiology**

In asthma, Th1 and Th2 cytokines are differentially regulated under conditions of oxidative stress[72]. That apoptotic death pathways, which are activated in asthmatic RTECs are affected by antioxidants[73,74], which decreases phagocytes and nonphagocyte NADPH oxidase activities[75] and also affects the generation of nitric oxide (NO)[76]. The antioxidant pathobiology in asthma is as follows-1. The role of pleiotropic nonphagocytic NADPH oxidases which normally influences the complicated network of signaling cascades affecting gene regulation and protein metabolism. In asthma as this level is less, the localized intracellular signaling levels of ROS gets affected[74,77]. 2. NO pathways, are dysregulated in asthma[78].
3. The role of the antioxidant micronutrients, including vitamin C\textsuperscript{[79,80]} and vitamin E\textsuperscript{[81]} function as mild pro-oxidants which influence cellular protective and adaptive antioxidant systems by enhancing GSH-related pathways and phase II detoxifying/metabolizing pathways.

CONCLUSION

Asthmatic adults on low-antioxidant diets were found to have lower FEV1 scores, lower forced vital capacity percentage predicted, more frequent exacerbation and higher plasma C-reactive protein compared to those on a high-antioxidant diet. Supplementation therapy markedly improved both symptoms and lung function in asthma induced by exercise.

Vitamin A, vitamin E, were found significantly lower in asthma than in controls, and vitamin E was negatively affected by MDA and FeNO. Vitamin E, is a major defense against ROS, and is a primary source of oxidant-induced membrane damage. Vitamin C maintains antioxidant capacity in the aqueous phase, and also contributes to the membrane-bound oxidative regeneration of vitamin E. Also studies have shown that vitamin A and vitamin A carotenoids-like α-carotene, β-carotene, lycopene, zeaxanthin and β-cryptoxanthin, have antioxidant action.

Most short term researches on the role of antioxidants in management of asthma were inconclusive since they examined only immediate effects. Long-term randomized control studies on vitamins A, C, and E supplementation are needed to get a clear idea about their role on the inflammatory process in asthmatic subjects. It is concluded that antioxidant agents like vitamins A, C, and E supplementation be beneficial in the management of asthma, along with routine pharmacological treatment.

CONFLICTS OF INTEREST

Author declares that there are no conflicts of interest.

REFERENCES


