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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 suggests 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 hyper reactivity. 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 socioeconomicstratas[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 symptoms than those on a high-antioxidant diet[2]. Both symptoms and lung function improved notably on in 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-Tocotrienolinhibited oxidative damage by enhancing endogenous antioxidant production in the lung and also increasing the level of Nrf_2 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 methacholinein 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[20,21].

Many epidemiological studies and population surveys from the UK[22,23], US[24,25], the Netherlands[26] and China[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[28] and bronchial sensitivity in adults[29]. Plasma concentrations of vitamin C were found to be lower in asthmatic patients, particularly those with severe asthma[30,31]. In mild asthmatic patients lung lining fluid and induced sputum concentrations of vitamin C were also found to be low[32,33].

Some studies on low vitamin E intake has reported skin sensitization to allergens and total serum IgE [34], with the onset of wheeze, and with asthma exacerbations[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 [22,35], or on bronchial reactivity[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) [25,37]. There are also some studies that have reported low intakes of vitamin A in asthmatic Patients [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[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[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[42]. β-Carotene exerts its antioxidant effect by quenching singlet oxygen and reduces airway inflammation in asthma[43]. Few studies have shown that hypovitaminosis A can predispose to respiratory infections[44,45] and cause respiratory epithelial changes, such as metaplasia[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, dehydroascorbicacid 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[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[47,48].

Epidemiological studies have shown that increased dietary intake of vitamin C is associated with a reduced risk of asthma[49-51] and vitamin C levels are diminished in mild asthma[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[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[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[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[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[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 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[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[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[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 tocopherols[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).

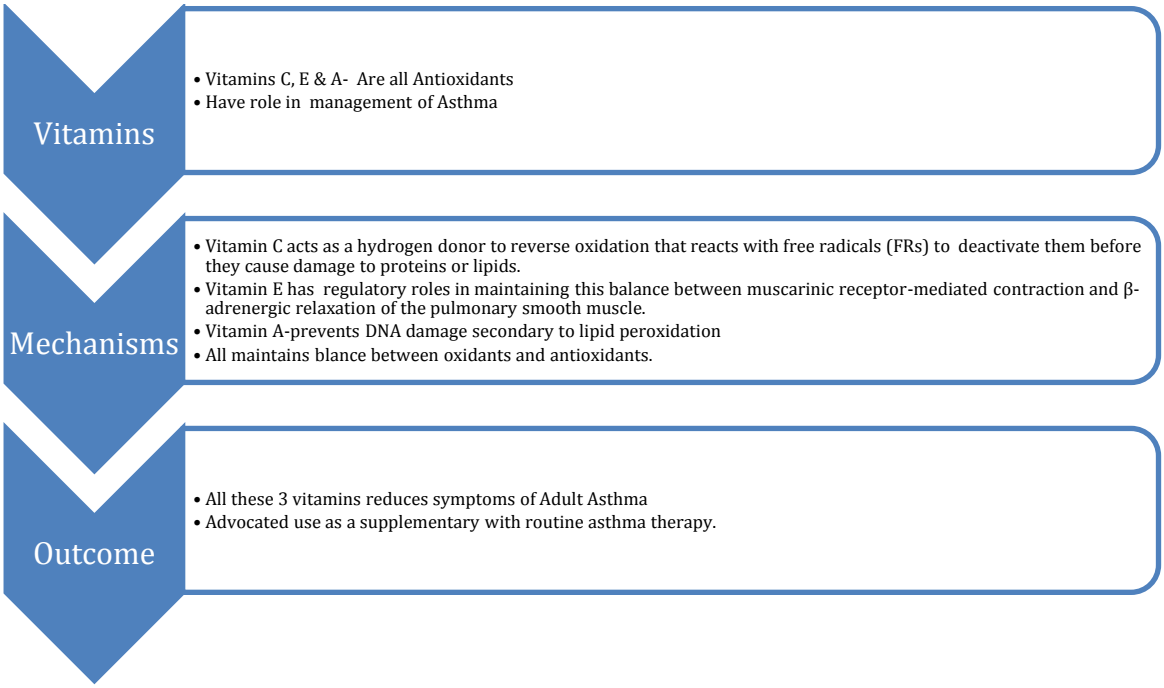

Figure 1: Effects of Vitamins C, E & A

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[79,80] and vitamin E[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

1. Zhu LY, Ni ZH, Luo XM, Wang XB. Advance of antioxidants in asthma treatment. World J Respirol. 2017;7(1):17-28.
2. Wood LG, Garg ML, Smart JM, Scott HA, Barker D, Gibson PG. Manipulating antioxidant intake in asthma: a randomized controlled trial. Am J ClinNutr. 2012;96(3):534-543.
3. Kurti SP, Murphy JD, Ferguson CS, Brown KR, Smith JR, Harms CA. Improved lung function following dietary antioxidant supplementation in exercise-induced asthmatics. Respir Physiol Neurobiol. 2016;220:95-101.
4. Tenero L, Piazza M, Zanoni L, Bodini A, Peroni D, Piacentini GL. Antioxidant supplementation and exhaled nitric oxide in children with asthma. Allergy Asthma Proc. 2016;37(1):e8-13.

5. Fabian E, Pölöskey P, Kósa L, Elmadfa I, Réthy LA. Nutritional supplements and plasma antioxidants in childhood asthma. Wien KlinWochenschr. 2013;125(11-12):309-315.

6. Peh HY, Ho WE, Cheng C, Chan TK, Seow AC, Lim AY, et al. Vitamin E Isoform γ-Tocotrienol Down regulates House Dust Mite-Induced Asthma. J Immunol. 2015;195(2):437-444.

7. Hernandez ML, Wagner JG, Kala A, Mills K, Wells HB, Alexis NE, et al. Vitamin E, γ-tocopherol, reduces airway neutrophil recruitment after inhaled endotoxin challenge in rats and in healthy volunteers. Free Radic Biol Med. 2013;60:56-62.

8. Hoskins A, Roberts JL, Milne G, Choi L, Dworski R. Natural-source d-α-tocopheryl acetate inhibits oxidant stress and modulates atopic asthma in humans in vivo. Allergy. 2012;67(5):676-682.

9. Kodama Y, Kishimoto Y, Muramatsu Y, Tatebe J, Yamamoto Y, Hirota N, et al. Antioxidant nutrients in plasma of Japanese patients with chronic obstructive pulmonary disease (COPD), asthma-COPD overlap syndrome, and bronchial asthma. Clin Respir J. 2017;11(6):915-24.

10. Moreno-Macias H, Romieu I. Effects of antioxidant supplements and nutrients on patients with asthma and allergies. J Allergy Clin Immunol. 2014;133(5):1237-44.

11. Mohsenin V, Dubois A, Douglas J. Effect of ascorbic acid on response to methacholine challenge in asthmatic subjects. Am Rev Respir Dis. 1983;127(2):143-147.

12. Kordansky D, Rosenthal R, Norman P. The effect of vitamin C on antigen-induced bronchospasm. J Allergy ClinImmunol. 1979;63(1):61-64.

13. Romieu I, Meneses F, Ramirez M, et al. Antioxidant supplementation and respiratory functions among workers exposed to high levels of ozone. Am J Respir Crit Care Med. 1998;158(1):226-232.

14. Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, et al. Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. Am J Respir Crit Care Med. 2002;166(5):703-709.

15. Grievink L, Zijlstra AG, Ke X, Brunekreef B. Double-blind intervention trial on modulation of ozone effects on pulmonary function by antioxidant supplements. Am J Epidemiol. 1999;149(4):306-314.

16. Trenga CA, Koenig JQ, Williams PV. Dietary antioxidants and ozone-induced bronchial hyper responsiveness in adults with asthma. Arch Environ Health. 2001;56(3):242-249.

17. Fogarty A, Lewis SA, Scrivener SL et al. Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial. Clin Exp Allergy. 2003;33(10):1355-1359.

18. Ram FS, Rowe BH, Kaur B. Vitamin C supplementation for asthma. Cochrane Database Syst Rev. 2004;(3):CD000993.

19. Pearson PJ, Lewis SA, Britton J, Fogarty A. Vitamin E supplements in asthma: a parallel group randomised placebo controlled trial. Thorax. 2004;59(8):652-656.

20. Currie GP, Lee DK, Anderson WJ. Vitamin E supplements in asthma. Thorax 2005;60(2):171-172.

21. Misso NLA, Thompson PJ. Oxidative stress and antioxidant deficiencies in asthma: potential modification by diet. Redox Rep. 2005;10(5):247-255.

22. Fogarty A, Britton J. The role of diet in the aetiology of asthma. Clin Exp Allergy. 2000;30(5):615-627.

23. Britton JR, Pavord ID, Richards KA et al. Dietary antioxidant vitamin intake and lung function in the general population. Am J Respir Crit Care Med. 1995;151(5):1383-1387.

24. Schwartz J, Weiss S. Relationship between dietary vitamin C and pulmonary function in the First National Health and Nutrition Examination Survey (NHANES I). Am J Clin Nutr. 1994;59(1):110-114.

25. Hu G, Cassano P. Antioxidant nutrients and pulmonary function: the third National Health and Nutrition Examination Survey (NHANES III). Am J Epidemiol. 2000;151(10):975-981.

26. Grievink L, Smit HA, Ocke MC, van't Veer P, Kromhout D. Dietary intake of antioxidant (pro)-vitamins, respiratory symptoms and pulmonary function: the MORGEN study. Thorax. 1998;53(3):166-171.

27. Hu G, Zhang X, Chan J, Peto R, Campbell TC, Cassano PA. Dietary vitamin C intake and lung function in rural China. Am J Epidemiol. 1998;148(6):594-599.

28. Bodner C, Godden D, Brown K, et al. Antioxidant intake and adult-onset wheeze: a case-control study. Eur Respir J. 1999;13:22-30.

29. Soutar A, Seaton A, Brown K. Bronchial reactivity and dietary antioxidants. Thorax. 1997; 52(2): 166-170.

30. Misso NL, Brooks-Wildhaber J, Ray S, Vally H, Thompson PJ. Plasma concentrations of dietary and nondietary antioxidants are low in severe asthma. Eur Respir J. 2005;26(2):257-264.

31. Ford ES, Mannino DM, Redd SC. Serum antioxidant concentrations among U.S. adults with self-reported asthma. J Asthma. 2004;41(2):179-187.

32. Kelly FJ, Mudway I, Blomberg A, Frew A, Sandstrom T. Altered lung antioxidant status in patients with mild asthma. Lancet. 1999;354(9177):482-483.

33. Kongerud J, Crissman K, Hatch G, Alexis N. Ascorbic acid is decreased in induced sputum of mild asthmatics. Inhal Toxicol. 2003;15(2):101-109.

34. Fogarty A, Lewis S, Weiss S, Britton J. Dietary vitamin E, IgE concentrations, and atopy. Lancet. 2000;356(9241):1573-1574.

35. Troisi R, Willett W, Weiss S, Trichopoulos D, Rosner B, Speizer F. A prospective study of diet and adult-onset asthma. Am J Respir Crit Care Med. 1995;151(5):1401-1408.

36. Baker J, Tunnicliffe W, Duncanson R, Ayres J. Dietary antioxidants and magnesium in type 1 brittle asthma: a case control study. Thorax. 1999;54(2):115-118.

37. Rautalahti M, Virtamo J, Haukka J, et al. The effect of alphatocopherol and beta-carotene supplementation on COPD symptoms. Am J Respir Crit Care Med. 1997;156(5):1447-1452.

38. Barasi ME. Water soluble vitamins. In: Human Nutrition. Arnold Press. London. 1997; 171-175.

39. Melendez GV, Okani ET, Kiertsman B, Roncada MJ. Vitamin A status in children with pneumonia. Eur J Clin Nutr. 1995;49(5):379-384.

40. Kükükbay H, Yakinci C, Kükükbay FZ, Tutgut M. Serum vitamin A and beta-carotene levels in children with recurrent acute respiratory infections and diarrhoea in Malarya. J Trop Pediatr. 1997;43(6):337-340.

41. Mayne ST. Beta-carotene, carotenoids, and disease prevention in humans. FASEB J. 1996;10(7):690-701.

42. Maier K. How the lung deals with oxidants. Eur Respir J. 1993;6(3):334-336.

43. Burton GW, Ingold KU. b-Carotene: An unusual type of lipid antioxidant. Science 1994;224(4649):569-573.

44. Chandra RK, Vyas D. Vitamin A, immunocompetence and infection. Fed Nutr Bull. 1989; 11:12-19.

45. Bloem MW, Wedel M, Egger RJ. Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhea in preschool and school children in northeastern Thailand. Am J Epidemiol. 1990;131(2):332-339.

46. Zachman RD. Role of vitamin A in lung development. J Nutr. 1994;125(6 Suppl):1634S-1638S.

47. Shanmugasundaram KR, Kumar SS, Rajajee S. Excessive free radical generation in the blood of children suffering from asthma. Clin Chim Acta. 2001;305(1-2):107-114.

48. Vural H, Uzun K. Serum and red blood cell antioxidant status in patient with bronchial asthma. Can Respir J. 2000;7(6):476-480.

49. McDermoth JH. Antioxidant nutrients: current dietary recommendations and research update. J Am Pharm Assoc. 2000;40(6):785-799.

50. Soutar A, Seaton A, Brown K. Bronchial reactivity and dietary antioxidants. Thorax 1997;52(2):166-170.

51. Hatch GE. Asthma, inhaled oxidants, and dietary anti-oxidants. Am J Clin Nutr. 1995;61(3 Suppl):625S-630S.

52. Kelly FJ, Mudway I, Blomberg A, Frew A, Sandstrom T. Altered lung antioxidant in patients with mild asthma. Lancet. 1999;354(9177):482-483.

53. Trenga C, Koenig JQ, Williams PV. Dietary antioxidants and ozone-induced bronchial hyper responsiveness in adults with asthma. Arch Environ Health. 2001;56(3):242-249.

54. Huang SL, Pan WH. Dietary fats and asthma: analyses of the First Nutrition and Health Survey in Taiwan (NAHSIT). Clin Exp Allergy. 2001;31(12):1875-1880.

55. Kongerud J, Crissman K, Hatch G, Alexis N. Ascorbic acid is decreased in induced sputum of mild asthmatics. Inhal Toxicol. 2003;15(2):101-109.

56. Troisi RJ, Willet WC, Weiss ST, Trichopoulos D, Rosner B, Spiezer FE. A prospective study of diet and adult-onset asthma. Am J Respir Crit Care Med. 1995;151(5):1401-1408.

57. Fogarty A, Lewis SA, Scrivener SL, Antoniak M, Pacey S, Pringle M, et al. Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial. Clin Exp Allergy. 2003;33(10):1355-1359.

58. Doelman CJ, Bast A. Oxygen radicals in lung pathology. Free Radic Biol Med. 2000;9(5):381-400.

59. Centanni S, Santus P, Di Marco F, Fumagalli F, Zarini S, Sala A. The potential role of tocopherol in asthma and allergies: modification of the leukotriene pathway. BioDrugs. 2001;15(2):81-86.

60. Fogarty A, Lewis S, Weiss S, Britton J. Dietary vitamin E, IgE concentration, and atopy. Lancet. 2000;356(9241):1573-1574.

61. Pletsityi KD, Vasipa SB, Daydova TV, Fomina VG. Vitamin E: immune correcting effect in bronchial asthma patients. Vopr Med Khim. 1995;41(4):33-36.

62. Picado C, Deulofeu R, Lleonart R, Agusti M, Mullol J, Quinto L, et al. Dietary micronutrients/antioxidants and their relationship with bronchial asthma severity. Allergy. 2001;56(1):43-49.

63. Troisi RJ, Willett WC, Weiss ST, Trichopoulos D, Rosner B, Speizer FE. A prospective study of diet and adult-onset asthma. Am J Respir Crit Care Med. 1995;151(5):1401-1408.

64. Dow L, Tracey M, Villar A, Coggon D, Margetts BM, Campbell MJ, et al. Does dietary intake of vitamins c and e influence lung function in older people? Am J Respir Crit Care Med. 1996;154(5):1401-1404.

65. Kalayci O, Besler T, Kilinc K, Sekerel BE, Saraclar Y. Serum levels of antioxidant vitamins (alpha tocopherol, beta carotene, and ascorbic acid) in children with bronchial asthma. Turk J Peds. 2000;42:17-21.

66. Kelly FJ, Mudway I, Blomberg A, Frew A, Sandstrom T. Altered lung antioxidant status in patients with mild asthma. Lancet. 1999;354:482-483.

67. Schunemann HJ, Grant BJ, Freudenheim JL, Muti P, Browne RW, Drake JA, et al. The relation of serum levels of antioxidant vitamins c and e, retinol and carotenoids with pulmonary function in the general population. Am J Respir Crit Care Med. 2001;163(5):1246-1255.

68. Al-Abdulla NO, Al Naama LM, Hassan MK. Antioxidant status in acute asthmatic attack in children. J Pak Med Assoc. 2010;60(12):1023-1027.

69. McCary CA, Abdala-Valencia H, Berdnikovs S, Cook-Mills JM. Supplemental and highly elevated tocopherol doses differentially regulate allergic inflammation: Reversibility of alpha-tocopherol and gamma-tocopherol's effects. J Immunol. 2011;186(6):3674-3685.

70. Berdnikovs S, Abdala-Valencia H, McCary C, Somand M, Cole R, Garcia A, et al. Isoforms of vitamin e have opposing immune regulatory functions during inflammation by regulating leukocyte recruitment. J Immunol. 2009;182(7):4395-4405.

71. Redlich CA, Grauer JN, Van Bennekum AM, Clever SL, Ponn RB, Blaner WS. Characterization of carotenoid, vitamin a, and alpha-tocopheral levels in human lung tissue and pulmonary macrophages. Am J Respir Crit Care Med. 1996;154(5):1436-1443.

72. Malmberg KJ, Arulampalam V, Ichihara F, Petersson M, Seki K, Andersson T, et al. Inhibition of activated/memory (CD45RO(+)) T cells by oxidative stress associated with block of NF-kappaB activation. J Immunol. 2001;167(5):2595-2601.

73. Vignola AM, Chiappara G, Gagliardo R, Gjomarkaj M, Merendino A, Siena L, et al. Apoptosis and airway inflammation in asthma. Apoptosis 2000;5(5):473-485.

74. Droge W. Free radicals in the physiological control of cell function. Physiol Rev. 2002;82(1):47-95.

75. Halliwell B. The antioxidant paradox. Lancet. 2000;355(9210):1179-1180.

76. Mak S, Egri Z, Tanna G, Colman R, Newton GE. Vitamin C prevents hyperoxia-mediated vasoconstriction and impairment of endothelium-dependent vasodilation. Am J Physiol Heart Circ Physiol. 2002;282(6):H2414-H2421.

77. Lambeth JD. Nox/Duox family of nicotinamide adenine dinucleotide (phosphate) oxidases. Curr Opin Hematol. 2002;9(1):11-17.

78. Guo FH, Comhair SA, Zheng S, Dweik RA, Eissa NT, Thomassen MJ, et al. Molecular mechanisms of increased nitric oxide (NO) in asthma: evidence for transcriptional and post-translational regulation of NO synthesis. J Immunol. 2000;164(11):5970-5980.

79. Vissers MC, Lee WG, Hampton MB. Regulation of apoptosis by vitamin C. Specific protection of the apoptotic machinery against exposure to chlorinated oxidants. J Biol Chem. 2001;276(50):46835-46840.

80. Carcamo JM, Borquez-Ojeda O, Golde DW. Vitamin C inhibits granulocyte macrophage-colony-stimulating factor-induced signaling pathways. Blood. 2002;99(9):3205-3212.

81. Ricciarelli R, Zingg JM, Azzi A. Vitamin E: protective role of a Janus molecule. FASEB J. 2001;15:2314-2325.