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Antioxidant Supplementation among Chronic Obstructive Pulmonary Disease (COPD): Is it Necessary?

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Abstract: The development of airflow limitation is related to inadequate antioxidant intake and hence dietary supplementation may be a beneficial therapeutic intervention. Antioxidants with good bioavailability or molecules that have antioxidant enzyme activity may not only protect cells against the direct injurious effects of oxidants, but may fundamentally alter the inflammatory events that play an important part in the pathogenesis of Chronic Obstructive Pulmonary Disease (COPD). We aimed to review highlights the role of antioxidant and antioxidant vitamins in respiratory health. This is a retrospective study which is reviewing twenty cross-sectional and nine interventional studies from years 1990 to 2007 which were journal publications on the benefits of antioxidants and antioxidant supplementation among COPD patients. The results and finding from reviewing the studies, revealed that antioxidant vitamins [e.g. Vitamin A, E, C and N-acetyl Cysteine (NAC)] had an important role in respiratory health and lung function.

Key words: Antioxidant, chronic obstructive pulmonary disease, dietary supplements, oxidative stress, oxidants

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease although not fully reversible, characterized by airflow limitation. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also associated with significant systemic consequences such as weight loss and muscle dysfunction (Celli *et al*., 2004). COPD is the fourth leading cause of death behind cardiovascular disease, cancers and stroke, leading to death of 120,000 Americans annually (National Vital Statistics Reports, 2004). It is estimated to be the third largest cause of death worldwide by the year 2020 (Murray and Lopez, 1998). The highest prevalence occurs in industrialized countries (except for China) although this has been disputed and reported to be higher in sub-Saharan Africa (4.41 per 1000 for men and 2.49 per 1000 for women) (Cheng *et al*., 1998). The lowest prevalence was noted in the Middle Eastern Crescent (2.69 per 1000 for men and 2.83 per 1000 for women) (Murray and Lopez, 1996). Incidence of COPD is estimated to be 6.2% in 11 Asian countries surveyed by the Asian Pacific Society of Respiratory Diseases (COPD International 16 March 2004). The number of COPD cases in Asia is approximately three times the total number of cases in the rest of the world and is closely associated with smoking and usage of biomass fuel (Pandey, 1984). Research estimates the prevalence of COPD in Malaysia to be 4.7% (Tan *et al*., 2003). The first National Health Morbidity and Mortality Survey showed 49%, 4% smoking prevalence in men and women respectively, thereby resulting in 448,000 COPD cases (4.7%) in Malaysia (Rampal *et al*., 2006).

Increase in COPD prevalence in developing countries is due to the rise in smoking and failure in cessation efforts. This rise in COPD could also be attributed to industrial exposure to noxious substances and air pollution. Despite the enormous global impact of COPD there are no current therapies that prevent disease progression. However, recently there has been enormous interest in COPD by researchers and pharmaceuticals who are involved in understanding the cellular and molecular mechanisms and in the identification of novel targets for therapy (Barnes, 2003). Among the various antioxidants tried so far, thiol antioxidants and mucolytic agents, such as glutathione, N-acetyl-L-cysteine, N-acystelyn, erdosteine, fudosteine and carbocysteine; Nrf2 activators and dietary polyphenols (curcumin, resveratrol and green tea catechins/ quercetin) have been reported to increase intracellular thiol status along with induction of GSH biosynthesis. Such an elevation in the thiol status in turn leads to detoxification of free radicals and oxidants as well as inhibition of ongoing inflammatory responses (Rahman, 2008).

COPD and oxidative stress: Reactive Oxygen (ROS) and reactive nitrogen species and other molecules, such as

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protein radicals and lipid peroxidation products which are derived from the formation of highly reactive and unstable hydro peroxides of both saturated and unsaturated lipids, lead to oxidant and antioxidant imbalance. These imbalances observed in cancer and most of chronic diseases such as COPD (MacNee, 2005). Cigarette smoke contains more than 5,000 different chemicals of which many are oxidants, including H_2O_2, O_2, OH and NO (Halliwell and Gutteridge, 1999). Cigarette smoke can be separated into a gas phase and a particulate phase (tar phase) and both of these contain abundant oxidants. The gas phase is less stable and is estimated to contain 1015 free radicals per puff. The tar phase by contrast is more stable and is estimated to contain 1017 free radicals per gram (Halliwell and Gutteridge, 1999). Both ROS species from inhaled cigarette smoke and those endogenously formed by inflammatory cells constitute an increased intrapulmonary oxidant burden. Structural changes to essential components of the lung are caused by oxidative stress, contributing to irreversible damage of both parenchyma and airway walls. In addition, oxidative stress results in alterations in the local immune response, increasing the risk of infections and exacerbations, which may accelerate the decline in lung function (Dekhuijzen, 2004). The three most common lung diseases (asthma, COPD; a term used to describe chronic bronchitis and emphysema and lung cancer) have a fairly well established etiology. In the case of asthma, genetic factors and exposure to allergens have been identified as playing a key role, while COPD and lung cancer are largely the result of cigarette smoking (Doll and Peto, 1976).

Antioxidant in lungs: Antioxidants are usually classified as either enzymatic or nonenzymatic and are the primary defenses against reactive oxygen and reactive nitrogen species. Antioxidant enzymes include the Superoxide Dismutase (SOD) family, catalase, glutathione (GSH) peroxidase, GSH S-transferase and thioredoxin (Halliwell and Gutteridge, 1990). The SOD family is one of the major antioxidant enzymes found in the lungs. GSH is the most abundant intracellular thiol-based antioxidant. It is concentrated in the epithelial lining fluid and plays a critical role in maintaining intracellular redox status, in addition to detoxifying compounds via conjugation reactions through GSH S transferase. Bronchoalveolar Lavage Fluid (BALF) contains 100 fold concentration of GSH compared with the blood (Van *et al*., 1999). GSH is also highly concentrated in intracellular spaces (Halliwell and Gutteridge, 1999). The nonenzymatic antioxidants include low molecular weight compounds, such as GSH, ascorbate, urate, alpha-tocopherol, bilirubin and lipoic acid. Concentrations of these nonenzymatic antioxidants vary in the lungs. Some, antioxidants such as GSH, are more concentrated in epithelial lining fluid compared with plasma (Van *et al*., 1999) while others, such as albumin, are found in high concentration in serum, but at much lower concentrations in the epithelial lining fluid (Reynolds and Newball, 1974) (Table 1).

Table 1: Concentration of low molecular weight antioxidants in normal subjects (Data presented as mean±SD, in μM)

Antioxidant	Plasma	Epithelial lining fluid
Glutathione	1.0±0.7	109±64
Urate	378±133	207±167
Ascorbate (Vitamin C)	67±25	40±18
α-tocopherol (Vitamin E)	16±5	0.7±0.3

COPD and antioxidants: As early as in 1960, studies had shown that high intake of fruits and vegetables were positively associated with pulmonary function. A high intake of three antioxidant vitamins E, C and β-carotene was positively associated with lung function (Tabak *et al*., 1999), while there was a positive effect of fruit and vitamin E intake against COPD (Walda *et al*., 2002). In a cross sectional study a strong positive association was observed between lung function and number of apples consumed per week suggesting a protective effect of hard fruit rather than soft/ citrus fruit (Butland *et al*., 2000). Also, dietary intake of fruits and vegetable rich in vitamin E and β-carotene had beneficial effects on COPD (Alahti *et al*., 1997). A diet rich in fruits, vegetables and fish may reduce the risk of COPD in both men and women whereas a diet rich in refined grains, cured and red meats, desserts and French fries may increase the risk of COPD (Varraso *et al*., 2007). In a cross sectional study high intake of vitamin C or β-carotene was not only protective for FEV_1, FVC but was also related to COPD symptoms. Vitamin C was inversely related to cough and vitamin E intake was positively associated with productive cough and intake of β-carotene was positive association with wheeze (Grievink *et al*., 1998). Therefore, vitamin C may help in protecting against the development of COPD (Britton *et al*., 1995). Most studies to date, have examined the efficacy of antioxidants on lung function and respiratory symptoms and few studies have examined the effect of antioxidant supplementation on oxidative stress in COPD patients and smokers. An eight week antioxidant supplementation drink has been shown to reduce lipid peroxidation and susceptibility of Low Density Lipoprotein (LDL) to oxidation in smokers and may improve the oxidative stress of cigarette smoker (Steinberg and Chait, 1998). In addition, the combination of vitamin C, E and β-carotene has been shown to reduce exhaled ethane in cigarette smokers while vitamin E alone failed to reduce exhaled ethane in those subjects. Exhaled ethane correlated to pack-years of smoking and there was a negative significant correlation existed between exhaled ethane and FEV_1/ FVC after vitamin E therapy as well (Habib *et al*., 1999).

Table 2: Summary of cross-sectional and clinical trial on antioxidant supplementation among COPD patients

References	Antioxidant	Type of study	Sample size	Results
NHANES (Celli *et al*., 2004)	Vit C	Observational study	Population study	Lower dietary intake of vitamin C related to lower
Schwartz and Weiss (1994)		Project for risk factor	survey	FEV_1
NHANES (NVSR, 2004)	Vit C	Observational study	Population study	Inverse relationship between both vit C and chronic
Schwartz and Weiss (1990)		Project for risk factor	survey	respiratory symptoms
NHANES (Murray and Lopez, 1998)	Level of vit C, E,	Observational study	Population study	Correlated positively with lung function
Hu and Cassano (2000)	selenium, beta carotene	Project for risk factor	survey	
Tabak *et al*. (2001)	Vitamin C and beta	Longitudinal study	2859 healthy	Higher intake of vitamin C and beta carotene was
Miedema *et al*. (1993)	carotene	Cross-sectional	subjects	associated with higher level of FEV_1. And association
Strachan *et al*. (1999)		Cross- sectional		between fruit intake and higher FEV and lower symptoms in COPD patients.
Stey *et al*. (2000), Grandjean *et al*. (2000)	NAC = 600 mg	Meta analysis	COPD studies	Positive effect on exacerbation COPD
Benedetto *et al*. (2005)	NAC = 600 mg, for 2 months	Randomized single blind, placebo controlled	55 clinical stable COPD	Reduced oxidant burden in airway of stable COPD (H_2O_2 content in exhaled air condensate).
Kasielski and Nowak (2001)	NAC = 600 mg, for 1 year	Double blind- double dummy	44 COPD subjects	Decreased H_2O_2 formation in the air ways of COPD
Zuin *et al*. (2005)	NAC = 1200 mg, for 10 days	Randomized double blind-double dummy, placebo controlled	123 COPD subjects	Decreased H_2O_2 formation in the air ways of COPD.
Altaf *et al*. (2007), Pela *et al*. (1999)	NAC = 600 mg	Randomized single blind, placebo controlled	100 COPD subjects	Reduction of exacerbations by 26% and lower number of 2 or more exacerbations.
Altaf *et al*. (2007)	NAC = 600 mg, 1 year	Randomized single blind, placebo controlled	100 COPD subjects	Readmission risk significantly lower by 30% in COPD.
Gerrits *et al*. (2003)	12 years	1 year follow up	1,219	
Altaf *et al*. (2007)	NAC 600 mg, 1 year	Randomized single blind placebo controlled	100 COPD subjects	Significant improvement in spirometric parameters FEV_1 and FEF
Pela *et al*. (1999)	6 months	Randomized controlled	196 COPD subjects	

Vitamin E supplementation did not show any significant effects on the level of oxidant and antioxidants and on the spirometric measurement in COPD. However, levels of Malondialdehyde (MDA) were reduced indicating attenuation in damage to the lung function (Daga *et al*., 2003). Serum MDA level was significantly higher in COPD patients during acute exacerbation and those in stable phase suggesting a systemic oxidant and antioxidant imbalance in COPD and this imbalance was probably independent of smoking (Calikoglu *et al*., 2002). Antioxidant supplementation decreased lipid peroxidation biomarker F_2-isoprostane in plasma of smokers showing that consuming vitamin supplement may help prevent smoking- related disease (Dietrich *et al*., 2002). In addition, six weeks of antioxidant therapy on lung clearance, pulmonary function tests and oxidant stress in patients with COPD indicated that antioxidant therapy as an adjunct to diet improved the oxidant and antioxidant balance, a slight but not significant decrease was observed on lung clearance (Demir *et al*., 2004). Vitamin E (400 mg/d and 200 mg/d) and vitamin C (250 mg/d) supplementation for a period of 12 weeks significantly suppressed the H_2O_2 - induced DNA breakages, suggesting that vitamin E and C supplementation may improve the resistance of DNA in whole blood against oxidative challenge (Tzu-Chin *et al*., 2007).

Antioxidant vitamins (C, E, Retinol and Carotenoids) not only improve the pulmonary function of COPD patients but also support the hypothesis that antioxidant vitamins may play an important role in respiratory health (Schunemann *et al*., 2001). Vitamin E and β cryptoxanthin appeared to be stronger correlates of lung function compared to other antioxidants vitamins. (Schunemann *et al*., 2001) Administration of vitamin A and E may be beneficial in the prevention and treatment of the harmful effects of COPD (Tug *et al*., 2004). Among the various antioxidants, N-Acetylcysteine (NAC) has been reported to increase intracellular glutathione leading to lung protection (Rahman, 2008). NAC has been shown to reduced oxidant burden (Benedetto *et al*., 2005) and decreased H_2O_2 formation (Zuin *et al*., 2005; Kasielski and Nowak, 2001), decrease exacerbations and significantly improve spirometric parameters FEV_1 and FEF (Altaf *et al*., 2007; Pela *et al*., 1999) in airway of stable COPD (Table 2).

Conclusion: Antioxidants and antioxidant vitamins improve lung function and respiratory health lending overwhelming support for antioxidant supplementation in COPD. The independent protective and palliative effects of antioxidants such as NAC and antioxidant vitamins, on respiratory function and respiratory health open avenues for further research using combination therapies.

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