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Plasma Antioxidants Are Associated with Impaired Lung Function and COPD Exacerbations in Smokers

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Abstract

Low molecule weight antioxidants such as uric acid (UA), glutathione (GSH), and ascorbate (ASC) counter the effects of oxidants produced by cigarette smoke. Although dietary intake of foods rich in antioxidants has been associated with a reduced risk of smokers developing chronic obstructive pulmonary disease (COPD), the association between plasma antioxidants and COPD is less clear. In this cross-sectional study we investigated the relationship among plasma antioxidants and COPD phenotypes (severity of airflow obstruction on spirometry and history of exacerbations) in 136 smokers with normal lung function and 367 smokers with COPD. In the multivariate analysis, a lower plasma UA was associated with more severe COPD ($P < 0.002$) and a lower GSH was associated with a history of COPD exacerbations ($P = 0.03$); ASC was not associated with any COPD phenotypes. This suggests that antioxidant balance is impaired in smokers with obstruction on spirometry or a history of COPD exacerbations.

Keywords

antioxidants; glutathione; uric acid; plasma; COPD; exacerbation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) develops in only 25–40% of cigarette smokers (1). The pathophysiologic factors that determine which of these smokers develop disease have been postulated to include oxidant/antioxidant imbalance, unopposed protease activity, inflammation, autoimmunity, and enhanced apoptosis (2–5). The oxidant/antioxidant imbalance theory has been supported by studies demonstrating elevated oxidative stress in smokers and COPD patients (2, 6). The role of antioxidants is also supported by associations between low lung function and diets that are low in antioxidants

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DECLARATION OF INTEREST

Authors Michael E. Nicks, Maureen M. O'Brien, and Russell P. Bowler have all stated that they have no conflict of interest. This includes financial, personal, academic and intellectual conflicts of interest. Michael E. Nicks contributed to the design, collection and analysis of data, and in the writing of the manuscript. Maureen M. O'Brien contributed to the analysis of data. Russell P. Bowler contributed to the design, analysis of data, and in the writing of the manuscript.

(7–10). In small studies, antioxidant concentrations and oxidative stress have been associated with both smoking and COPD (5, 11–15).

The two broad classes of antioxidants include high molecular weight antioxidants (e.g., enzymes such as superoxide dismutase or catalase) and low molecular weight antioxidants that directly react with ROS. In human plasma, low molecular weight water soluble antioxidants include glutathione (GSH), uric acid (UA), and ascorbate (vitamin C or ASC). Other lipid soluble antioxidants such as tocopherols (e.g., Vitamin E) are also present in high concentrations.

UA is the most abundant antioxidant in the plasma and may play an important role in protecting the lung from oxidative stress by inhibiting lipid peroxidation and scavenging ROS/RNS (reactive nitrogen species) (16). In small studies UA has been associated with low lung function (11, 17). GSH is another antioxidant important to the lung (18) and GSH sensitive pathways have been shown to play an important role in host defense and redox signaling (19, 20). GSH is oxidized by reactive oxygen species (ROS) to form oxidized glutathione (GssG). ASC is one of the most abundant intracellular antioxidants in cells and has been suggested to help maintain both UA and GSH in a reduced state (21). ASC has been shown to prevent the pro-oxidant effects of UA on the oxidation of human low density lipoprotein *in vitro* (22). In a study of 218 subjects from western New York who had COPD or asthma, dietary ascorbate intake was positively associated with forced expiratory volume at one second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC (23). In the MORGEN study, a higher ASC dietary intake was associated with better lung function (FEV₁) (9); however a 20-year longitudinal study showed no relationship between dietary ASC and COPD mortality (8).

These studies, although somewhat conflicting, suggest an association between dietary antioxidants and COPD. Some of the limitations of these studies include small size and lack of a proper control group (smokers with normal lung function). Other limitations include the lack of blood measurements of these antioxidants. Furthermore, there are few studies examining the association between antioxidants and other important COPD outcomes such as exacerbations, despite evidence to suggest that N-acetylcysteine (a precursor of GSH) supplementation may reduce exacerbation rates (24, 25). In the present study we determined whether plasma levels of three low molecular weight antioxidants ASC, UA, and GSH were associated with either lung function or COPD exacerbations in more than 500 smokers.

MATERIALS AND METHODS

Selection and description of participants

All subjects (N = 503) were studied under protocols approved by the Institutional Review Board at National Jewish Health with guidelines by the National Institutes of Health. Subjects were recruited from the local community in Denver Colorado by advertising or clinic referrals. All patients had at least a 10-pack year smoking history and no respiratory symptoms or disease other than COPD. The diagnosis of COPD was made using Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria: post-bronchodilator (BD) maximum volume of air expired in one second (FEV₁) divided by forced vital capacity

(FVC) less than 0.7 (26). The FEV₁ percent predicted (FEV₁%) was based on a sample of the general U.S. population (27). A COPD exacerbation was defined a respiratory illness that required the use of antibiotic, steroids or hospitalization. Subjects who reported at least one COPD exacerbation within the past 12 months (but not within the previous 30 days) were classified as having had a recent exacerbation. Data were self-reported. Demographics of the subjects are reported in Table 1.

Blood collection

Six ml of blood were withdrawn from the antecubital vein into a sterile 13 × 1000 mm sodium heparin Vacutainer Plus (BD, New Jersey, USA). The sample was immediately spun at 2100 × g for 10 minutes at room temperature. The plasma was removed and precipitated with 1:1 5% meta-phosphoric acid and placed on ice for 20 minutes. The samples were then centrifuged at 10,000 g for 10 minutes. The sample was placed into aliquots in HPLC vials and stored at −80°C.

Antioxidant determination

Individual concentrations of ascorbate and urate were determined by high performance liquid chromatography (HPLC) with electrochemical detection using an ESA Coullarray (Chelmsford, MA). Detector potentials were set at 100, 250, 600, and 670 mV. Five µl of sample was injected onto a 4.6 × 250 mm YMC ODS-AQ S5 µM 120Å column (Waters Co, Milford, MA). Antioxidants were eluted with mobile phase (potassium phosphate 125 mM, acetonitrile 1%, pH 3.0) at 0.75 ml/min. For UA measurements, samples were diluted 1:1 or 1:4 because of high initial concentrations. Total glutathione and oxidized glutathione were measured by colorimetric determination using a Bioxytech GSH/GSSG-412 kit (Oxis Research, Portland, OR). The linear range of this assay was approximately 0.05–2 µM.

Data analysis

Data analysis was done with SAS version 9.2 (SAS Institute Inc., Cary, NC) and Prism GraphPad 4 (Graphpad Software, La Jolla, CA). The 2-sample—test was used to compare means of normally distributed data and the Chi-squared test for dichotomous outcomes was used for categorical variables. The Kruskal-Wallis nonparametric test was used for smaller groups with large variation or data that was not normally distributed. Multivariate analysis was performed using backward stepwise regression with the following covariates: age, sex, smoking status (current or former), body mass index (BMI), pack-year history, percent predicted diffusing capacity of carbon monoxide (DL_{CO}%), arterial oxygen and carbon dioxide (Pa O₂ and Pa CO₂ in 5 mm Hg).

RESULTS

Demographics

Smokers without COPD tended to be slightly younger, heavier, more often current smokers, female and had fewer pack-years compared to those with COPD (Table 1, $p = < 0.001$). Thus, these parameters were included as covariates in the multivariate regression analysis.

Plasma antioxidants and lung function

Table 2 lists the plasma antioxidant concentrations for control and COPD groups. There were no significant differences by 2-sample *t*-test; however, GOLD stage IV (very severe COPD) was associated with lower uric acid levels compared to smokers with normal lung function (Figure 1 and Table 3). In univariate and multivariate analysis of lung function, only UA was significantly associated FEV₁ and FEV₁/FVC ratio in the COPD subjects. A univariate regression model with UA alone revealed an adjusted R² of 0.02 accounting for 2% of the change in FEV₁ (P = 0.011) and FEV₁/FVC in COPD (P = 0.024). The final multivariate model with covariates UA, pack-years and a history of exacerbations had an R² of 0.07 accounting for 7% of the change in FEV₁ in COPD (p = 0.011 for UA, p = 0.004 for pack-years, and p = 0.018 for exacerbations).

Plasma GSH was significantly lower in COPD patients who reported at least one exacerbation in the previous 12 months compared to COPD patients without exacerbations (0.322 μ M and 0.454 μ M, respectively, p = 0.035). The ratio of reduced to oxidized glutathione (GSH/GssG) was significantly lower in COPD patients with a history of COPD exacerbations (GSH/GssG of 1.13 and 2.72, respectively, p = 0.0136) (Figure 2). There were no statistical differences for either GSH or GssG in the smoking subjects who did not have COPD.

DISCUSSION

Local and systemic oxidative stress are prominent features of COPD even after smoking cessation (2, 5, 23, 28, 29). The antioxidant defense system, composed of both low molecular weight antioxidants and antioxidant enzymes, is the primary defense against these types of oxidative stress. This study focused on the water-soluble antioxidants UA, ASC, and GSH. Acutely, cigarette smoking depletes these antioxidants (30, 31); however, the adaptive response to chronic oxidative stress is usually to increase antioxidants. We found that subjects with milder COPD (GOLD stages 1 and 2) had higher levels of the UA compared to subjects with severe COPD (GOLD stages 3 and 4) suggesting that antioxidant responses may be inadequate in subjects with more severe COPD. Additionally GSH levels were lower in COPD patients with a history of exacerbations. These findings persisted after adjustment for covariates such as age and pack-years and suggest that low systemic antioxidant levels are associated with worse COPD and more exacerbations.

This is the first study to demonstrate an association between lung function and UA in COPD patients. UA is the most abundant antioxidant in plasma (range 300–400 mM). In 1981 Ames proposed that UA was not a by-product of metabolism but a powerful antioxidant whose purpose was to defend humans against oxidants and free radicals that cause aging and cancer (32). UA recently been shown to be a powerful scavenger of O₃ and NO₂. (33). UA is also capable of scavenging singlet oxygen, peroxy radicals, and hydroxyl radicals *in vitro* (13). UA could play a particular important role in COPD because α_1 -antitrypsin is protected from nitration by UA *in vitro* (33). Two small studies have reported conflicting results between COPD and plasma (5, 11). Garcia-Pachon et al. (11) showed that a high serum UA (above median) was associated with low FEV₁, but Hageman et al. (5) reported that UA was lower in COPD patients. These differences may have been due to chance since both these

studies were both very small (59 and 58 subjects, respectively) compared to our study (503 subjects).

Unlike UA, GSH is a major low molecular weight antioxidant that has been extensively studied in COPD. GSH plays an essential role in mitigating oxidative stress by donating hydrogen to form a glutathione disulfide (GssG) or from direct scavenging of free radicals (20). In our study, there was no association between plasma levels of GSH and lung function. Premanand also failed to show a difference in plasma levels of GSH in smokers with and without COPD (14). On the other hand, intracellular erythrocyte GSH (normally 1–3 mM) has been shown to be significantly decreased in stable COPD patients and during acute exacerbations of COPD (34). Also, glutathione peroxidase activity, which converts GSH to GssG, has been shown to be lower in both stable COPD patients and during acute exacerbations of COPD (35, 36). GSH is concentrated in the lung epithelial lining fluid, and has shown to be increased in the BALF of COPD patients and smokers, but decreased during exacerbations (37–39).

This study is the first to report that COPD patients with a history of exacerbations have lower levels of plasma GSH. This is consistent with the hypothesis that a defective adaptive GSH response may result in the systemic inflammation and oxidative stress that are associated with acute exacerbations (35, 40). An alternative interpretation of these results is that GSH stores are depleted after an exacerbation and that it takes time to replete the stores. The BRONCUS study (25) and other meta-analyses (24) supports the idea that boosting GSH pathway defenses with N-acetylcysteine may prevent exacerbations for those not on inhaled corticosteroids.

A problem with comparing GSH and GSSG studies is that reported plasma levels can vary widely due to collection techniques or sample processing (41). In this study, blood was drawn through a butterfly needle and samples were immediately processed by remove proteins and, although the samples were collected in a vacuutainer tube and not a syringe, there was minimal hemolysis visibly detectable. Despite this, we report glutathione levels slightly lower than those reported by Samiec et al. (42), who reported plasma GSH concentration of 1.32 μ M. The lower values in our study may be related to oxidation of GSH during processing or storage. Other differences with our study are that all of our subjects had a history of smoking that may have resulted in lower plasma GSH (43).

Unlike UA and GSH, we did not find any associations between ASC and lung function. These results are similar to other publications such as Tuncer et al., who showed that ASC levels did not differ in stable COPD patients or acute exacerbations of COPD (44). ASC is a unique antioxidant in humans because unlike other mammals, primates have lost the ability to synthesize ASC and must rely entirely on diet to obtain this vitamin (45). However, some dietary studies such as the Morgen study have shown that high intake of ascorbate is associated with improved FEV₁ and FVC (9). Unlike the Morgen study, our findings and other publications suggest that dietary antioxidants other than ASC be responsible for this effect.

The main limitation of this study was that it is cross sectional. Thus, although some plasma antioxidants were associated with worse severity of COPD and a history of exacerbations, it is unknown whether increasing systemic antioxidants prevents progression of COPD or if more severe COPD and exacerbations cause more oxidative stress. Other potential confounding factors that we could not assess were the role of a healthier lifestyle (exercise, less caloric intake of food, vitamin supplementation and quality foods high in antioxidants). For instance, all freshly prepared fruit and vegetables, nuts and meats are high in GSH while processed foods, cereals, grains and dairy products are deficient in GSH (46).

In summary, the strengths of this study were large sample size, use of a better control group (i.e., smokers), evaluation of multiple antioxidants, and a determination of the relationship between plasma antioxidants and a history of COPD exacerbations. We found that a higher level of uric acid was associated with better lung function and lower levels of GSH were associated with a history of exacerbations. These results suggest continued study of the antioxidant pathways for therapy in COPD; however, previous studies using NAC and other direct dietary antioxidant supplementation in smoking related lung diseases have been ineffective (47, 48). A new approach including indirect stimulation of antioxidant defense may be more appropriate (49).

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ABBREVIATIONS

ASC	Ascorbate
BD	Bronchial dilator
COPD	Chronic obstructive pulmonary disease
FEV₁	Forced expiratory volume at one second
FVC	Forced vital capacity
GOLD	Global initiative for Chronic Obstructive Lung Disease
GSH	Glutathione
GssG	Oxidized glutathione or glutathione disulfide
HPLC	High performance liquid chromatography
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
UA	Uric acid

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Figure 1.

Plasma uric acid levels (UA) are lower in smokers with more severe airflow obstruction. Smokers without COPD (SC) and by GOLD stage (1–4). Means and interquartile range are shown. Smokers with GOLD 4 COPD had significantly lower plasma UA.

Figure 2. COPD patients with a history of exacerbation in the past year have a lower ratio of reduced to oxidized glutathione. Means and interquartile range are shown.

Table 1

Demographics

	Smokers without COPD (N = 136)	COPD (N = 367)	p-value
Age (years)	57 (11)	66 (10)	<0.001
Sex (female)	75 (55%)	163 (44%)	0.032
Body Mass Index	29.2 (7.0)	27.2 (6.2)	0.005
Pack-years	42 (28)	57 (31)	<0.001
Current smokers	70 (51%)	78 (21%)	<0.001
FEV ₁ % predicted	80% (16%)	50% (22%)	N/A
FEV ₁ /FVC	0.77 (0.05)	0.48 (0.12)	N/A

Shown are mean ($\pm$ standard deviation); p-value by 2 sample *t*-test of the means or by χ^2 test; spirometry measurements are post-bronchodilator; N/A – not applicable.

Table 2

Plasma antioxidant concentration by group

	Smokers without COPD (N = 136)	COPD (N = 367)	p-value
Uric Acid uM	560 (278)	555 (295)	0.85
Ascorbate uM	52.1 (33.9)	57.9 (34.4)	0.10
GSH uM	0.53 (0.34)	0.50 (0.42)	0.74
GssG uM	0.24 (0.13)	0.23 (0.17)	0.67

Shown mean ($\pm$ standard error); p-value by 2 sample *t*-test of the means.

Table 3

Uric acid (mM) by GOLD stage

GOLD stage	uM Uric Acid	p-value (versus no COPD)
Smokers without COPD (N = 136)	506 (248)	
GOLD 1 (N = 41)	591 (281)	0.45
GOLD 2 (N = 130)	561 (266)	0.57
GOLD 3 (N = 116)	494 (285)	0.95
GOLD 4 (N = 80)	439 (272)	0.009

Median (interquartile range); Kruskal-Wallis p-value.