Comparison of Plasma Antioxidant Levels and Related Metabolic Parameters Between Smokers and Non-smokers

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The relationship between cigarette smoking and cell damage is complicated, particularly considering the role of oxidative stress. The aim of this study was to identify the relationships among plasma nicotine metabolites, lipophilic antioxidants, and metabolic parameters in smokers and non-smokers. This cross-sectional study recruited 100 subjects who visited the Department of Family Medicine at Kaohsiung Medical University Hospital. Excluding 14 ineligible cases, 46 smokers and 40 non-smokers were enrolled. Plasma nicotine metabolites, lipophilic antioxidants (including retinol, lycopene, α-carotene, β-carotene, δ-tocopherol, γ-tocopherol and α-tocopherol), related metabolic parameters, and body composition (including height, weight, body mass index, body fat, and waist circumference) were examined by comparison of means, correlations and regressions. Significant correlations among nicotine metabolites, age, sex, body composition and plasma lipophilic antioxidants were noted. Nicotine metabolites, age, body height and body weight were closely associated with plasma antioxidant levels ($p < 0.05$) in multiple linear regression. The levels of α-carotene, β-carotene, γ-tocopherol and lycopene were lower in smokers than in non-smokers ($p < 0.01$). The plasma level of high-sensitivity C-reactive protein (hsCRP), which is a marker for high cardiovascular risk, was higher in smokers than in non-smokers ($p = 0.003$). We conclude that the lower plasma antioxidant levels and the higher level of hsCRP in smokers may lead to decreased protective efficacy compared with non-smokers. Further studies are warranted to support our hypothesis.

Key Words: antioxidant, cigarette smoking, nicotine metabolites
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Cigarette smoking is known to contribute to many diseases, including cancer, chronic obstructive pulmonary disease, stroke, cardiovascular disease and peptic ulcers [1–5]. Investigators have attempted to elucidate the mechanisms of the pathogenesis associated with cigarette smoking, but the conclusions were not consistent. A basic hypothesis is that free radicals cause oxidative damage to macromolecules such as lipids, proteins and DNA; therefore, free radicals are believed to be instrumental in the pathogenesis of diseases [6,7]. In accordance with this theory, antioxidants such as

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carotenes are believed to play important roles in resisting damage from oxidative stress resulting from cigarette smoking. Although the inferences to date regarding the relationship between smoking and antioxidants are equivocal, differences in the effects of antioxidants between smokers and non-smokers have been studied [8–13]. For instance, Alberg demonstrated that the circulating concentrations of ascorbic acid, α-carotene, β-carotene, and cryptoxanthin are, on average, 25% lower in smokers compared with non-smokers [8]. A study by Mezzetti et al showed that plasma vitamin C and lipid peroxide levels were lower and higher, respectively, in smokers than in non-smokers when these subjects were undergoing coronary bypass surgery [13]. However, there is still limited information regarding the relationship between cigarette smoking and plasma antioxidant concentrations in disease-free individuals.

Nicotine is the main substance that results in addiction to smoking. Because nicotine is a substance specific to cigarette smoking, it can be used as a marker for how many cigarettes are consumed by the smoker. Therefore, it allows us to quantify the amount that a subject smokes. Nicotine metabolites, including cotinine, nicotine-N-oxide and a number of derivatives, offer a priority consideration. These are more accurate than other biomarkers such as carboxyhemoglobin or carbon monoxide, which are do not predictor the amount smoked. In addition, such biomarkers may be present as a result of exposure to other environmental factors [14].

Cigarette smoking is related to cardiovascular diseases. Elevated levels of high-sensitivity C-reactive protein (hsCRP) or homocysteine appear to indicate risk for cardiovascular diseases [15–18]. Even though the associations between cardiovascular disease and hsCRP and homocysteine are well known, very few studies have assessed the association between cigarette smoking and hsCRP and homocysteine levels. Two studies have demonstrated that hsCRP levels were higher in smokers than in non-smokers [19,20], while another two studies have reported that there was no significant association between hsCRP and smoking status itself and that there was no difference in hsCRP levels between smokers and non-smokers [21,22]. In studies that assessed the relationship between homocysteine levels and cigarette smoking, some investigators suggested that the plasma homocysteine level is higher in smokers than in non-smokers [22–24], while others demonstrated the opposite [25]. Therefore, the research indicates that the associations between hsCRP and cigarette smoking and between homocysteine and cigarette smoking may be complicated.

Therefore, the aim of this study was to determine the differences in body composition, metabolic characteristics, and levels of hsCRP, homocysteine and plasma lipophilic antioxidants between smoking and non-smoking subjects.

Methods

This cross-sectional study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital. One hundred subjects who visited the Department of Family Medicine at Kaohsiung Medical University Hospital were recruited initially. The smoking subjects were selected from people who visited for smoking-cessation consultations in 2002 and 2003. Non-smokers were selected to match the age of the smoking participants. Our exclusion criteria included the following: subjects with any identified disease (e.g. diabetes, hypertension and coronary artery disease); those already under nicotine replacement therapy; those regularly taking vitamin supplements; vegetarians; and those taking medicine. Excluding 14 ineligible individuals, a total of 86 participants (16–78 years old), including 46 smokers and 40 non-smokers, were enrolled.

Participants were asked to record their regular dietary habits before blood sample collection. Participants were blinded as to which blood examination was performed to reduce the possibility of deliberate food intake. Fasting blood samples were drawn in the morning and were stored immediately in an ice chest and kept out of sunlight. At the same time, demographic data were collected via questionnaires, and body composition was measured by well-trained examiners employing a bioelectric impedance analysis meter [26,27]. Heparinized blood samples were centrifuged at 3,000 revolutions per minute for 10 minutes at 4°C within 1 hour of being drawn. Plasma was separated and stored in aliquots at –80°C until required for analysis. During transportation, the plasma aliquots were stored at –20°C, which was maintained by dry ice. Blood analysis included plasma nicotine metabolites, metabolic parameters (blood sugar, cholesterol, triglyceride, glutamate pyruvate transaminase

[GPT], creatinine, uric acid [UA], hsCRP and homocysteine), and antioxidants (α-carotene, β-carotene, δ-tocopherol, γ-tocopherol, α-tocopherol, retinol and lycopene).

Samples were thawed and mixed well before analysis. Antioxidants were analyzed by high-pressure liquid chromatography [28–30]. Aliquots of plasma were mixed with ethanol and hexane. The sample was then centrifuged at 10,000 revolutions per minute for 5 minutes and the hexane layer was collected and evaporated under nitrogen, and finally dissolved in a mobile phase in the high-pressure liquid chromatography system. The mobile phase consisted of a solvent system of 68:22:7 (v/v/v) acetonitrile-tetrahydrofuran-methanol with 1% (v/v) ammonium acetate. The separation module (Waters 2695; Waters Corp., Milford, MA, USA) was equipped with a Waters Novapak C18 column (150 × 3.9 mm) and two programmable multi-wavelength detectors (Dual λ Absorbance Detector and Scanning Fluorescence Detector; both from Waters Corp.). The detection wavelength was set at 295 nm for tocopherols, 325 nm for retinol and 450 nm for carotenoids. The column was fitted with a pre-column module (Guard-Pak Pre-column; Waters Corp.) and all samples were pre-filtered through a 0.45-μm filter (Waters Corp.). The analysis procedure used in this study was modified from a previously reported protocol [31]. Plasma nicotine metabolites were measured by a competitive chemiluminescent immunoassay method using IMMULITE 1000 [32], which can detect plasma nicotine metabolites at the same time, which corresponds to the amount of nicotine absorbed *in vivo*. Homocysteine and hsCRP were also measured by a competitive chemiluminescent immunoassay [33,34]. Cholesterol, triglyceride, blood sugar (AC sugar), creatinine, GPT, and UA were detected by a nephelometric method using the Beckman Coulter LX-20 (Beckman Coulter Inc., Fullerton, CA, USA).

SPSS version 14.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for statistical analysis. Descriptive analyses were examined to identify differences in demographic characteristics, metabolic parameters and plasma antioxidant levels between smokers and non-smokers. Correlation coefficients and multiple linear regression were used to identify associations among plasma nicotine metabolites, age, sex, body composition and plasma antioxidants.

Results

Demographic and metabolic characteristics of the participants

Age, sex, smoking duration, and body composition (height, weight, body mass index [BMI], waist circumference and body fat) are summarized in Table 1.

Table 1. Comparison of demographic characteristics and metabolic parameters between smokers and non-smokers

	Smokers ($n = 46$)	Non-smokers ($n = 40$)	p
Demographic characteristics			
Age (yr)	33.5 ± 15.6	40.7 ± 18.6	0.184*
Male/female (n)	37/9	22/18	0.020†‡
Smoking (yr)	14.1 ± 11.9	0	< 0.001*§
Height (cm)	170.5 ± 5.3	161.9 ± 6.9	0.088*
Weight (kg)	69.1 ± 16.2	63.2 ± 12.0	0.499*
BMI (kg/m^2)	23.7 ± 4.8	24.1 ± 4.5	0.622*
Body fat (%)	24.1 ± 3.3	28.9 ± 10.4	< 0.001*§
Waist circumference (inches)	29.5 ± 5.2	30.3 ± 5.4	0.697*
Metabolic characteristics			
Cholesterol (mg/dL)	183.8 ± 24.2	186.1 ± 32.3	0.072*
Triglyceride (mg/dL)	118.5 ± 37.8	126.3 ± 36.1	0.311*
Blood sugar (mg/dL)	99.3 ± 23.5	109.2 ± 34.6	0.254*
Creatinine (mg/dL)	0.71 ± 0.26	0.77 ± 0.31	0.588*
Glutamate pyruvate transaminase (IU/L)	25.0 ± 16.7	26.2 ± 10.9	0.036*‡
Uric acid (mg/dL)	5.1 ± 1.2	4.9 ± 1.2	0.794*
Nicotine metabolites (ng/mL)	339.0 ± 194.4	0	< 0.001*§
High-sensitivity C-reactive protein (mg/dL)	0.64 ± 1.20	0.18 ± 0.35	0.003*§
Homocysteine (μmol/L)	10.1 ± 2.1	9.3 ± 2.4	0.117*

*t test; †χ^2 test; ‡$p < 0.05$; §$p < 0.01$.

Table 2. Comparison of plasma antioxidant levels between smokers and non-smokers, as analyzed by *t* test

	Smokers ($n=46$)	Non-smokers ($n=40$)	p
α-carotene (μg/dL)	3.3 ± 1.2	6.7 ± 4.0	< 0.001*
β-carotene (μg/dL)	11.7 ± 6.7	34.9 ± 22.8	< 0.001*
γ-tocopherol (μg/mL)	1.2 ± 0.4	1.4 ± 0.7	< 0.001*
Lycopene (μg/dL)	4.3 ± 1.7	6.3 ± 3.8	0.002*
δ-tocopherol (μg/mL)	0.085 ± 0.030	0.100 ± 0.046	0.106
α-tocopherol (μg/mL)	7.6 ± 2.5	9.6 ± 3.2	0.172
Retinol (μg/dL)	49.3 ± 11.7	47.8 ± 14.5	0.236

*$p < 0.01$.

Table 3. Relationships (Pearson's correlation coefficients) between plasma levels of antioxidants and nicotine metabolites, age and body composition

	α-carotene	β-carotene	α-tocopherol	δ-tocopherol	γ-tocopherol	Retinol	Lycopene
Nicotine metabolites	–0.472*	–0.501*	–0.367*	–0.279*	–0.321*	–0.061	–0.262†
Age	0.388*	0.485*	0.657*	–0.079	–0.104	0.402*	0.128
Height	–0.420*	–0.532*	–0.138	0.010	–0.113	0.185	–0.108
Weight	–0.220†	–0.329*	0.179	0.126	0.071	0.279*	0.055
BMI	–0.049	–0.130	0.235†	0.139	0.130	0.229†	0.101
Body fat	0.168	0.046	0.034	0.118	0.178	–0.044	0.172
Waist circumference	0.091	0.017	0.340*	0.063	0.049	0.308*	0.122

*$p < 0.01$; †$p < 0.05$. BMI = body mass index.

There were no statistically significant differences between the two groups in terms of age, height, weight, BMI or waist circumference. However, there was a difference in body fat between the two groups ($p < 0.001$). The body fat percentage of smokers (mean = 24.1%) was significantly lower than for non-smokers (mean = 28.9%). Metabolic parameters of participants are also displayed in Table 1. There were no statistically significant differences between the two groups in terms of cholesterol, triglyceride, blood sugar, creatinine, UA and homocysteine. HsCRP was higher in smokers (mean = 0.64 mg/dL) than in non-smokers (mean = 0.18 mg/dL) ($p = 0.003$).

Relationships among plasma nicotine metabolites, body compositions and plasma antioxidant levels

Comparisons of plasma antioxidant levels between smokers and non-smokers are shown in Table 2. There were statistically significant differences between the two groups in terms of α-carotene, β-carotene, γ-tocopherol and lycopene levels. The plasma α-carotene (smokers *vs*. non-smokers, mean = 3.3 μg/dL *vs*. 6.7 μg/dL, $p < 0.001$), β-carotene, γ-tocopherol and lycopene levels (all $p < 0.01$) were lower in smokers than in non-smokers.

We performed correlation analysis to identify correlations among nicotine metabolites, age, sex, body composition and antioxidant levels, and the results are shown in Table 3. Nicotine metabolites were inversely related to α-carotene, β-carotene, α-tocopherol, δ-tocopherol, γ-tocopherol and lycopene levels. With regard to age, correlations were evident between age and α-carotene, β-carotene, α-tocopherol and retinol levels ($p < 0.01$).

Table 4 shows the relationships among dependent variables (α-carotene, β-carotene, α-tocopherol and retinol) and independent factors such as age, body height, body weight, and nicotine metabolite levels by multiple linear regression. Age was positively correlated with α-carotene, β-carotene, α-tocopherol and retinol levels. Nicotine metabolites were negatively correlated with β-carotene and α-tocopherol levels.

Discussion

Our study demonstrated that plasma antioxidant levels (lycopene, α-carotene, β-carotene and γ-tocopherol) were significantly lower in smokers than in non-smokers. Our results are consistent with these of a previous study, which compared the antioxidant

Table 4. Multiple linear regression models of relationships among dependent variables (plasma antioxidant levels) and independent factors

Models; factors	B (SE)	95% CI	*p*
Dependent variable: α-carotene			
Age	0.058 (0.019)	0.021 to 0.094	0.003
Height	–0.153 (0.043)	–0.239 to –0.067	0.001
Adjusted R^2 = 24.4%			
Dependent variable: β-carotene			
Nicotine metabolites	–0.036 (0.007)	–0.050 to –0.021	< 0.001
Age	0.473 (0.092)	0.291 to 0.656	< 0.001
Weight	–0.416 (0.107)	–0.630 to –0.203	< 0.001
Adjusted R^2 = 48.0%			
Dependent variable: α-tocopherol			
Nicotine metabolites	–0.003 (0.001)	–0.005 to –0.001	0.003
Age	0.104 (0.014)	0.077 to 0.131	< 0.001
Adjusted R^2 = 47.7%			
Dependent variable: retinol			
Age	0.299 (0.072)	0.155 to 0.442	< 0.001
Weight	0.243 (0.086)	0.073 to 0.414	0.006
Adjusted R^2 = 21.7%			

SE = standard error; CI = confidence interval.

levels according to smoking exposure [9]. They suggested that subjects exposed to smoking had lower plasma β-carotene levels than those who were not. However, Dietrich et al's study demonstrated that the γ-tocopherol level was higher in smokers than in non-smokers [9], which contrasts with our study. In the study done by Wei et al, smokers had significantly lower plasma levels of α-carotene and β-carotene, whereas the reduction in tocopherol and lycopene levels in smokers was very limited [35]. Chronic cigarette smokers have lower concentrations of many dietary antioxidants (β- and α-carotene) in serum and buccal mucosa cells compared with nonsmokers, an effect which is not entirely ascribable to diet [11]. There is no doubt that the levels of β- and α-carotene were lower in smokers compared with non-smokers. However, the findings of higher and lower levels of γ-tocopherol in smokers are still contentious. The studies of Gabriel et al [11] and Dietrich et al [9] revealed that γ-tocopherol was higher in smokers than in non-smokers. However, we found the opposite. Similarly, Wei et al's study [35] also demonstrated that the reduction of tocopherol was very limited. However, no clear mechanism for the relationship between the amount of γ-tocopherol and smoking status has been described in the literature. Therefore, further studies are needed to clarify this finding.

Plasma antioxidant levels were closely, but inversely related to levels of plasma nicotine metabolites in our study. We propose the explanation that more regular cigarette smoking would markedly affect plasma nicotine metabolites and thus decrease plasma antioxidant levels. Furthermore, our finding suggests that plasma nicotine metabolites are appropriate as biomarkers for smoking consumption. These biomarkers should be applicable use in future studies of cigarette smoking.

The associations between hsCRP and cigarette smoking were inconclusive in the previous studies [19–24]. Our finding that the hsCRP levels were significantly higher in smokers than in non-smokers indicates that cigarette smoking causes greater burden in terms of vascular diseases mediated by elevated hsCRP.

The relationship between cigarette smoking and body weight change is also controversial in the literature. Our clinical experience suggested that subjects who smoked would have a lower body weight. This study found that the body fat of smokers (24.1 ± 3.3%) was lower than that of non-smokers (28.9 ± 10.4%) ($p < 0.001$). A statistical linear relationship between plasma nicotine metabolites and body fat was also found (data not shown). However, the differences between the two groups in terms of body weight, BMI

and waist circumference were not clear. A previous study demonstrated that average cigarette smokers have a lower BMI than non-smokers [36]. The small sample size in this study probably limited reaching an equivocal outcome. Further studies with a larger sample size are needed to clarify this hypothesis.

An interesting outcome of this study was that age was positively related to levels of plasma antioxidants including α-carotene, β-carotene, α-tocopherol and retinol. This can be explained in three ways: (1) people with older age have healthier lifestyles, meaning that their nutrition is more balanced than younger people; (2) the use of and need for antioxidants in younger people are greater than in older people; (3) lipophilic antioxidants can accumulate in the body by aging; therefore they can be detected more frequently in older people than in younger people.

A notable feature of our study is that we did not restrict the diet of the study subjects because diet control *per se* would change the dietary habits of the individuals. Individuals may have a different need and capacity for nutrient consumption. If we restrict the diet of our study subjects, we may alter the balance in antioxidant levels. Nevertheless, we recognize that the cross-sectional study design is a weakness because of the presence of potential confounding factors. On the other hand, our careful and comprehensive surveys of the participants, particularly the rigorous and comprehensive laboratory examinations, are strengths of this study.

In this study, the levels of antioxidants (including α-carotene, β-carotene, γ-tocopherol and lycopene) were lower in smokers than in non-smokers. The level of hsCRP was higher in smokers than in non-smokers. Levels of nicotine metabolites were inversely associated with plasma levels of lipophilic antioxidants. Therefore, cigarette smoking may influence oxidative stress by affecting the levels of plasma antioxidants, which may be involved in the mechanisms underlying various diseases. Our study is the first attempt to determine the relationship among cigarette smoking, plasma antioxidants, plasma nicotine metabolites and body composition in healthy subjects in Taiwan.

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吸菸者和非吸菸者在血漿中抗氧化劑濃度的差異

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吸菸和細胞傷害之間的關聯性是很複雜的，其中氧化壓力也被認為有關聯。本研究的目的在研究血漿中尼古丁代謝物、脂溶性抗氧化劑、生化代謝指標、以及吸菸的相關性。這個橫斷式研究將 **100** 位在高雄醫學大學家庭醫學科看診的個案納入研究。排除掉不符合收案條件的 **14** 位個案，**46** 位吸菸者和 **40** 位非吸菸者完成收案。測量的項目包括：血漿尼古丁代謝物、脂溶性抗氧化劑 (包括維他命 **A**、蕃茄紅素、α **-** 胡蘿蔔素、β **-** 胡蘿蔔素、δ **-** 維生素 **E**、γ **-** 維生素 **E** 和 α **-** 維生素 **E**)、代謝性生化指標，和生體結構組成 (包括身高、體重、身體質量指數、體脂肪、以及腰圍)。統計方法包括平均數比較、相關係數分析、以及回歸檢定。血漿尼古丁代謝物、年齡、性別、生體結構組成、和血漿脂溶性抗氧化劑濃度呈現統計顯著的相關性。複回歸分析則顯示：血漿尼古丁代謝物、年齡、身高和體重，是主要影響血漿抗氧化劑濃度的因素 ($p < 0.05$)。吸菸者血漿中 α **-** 胡蘿蔔素，β **-** 胡蘿蔔素，γ **-** 維生素 **E** 和蕃茄紅素的量低於非吸菸者 ($p < 0.01$)。與心血管危險性相關的生物指標：血漿中高敏感性 **C-** 反應蛋白 (**hsCRP**) 在吸菸者的濃度比非吸菸者高。我們認為這些現象解釋了：吸菸者因為血漿中較低的抗氧化物濃度及較高的 **hsCRP** 濃度可能會造成較低的細胞保護效果。需要進一步的研究來支持我們的假說。

關鍵詞：抗氧化劑，吸菸，尼古丁代謝物

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