Association of C-reactive protein and total antioxidant capacity in smoker

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Abstract

Cigarette smokers demonstrate elevated oxidative stress (OXS) levels and increased pro-inflammatory cytokines. In this study, Relationships between serum C-reactive protein (CRP) and total antioxidant capacity (TAC) were examined in smoker men. For this purpose, venous blood samples (5ml) were collected from sedentary smoker males aged (41.8 ± 4.36) after an overnight fast (K 12 h) between 8:30 and 9:30 AM. Pearson correlation coefficients were used to determine the association between CRP and TAC. A P-value of < 0.05 was considered to be statistically significant. Data analyses showed that CRP is negatively related with TAC in studied subjects. Based on these data, we can say systemic inflammation is associated with stress oxidative in smoking.

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Introduction
The relationship of cigarette smoking (smoking) with systemic inflammation and cardiovascular diseases has been frequently reported (Virginia et al., 2011). Release of inflammatory mediators by cigarette smoking has been introduced as the underlying cause of most chronic inflammatory diseases (Walters et al., 2005; Barbieri et al., 2007). On the other hand, decreased antioxidant protective systems following cigarette smoking is also introduced as being responsible for most pathological conditions. This is due to the fact that in addition to decreased total antioxidant capacity, increased levels of free radicals and most oxidants is also caused by cigarette smoking (Rouzbahani et al., 2009).

Although some changes caused by smoking are reversible after quitting smoking, it has been reported that smoking has so powerful inflammatory effects that high levels of some inflammatory mediators such as C - reactive protein (CRP) can still be preserved even 10-20 years after quitting smoking (Dilyara et al., 2007). In this regard, academic resources have frequently shown that levels of CRP as a proinflammatory cytokine and cardiovascular risk factor are higher in smokers than in non-smokers (Karadag et al., 2008; Groenewegen et al., 2008). Findings show that antioxidant mechanisms in living organisms compete with adverse reactions caused by oxidative stress (Aycicek et al., 2005).

According to existing evidence, smoking results in increased free radicals and oxidants and decreased total antioxidant capacity (TAC) (Polidori et al., 2003). It seems that increased levels of CRP along with decreased TAC in smokers are underlying causes of most diseases caused by smoking. Therefore, identifying and creating appropriate pharmaceutical or non-pharmaceutical strategies to reduce the harm caused by smoking has attracted the attention of health and wellbeing researchers. However, few studies have been conducted on the relationship between them in smokers. Hence this study aims to determine the relationship between serum CRP levels and TAC in non-athlete male smokers.

Method and Subjects
Human Subjects
As previously mentioned, this study aimed to determine whether serum CRP concentration is associated with total antioxidant capacity in adult males with cigarette smoking. Subjects was thirty six sedentary healthy smoker male aged 41.8 ± 4.36 year of old, BMI 29.8 ± 1.99 kg/m2 that participated by accessible sampling in present study. Approval for the study had been given in 2013 and 2014 by the Ethics Committees of Islamic Azad University, Islamshahr branch, Iran. Each participant received written and verbal explanations about the nature of the study before signing an informed consent form.

Inclusion and exclusion criteria
Participants were non-athletes and non-alcoholics. Having history of at least 10 cigarettes a day for 5 years was the main criterion for inclusion. All subjects were non-smokers and had not participated in regular exercise/diet programs for the preceding 6 months. The exclusion criteria were as follows: Patients with known history of acute or chronic respiratory infections, neuromuscular disease, and cardiopulmonary disease. Furthermore patients with overt diabetic were also excluded from the study.

Anthropometry
All anthropometric measurements were made by the same trained general physician and under the supervision of the same pediatrician following standard protocols. Body composition monitor (BF508-Omron made in Finland) with a precision error of less than 100 g was used to measure weight and body fat percentage of the subjects. Height of the barefoot subjects was measured to the nearest 0.1 cm. Body mass index was measured for each individual by division of body weight (kg) by height (m2).

Biochemical measurement
All blood samples were taken following an overnight 12-hour fast between 8:30 and 9:30 AM. Subjects were advised not to perform serious physical activity 48 hours prior to blood samples. Part of blood samples were dispensed into EDTA-coated tubes and
centrifuged for 10 minutes in order to separate serum. Serums were analyzed for CRP. Serum CRP was determined by ELISA method (Diagnostics Biochem Canada Inc. High sensitivity C-reactive protein (Hs-CRP)). Intra-assay and inter-assay coefficient of variation of the method were 8.3% and 7.8 respectively. FRAP method was used to determine the plasma total antioxidative capacity (the sensitivity of method was 0.1 Units/ml).

Data analysis
Statistic analysis was done with SPSS 15.0 for Windows. The Kolmogorov-Smirnov test was applied to determine the variables with normal distribution. Pearson correlations were used to establish the relationship between serum CRP and TAC in smoker subjects. A p-value less than 0.05 were considered statistically significant.

Results
Anthropometric and clinical characteristics of the study participants are shown in Table 1. Data were expressed as individual values or the mean and standard deviation.

Table 1. The descriptive anthropometric and clinical features of studied smokers.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>41.75</td>
<td>4.36</td>
<td>33 – 52</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91.4</td>
<td>5.30</td>
<td>81 – 100</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175</td>
<td>2.63</td>
<td>168 – 180</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.8</td>
<td>1.99</td>
<td>26.8 – 34.7</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>28.9</td>
<td>1.88</td>
<td>26.3 – 33.1</td>
</tr>
<tr>
<td>C-reactive protein (ng/ml)</td>
<td>2036</td>
<td>914</td>
<td>445 – 4921</td>
</tr>
<tr>
<td>Total antioxidant capacity (mmol/L)</td>
<td>0.311</td>
<td>0.242</td>
<td>0.12 – 0.93</td>
</tr>
</tbody>
</table>

Data of Pearson coefficient correlation showed a significant negative correlation between serum CRP with total antioxidant capacity in studied smokers (p = 0.001, r = 0.55). On the other hand, increased TAC in smoker males is associated with decreased serum CRP. Their relationship is showed in Fig 1. TAC was also negatively correlated with age in smokers (p = 0.002, r = 0.50).

Discussion
A significant inverse relationship was observed between serum CRP levels and TAC in smoker subjects before. In other words, in this study, a significant inverse relationship was observed between serum CRP levels and TAC in adult male smokers. These findings somehow support the relationship between systemic inflammation and antioxidant levels in smokers. CRP is secreted by hepatocytes as an acute phase response sensitive to infectious harms and some other internal and external stimuli that have been introduced as a non-specific inflammatory marker (Pepys et al., 2003). Scientific evidence has mostly shown that both smoking and depression are accompanied by increased levels of inflammatory markers (Nunes et al., 2012).

![Fig. 1. Relationship between serum CRP and total antioxidant capacity in smoker: A negative significant correlation.](image-url)
study showed that although CRP levels in smokers tended to increase, no statistically significant difference between smokers and non-smokers was observed (Bergmann et al., 2009). Moreover, there was a significant inverse correlation between the levels of antioxidants with duration of smoking and number of cigarettes smoked per day (Bahmani et al., 2006). In fact, as the duration of cigarette smoking and number of cigarettes smoked increase, more free radicals is produced, this results in increased oxidative stress. Consequently, more antioxidants are involved to deal with these free radicals, which in turn lead to decreased antioxidant levels in smokers.

Release of free radicals during smoking causes damage to the structure and activity of enzymes present in erythrocytes with sensitive structures similar to other proteins. In contrast, antioxidants maintain and enhance the structure and activity of existing enzymes by eliminating and reducing free radicals and other oxidants (Cotgreave et al., 1998). Imbalance between oxidants and antioxidants has been frequently reported in smokers (Rahman et al., 2006), which leads to tissue damage. Such damages can be attributed to the presence of $10^{14-10^{18}}$ oxidant molecules in cigarette (Pryor et al., 1999). For example, 4-hydroxy-2-nonenal (4HNE) is one of the end products of lipid peroxidation with high dispersion capability, which is also considered as one of the markers of oxidative stress that is able to be absorbed even by target cells in tissues away from where free radicals are formed (Doorn et al., 2002). 4HNE is in fact an effective alkylating material that reacts with DNA and proteins and finally produces different types of toxic substances capable of causing cell death and stimulating stress signaling pathways (Uchida et al., 1999). It is possible that 4HNE is produced directly or indirectly by smoke-induced lipid peroxidation of cell membranes (Aruna et al., 2006). However, it is also noted that smoking independently increases oxidative stress in all airway/airspace epithelium cells (Rahman et al., 2002). These observations have also been reported in some other studies pointing to increased 4HNE in smokers’ alveolar epithelium and airways or in patients with chronic obstructive pulmonary (Floegel et al., 2011).

In addition to other factors, appropriate dietary factors play a significant role in modifying and improving CRP profile as well as its blood circulation levels. It seems that appropriate dietary factors are closely associated with serum or plasma levels of this cytokine. In this regard, several studies have revealed that increased intake of dietary antioxidants such as vitamins E and C as well as eggs, tea, fruits, and vegetables decreases CRP concentration (Nanri et al., 2007; Floegel et al., 2011). Accordingly, a recent study has shown a significant inverse relationship between CRP and dietary TAC (Kobayashi et al., 2012). Some other studies, however, have reported that these dietary antioxidants have no effect on CRP levels and there is no relationship between dietary antioxidants and CRP levels (Nanri et al., 2007; de Oliveira Otto et al., 2011). In this regard, a recent study has shown no significant relationship of glutathione, as a potent antioxidant, with CRP and other inflammatory cytokines such as IL-6 and TNF-α (Samadian et al., 2007). On the other hand, some other laboratory studies have shown that antioxidants are effective in reducing CRP levels not only individually but also simultaneously and in collaboration with other effective factors (Stanner et al., 2004).

It seems that the relationship between CRP and antioxidants or TAC appears more in patients, especially in those diseases associated with inflammatory damages. In this regard, a study showed a significant relationship between glutathione, as an antioxidant, and serum CRP levels in hemodialysis patients (Samadian et al., 2004). However, the combined effect of dietary antioxidants or antioxidant vitamins on CRP concentrations has not yet been fully identified. Recently, it has been found that the effects of TAC do not appear by taking only one dietary antioxidant, and new studies use a combination of dietary antioxidants in order to determine the level of TAC (Serafini et al., 2002). Moreover, according to a recent study, a significant inverse relationship was observed between dietary...
TAC and chronic diseases (Wang et al., 2012). These researchers also pointed out that dietary TAC is an independent predictor for plasma TAC in healthy individuals (Li et al., 2013).

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