



A study of high-sensitivity C-reactive protein in relation to respiratory symptoms in mild to moderate asthma

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Abstract

To determine the role high-sensitivity C-reactive protein (CRP) as a inflammation cytokine in the severity of asthma, a resting spirometry test and fasting blood sampling was performed in 42 middle-aged males with mild to moderate severity of asthma for measuring serum CRP and respiratory functional. Also, a total 33 healthy males participated in study as control group. Pearson correlations were used to establish the relationship between serum CRP concentrations with spirometry markers in asthma patients. Serum CRP concentration in asthmatic patients was significantly higher than healthy subjects. Serum CRP correlated negatively with FEV₁ ($p = 0.021$), FVC ($p = 0.026$) and FEV₁/FVC ($p = 0.034$). Based on our results, we can say asthma is a inflammation disorder and these date support the hypothesis that the measurement of serum levels of hs-CRP may be useful tool for detecting systemic inflammation in asthma.

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Introduction

Asthma is a disorder characterized by inflammation of the airways. There is considerable evidence that this disease is a chronic condition that is on the increase in adolescents as it is among other age groups; often under-diagnosed it prevalently affects males and is 10% sustained by an allergic diathesis (Marchi et al., 2002). Another important point is that adolescence, with its peculiarities and characteristic psychological and physical changes affects the clinical expression of asthma and above all requires particular diagnostic and therapeutic attention from the treating pediatrician (Amina et al., 2010). Reported studies have found an inverse relationship between lung function and markers of systemic inflammation (Amina et al., 2010). So that, impaired respiratory function such as forced expiratory volume in one second (FEV₁) is strongly related with cardiovascular risk factors, atherosclerosis, arterial stiffness, cardiovascular disease and mortality, although the mechanisms underlying this response are a matter of some debate. These changes are associated with disturbance in immune response in the lung. This immune response is characterized by the secretion some inflammation cytokines such as C- reactive protein (CRP) and IL-6 (Georas et al., 2005). It was reported that reduced lung function has been associated with various inflammation sensitive plasma proteins. In addition, increased levels of systemic markers of inflammation have been reported in patients with impaired lung function due to obstructive or restrictive lung disease (Aronson et al., 2006). Some studies have indicated a positive correlation between asthma and increased CRP levels (Ebrahim et al., 2011; Ford, 2003; Jousilahti et al., 2002; Olafsdottir et al., 2005). On the other hand, a recent study report that CRP is elevated in clinically stable COPD patients (de Torres et al., 2006). Additionally, it was observed that an increased hs-CRP level is associated with current asthma, respiratory impairment and bronchial hyper-reactivity (Kony et al., 2004, Jousilahti et al., 2002). In contrast, a recent study showed that there is not a

significant relation between CRP and respiratory functional in asthma patients (Ebrahim et al., 2012). Review of research evidence shows that asthma patients have circulation CRP more than normal subjects. But, the question is that whether a serum concentration of high sensitivity C reactive protein (hs-CRP) is related with spirometry markers as respiratory functional in asthma patients. Therefore, the aim of present study is determining the relationship between serum CRP and indicator markers of respiratory functional in a group of men with asthma.

Materials and Methods

Forty two middle-aged men with mild to moderate severity of asthma and 40 healthy males aged that matched for aged (37 to 48 years) participated in this study by randomly in order to compare serum CRP between them and also to examine its relationship with markers indicative of respiratory functional in asthma patients . The study was conducted with the approval of the Ethics Committee of the Islamic Azad University, Iran. After the nature of the study was explained in detail, informed consent was obtained from all participants. Asthma severity was determined by specialist physicians measuring spirometry indices (Minispire model, Made in Italy).

Inclusion and exclusion criteria

Participants were included if they had not been involved in regular physical activity/diet in the previous 6 months. Subjects were reported to be non-smokers, not currently taking supplements of any kind, and having no major health problems (i.e., diabetes, cardiovascular disease, etc.). Daily food records were kept for 48 h preceding each test session, and subjects were instructed to refrain from caffeine consumption and intense physical activity for 24 h before testing. No difference was observed in the subjects' diets 48 h before each trial.

Anthropometric and spirometry measurements

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. Body weight was measured with a standard physician's scale respectively when subjects were in a fasting state. Subjects' height was carefully measured while standing along the wall without shoes while their shoulders were in normal conditions. Body mass index (BMI) was calculated using weight divided by squared height. Spirometry tests were performed in order to asthma diagnosis as well as to determine the asthma severity. Spirometry test were also reformed for measuring forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC). Patients were asked to avoid having tea or coffee as well as other airways dilator food for at least 3 hours prior to spirometry test.

Table 1. Descriptive anthropometric and spirometry markers of the study groups.

Variables	Asthma patients	Healthy subjects
Age (year)	44 ± 7	45 ± 6
Weight (kg)	95 ± 11	97 ± 9
Height (cm)	175 ± 8	176 ± 9
BMI (kg/m ²)	31.02 ± 2.34	31.31 ± 2.13
BF (%)	30.9 ± 2.14	31.2 ± 3.04
FEV1	77 ± 4	97 ± 11
FVC	90 ± 5	96 ± 8
FEV1/FVC	69 ± 6	82 ± 7
CRP (ng/ml)	2311 ± 340	1635 ± 211

BMI: body mass index, BF: Body fat percentage, FEV1: forced expiratory volume in 1 s, FVC: forced vital capacity, CRP: high-sensitivity C-reactive protein, FEV1/FVC: forced expiratory volume in 1 s / forced vital capacity

Blood sampling

Venous blood was collected from subjects after an overnight fast in order to measuring serum CRP. Serum CRP was determined by ELISA method (Diagnostics Biochem Canada Inc. High sensitivity C-reactive protein (Hs-CRP)). The Intra- assay coefficient

of variation and sensitivity of the method were 5% and 10 ng/mL, respectively.

Statistical analyses

Experimental data are presented as means ± SD and were analyzed with the SPSS software version 15.0. The statistical significance of differences between the means in the two groups were evaluated using an independent sample T-test in the case of normal distribution of data sets, and using the Kolmogorov-Smirnov's test when at least in one of the data sets the normal distribution was excluded. The bivariate association between serums CRP with markers indicative of respiratory functional were examined with the Spearman rank correlation analysis in asthma patients.

Results

Table 1 show the descriptive anthropometric and spirometry markers of the study groups. Significant differences were not found in body weight, body fat percentage, BMI in subjects with and without asthma ($p \geq 0.05$). But we have observed that in asthma patients the CRP concentration in serum was significantly higher than in those without asthma symptom ($p = 0.012$). In addition, our findings showed that the level of FEV1 ($p = 0.023$), FVC ($p = 0.019$) and FEV1/FVC ($p = 0.035$) in asthma patients were significantly lower than healthy subjects group. There was no evidence that serum CRP was associated with FEV1 ($p = 0.123$, $r = 0.19$). Also, there was no significant relationship between Serum CRP with FVC ($p = 0.213$, $r = 0.14$), FEV1/FVC ($p = 0.216$, $r = 0.21$) and the other respiratory symptoms.

Discussion

Main finding of this study was serum CRP was not significantly correlated with indicator markers of respiratory functional in asthma patients. Asthma is a syndrome characterized by intermittent narrowing of the small airways of the lung, with subsequent airflow obstruction and symptoms of wheeze, cough and breathlessness. It has been long known that an

important characteristic of asthma is airways hyper-responsiveness, which is the exaggerated narrowing of the airways in response to provocative agents (Kishimoto, 2005). It has been hypothesized that Systemic inflammation is also a possible element in the link between respiratory impairment and cardiovascular events (Amina et al., 2010). Although the psychopathological mechanisms underlying these associations are largely unknown. C-reactive protein is an inflammation cytokine in humans. Its synthesis by the liver is regulated to a large extent by the pro-inflammatory cytokine interleukin (IL)-6 (Amina et al., 2010). Our study showed that CRP level in asthma patients was significantly higher than normal subject. These results were supported by other authors (Sahoo et al., 2009, Amina et al., 2010). In recent years, there have been some reports concerning the measurement of serum levels of hs-CRP as a useful tool for detecting systemic inflammation in asthma (Takemura et al., 2006, Fujita et al., 2007). In addition to cardiovascular disease or diabetes mellitus, plasma hs-CRP levels also obesity increase in presence of obesity and some the other chronic diseases which may be due to adipocyte-derived interleukin-6 (Fujita et al., 2007, Visser et al., 1999, Ford, 2003,). This cytokine can also act as a potent proinflammatory agent and activates the classical complement cascade by binding directly to the complement fragment C1q (Pepys et al., 2003, Aronson et al., 2006). There have been some reports concerning the measurement of serum levels of hs-CRP as a useful tool for detecting systemic inflammation in asthma. Significant association between increasing CRP levels with asthma and other respiratory diseases has been observed. There is an association between increased hs-CRP levels and non-allergic asthma even when adjusted for body weight. The results of another study demonstrated that serum hs-CRP levels were significantly higher in patients with mild-to moderate asthma than in healthy controls (Süvykoski et al., 2004). These findings in consist of previous studies support of systemic inflammation in asthma.

Our study also showed that the spirometry markers such as FEV₁ and FVC or FEV₁/FVC in asthma patients were significantly higher than normal subjects. There is considerable evidence that that impaired lung function as measured by FVC or FEV₁ is a powerful predictor of nonfatal ischemic heart disease and of mortality due to cardiovascular disease (Sin et al., 2005, Schroeder et al., 2003). The majority of patients with reduced FEV₁ have asthma, chronic obstructive pulmonary disease (COPD), or fibrotic lung disease (Mannino et al., 2003). In these conditions, cytokines are over expressed in lung tissue, potentially resulting in systemic low-grade inflammation (Mannino et al., 2003, Sin et al., 2003, Sin et al., 2004).

Present study showed that serum CRP has not correlated with FEV₁, FVC or FEV₁/FVC. These finding were observed in the other previous study. To support these findings, a recent study showed that in patients with asthma, serum levels of hs-CRP were increased compared with healthy controls, and no significant correlations were found between hs-CRP levels and indices of pulmonary function, total serum IgE levels, white blood cell count or eosinophil count (Ebrahim et al., 2012). In addition, in study by Ramirez et al. on patients with mild asthma, no significant correlation was detected between hsCRP and FEV₁ (Ramirez et al., 2010). Study by Doron and collegus also showed no significant relationship between CRP and FEV₁/FVC (Aronson et al., 2006). In other words, despite the observed higher levels of CRP and lower levels of respiratory functional indexes in the asthmatic patients studied, the findings showed that although there is an inverse linear relationship between serum CRP levels and respiratory performance indicators, this relationship not statistically significant. In fact this study confirms previous studies indicating systematic inflammation in these patients and the findings of this study showed that serum CRP levels as a precursor of systemic inflammation is higher in asthmatic patients than in healthy individuals. Moreover, lower levels of respiratory performance indices are observed in these

patients than in healthy subjects. But unlike some previous studies, the present study does not support a significant association between CRP and spirometric indices. These findings are somewhat suggestive of the hypothesis that systemic inflammation and inflammation of the respiratory pathways, each independently influence outbreak or severity of asthma. Of course it is possible that systemic inflammation and respiratory performance in these patients are associated with each other through other inflammatory mediators such as IL-6 or TNF- α , which necessitates further studies in this field. However, the absence of a significant relationship between CRP and respiratory performance indices in the present study, can be attributed perhaps to the low number of patients studied which was the main limitations of this study. Further studies are necessary to elucidate the significance of serum CRP concentration in pathophysiology asthma and the other respiratory diseases.

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