

## Correlation between hs-CRP and Asthma Control Indices

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**Background:** Local and systemic inflammation occur at the same time in asthma and high sensitive CRP may play a role in the pathogenesis of this disease. Conventional approaches to monitor and control asthma involve no direct assessment of airway inflammation. There are some recent data postulating a discrepancy between the markers of airway and systemic inflammation and asthma control test (ACT) scores. In this study we evaluate the correlation between the serum levels of hs-CRP in patients with different levels of asthma control based on ACT scores and spirometric indices.

**Materials and Methods:** The validated Persian version of ACT was administered to one-hundred asthmatic patients. Spirometry was performed and prebronchodilatory FEV1 was measured. Blood samples for CRP measurement were taken and hs-CRP levels were analyzed. Fifty age-matched healthy volunteers comprised the control group.

**Results:** A total of 100 asthmatic patients (57 females and 43 males) and 50 controls were participated. hs-CRP in asthmatics was higher than in controls. No significant differences were found in hs-CRP levels in patients with different levels of asthma control based on ACT ( $\geq 20$ , 16-19,  $\leq 15$ ), GINA classification of asthma control (well controlled, partly controlled, uncontrolled) or FEV1.

**Conclusion:** We found no correlation between degree of systemic inflammation estimated by hs-CRP and other clinical indices of asthma control such as ACT scores, FEV1 and GINA classification of asthma control and even in patients with clinical and spirometric indices of controlled asthma, markers of systemic inflammation were still present.

**Key words:** hs-CRP, Asthma Control Test, Asthma

### INTRODUCTION

C-reactive protein is a sensitive marker of inflammation, infection, and tissue damage (1). Its synthesis by the liver is regulated to a large extent by the proinflammatory cytokine interleukin (IL-6) (2). The rise in CRP is driven by its rate of synthesis and falls rapidly when the pathologic stimulus ceases (3). High sensitivity assays for CRP (hs-CRP) have become available in clinical laboratories (4). hs-CRP is a strong independent predictor of future myocardial infarction, stroke and peripheral arterial diseases and is a prognostic marker for the development of diabetes mellitus (5, 6). Furthermore, it is

increased in COPD in stable condition and during exacerbations (7).

Asthma is a chronic inflammatory disease of the airways with multiple dimensions and phenotype expressions. In asthma, local and systemic inflammation occur and hs-CRP may play a role in its pathogenesis (8). Other studies have shown that increased level of hs-CRP is associated with respiratory symptoms in non-allergic asthmatic adults (9) and the serum level of hs-CRP during exacerbation is significantly higher than the serum level during remission (10). There is a direct correlation between the serum levels of hs-CRP and severity of asthma (11).

Recent international guidelines indicate that the primary goal of asthma treatment is to obtain optimal control and reduce the risk of exacerbations (12). There are several questionnaires that may be useful for assessing asthma control. In 2004 Nathan et al. developed Asthma Control Test (ACT) for the assessment of asthma control (13). The ACT contains five items: the effect of asthma on daily activities, daytime and nocturnal symptoms, use of rescue medications and self assessment of asthma control. Each question has a 5 point scale and the ACT score is the sum of the five scores (13, 14). Pulmonary function assessment by spirometry is another simple and practical tool for assessing asthma control.

While achievement of asthma control and suppression of airway inflammation are considered as important goals, conventional approaches to monitor and control asthma involve no direct assessment of airway inflammation. A positive association was found between inflammatory markers and ACT scores in stable asthmatic patients (5,15) but there are some recent data postulating a discrepancy between the markers of airway and systemic inflammation and ACT scores (16-19).

In this study, we evaluate the correlation between the serum levels of hs- CRP in patients with different levels of asthma control based on ACT scores and spirometric indices.

## MATERIALS AND METHODS

This prospective, case-control study was performed from December 2011 to May 2012 in Kurdistan University of Medical Sciences. One-hundred patients diagnosed with bronchial asthma according to clinical and functional criteria established by GINA were included in this case control study. We excluded subjects with conditions that could affect CRP measurement for reasons other than asthma, such as patients with respiratory tract infection in the previous 6 weeks, smokers, patients with a history of renal, hepatic, cardiovascular, and collagen vascular diseases, cancer, COPD and other lung disorders and obesity (body mass index  $\geq 30\text{kg/m}^2$ ).

The following information was collected for each patient: age, gender, asthma medication and history of hospitalization during a year prior to current presentation.

The validated Persian version of ACT was administered to the subjects (20). Spirometry was performed using Spirolab 3 (MIR, Italy) and prebronchodilatory FEV1 was measured. Blood samples for CRP measurement were taken after 4 hours of fasting. hs-CRP levels were analyzed with ELISA method using the commercial kit (IBL Germany). Fifty age-matched healthy volunteers were used as the control group. The study was approved by the Ethics Committee of Kurdistan University of Medical Sciences. All patients provided written informed consent.

SPSS statistical software version 18 (SPSS Chicago, IL, USA) was employed for data analysis. Descriptive statistics were used to summarize the demographic characteristics of patients. One-way ANOVA or t-test was used to test the significance of differences between mean hs-CRP levels among the groups. Correlations between data were analyzed using Spearman's rank correlation test. A p-value of  $<0.05$  was considered significant.

## RESULTS

A total of 100 asthmatic patients and 50 healthy controls participated in this study. The mean age was 42.34 years (range 15 to 72 years). There were 57 females and 43 males. One third of patients had a family history of asthma in their first-degree relatives.

hs-CRP level was significantly higher in asthmatic patients (11.5 mg/l) as compared to the control group (4.32 mg/l) ( $P < 0.05$ ). There were no significant difference in hs-CRP level between males and females (11.1 and 11.23 mg/l respectively).

According to GINA degrees of asthma control (21), asthma was controlled in 59% of patients, partly controlled in 30% and uncontrolled in 11%. There were no significant differences in hs- CRP levels between these three groups ( $P=0.81$ ) (Table 1). In addition, no significant correlation was found between hs-CRP and FEV1 ( $P=0.5$ ,  $r = - 0.68$ ).

Asthmatic patients were divided into three groups based on their ACT scores: well controlled (ACT  $\geq$ 20, n=61), partially controlled (ACT=16-19, n=26) and uncontrolled (ACT  $\leq$ 15, n=13). No significant differences were seen in hs-CRP levels between these groups [(ACT  $\geq$  20, hs-CRP 10.2mg/l), (ACT 16-19, hs-CRP 9.97mg/l), (ACT  $\leq$  15, hs-CRP 13.67mg/l)] (P=0.27 F= 1.32). (Table 2)

**Table 1.** Correlation between GINA classification of asthma control and serum level of hs-CRP.

GINA Classification	No. of Patients	Hs- CRP level	
Well Controlled	n=59	10.6	P= 0.81
Partly Controlled	n= 30	11.41	
Uncontrolled	n=11	11.20	

**Table 2.** Correlation between ACT score and serum level of hs-CRP

ACT Score	No. of Patients	Hs- CRP level	
ACT $\geq$ 20	n=61	10.2	P= 0.27
ACT = 16 – 19	n= 26	9.97	F = 1.32
ACT $\leq$ 15	n=13	13.67	

The five ACT items were not significantly associated with hs-CRP levels; however, the correlation of hs-CRP with nocturnal symptoms was greater than other items.

## DISCUSSION

The present study results showed no association between the clinical indices of asthma control and the hs-CRP levels in asthmatic patients.

Asthma is a heterogeneous complex inflammatory disease and low-grade systemic inflammation is probably part of the manifestations of this disease. There is now sufficient evidence to support the presence of extra-pulmonary inflammation in asthma that could be measured by the determination and level of increased systemic inflammatory markers such as hs-CRP, serum amyloid A and plasma fibrinogen (1, 2, 22, 23).

Achievement of asthma control and suppression of airway inflammation are considered as important management goals in asthmatic patients, but there is no consensus regarding a tool for assessing asthma control. There are several published questionnaires that may be useful for assessing asthma control. The ACT questionnaire has been previously assessed by specialist consultations (13) and has been validated in Persian language (20). It has shown a good relationship with therapeutic decisions made by specialists (24); however, the correlation between the ACT scores and markers of inflammation is not well clear. Kilic et al (5) showed a negative association between hs-CRP and ACT scores in two groups of asthmatic patients based on ACT  $\geq$ 20 and ACT <20. Piacentini et al. (19) confirmed the concept that childhood ACT is complementary to but not a substitute for other markers of disease control in asthmatic children.

Correlation between other markers of inflammation and indices of asthma control has been evaluated in other studies. The study carried out by Khalili et al (25) showed that up to 38% of patients with appropriately controlled asthma had high levels of fractional exhaled nitric oxide (FeNO). This study failed to found a significant association between FeNO and asthma control based on ACT and asthma control questionnaire (ACQ). Study on 68 asthmatic patients by Melosini et al. (17) confirmed that ACT scores significantly correlated with symptom scores but not with markers of airway inflammation.

We could not find a correlation between hs-CRP and FEV1. This relationship has been evaluated in other studies. Takemura (4) showed an association between systemic inflammatory markers and decreased pulmonary function. Soferman (9), Fujita (10), Pinto-plata (26) and Al Obaidi et al. (27) showed that serum levels of hs-CRP were inversely correlated with FEV1. On the other hand, other studies showed that PFT values might be within normal range when the inflammatory process of the airways is still ongoing and anti-inflammatory treatment is still indicated (9). Senna et al. (28) postulated that the degree of bronchial inflammation is more sensitively detected by FeNo than by

FEV1. Kilic (5), Melosini (17) and Buyukozturk (23) found no significant correlation between hs-CRP and FEV1 values.

The rise in CRP is driven by its rate of synthesis, reaches a peak at around 48 hours and falls rapidly when the pathologic stimulus ceases (29). The elevation levels of hs-CRP in well controlled patients suggests a theory that asthmatic patients could have subclinical inflammation that could subsequently cause problems. Even in asthmatic patients with controlled disease eosinophilic inflammation in the airways is still present (27). A Cochrane review stated that a treatment strategy based on the sputum eosinophil reduction in contrast to a strategy using international guidelines, leads to a greater decrease in the overall risk of exacerbation (30).

These results provide us with a strong argument to develop and institute therapies aimed at decreasing the inflammatory state in asthmatics not only based on clinical markers but also on systemic inflammatory markers.

In conclusion, we found no correlation between degree of systemic inflammation estimated by hs-CRP and other clinical indices of asthma control such as ACT scores, FEV1 and GINA classification of asthma control and even in patients with clinical and spirometric indices of controlled asthma, markers of systemic inflammation were still present.

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