

# Association Between C Reactive Protein and Asthma

## C Reaktif Protein ve Astım Arasındaki İlişki

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### ABSTRACT

**Objective:** Reported studies have found an inverse relationship between lung function and markers of systemic inflammation. The aim of this study was to clarify the relationship between C-reactive protein (CRP) serum levels, body mass index and asthma.

**Material and Method:** In the present study, CRP was determined in 178 patients with asthma and 50 healthy control subjects. Of all asthmatics, 126 had stable asthma and 52 had asthma during exacerbation.

**Results:** CRP was significantly higher ( $p<0.05$ ) in asthmatic patients as compared to the control group. In asthmatics with exacerbation, serum CRP was significantly higher than in stable asthmatic patients and control subjects. FEV<sub>1</sub> was significantly inversely correlated with serum CRP in asthmatic patients. In asthmatic patients there was a significant ( $p<0.0001$ ) association between serum level of CRP and body mass index. Furthermore, the mean BMI was significantly higher in asthmatic patients than that in control subjects.

**Conclusion:** Serum CRP may be a non specific marker of asthma and its exacerbation. In addition, obesity could be a risk factor for asthma. (*Tur Toraks Der 2010; 11: 98-104*)

**Key words:** Asthma, CRP, body mass index

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### ÖZET

**Amaç:** Yapılan çalışmalar sistemik inflamasyon belirteçleri ve akciğer fonksiyonları arasında ters bir orantı olduğunu göstermektedir. Bu çalışmada C- reaktif proteinin (CRP) serum düzeyi, vücut kitle indeksi ve astım arasındaki ilişkiyi belirlemeyi hedefledik.

**Gereç ve Yöntem:** Bu çalışmada 178 astım hastasında ve 50 sağlıklı kontrol grubunda CRP düzeyi belirlendi. Astım hastalarının 126'sı stabil evrede ve 52'si ise atak dönemindeydi.

**Bulgular:** Astım hastalarında kontrol grubuna göre CRP düzeyinin istatistiksel düzeyde anlamlı derecede ( $p<0.05$ ) daha yüksek olduğu görüldü. Atak dönemindeki astım hastalarında ise serum CRP düzeylerinin stabil devredeki astım hastalarından anlamlı derecede daha yüksek olduğu görüldü ( $p<0.05$ ). Astım hastalarında FEV<sub>1</sub> değeri serum CRP düzeyi ile ters bir orantı gösteriyordu. Astım hastalarında, serum CRP düzeyi ve vücut kitle indeksi arasında istatistiksel düzeyde anlamlı bir ilişki vardı ( $p<0.0001$ ). Ayrıca ortalama vücut kitle indeksinin astım hastalarında kontrol gruba göre daha yüksek olduğu görüldü.

**Sonuç:** Serum CRP düzeyi astım ve atakları için özgün olmayan bir belirleyici olarak tanımlanabilir. Ayrıca, obezite astım için bir risk faktörü olabilir. (*Tur Toraks Der 2010; 11: 98-104*)

**Anahtar sözcükler:** Astım, CRP, vücut kitle indeksi

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### INTRODUCTION

C-reactive protein (CRP) is a major inflammation sensitive plasma protein in humans. Its synthesis by the liver is regulated to a large extent by the pro-inflammatory cytokine interleukin (IL)-6 [1]. The measurement of CRP levels in the blood is simple and has been used for decades in clinical practice to follow the progression of inflammatory processes [2]. Impaired respiratory function (expressed by FEV<sub>1</sub>) is strongly associated with cardiovascular risk factors, atherosclerosis, arterial stiffness, cardiovascular disease and mortality, although the physiological mechanisms underlying these associations are largely unknown [3]. Some hypotheses have been put forward, including the possibility that respiratory and

cardiovascular alterations may share common risk factors such as aging and smoking status [4]. Systemic inflammation is also a possible element in the link between respiratory impairment and cardiovascular events. Reduced lung function has been associated with various inflammation sensitive plasma proteins [5,6]. The factors they found to be associated with FEV<sub>1</sub> and bronchial hyper responsiveness (BHR) were reported to be the same in numerous other studies [7-11]. They found that FEV<sub>1</sub> was independently associated with CRP and BHR was inversely associated with FEV<sub>1</sub>, in agreement with results of previously published studies [10,11]. The association between FEV<sub>1</sub> and CRP found in their study is consistent with previous studies that found a relationship

between lung function and other markers of systemic inflammation.

C-reactive protein (CRP), a marker of systemic inflammation, is a powerful predictor of adverse cardiovascular events. Respiratory impairment is also associated with cardiovascular risk [12]. Although some studies have found an inverse relationship between lung function and markers of systemic inflammation, only one study has reported a relationship between lung function and CRP levels [5]. In contrast, little is known about the relationship between bronchial hyper responsiveness (BHR) and systemic inflammation. The associations between lung function and CRP and between BHR and CRP have been investigated. Increased CRP levels are strongly and independently associated with respiratory impairment and more frequent BHR. These results suggest that both respiratory impairment and BHR are associated with a systemic inflammatory process [5]. To our knowledge, no previous study has been performed to evaluate the association between CRP serum levels and asthma. The purpose of the study was to clarify the relationship between CRP serum levels, body mass index and asthma.

## MATERIAL and METHOD

### Patients

The study was performed on asthmatic patients and healthy non asthmatic control subjects. Acute phase reactants have been implicated as being involved as proinflammatory molecules in various inflammatory diseases. However, little is known regarding their role in allergic airway disease. Thus, in the present study CRP was determined in 178 patients with asthma and 50 healthy control subjects. Of all asthmatics, 126 had stable asthma and 52 had asthma with exacerbation. Their age range was from 17 to 52 years. The subjects included in the study were outpatients from the Asthma and Allergy Centre of Samara General Hospital Outpatients Clinic. The diagnosis and classification of asthma was performed by a specialist physician and was established according to the National Heart Blood and Lung Institute / World Health Organization (NHLBI/WHO) workshop on the Global Strategy for Asthma [13]. Patients were excluded if they were smokers, had respiratory infection within the month preceding the study, a rheumatologic illness, malignancy, diabetes, heart failure, history of venous embolisms, coronary heart disease and liver or kidney diseases.

At enrolment, they all underwent full clinical examination, pulmonary function tests, and blood sampling. Normal volunteers were also enrolled in the study as healthy controls. None of them had any previous history of lung or allergic disease and were not using any medication. They had a normal lung function test ( $FEV_1 > 80\%$ ) and negative skin allergy test. General stool examination was performed for all patients and controls to exclude parasitic infections.

Acute asthma exacerbation was defined as dyspnea and wheezing with or without increased coughing [14].

The sampling was performed during the period from May 2004 to December 2005. All samples were collected in the morning following overnight fasting.

### Determination of serum CRP

Serum CRP was determined using a rheumajet kit from BLOKIT, Spain. The test was an agglutination test and was used for qualitative and quantitative determination of serum CRP. The test was performed according to the manufacturer's instructions.

### Statistical Analysis

The values are reported as mean $\pm$ SD and 95% confidence interval. For statistical analysis between groups unpaired t test was used. Pearson test was used for correlation analysis. The levels of each marker were compared between the study groups and control group, using SPSS computer package. P values of  $<0.05$  were considered significant.

## RESULTS

CRP was significantly higher ( $p < 0.05$ ) in asthmatic patients ( $81.05 \pm 61.29$  mg/l) as compared to the control group ( $6.40 \pm 1.14$  mg/l). In asthmatics with exacerbation, serum CRP was significantly higher ( $225.23 \pm 190.47$  mg/l,  $p < 0.001$ ) than in stable asthmatic patients ( $16.97 \pm 7.98$  mg/l) and control subjects ( $6.4$  mg/l) (Table 1).

$FEV_1$  was significantly inversely correlated with serum CRP in all asthmatic patient groups ( $r = -0.76$ ,  $p < 0.0001$ ), stable asthma group ( $r = -0.55$ ,  $p < 0.0001$ ), and in the exacerbation asthma group ( $r = -0.64$ ,  $p < 0.0001$ ) (Table 2). In asthmatic patients there was a significant ( $p < 0.0001$ ) association between serum level of CRP and body mass index (Table 3). Furthermore, for asthmatics, the mean BMI was significantly higher ( $p < 0.01$ ) in asthmatic patients (28.3) than in control subjects (24.8) (Table 4).

## DISCUSSION

C reactive protein (CRP) is a highly sensitive marker of inflammation, infection and tissue damage which contribute to host defense against infection by activating the complement pathways [15]. A positive relationship has

**Table 1.** Serum concentration of C reactive protein (mg/l) in asthmatic patients

Group [No.]	Mean	SD	95% CI
Stable asthma [126]	16.97	7.98	15.56-18.37
Exacerbating asthma [52]	225.23	190.47	172.4-278.06
All asthma [178]	81.05	61.17	72.07-90.03
Control [50]	6.4	1.14	6.07-6.73

p value:  
Stable Vs Exacerbation  $<0.0001$   
Exacerbation Vs Control  $<0.0001$   
All asthma Vs Control  $<0.001$   
Stable Vs Control  $<0.001$

been reported between raised CRP levels and current asthma [16,17], respiratory impairment [18-21], and bronchial responsiveness [5]. The association between asthma and CRP is by no means clear, however, and could at least in part reflect the role of obesity in CRP production [22,23], as asthma in young adults is significantly more common in subjects with a raised body mass index (BMI) [24-26]. Whether there is a difference in the association between CRP level and asthma severity is unknown.

In the present study, asthma exacerbation was strongly related to high CRP levels, whereas stable asthma was related with lower levels of CRP. The difference in CRP was very significantly higher during exacerbation than in stable asthma and control subjects. Furthermore, the CRP level in stable asthma was significantly higher compared to that of control subjects. There was a strong association between CRP level in asthmatic patients and disease stability. The present study findings support the hypothesis that not only local but also systemic inflammation exists in bronchial asthma. In a population based study, Jousilhti et al [16] demonstrated that asthma increased gradually with increasing CRP.

Obesity, a state that may be characterized by a low grade inflammation, has been associated with asthma [17,26-29]. CRP, an acute phase reactant, is elevated in obese people, however little is known about how asthma affects CRP concentration [17]. The prevalence of both obesity and asthma [30-32] has increased dramatically in recent decades. The concordant increase of these condi-

tions has raised speculation that the two are causally correlated. A prospective study supports this possibility [33].

Although the mechanisms by which obesity is linked to asthma remain to be fully elucidated, several factors could link the two conditions. For example, IL-6 and TNF- $\alpha$ , which are elevated in obese people, are thought to be important agents in the pathophysiology of asthma [17]. Because IL-6 is a potent stimulant of hepatic CRP, its concentration may be regarded as a proxy for IL-6 activity [29]. Little is known about CRP concentrations among people asthmatics. People with asthma have a higher prevalence of obesity than people who do not have asthma [34,35].

Speculation that people with asthma are more likely to have elevated CRP concentrations seems reasonable. This study indicated the positive relationship between asthma and high CRP concentrations. The results from a study of a representative sample of the US population show that adults with asthma are more likely to have elevated CRP concentrations than are persons who formerly had asthma or who never had asthma [17,29]. This was consistent with the findings of the present study, which show that asthmatics with exacerbation were more likely to have elevated CRP concentration than persons with stable asthma or healthy control. This study also indicated that body mass index correlated strongly with CRP concentration in asthmatic patients.

Ford studies [17,29] also show that adults with asthma are more likely than non asthmatics to be obese. Because BMI correlates strongly with CRP, as this study and the finding reported above indicated, much of the association between asthma status and CRP was accounted for by the high prevalence of obesity among asthmatics.

The links between asthma and obesity have not been adequately explained. However, mounting evidence now implicates obesity as a major risk factor for asthma, thus linking these two major epidemics [30-32].

Moreover, both in human subjects and in mice, obesity appears to predispose to BHR. The mechanisms by which obesity might modify ASM functions include both static and dynamic mechanical factors attributable to decreases in tidal volume that are observed in the obese. They include also obesity related changes in lung development, chronic systemic inflammation, and adipocyte derived factors, including leptin, adiponectin and plasminogen activating factor [36].

Summarizing a number of studies, Camargo and colleagues [33] suggested that obesity causes histologi-

**Table 2.** Correlation between serum C reactive protein and FEV<sub>1</sub> predicted percent in asthmatic patients

Group	r value	p value
All asthma	-0.76	<0.0001
Stable asthma	-0.55	<0.0001
Exacerbating asthma	-0.64	<0.0001

**Table 3.** Relationship between body mass index [BMI] and serum C reactive protein (CRP) levels in serum of asthmatic patients

Body mass index	Serum CRP	
	Mean	SD
Less than 25	36.91	24.51
25-30	68.17	40.21
More than 30	132.9	91.32

P value < 0.0001 for all BMI index groups

**Table 4.** Relationship between body mass index (BMI) and serum C reactive protein (CRP) in asthmatic patients and control

Group	Number	Serum CRP		Body Mass index	
		Mean	SD	Mean	SD
Asthma	178	81.05	61.17	28.3	5.2
Control	50	6.40	1.14	24.8	7.4
P value		<0.001		<0.001	

cal changes in the lungs of obese rats, reduction in airway caliber and increased bronchial hyper reactivity. Furthermore, they suggested that obese people may be more sedentary, thus spending more time indoors with continued exposure to potential allergens; are more likely to have gastro-esophageal reflux, which has been associated with asthma, and may have diets that are more likely to lead to asthma. Finally, they speculate that effects of obesity on hormonal patterns could be related to the risk of developing asthma.

Several additional possibilities could be suggested. Obesity affects immune function [36,37]. Because the immune system is critically involved in the pathophysiology of asthma, some of these immune alterations may be linked to asthma. For example, leptin, which is elevated in obese persons, can affect the immune response [38]. In addition to producing hormones such as leptin, adipose tissue is an important source of cytokines, such as TNF- $\alpha$ , IL-1 and IL-6 [39-41]. Both TNF- $\alpha$  and IL-1 affect numerous processes that may be important in asthma. These cytokines increase adhesion of eosinophils to epithelial cells [42], cause release of eotaxin, a potent chemotactic agents for eosinophils from lung fibroblast [43] and epithelial cells [44,45], cause release of IL-9 from eosinophils [46], up regulate IL-8 production by alveolar macrophages [47] increase IL-8 mRNA of bronchial epithelial cells [48], damage bronchial epithelial cells [49], activate endothelial cells [50], increase cyclooxygenase -2 activity [51] and cause bronchoconstriction [52].

Furthermore, TNF- $\alpha$  or IL-1 may up regulate the expression and release of various interleukins, such as IL-1, IL-6, IL-8, IL-11 and IL-15, some of which affect asthma activity. IL-6, which stimulates humeral immunity and prostaglandin-E<sub>2</sub>, a product of the cyclooxygenase-2 pathways that stimulate humeral immunity and promotes various cytokine responses that have been implicated in asthma pathophysiology, may be linked to asthma [53]. Although it remains unclear whether IL-6 is an important mediator in asthma, IL-6 concentrations were higher in BALF from patients with status asthmaticus than from control subjects [54]. However, whether TNF- $\alpha$ , IL-1 and IL-6 produced by adipocytes are biologically active in lung tissues remain uncertain [17].

Whether elevated CRP concentration among overweight and obese adults with asthma potentially affects the course of their disease is unclear [26]. Research thus far has not implicated CRP as a factor in asthma severity or prognosis. However, CRP can trigger the complement cascade through activation of the classical pathway. Although the role of the complement system in asthma remains to be fully worked out, researchers have suggested that it may be involved in the pathophysiology of asthma [55-57]. Recently, Nakano et al [58], reported that the concentration of the complement components C3a, which can induce airway inflammation and bronchoconstriction, were associated with a difference in response to emergency treatment of severe exacerbation.

Complement has a vital role in innate immunity. Several biologic interactions in the complement pathway that are likely to participate in acute asthma involve the C3a anaphylatoxin, a potent proinflammatory mediator generated early in inflammatory reactions by proteolytic cleavage of complement C3 [12]. Many features of asthma exacerbations such as smooth muscle contraction, mucus hypersecretion, and recruitment of inflammatory cells are consistent with actions of C3a [14]. In addition, C3a can stimulate the release of histamine and leukotrienes from basophils and mast cells as well as regulate synthesis of ECP by eosinophils [58]. High potency, early timing, and the overall pattern of the reaction suggest involvement of C3a in the pathophysiology of asthma. Several recent reports have implicated complement anaphylotoxins as likely effectors in animal models or mildly asthmatic individuals [59,60]. These data support the hypothesis that, in addition to acquired immune responses, the innate immune system, that is, the complement system, is involved in the pathophysiology of asthma. Furthermore, recent research suggests that CRP can affect endothelial function [61].

If high CRP concentrations in adults with asthma are not biologically inert and if the source of some of the CRP concentration is excess weight, weight control among overweight and obese adults with asthma is clearly desirable. Weight loss among obese patients with asthma results in improvements in clinical measures and quality of life [62,63].

A strong inverse correlation was achieved in this study between CRP serum levels and FEV<sub>1</sub> in asthma, whether with stable or exacerbation status. Furthermore, CRP was associated with BMI, and reduced FEV<sub>1</sub> was strongly associated with high CRP levels. This finding was consistent with previously published results [5,64]. The association between FEV<sub>1</sub> and CRP found in this study is consistent with previous studies which found a relationship between lung function and other markers of systemic inflammation. Kauffmann et al [65] found a negative association between FEV<sub>1</sub> and haptoglobin level in men. Dahl et al [66] reported that lower FEV<sub>1</sub> and increased risk of chronic obstructive pulmonary disease were associated with increased plasma fibrinogen levels. Finally, Engstrom et al [67] showed that forced vital capacity in men was inversely associated with levels of inflammation sensitive plasma proteins (fibrinogen,  $\alpha$ -1 antitrypsin, haptoglobin, ceruloplasmin and orosomucoid). They also showed that the levels of these inflammation markers partially accounted for the relationship between lung function and cardiovascular events. Only two studies investigated the relationship between CRP and FEV<sub>1</sub> [5,64]. This study and the previous two studies support the hypothesis that systemic inflammation may be the missing link in the association between pulmonary and cardiovascular alterations [3,68-71].

The study of Kony et al. [5] provides first evidence of an association between higher frequency of BHR and high



CRP levels. However, this study indicated a strong association between FEV<sub>1</sub> and CRP. BHR was inversely associated with FEV<sub>1</sub>, as reported previously [5,10,11]. The result of the present study is consistent with those of studies showing that asthmatic patients who commonly present with BHR or reduced FEV<sub>1</sub> have both systemic inflammation and local inflammation in the bronchus [5,16,72,73]. However, most of these studies included a small number of patients and used markers of inflammation usually associated with allergic inflammatory response, such as eosinophils and interferon gamma [72,73]. Closer to the present study are the two recent population based studies [21,26] showing that CRP levels were higher in asthmatic subjects than in non asthmatics.

A few epidemiological studies have investigated the relationship between BHR and other systemic inflammation sensitive proteins or cytokines. Kauffmann et al. [65] found a positive relation in man between BHR and haptoglobin levels, and Tusoda et al. [74] recently reported a positive association in pregnant women between BHR and some cytokines - including IL-6 and granulocyte-macrophage colony stimulating factor. Recently, the Buyukozturk et al. [75] study demonstrated that acute phase reactant serum amyloid A is raised in patients with asthma, which may indicate the presence of systemic inflammation.

The Kony et al. [5] population based study and the previous studies suggest that BHR may reflect not only local inflammation in the bronchus but also non specific systemic inflammation. The mechanisms underlying the association between respiratory function and BHR with systemic inflammation are unknown and the study of Kony et al. [5] does not shed light on the nature of this association. A number of hypotheses have been suggested. It has been reported that Alfa -1 antitrypsin is inversely associated with an alteration of gas exchange in the lungs [76]. As the pro inflammatory IL-6 is largely implicated in the synthesis of CRP and also alfa-1 antitrypsin, fibrinogen, and haptoglobin, IL-6 may play a particularly important role in the mechanisms leading to reduced pulmonary function.

The higher level of CRP observed in some subjects may result from higher exposure to some irritant or infectious agents-for example, in the occupational environment-and may therefore reflect the effects of these agents in the lungs [67]. The genetic determinants of systemic markers of inflammation and predisposition to an exaggerated inflammatory response may also be involved [5] in the association between lung function and CRP. Consistent with this hypothesis, a number of studies have provided evidence of heritability for CRP levels [77,78]. More generally, systemic inflammation may reflect a poorer general state of healthy, hence its association with respiratory and cardiovascular health, which are two vital functions. Interestingly, some recent studies have suggested that individuals who are able to produce high levels of IL-6 are at a disadvantage regarding

longevity [79]. The mechanism underlying the association between BHR and CRP levels may involve environmental and genetic factors [5].

In conclusion, the FEV<sub>1</sub> impairment and high frequency of BHR were strongly associated with increased CRP levels, independent of potential confounding factors, which suggest that both reduced lung function and BHR are related to systemic inflammatory process. This means that in asthma there are local and systemic inflammatory reactions which may lead to the deterioration in pulmonary function. Further studies are needed to determine the mechanisms underlying these associations.

### Conflict of Interest

None declared.

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