



Does systemic inflammation and allergen-specific IgE are related to each other in presence asthma

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Abstract

High sensitivity C-reactive protein (hs-CRP) is an inflammatory cytokine known to be related to inflammation diseases and elevated immunoglobulin E (IgE) is considered as an objective marker of allergy and has been associated with a number of respiratory disorders. Recently, it has been hypothesized that there is a strong significant between systemic and allergic responses in adult asthma patients. To test the hypothesis, we compared fasting serum IgE and hs-CRP in middle-aged men with asthma and those with healthy subjects. In addition, the relationship between IgE and hs-CRP were observed in asthma patients. Serum IgE and hs-CRP in asthma patients was significant higher than healthy subjects. There is a significant positive correlation between serum CRP and IgE in asthma patients ($p = 0.023$). These data support of asthma as an inflammation disease. Additionally, our study to support previous study demonstrated that inflammation mechanism play important role in pathogenesis of impaired airway in respiratory diseases.

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Introduction

There is considerable evidence that the recognition of asthma disease led to a search for soluble markers that would be useful in assessing airway inflammation (Venge, 1994). Asthma is inflammation disease with some clinical phenotypes in both adults and children. Its characteristics are BHR (bronchial hyper-responsiveness) and chronic airway inflammation and airflow obstruction (Buses et al., 2001). Review of research findings show that asthma is accompanied with pathological changes that occur in the lung such as airway eosinophilia, mucus metaplasia and mucus hypersecretion. 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). There is considerable evidence that immunologic stimulus leading to degranulation of human mast cells is their activation when the immunoglobulin E (IgE) molecules on their surfaces bind a relevant antigen (Ishizaka et al., 1984). It has been suggested that Mast cells are essential components of asthma and allergic responses (Theoharides et al., 2006, Bradding et al., 2006). One of the best-known mechanisms of mast cell activation is the binding of IgE to its high-affinity receptor FcεR1 on the mast cell surface. After IgE binding, mast cells release histamine, mast cell protease, proteoglycan, chemokines and some cytokines such as CRP (MacGlashan et al., 1998, Gruber, 1989). Many of these inflammatory mediators associate with respiratory diseases such as asthma. The chronic airway inflammation present in asthma is a predominantly helper T-cell type 2 (Th2) response characterized by high levels of total and allergen-specific IgE and bronchial eosinophilia (Bryce et al., 2006, Feleszko et al., 2006). A recent study report that CRP is elevated in clinically stable COPD patients. They reported that elevated CRP levels are negatively correlated with lung function (forced expiratory volume in one second (FEV₁), FEV₁ per cent predicted (% pred), forced vital capacity (FVC) (de Torres et al., 2006). But, a recent

study showed that there is not a significant relation between CRP and IgE (Ebrahim et al., 2012). 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). Although the molecular mechanisms for this are less understood. Accumulating evidence indicates that both hs-CRP and IgE levels are increased in asthma patients. But, it is still not completely clear which way there is a relationship between them in these patients. Therefore, the main objective of this study is determined hs-CRP in relation to IgE in a group of middle-aged asthma patients.

Material and methods

The Study Protocol was approved by the Ethics Committee of Islamic Azad University, Iran. The primary aim was to determine whether a serum concentration of IgE is related with CRP in asthma patients. This study conducted on 43 middle-aged men with asthma, between 35 and 50 years old who voluntarily participated in this study. Also, forty non-obese male matched for age and BMI participated in study by accidentally. Each participant received written and verbal explanations about the nature of the study before signing an informed consent form. All subjects were non-smokers. All participants had not participated in regular exercise/diet programs for the preceding 6 months. Subjects with a history or clinical evidence of impaired fasting glucose or diabetes, orthopedic abnormalities, recent myocardial infarction, congestive heart failure, active liver or kidney disease, growth hormone deficiency or excess, neuroendocrine tumor and anemia were excluded. Subjects were instructed to refrain from caffeine consumption and intense physical activity for 24 h before testing. Anthropometric measurements were performed with the subjects wearing light underwear and without shoes. Abdominal circumference was measured in the most condensed part using a non-elastic cloth meter. Body mass index (BMI) was calculated as weight (kg) divided by squared height

(m). Percent body fat was calculated from skin fold measurements. A resting spirometry test was performed to asthma diagnosis and its severity.

In addition, Blood samples were obtained after a 12-hour overnight fast in order to measuring serum IgE and CRP in all subjects. Serum IgE was determined by ELISA method (Monobind Inc, CA 92630, USA). The Intra- assay coefficient of variation and sensitivity of the method were 5.87% and 1/0 IU/mL, respectively. 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

Independent t-test was used to compare the means of all variables between asthma and non-asthma groups. Pearson correlation method used to determine the relationship between IgE with CRP. A p-value < 0.05 was considered to be statistically significant.

Results

The primary aim of present study was to determine serum CRP in relation to IgE in asthma patients. The finding of resting spirometry testing revealed that asthma patients were in mild to moderate of asthma severity. At baseline there were no differences in the age, body weight or BMI between asthma and non-asthma groups ($p \geq 0.05$). The finding of Statistical analysis showed that serum CRP (2356 +/- 349 versus 1669 +/- 269 ng/ml, $P = 0.011$) and IgE (349 +/- 66 versus 90 +/- 27 IU/ml, $P = 0.006$) in asthma patients group was significantly greater than healthy subjects. In other words, this data indicate asthma is an inflammation disorder. IgE was found to be positively associated with CRP in patients with asthma ($p = 0.011$, $r = 0.59$).

Discussion

The major finding of this investigation was a high positive relationship between serum CRP and IgE in patients with asthma. Indeed, the finding of present study show that in the asthma patients with mild to moderate severity increased CRP is associated with increased serum IgE. Although, the specific mechanisms responsible for these observations are not fully understood. 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).

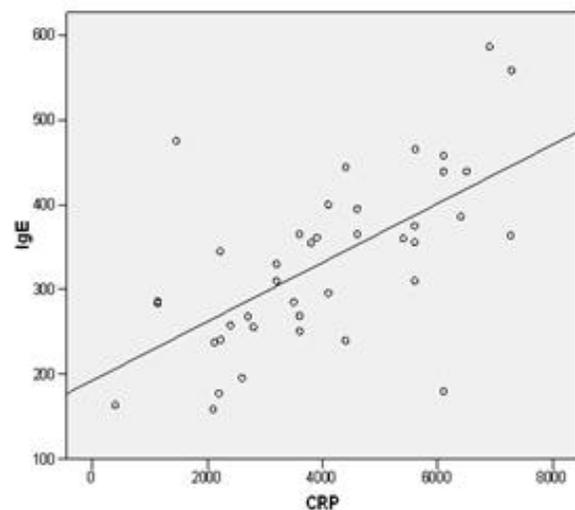


Fig 1. The relationship pattern between IgE and CRP in asthma patients.

Immunoglobulin E is a key mediator of the inflammatory reactions that are central to the pathogenesis of respiratory diseases such as Asthma. There is evidence that IgE plays a central role in allergic responses to allergens in asthma and rhinitis patients (Bousquet et al., 2006). Immunoglobulin E is predominantly produced by B cells in response to an allergen and has a short half-life (MacGlashan et al., 1999). In contrast to other immunoglobulin that binds to immunoglobulin Fc receptors only when antigen has

been bound by an antibody, IgE will bind to FcεR in the absence of antibody. Immunoglobulin E binding to mast cells “sensitizes” the mast cells to degranulate when multivalent antigens cross-link FcεR-bound IgE. Despite its low levels in the blood, IgE is immunologically highly active due to the large number of high-affinity IgE receptors on mast cells and basophiles (Bousquet et al., 2006). There is considerable evidence that, IgE up-regulates receptors on several cell types, including basophiles and mast cells (MacGlashan^a et al., 1999, MacGlashan^b et al., 1999). The IgE binding to the receptors on these cells results in the formation of cross links between the allergen and the IgE molecule and initiates the inflammatory cascade through release of a variety of mediators, including histamine, leukotrienes (LT), and platelet-activating factor (Arshad et al., 2001) and some inflammation cytokines.

Another important point is that asthma is a chronic inflammatory disorder of the airways in which mast cells, eosinophils and T- lymphocytes play a major role. On the other hand, hs-CRP is a sensitive indicator for inflammation, infection and also contributes to the host defense against infection by activating the complement pathway. The C-reactive protein is mainly secreted in the liver and is regulated by pro-inflammatory cytokines particularly tumor necrosis factor-α and interleukin-6. The plasma half-life of CRP is approximately 19 hours. Although its function is not completely understood, the CRP may play an important role in opsonisation, phagocytosis, and cell-mediated cytotoxicity. This cytokine can also act as a potent proinflammatory agent and activates the classical complement cascade by binding directly to the complement fragment C1q (Anderson, 2006) 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. This study demonstrated that elevated hs-CRP levels and respiratory symptoms,

such as wheeze, attack of breathlessness and nocturnal cough (Olafsdottir et al., 2005). Circulation IgE is increased in asthma patients (Heidenfelder et al., 2010). A number of studies have demonstrated that the role of IgE and IgE-dependent mast cell activation in asthma is underlined by the close correlation of increased serum IgE levels and the prevalence of asthma (Burrows et al, 1989). Another important point is that secreted IgE molecules bind to mast cells and stimulate them to release histamine, leukotrienes, and cytokines which further play major roles in perpetuating the inflammatory response (Buses et al., 2001, Szczeklik et al., 1998). Based on this data, it was concluded that A simple way to detect a mast cell-mediated reaction is possible by demonstrating an increased level of IgE which is the signal turning the mast cells on. In our study, serum CRP concentrations were positively correlated with IgE in asthma patients studied. It appears that the increased IgE levels stimulate mast cells and fat tissues to release CRP into circulation. On the other hand, a recent study showed that the peak value of IgE occurred a day earlier than CRP and gradually subsided along with CRP over several days (Erdogan et al., 2004). If high CRP or IgE levels persist for days or months, it might be related with ongoing intense inflammation as a reaction to the stent and possible neointimal muscle cell proliferation, in other words in-stent restenosis (Erdogan et al., 2003). Increased serum levels of both IgE and CRP in asthmatic patients suggests that asthma in addition to being known as an allergic disease developed in response to stenosis of respiratory pathways and increased levels of certain allergic mediators such as IgE, increased levels of inflammatory cytokines such as CRP, in these patients also confirms that asthma is an inflammatory disease. But the question is which of the inflammatory or allergic mediators plays a more important role in respiratory pathways inflammation or narrowing of the bronchus and eventually the outbreak of this disease. Future studies should examine the potential role of inflammation and allergic mediators on respiratory function.

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