High sensitivity C-reactive protein: Its correlation with sputum cell counts in bronchial asthma

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Summary

Background: Two major acute-phase proteins were identified in human, C-reactive protein and serum amyloid A. There are 3 types of C-reactive protein assays: conventional C-reactive protein, high sensitivity C-reactive protein and cardiac C-reactive protein. High sensitivity C-reactive protein assays can detect minor inflammatory changes that could be missed by other indices of inflammation. Induced sputum cell counts are relatively non-invasive, safe and reliable method for identifying the presence and type of airway inflammation in asthmatic patients.

Purpose of the work: This study was designed to detect the role of serum levels of high sensitivity C-reactive protein in asthmatic patients with or without inhaled corticosteroids treatment. Also to determine the relationship of serum high sensitivity C-reactive protein levels to clinical indices of asthma and inflammatory cell counts in induced sputum.

Subjects & Methods: Serum high sensitivity C-reactive protein level, pulmonary function tests, body mass index and induced sputum cell counts were estimated in 50 asthmatic patients (26 steroid inhaled and 24 steroid naive). Fifteen healthy volunteers, who matched in age and sex with the other groups, were used as a control group.

Results: There was an increase of high sensitivity C-reactive protein in asthmatic patients among both steroid inhaled and steroid naive patients compared to the healthy controls. Serum high sensitivity C-reactive protein correlated negatively with pulmonary function tests and positively with sputum eosinophil % in both inhaled steroid and steroid naive groups.

Conclusion: High sensitivity C-reactive protein is one of the markers of systemic inflammation that can be indirectly reflecting the degree of severity of airway inflammation in bronchial asthma.

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Introduction

C-reactive protein (CRP) is the first acute-phase protein to be described and is highly sensitive systemic marker of inflammation, infection and tissue damage. CRP is predominantly produced and secreted by hepatocytes, although other cells including alveolar macrophages may also synthesize it under control of cytokines mainly interleukin-6 (IL-6). A positive CRP may be an indicator of several conditions including rheumatoid arthritis, rheumatic fever, cancer, tuberculosis, pneumonia, heart attack and systemic lupus. There is also a high sensitivity CRP (hs-CRP) assay in addition to the conventional CRP test. The hs-CRP measures very low amount of CRP in the blood (below 0.2 mg/L) and is typically used to assess risk for heart problems and can be used as prognostic marker for development of diabetes mellitus. A population based study showed an association of increased level of serum hs-CRP with a high frequency of airway hyper responsiveness and low forced expiratory volume in one second FEV1 among subjects without heart disease, suggesting that systemic inflammation may be associated with respiratory impairment.

Asthma is a chronic inflammatory airway disorder characterized by airway hyper responsiveness and inflammation, in which various cells as eosinophils, neutrophils, macrophages, T lymphocytes, cytokines and mediators play a role. Besides local inflammation, systemic inflammation is present in asthma as shown by increased level of plasma fibrinogen and serum myeloid A (SAA). Thus hs-CRP could be a useful tool for detecting systemic inflammation in asthma.

Aim of the work

The aim of this study was to detect:

1. The role of serum levels of hs-CRP in asthmatic patients with and without inhaled corticosteroids treatment.
2. Relationship of serum hs-CRP levels to clinical indices of asthma and inflammatory cell differential counts in induced sputum.

Subjects and methods

Fifty cases of bronchial asthma were recruited from those attending the outpatient Chest clinic in Minia University hospital from January 2007 to August 2007. This study was approved by the ethical committee of Faculty of Medicine, Minia University and a written consent was obtained from patients and controls. Patients were selected according to the global initiative for asthma on the basis of symptoms such as: episodic breathlessness, wheezing, chest tightness, seasonal variability of symptoms with or without positive family history of asthma and post bronchodilator increase in FEV1 (more than 12%) or increase of peak expiratory flow (PEF) > 15%. Current smokers, patients with recent respiratory tract infection or exacerbation of less than one month prior to study were excluded. Besides, patients with heart diseases, diabetes mellitus collagen vascular disorder, obesity with body mass index (BMI) > 30 kg/m2 and semi quantitative CRP > 10 mg/L were also excluded.

According to the severity of asthma based on symptoms and lung function tests; asthmatic patients were classified into intermittent, mild persistent, moderate persistent and severe persistent cases. Patients included in this study were those of moderate persistent (pre-bronchodilator FEV1 60–80% predicted) and severe persistent asthma categories (pre-bronchodilator FEV1 < 60% predicted) as they were the usual groups presenting to the outpatient chest clinic.

Patients were divided into the following groups:

Group (A): Included (26) asthmatic patients who were on inhaled corticosteroids (ICS+ve) in their usual treatment of asthma besides bronchodilators. This group was divided into 2 subgroups according to asthma severity: subgroup (A1): included 11 cases of moderate persistent asthma and subgroup (A2): included 15 cases of severe persistent asthma.

Group (B): Comprised (24) steroid naïve asthmatic patients (not on inhaled corticosteroids) (ICS–ve). This group was further divided also into 2 subgroups according to asthma severity: subgroup (B1) which included 12 patients of moderate persistent asthma and subgroup (B2) which included 12 patients of severe persistent asthma.

Control group

(group C): Included 15 apparently healthy nonsmoker individuals matched in age and sex with the other 2 groups.

All the patients and healthy controls had been subjected to the following:

- Full detailed history taking including: (age, sex, duration of bronchial asthma, patient’s medications and family history of allergic diseases).
- Clinical examination, including: vital signs and BMI. The latter is defined as weight in kilograms divided by square of height in meters (wt in kg/(height in meter)2).
- Local chest examination.
- Investigations included:
  1. Plain chest X-ray (PA view).
  2. Complete blood count (CBC), total white blood cell counts (WBCS) and differential cell count.
  3. Electrocardiogram (ECG).
  4. Pulmonary function tests (PFTs) using (Vitallograph compact device), which is calibrated daily. Patient’s maximum effort had been used in performing the test so as to avoid any expected error in diagnosis. Results were obtained for forced vital capacity (FVC), FEV1, FEV1/FVC percentage and forced expiratory flow at 25–75% of FVC (FEF 25–75%).
  5. Sputum induction: Patients and controls had been medicated with inhaled salbutamol 200 µg, in hypertonic saline 5% administered for 15 min by ultrasonic nebulizer. Before expectoration, they were instructed to rinse their mouth to minimize saliva and then asked to expectorate sputum into a sterile plastic dish.
  6. Sputum processing and staining: Sputum samples were processed within two to seven hours of expectoration as delayed processing and examination more than nine hours may be an indicator of several conditions including rheumatoid arthritis, rheumatic fever, cancer, tuberculosis, pneumonia, heart attack and systemic lupus. There is also a high sensitivity CRP (hs-CRP) assay in addition to the conventional CRP test. The hs-CRP measures very low amount of CRP in the blood (below 0.2 mg/L) and is typically used to assess risk for heart problems and can be used as prognostic marker for development of diabetes mellitus. A population based study showed an association of increased level of serum hs-CRP with a high frequency of airway hyper responsiveness and low forced expiratory volume in one second FEV1 among subjects without heart disease, suggesting that systemic inflammation may be associated with respiratory impairment.

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hours are associated with significant reduction in cell viability. Sputum was treated with 15 ml HCl 8% and left for two to four hours to separate sputum from saliva. Sputum was put in a test tube and centrifuged at 2000 rpm for ten minutes. The precipitate was taken on slide and fixed with ethyl alcohol 95% in order to preserve cell details, without distortion. Staining was done using papanicolaou stain according to Bancroft and Gamle protocol.

7. Differential cell counts: The quality of induced sputum samples was assessed according to Gibson et al., which is based upon a slide quality assessment that evaluated the presence of three parameters: Adequate number of cells for enumeration, the presence of pulmonary macrophages on the slide, and the proportion of squamous epithelial cells.

Cell number was scored as (0) if there were fewer than 200 cells, (1) if there were 200–399 cells, and (2) if 400 or more cells were present. Pulmonary macrophages were scored as present (2) or absent (1). The proportions of squamous epithelial cells were scored as (2) if less than 20%, and (1) if 20% or greater. This gave a quality score ranging from 0 (poor quality) to 6 (good quality). Slides with low score <4 were excluded.

8. Measurement of serum hs-CRP: Under complete aseptic venipuncture, three ml venous blood samples were withdrawn, blood left to be clotted and centrifuged for ten minutes. The separated serum was kept frozen at −20 °C till assay of hs-CRP by ELISA.

Assay of hs-CRP by ELISA

Serum hs-CRP levels were measured using ultra Sensitive CRP assay, which is enzyme immuno-assays diagnostic kits supplied by (DiaMed eurogen company, 2300 Turnhout, Belgium) for the quantitative determination of hs-CRP in human serum.

A separate disposable tip for each sample transfer was used to avoid cross-contamination. All reagents were mixed without foaming in room temperature. Processing was done without any interruption.

Statistical analysis

All obtained data were analyzed statistically by SPSS software version 14. Data were presented as range and mean ± SD (standard deviation) for numerical data or number and percent (%) for categorical data. Mann–Whitney U-test was used to compare means between two groups of numerical data. Correlations between data were analyzed using Spearman correlation test. The significance was considered according to the level of significance (P-value) as follows:

- $P > 0.05$ = no significance (NS).
- $0.05 < P < 0.01$ = significant difference (*).
- $P < 0.01$ = high significant difference (**).
- $P < 0.001$ = very high significant difference (***).

Results

On studying the general characteristics of all studied subjects, it was found that there was no difference in the mean age in group A & B (33.3 ± 11) and (35.1 ± 12.1) respectively ($P > 0.05$). There was no difference between both groups of bronchial asthma regarding duration of the disease ($P > 0.05$). Considering BMI, there was no significant difference in BMI among all of the asthmatic patients and healthy control ($P > 0.05$).

Fig. 1 shows hs-CRP levels among the studied groups. It was found that group B had a mean value of hs-CRP of 2.63 ± 2.1 mg/L which was higher than that of group A and healthy control group. The difference of hs-CRP mean value between group A (2.35 ± 1.66) and B (2.63 ± 2.1) was not significant ($P > 0.05$). On the other hand, the difference between both groups A and B in comparison with control group (0.70 ± 0.67) showed a highly significant difference ($P < 0.01$) (Fig. 1).

Correlation between age, duration of bronchial asthma, BMI and hs-CRP using Spearman correlation was done. There was no significant correlation of age, duration of bronchial asthma, BMI and hs-CRP among all studied patients and healthy controls.

Correlation of hs-CRP to pulmonary function tests using Spearman correlation is illustrated in Table 1. Among group A, hs-CRP had a significant negative correlation with FEV1/FVC, PEF and FEF 25–75%. In group B, hs-CRP had
A significant negative correlation to FEV₁ and high significant negative correlation to FEV₁/FVC, PEF and FEF 25–75%. In the control group, hs-CRP had no significant correlation to any of pulmonary function test parameters (Fig. 2).

Table 2 shows range and means ± SD of sputum cell counts among studied groups. The mean value of sputum macrophage % was higher among healthy control group. The difference between this value with groups A & B showed a very highly significant difference (P < 0.001). The mean value of neutrophils was very highly significant (P < 0.001) in group A when compared with group B and healthy controls. The mean value of sputum eosinophil % was higher among steroid naive asthmatics (group B) than other groups and this difference was very highly significant as compared with group A and healthy controls (P = 0.0001). The sputum percentage of lymphocytes showed a very highly significant difference between inhaled corticosteroids group (group A) and steroid naive asthmatics (group B) vs. healthy control group (P = 0.0001).

Correlation of hs-CRP to sputum cell counts is shown in (Table 3). It was found that in group A, hs-CRP had no significant correlation to macrophages, neutrophils, and lymphocyte %, while it had a significant positive correlation to eosinophil % in induced sputum (r = 0.44, P = 0.025). In group B, hs-CRP had a very highly significant positive correlation to eosinophil % in induced sputum (r = 0.66, P = 0.001), highly significant positive correlation to macrophage % (r = 0.56, P = 0.005) and lymphocytes % (r = 0.55, P = 0.006). There was no significant correlation between hs-CRP and sputum cell counts in the control group (Fig. 3).

Discussion

CRP production is part of the nonspecific acute-phase response to most forms of inflammation and infection. High sensitivity CRP assays may be used to diagnose conditions with low grade inflammation in apparently healthy individuals. hs-CRP value ranges between 0.3 and 8.6 mg/L in healthy men and between 0.2 and 9.1 mg/L in healthy women not taking hormonal replacement therapy. A positive relationship has been reported between raised CRP levels and current asthma, respiratory impairment, and bronchial hyper responsiveness.

Asthma is characterized by inflammatory changes in the airway mucosa. The importance of local inflammation in the pathogenesis of asthma is well established. However, only limited data is available on whether systemic inflammation is also associated with asthma or not. Sensitive markers of systemic inflammation, particularly SAA and fibrinogen, were positively and significantly associated with asthma prevalence. These findings support the hypothesis that not only local but also systemic inflammation exist in bronchial asthma and may play a role in its pathogenesis.

The present study was designed to detect firstly, the role of serum levels of hs-CRP among asthmatic patients with and without inhaled corticosteroids treatment. This study had shown that serum levels of hs-CRP were significantly higher in asthmatic patients than among healthy controls.

Steroid naive patients (group B) showed higher mean value of hs-CRP than those on inhaled steroid (group A) but the difference between group A & group B was not significant. This agrees with the results of Takemura et al. who showed that patients with ICS–ve represented a higher mean value of hs-CRP. On the other hand, the present study showed that in ICS+ve patients, the serum hs-CRP levels differ with high significance (P = 0.002) from those of healthy controls. This was different from Takemura et al. findings who found that in ICS+ve patients, serum hs-CRP levels did not differ from those of healthy controls, due to the well characterized anti-inflammatory properties of inhaled steroid which reduced serum hs-CRP.

In this study, the apparent controversy with Takemura et al. study could be explained by either the non compliance of the studied patients with the use of steroid inhalers or may be due to development of steroid resistant form of asthma. Elevated CRP in stable asthma can be
explained by considering asthma as a chronic inflammatory disease leading to a damage of lung tissue. This might generate endogenous ligands such as fibronectin or heat shock protein triggering direct inflammation. IL-6 and interleukin-1 beta (IL-1β) are secreted by activated monocytes and macrophages. These cytokines have been found in asthma and chronic obstructive pulmonary disease (COPD) and are directly implicated in elevating CRP level. It is also postulated that elevated CRP level in stable asthma and COPD may be due to lung colonization in 30% of the patients with chronic obstructive airway diseases.

The second aim of this study was to determine the relationship of serum hs-CRP to clinical indices of asthma and inflammatory cell differentials in induced sputum among asthmatic patients. It was found that there was no significant correlation between serum hs-CRP and age of asthmatic patients. As the mean age of ICS-ve and ICS-ve patients was 33.3 ± 11 and 35.1 ± 12.1 respectively so most of the patients of this study were in their middle age, thus avoiding the effect of aging on hs-CRP levels. Nakamura and Yamashita showed that aging and its associate atherosclerotic changes are contributing factors of elevated hs-CRP. Smokers show elevation of hs-CRP levels and smoking cessation leads to a reduction in hs-CRP level. For this reason current smoker whether patients or controls were excluded from this study.

There was no correlation between the duration of bronchial asthma and BMI with serum hs-CRP levels in the present study and this was consistent with Takeumura et al. Obese asthmatic patients with BMI > 30 kg/m² were excluded from this study to avoid effect of obesity on serum hs-CRP levels. Higher BMI is associated with higher hs-CRP values even among healthy persons, which suggests a state of low grade systemic inflammation in over weight and obese persons.

In the present study, serum hs-CRP levels correlated negatively with pulmonary function test parameters and this negative correlation was highly significant among those of steroid naı ¨ ve patients. These findings are in accordance with Takeumura et al. who found also that the degree of negative correlation of hs-CRP and pulmonary function test parameters were more in steroid naive than in steroid inhaled patients.

The negative correlation between pulmonary function tests and hs-CRP in our study is consistent with previous studies that have found a relationship between lung function and other markers of systemic inflammation. Kauffmann et al. found a negative association between FEV₁ and haptoglobin levels in men. Also Dahl et al. reported that a lower FEV₁ and increased risk of chronic obstructive pulmonary disease were associated with increased plasma fibrinogen levels. Finally, Engstrom et al. showed that the FVC was inversely associated with levels of inflammatory markers as (fibrinogen, α1-antitrypsin, haptoglobin and ceruloplasmin). They also showed that the levels of these inflammatory markers partially accounted for the relationship between lung function and cardiovascular events.

The current study showed that sputum neutrophil % was higher in asthmatic patients when compared with that of healthy controls and that increase showed higher significant level in ICS-ve (group A) (71.8 ± 12.1) patients than ICS-ve (group B) (52.5 ± 19.5). The same results were obtained by Takeumura et al. Gibson et al. used induced sputum to assess 56 patients with persistent asthma taking high doses of inhaled corticosteroids and found that 59% of patients had suppressed sputum eosinophil counts but they showed evidence of neutrophilic inflammation. The increase of sputum neutrophils % in bronchial asthma may be due to the use of high doses of steroid, severity of asthma, subtle sub-clinical bronchiectasis or lower respiratory tract infections.

Sputum lymphocyte % in the present study was significantly higher among asthmatic patients than healthy control group. The present study showed that there was a highly significant increase in sputum eosinophil % among steroid inhaled and steroid naive patients compared to healthy control group. The increase in steroid naive patients was highly significant than steroid inhaled group. On the other hand, Takeumura et al. reported that the number of sputum % of eosinophils was increased in ICS-ve group than ICS-ve group (7.0 ± 11.9 vs. 3.5 ± 9.2).

In regards to the correlation of serum hs-CRP to sputum cell %, it was found that in ICS-ve group there was

| Table 2 | Shows range and means ± SD of sputum cell counts among the studied groups. |
|---------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|         | Macrophage % | Neutrophil % | Eosinophil % | Lymphocyte % |
|         | Range | Mean ± SD | Range | Mean ± SD | Range | Mean ± SD | Range | Mean ± SD |
| Group A (n = 26) | 0–39 | 13.2 ± 9.5 | 41–88 | 71.8 ± 12.2 | 1–22 | 6.8 ± 5.2 | 2–24 | 8.1 ± 5.6 |
| Group B (n = 24) | 1–34 | 6 ± 7.6 | 1–84 | 52.5 ± 19.5 | 13–78 | 33 ± 14.6 | 1–80 | 8.8 ± 16.3 |
| Control group (n = 15) | 40–69 | 57.06 ± 9.01 | 30–60 | 40.73 ± 8.50 | 0–6 | 1.40 ± 2.02 | 0–3 | 1.20 ± 1.08 |

| Table 3 | Spearman correlation of hs-CRP to sputum cell counts. |
|---------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|         | Macrophage% | Neutrophils% | Eosinophils% | Lymphocytes% |
|         | r | P-value | r | P-value | r | P-value | r | P-value |
| Group A Total (n = 26) | −0.05 | 0.8 | 0.11 | 0.6 | 0.44 | 0.025* | 0.38 | 0.06 |
| Group B Total (n = 24) | 0.56 | 0.005* | −0.18 | 0.4 | 0.66 | < 0.001** | 0.55 | 0.006* |
| Control group (n = 15) | 0.15 | 0.57 | −0.154 | 0.58 | 0.08 | 0.78 | −0.04 | 0.89 |

* denotes significant difference; ** denotes high significant difference; and *** denotes very high significant difference.
a significant positive correlation between serum hs-CRP and sputum eosinophil % with no significant correlation with other sputum inflammatory cells.

Takemura et al.\textsuperscript{19} found that there was no significant correlation between serum hs-CRP and any sputum inflammatory cells among ICS-ive group. This apparent controversy could be explained as mentioned before, i.e. non-compliance or inefficient utilization of inhaled steroid, use of suboptimal doses of inhaled steroid or finally the asthma became steroid resistant.

Regarding steroid naïve patients, the current study demonstrated a very highly significant positive correlation between serum hs-CRP and sputum % of eosinophils, macrophages and lymphocytes. The positive correlation between hs-CRP and sputum % of eosinophils can reflect the degree of severity affecting airway inflammation. Takemura et al.\textsuperscript{19} found similar result; significant positive correlation between hs-CRP and sputum eosinophil % and marginally positive correlation with both of neutrophils and macrophages % among steroid naïve asthmatic patients.

Conclusion

- hs-CRP is a sensitive, easily measured inflammatory marker and is a useful systemic biomarker of airway inflammation in asthmatic patients.
- It is obviously less complicated than other exhaled biomarkers of inflammation.
- Asthma has a systemic aspect of inflammation besides the local inflammation as documented by the increase level of hs-CRP among steroid inhaled and steroid naïve patients in comparison with the control group.
- Increased eosinophil number and decreased pulmonary function are associated with higher serum hs-CRP level more in steroid naïve patients. Therefore serum hs-CRP can be used as one of the parameters indirectly detecting the degree of severity affecting the airways.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. None of the authors had a financial support for this paper.

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