Original Article

Correlation of hs-CRP, Exhaled Nitric Oxide and Atopic Status in Non-Obese and Obese Bronchial Asthma Patients

Raj Kumar, Anil Kumar Mavi, Kamal Singh and Manoj Kumar

National Centre of Respiratory Allergy, Asthma and Immunology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India

Abstract

Objectives. Obesity and asthma are the common conditions that describe the distinctive nature of inflammation. The high-sensitivity C-reactive protein (hs-CRP) and fraction of exhaled nitric oxide (FENO) levels are known to influence the atopic status. This study was undertaken to compare these inflammatory markers and atopic profile between non-obese and obese asthmatic patients.

Methods. Two hundred asthma patients aged between 11-58 years were enrolled for this study and divided into two groups: non-obese [body mass index (BMI) <25 kg/m^2) (n=100) and obese (BMI>30 kg/m^2) (n=100)]. All the subjects were assessed for the pulmonary function test (PFT), hs-CRP from blood serum, FENO and skin prick test (SPT) against the battery of 58 common aero-allergens and subjects having at least one SPT positive were labelled as atopics.

Results. Of these 200 patients, 135 (67.5%) were atopics [n=80 (59.3%) non-obese; and n=55 (40.7%) obese]. The BMI for the non-obese and obese group was 22.4 and 33.9 Kg/m^2, respectively. The functional residual capacity percent (FRC%) of non-obese and obese were (111.2±24.6 *versus* 88.54±19.99 (P<0.001) and expiratory reserve volume (ERV%) predicted was (97.750±33.571 *versus* 70.9±24.8; P<0.001). Both FRC% and ERV% were significantly lower in the obese group. Levels of FENO of non-obese were significantly higher than the obese (38.08±3.13 *versus* 30.77±3.02; P=0.0685). The hs-CRP was significantly higher in obese atopics in comparison to non-obese (15.33±23.66 *versus* 21.60±45.35; P<0.001).

Conclusions. Obese patients with asthma have a higher hs-CRP level. Thus, while interpreting hs-CRP level in obese patients, atopic status must be evaluated. **[Indian J Chest Dis Allied Sci 2021;63:7-12]**

Key words: Atopic status, Skin prick test, Aeroallergens, BMI, Inflammation.

Introduction

Obesity and asthma are the common conditions which describe the distinctive nature of inflammation.[1] The relationship between obesity and asthma is complex and from the past studies it is understood that prevalence of asthma and obesity increases dramatically.[2] Obesity even in the absence of intrinsic lung disease causes physiological impairment in lung functions due to mass loading of the respiratory system.[3] Obesity is a well-established risk factor for diabetes mellitus, hypertension, sleep apnoea, stroke, cardiovascular disease, arthritis, and many other diseases. This finding supports, adds asthma to this list and should provide yet one more piece of information to force obese individuals to lose weight and to support the aggressive implementation of public health measures to support the attainment to this goal.[4,5]

Inflammatory markers like C-reactive protein (CRP) levels and fraction of exhaled nitric oxide (FENO) levels are actively and independently linked with the respiratory impairment and more frequently hyper-responsiveness. These markers suggest that both respiratory impairment and bronchial hyper-responsiveness are associated with a systemic inflammatory process in patients with bronchial asthma.[6] Obesity aggravates inflammation in bronchial asthma leading to increased severity of asthma and decreased hyper-responsiveness to the treatment, thus, leading to an increase in morbidity and mortality in obese asthmatics compared to non-obese asthmatics. Studies[7] have established differential expression of inflammatory genes including cytokines, chemokines, and complement protein collectively termed as adipokines in the adipose tissue of obese in comparison

[Received: September 9, 2019; accepted after revision: February 21, 2020]

Corresponding author: Dr Raj Kumar, Professor and Head, National Centre of Respiratory Allergy, Asthma and Immunology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110 007, India; E-mail: rajkumarvpci@gmail.com, ncraaivpci@gmail.com

to lean human-beings. The present hypothesis is that this inflammation spills over into the blood, leading to inflammatory stimulation at sites distant to the adipose tissue.[7] Adipokines like interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) plasminogen activator inhibitor 1, vascular endothelial growth factors (VEGF) and monocyte chemotactic protein have been independently associated with inflammation in bronchial asthmatic patients, and thus, could be a link between obesity and asthma.[8]

This study was undertaken to measure the parameters, like complete pulmonary function test, atopic profile and inflammatory markers like (hs-CRP and FENO) of obese and non-obese asthma patients and to show that the inflammation of asthma is aggravated by the obesity.

Material and Methods

Patients diagnosed with bronchial asthma as per Global Initiative for Asthma (GINA) guidelines (2016)[9] were enrolled for this study from the out-patient department of Vallabhbhai Patel Chest Institute. Two hundred asthmatics (120 females) aged between 11-58 years were recruited and divided into two groups. Group 1 included 100 non-obese (body mass index [BMI] <25.0 kg/m^2) asthma patients (52 females) and Group 2 included 100 obese (BMI >30.0 kg/m^2) asthma patients (68 females). Investigations including complete pulmonary function test with diffusion capacity, blood (serum) sampling for hs-CRP, skin prick test (SPT) and FENO level measurements were done.

Pulmonary function testing was performed on a dry, rolling-seal spirometer of the Benchmark model/ CPL lung function machine (P.K. Morgan, Kent, UK). The procedure was done as per the guidelines of the American Thoracic Society (ATS).[10] Maximal expiratory flow volume curves were obtained as per the ATS recommendations. Dynamic lung volumes, like forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) was measured and static (or absolute) lung volumes, like vital capacity, residual volume and total lung capacity were measured as per the guidelines.[11] The diffusion capacity of the lungs was analysed by using single breath method (SBDLCO). Helium gas is used to calculate total lung capacity and the exhaled carbon monoxide was used to calculate the amount of carbon monoxide transferred to the blood.

Skin prick testing to common aeroallergens and food allergens was done in all the patients as per the standard guidelines of ATS.[11] Atopy was defined as a positive SPT (wheel diameters of >3 mm areas compared to buffer saline as a negative control) for at least ≥1 aeroallergens.[12] Before performing SPT, oral drugs including anti-histamines, steroids and any other drugs considered to affect SPT will be stopped two weeks prior to the tests, but inhaled drugs were continued as per requirement of the patient.

The hs-CRP levels were quantitatively measured by enzyme-linked immunosorbent assay (ELISA) using the ACCUBIND automated (URIT-660) analyzer. The mean absorbance value for each set of references, *i.e.* standard, controls and sample were calculated. The absorbance for serum reference was plotted (y-axis) *versus* the corresponding CRP concentration (x-axis) in mg/L. The assessment of exhaled nitric oxide was performed using breath exhaled NO analysis (online method) on breath analyser CLD 88SP (M3014) chemiluminescence (NIOX) analyser in accordance with 2005 ATS/ERS (European Respiratory Society) recommendations.[12]

Statistical Analysis

Statistical analysis was done by using Statistical Package for the Social Sciences (SPSS; 16.0 version windows; SPSS, Chicago, IL, USA). The data are presented as mean ± standard deviation. The difference in the mean baseline values of various assessment among group 1 (non-obese) and group 2 (obese) was done using student's t-test. The correlation between any two parameters between the groups or within the same group were made by using Pearson's correlation coefficient. A P-value of <0.05 was considered as statistically significant.

Results

The demographic characteristics of 200 study patients (80 males and 120 females) of both the groups are shown in table 1. The patients were divided into two groups: Group 1 non-obese patients (n=100) with bronchial asthma with normal weight and Group 2 obese patients (n=100) with bronchial asthma. The mean of age in group 1 and group 2 was (29.2±9.3 *versus* 36.4±8.4 years). Overall, 135 (67.5%) patients were atopic, of which 80 (59.3%) patients were non-obese and 55 (27.5%) were obese. The duration of the disease illness in group 1 and group 2 was (6.242±5.76 *versus* 6.367±4.66 years; P<0.001), and it was statistically significant.

The mean levels of PFT parameters in both the groups are presented in table 2. The levels of FEV_1/FVC ratio (74.73±12.16 *versus* 72.21±12.16; P=0.014), forced expiratory flow at 25-75% ($FEF_{25-75\%}$), (57.84±28.59 *versus* 53.28±27.91; P=0.025), peak expiratory flow rate (PEFR) (87.77±23.06 *versus* 83.34±26.11; P=0.020), slow vital capacity (91.98±14.24 *versus* 86.79±17.61; P=0.023), and functional residual capacity (FRC) (111.2±24.60 *versus* 88.54±19.99; P<0.001) was significantly high in patients of group 1. Inspiratory capacity (IC) of group 1 patients

was lower compared to group 2 and also shows a statistical significance between these two groups (88.69±22.80 *versus* 96.75±23.36; P=0.014). Expiratory reserve volume (ERV) (97.75±33.57 *versus* 70.90±24.80; P=0.014), residual volume (RV) (121.86±36.68 *versus* 102.16±34.68; P=0.050), total lung capacity (87.12±4.39 *versus* 51.53±2.83; P<0.001), and alveolar volume (VA) (83.99±15.15 *versus* 72.20±13.32; P=0.019), of the group 1 was significantly higher compared to group 2. Single breath diffusing capacity corrected for VA (DLCO/VA) for the group 1 patients was significantly lower compared to group 2 (113.39±20.79 *versus* 115.94±25.57; P=0.044), which is statistically significant.

On the correlation of lung volumes, group 2 had lower levels of functional residual capacity, the difference being statistically significant (P<0.001). The residual volume/total lung capacity ratio was statistically higher in group 2 (P<0.050). A statistical significant difference was observed for diffusion capacity (P=0.059), alveolar volume (0.019) and their ratio (P=0.044). The severity of asthma in patients of both the groups is shown in table 3.

The difference of atopic profile between non-obese (n=80) with normal BMI and obese (n=55) asthmatic individuals for common aeroallergens was not found to be statistically significant (P=<0.050). Similarly, on analysis of SPT for food allergens, the P-value that derived for these variables between non-obese (n=49) and obese (n=46) patients is not statistically significant.

The mean level of exhaled breath analysis of FENO in group 1 was 38.00±3.13 ppb (parts per billion) and 30.77±3.02 ppb in group 2; the difference being statistically insignificant (P=<0.050) (Table 1). The mean

Table 1. Demographic characterstics of the patients of both the groups

Variables	Group 1 (n=100) (Non-obese)	Group 2 (n=100) (Obese)	P-value
Sex (Male/Female)	48/52	32/68	P<0.001
Age (years)	29.2±9.3	36.4±8.4	P<0.001
Height (cm)	160.4±9.6	158.1±9.9	P<0.001
Weight (kg)	58.1±10.7	84. 5±13.1	P<0.001
BMI (kg/m^2)	22.4±3.2	33.9±4.4	P<0.001
Duration of illness (years)	6.242±5.76	6.367±4.66	P<0.001
hs-CRP (mg/L)	15.33±2.36	21.60±4.53	P<0.001
FENO (ppb)	38.00±3.13	30.77±30.23	0.068

Data are presented as mean± standard deviation

Definition of abbreviations: BMI=Body mass index, CRP=C-reactive protein, FENO=Fraction of exhaled nitric oxide, ppb=Parts per billion

Table 2. Comparison of pulmonary function tests in Group 1 and Group 2

Variables	Group 1 (n=100) (Non-obese)	Group 2 (n=100) (Obese)	P-value
FVC (% Predicted)	91.96±13.94	85.77±15.54	0.065
FEV_1 (% Predicted)	78.39±18.06	72.94±17.44	0.079
FEV_1/FVC (% Predicted)	74.73±12.16	72.21±12.16	0.014
$PEFR_{25-75}$ (% Predicted)	87.77±23.06	83.34±26.11	0.020
FEF_{25-75} (% Predicted)	57.84±28.59	53.28±27.91	0.025
SVC (% Predicted)	91.98±14.24	86.79±17.61	0.023
FRC (% Predicted)	111.2±24.60	88.54±19.99	0.00
IC (% Predicted)	88.69±22.80	96.75±23.36	0.014
ERV (% Predicted)	97.75±33.57	70.90±24.80	0.014
RV (% Predicted)	121.86±36.68	102.16±34.68	0.050
TLC (% Predicted)	87.12±4.39	51.53±2.83	0.000
RV/TLC (% Predicted)	50.62±3.10	51.50±2.80	0.082
DLCO (% Predicted)	108.96±26.29	98.18±25.80	0.059
VA (% Predicted)	83.99±15.15	72.20±13.32	0.019
DLCO /VA (% Predicted)	113.39±20.79	115.94±25.57	0.044

Definition of abbreviations: FVC=Forced vital capacity, FEV_1=Forced expiratory volume in one second, PEFR=Peak expiratory flow rate, FEF=Forced expiratory flow, SVC=Slow vital capacity, FRC=Functional residual capacity, IC=Inspiratory capacity, ERV=Expiratory reserve volume, RV=Residual volume, TLC=Total lung capacity, DLCO=Single breath diffusing capacity, VA=Alveolar volume, DLCO/VA=Single breath diffusing capacity corrected for alveolar volume.

Table 3. Severity of asthma in Group 1 and Group 2

Variable	Group 1 (n=100) (Non-obese) No. (%)	Group 2 (n=100) (Obese) No. (%)	P-value
Obstruction (<80% FEV_1/FVC)	64 (64)	69 (69)	0.456
Mild (≥70 FEV_1) (% Predicted)	36 (36)	32 (32)	0.553
Moderate (60-69 FEV_1) (% Predicted)	12 (12)	17 (17)	0.318
Moderately severe (50-59 FEV_1) (% Predicted)	10 (10)	6 (6)	0.300
Severe (35-49 FEV_1) (% Predicted)	5 (5)	12 (12)	0.077
Very Severe (<35 FEV_1) (% Predicted)	1 (1)	2 (2)	0.563

Definition of abbreviations: FEV_1= Forced expiratory volume in 1 second, FVC=Force vital capacity

hs-CRP level for the group 1 was 15.33±2.36 mg/L and for the group 2 was 21.60±4.53 mg/L. The difference was statistically significant and higher in group 2 in comparison to group 1 (P<0.001).

Discussion

The present investigation demonstrated a strong correlation between hs-CRP and exhaled nitric oxide and atopic status in non-obese and obese bronchial asthmatic patients. Asthma and obesity curve is J-shape,[8] the prevalence increases at both extremes of BMI.[8-13] These conclusions have been consistently shown not only in western population but also in Chinese population in previous studies.[14,15] These factors influencing the development and expression of asthma are divided into host and environment, among which the host factor that includes are genetically predisposing genes to atopy and airway hyper-responsiveness, obesity and sex.[16,17] Obesity is a systematic pro-inflammatory state correlated with increased levels of inflammatory markers.

In our study, we observed that obese group had significantly decreased FRC and ERV in comparison to the non-obese group. These findings are in contrast with previous studies.[18,19] The presumable explanation for this is an increase in intra-abdominal pressure on the diaphragm and in fat mass on the chest wall leading to mass loading of the thorax, thus increases the deflationary pressure and reducing the conformity of the lung and the respiratory system. Patients may be mildly hypoxaemic, possibly due to ventilation-perfusion mis-match at the base of the lungs, where micro-atelectasis is likely to occur.[19] Weight loss leads to a reversal of these changes.[20] For all of these changes, the distribution of fat, that is, upper *versus* lower body may be more important than BMI.

In a study, it was observed that there was a significant reduction in FVC, FEV_1 and FEF 25-75% in the obese patients compared to normal lean individuals.[21] There was a significant difference in the lung functions between obese and normal lean subjects.[21] However, dynamic lung volume including vital capacity (VC) and total lung capacity is often normal in obese individuals.[22,,23] In the present study, these volumes were within 95% confidence limits for the predicted value.

The mechanisms include the possibility that abdominal fat deposition leads to re-distribution of blood to the thoracic compartment that reduces VC. In obese patients, the diaphragm is in the upper position, which results in a low FRC. Such modification in resting end-expiratory lung volume may result in a massive change in airway resistance related to an increase in transmural pressure across the bronchial wall. In addition, chest wall resistance and increased respiratory resistance could also be due to the existence of upper airway obstruction and fat deposition or lax pharyngeal muscle tone in obesity.[24, 25] A study reported that in obesity there is a disproportionate reduction in FVC, demonstrating BMI is significantly associated with the FEV_1/FVC ratio.[26] In the present study, the FEV_1/FVC ratio in obese group was reduced. However, the difference with non-obese asthmatics group was not significant. In a correlative study[27] of obese and non-obese asthmatics, it was reported that there were no significant differences in FEV_1/FVC ratio between the groups. The system of the small airway collapsibility has been co-related to the lower content of collagen in small airways, greater inflammation in the outer wall in comparison to the inner wall and inflammation of peribronchiolar region.[28, 29]

Results of the present study did not find any significant difference in the atopic profile of non-obese and obese patients with bronchial asthma in contrast with another study.[27] However, there are few reports of cross-sectional data showing a correlation between BMI and increase in skin reactivity.[29] The results of the present study did not show any significant difference in positive reactivity to food allergens between the groups. Asthma developed in about 5% of individuals who suffer from food allergy and current asthma was reportedly triggered by food among 6-8% of children and 2% of adults.[30,31]

Obesity is connected with an increase in plasma hs-CRP levels which may be due to the presence of adipocyte-derived interleukin-6.[32,33] The hs-CRP is also associated with the degree of airway inflammation and airflow obstruction serves as a surrogate marker of this condition. These studies identified a significant interaction between obesity and asthma on hs-CRP and states that the presence of asthma further increased CRP levels (P=0.013). Concurrently, significantly raised the level of IL-6 was observed in obese asthma as compared to non-obese asthma group (P<0.0001). Both[34,35] the overweight (BMI, 25-29.9 kg/m^2) and obese (BMI, ≥30 kg/m^2) person were more likely to have increased CRP levels than their normal weight equivalent to (BMI< 25 kg/m^2) more so on obese women.[36] In the present study, the obese groups also had higher hs-CRP levels in comparison to non-obese groups, so these results reach the statistically significant difference between these groups.

Exhaled nitric oxide assessment is relatively simple, non-invasive and well-tolerated method and is commonly used as a clinic for the assessment of airway inflammatory biomarkers. Other studies showed that excess of body weight might be associated to

abnormalities of respiratory NO levels, as an impaired systemic NO in production has been reported in obese with a sub-clinical low-grade inflammation or by interacting with the change in conducting airway and lung volume.[37,38] However, in our study exhaled FENO level did not show any significant difference between obese and non-obese asthmatics.

Conclusions

In the present study, we observed that in obese asthmatic patients, the hs-CRP level was higher in comparison to non-obese asthmatics. There was no significant difference in between the groups for non-invasive inflammatory marker (FENO) and skin prick test to common aeroallergens and food allergens. The parameters, like FRC and ERV in obese asthmatics is significantly lower. Obesity and asthma have been shown to co-exist together but systemic and airway inflammation appears to operate independently of each other. Thus, while interpreting hs-CRP and FENO levels in obese and non-obese patients, atopic status must be evaluated.

References

1. Anne E, Fernando H, Aksay S, Cheryl MS, Richard EP. An American thoracic work shop report: obesity and asthma. *Am Thorac Soc* 2010;7:325–35.
2. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Low grade systemic inflammation in overweight children. *Pediatrics* 2001;107:E13.
3. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest* 2006;130:827–33.
4. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. *Arch Intern Med* 2000;160:898–904.
5. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH.The disease burden associated with overweight and obesity. *JAMA* 1999;282:1523–9.
6. Golden MP, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response of asthma controller agents. *Eur Respir J* 2006;27:495–503.
7. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated macrophage accumulation in adipose tissue. *J Clin Invest* 2003;112:1796–30.
8. Xu H, Barnes GT, Yang Q, Tan G Yang D, Chou CJ, *et al*. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistant. *J Clin Invest* 2003;112:821–30.
9. GINA Report, Global Strategy for Asthma Management and Prevention [Internet]. [place unknown] The Global Initiative for Asthma (GINA); 2016 update 4.2MB pdf. *Available from URL:* www.ginaasthma.org Accessed on April 4, 2016.
10. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al*, ATS/ERS Task Force: Standardisation of lund function testing: standardization of spirometry. *Eur Respir J* 2005;26:319–38.
11. Kumar R, Sharan N, Kumar M, Gaur SN. Pattern of skin sensitivity to various aero-allergens in patients of bronchial asthma and/or allergenic rhinitis in India. *J Allergy Asthma Immunol* 2012;26:66–72.
12. American Thoracic Society, European Respiratory Society. ATS/ERS recommendation of standardized procedure for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide 2005. *Am J Respir Crit Care Med* 2005;171:912–30.
13. Mishra V. Effect of obesity on asthma among adult Indian women. *Int J Obes Relat Metab Disord* 2004;28:1048–58.
14. Celedon JC, Palmer LJ, Litonjua AA, Weiss ST, Wang B, Fang Z, *et al*. Body mass index and asthma in adults in families of subjects with asthma in Anqing China. *Am J Respir Crit Care Med* 2001;164:1835–40.
15. Anandha KR, Nitesh G, Raj K. Impact of obesity on bronchial asthma in Indian population. *Lung India* 2014;31:121–6.
16. Nystad W, Meyer HE, Nafstad P, Tverdal A, Engeland A. Body mass index in relation to adult asthma among 135,000 Norweign man and women. *Epidemiol* 2004;160:969–76.
17. Shaheen SO, Sterne JA, Montgomery SM, Azima H. Birth weight, body mass index and asthma in young adults. *Thorax* 1999;54:396–402.
18. Shawn D, Aaron, Katherine L, Louis-philippe B, Andrew MR, Hernandez P, Catherine L, Stephen K. Over diagnosis of asthma in obese and non-obese adults. *Canadian Med Assoc J* 2008;179:1121–31.
19. Watson RA, Pride NB. Postural changes in lung volumes and respiratory resistance in subjects with obesity. *J Appl Physiol* 2005;98:512–7.
20. Little S. Impact of obesity on respiratory function. *Respirology* 2011;17:43–49.
21. Shinde PU, Irani FB, Heena K. The effect of body mass index on dynamic lung volumes. *Int J Health Sc R* 2014;4:42–46.
22. Fredberg JJ. Airway smooth muscle in asthma: flirting with disaster. *Eur Respir J* 1998;12:1252–6.
23. Ray CS, Sue DY, Bray G, Hanseb JE, Wasserman K. Effect of obesity on respiratory function. *Am Rev Respir Dis* 1983;128:501–6.
24. Collins LC, Hoberty PD, Walker JF, Fletcher EC, Peiris AN. The effect of body fat distribution on pulmonary function test. *Chest* 1995;107:1298–302.
25. Heena KG, Irani F, Shinde P. Effect of obesity on ventilator function of medical student. *Int J Cur Res* 2014;6:67–70.
26. Lazarus R, Sparrow D, Weiss ST. Effects of obesity and fat distribution on ventilatory function: the normative aging study. *Chest* 1997;111:891–8.

27. Scott HA, Gibson PG, Garg LM, Wood LG. Airway inflammation is augmented by obesity and fatty acid in asthma. *Eur Respir J* 2011;38:594–602.
28. Hauber HP, Gotfried M, Newman K, Danda R, Servi RJ, *et al.* Effect of HFA-flunisolide on peripheral lung inflammation in asthma. *J Allergy Clin Immunol* 2003;112:58–63.
29. Haley KJ, Sunday ME, Wigg BR, Kozakewich Hp, Reilly JJ, *et al.* Inflammatory cell distribution within and along asthmatic airways. *Am J Respir Crit Care Med* 1998;158:565–72.
30. Simard B, Turcotte H, Marceau P, Biron S, Hould FS, *et al.* Asthma and sleep apnoea in patients with morbid obesity: outcome afterbariatric surgery. *Obes Surg* 2004;14:1381–8.
31. Ozol D, Mete E. Asthma and food allergy. *Curr Opin Pulm Med* 2008;14:9–12.
32. Von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation to body mass index to asthma and atopy in children: The National Health and Nutrition Examination Study III. *Thorax* 2001;56:835–8.
33. Tracy RP, Inflammation in cardiovascular disease: cart, horse, or both? *Circulation* 1998;97:2000–2.
34. VisserM, Bouter LM, McQuillen GM, Wener MH, Harris TB. Elevated c-reactive protein levels in overweight and obese adults. *JAMA* 1999;282:2131–5.
35. Qian FH, Zhang Q, Zhou LF, Liu H, Huang M, Zhang XL, *et al.* High-sensitivity c-reactive protein: a predictive marker in severe asthma. *Respirology* 2008;13:664–9.
36. Olafsdottri IS, Gislason T, Thjodleifsson B, Olafsson I, Jogi R, *et al*. Creative protein levels are increased in non-alergic but not allergic asthma: a multicentre epidemiological study. *Thorax* 2005;60:451–4.
37. Dweik RA, Boggs PB, Erzurum Sc, Irvin CG, Leigh MW, *et al.* American Thoracic society Committee on interpretation of exhaled nitric oxide levels (FENO) or clinical applications: An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels of clinical application. *Am J Respir Crit Care Med* 2011;184:403–8.
38. Van Rensen EL, Straathof KC, Veselic-Charvat MA, Zwinderman AH, Bel. EH, Sterk PJ. Effect of inhaled steroid on airway hyperresponsiveness, sputum eosinophis, and exhaled nitric oxide levels in patients with asthma. *Thorax* 1999;54:403–8.