Research Article

Plasma fibrinogen as biomarker in asthmatic patients in Hila city

Ameera Jasim AL-Aaraji[1], Monqith Abdulmohsin Aljanabi[2], Ahmed Abdulzahra Jeyad Almurshidy[2]*, Noor Moqdad Mohammed[2], Ayaat Mohammed Khaleel[2], Mays Abbas Mohammed[2]

ABSTRACT

Background: Asthma is a chronic inflammatory process characterized by airway obstruction with hyper responsiveness to variable stimuli which reversible by drugs or by itself. A more new evidences, coagulation activation has been established in the bronchial tree of asthmatic patients. **Objectives:** The objective of the study was to evaluate the role of plasma fibrinogen as inflammatory biomarker in asthmatic patients. **Patients and Methods:** A case–control study was carried out in this study which includes 90 individuals. These subjects were divided into two groups: The first group includes 50 asthmatic patients and the second group includes 40 apparently healthy individuals. Student's *t*-test was used to determine the difference in means between control and asthma groups for numerical variables using SPSS version 20.0 software. **Results:** The current study shows a significant changes between patients and control group parameters (forced expiratory volume in 1 s [FEV1], FEV1/forced vital capacity [FVC], fibrinogen level, and asthma control test [ACT]). Furthermore, the study reveals a significant negative correlation between plasma fibrinogen level and FEV1/FVC in patients group. The study reveals a significant negative correlation between plasma fibrinogen level and FEV1 in patients group. Furthermore, the study reveals a significant negative relationship between plasma fibrinogen level and ACT in patients group. **Conclusions:** The results of this study indicated increased plasma fibrinogen concentration in asthma compared to control group. This increasing correlates positively with severity of asthma and thus can be considered as biomarker in predicting status.

KEY WORDS: Asthma control test, Asthma, Fibrinogen

INTRODUCTION

Asthma is a chronic inflammation of the bronchial tree, characterized by contraction of smooth muscle, overproduction of mucus, and remodeling of the airway wall.[1] However, asthma has become a major cause of morbidity and mortality worldwide, and its occurrence has amplified.[2] Spirometry is an extremely useful investigation in such disease, it is grossly under-utilized, in many countries.[3] A demonstration of airways obstruction and its reversibility (a <12% and 200 ml increase in forced expiratory volume in 1 s [FEV1]) following inhalation of a bronchodilator is recommended to approve the clinical diagnosis of asthma.[3,4] A reduced ratio of FEV1 to forced vital capacity (FVC) indicates airflow obstruction.[5] Asthma control test (ACT): Assessment of asthma control is required on every follow-up visit to take a decision on any change in treatment. The proposed method in the current global initiative of asthma (GINA) guidelines is based on the assessment of daytime and night-time symptoms, use of rescue bronchodilator and daily activity limitation. Spirometry is not required to step-up the treatment.[3,6]

The FEV1 is the most commonly applicable marker of asthma severity and progression. However, FEV1 shows poor relationship with both symptoms and other parameters of disease progression and may, therefore, not be a useful indicator of disease severity. Therefore, new approaches are mandatory to define the disease, observe its evolution and describe clinically related endpoints. Biomarkers could come to be appropriate substitutes in the early detection of diseases, topics stratification, and as clinical trial endpoints.[7] According to the last evidences, the activation of coagulation within the asthma patients bronchial tree may magnify inflammatory process.[8] Patients with asthma were found to have raised concentrations of thrombin-antithrombin complexes, soluble tissue factor (TF),

Access this article online

Website: jprsolutions.info | ISSN: 0975-7619

[1]Department of Basic Science, College of Nursing, University of Babylon, Iraq, [2]Alsadik General Teaching Hospital, Babil Health Directorate, Ministry of Health of Iraq, Iraq

***Corresponding author:** Ahmed Abdulzahra Jeyad Almurshidy, Ministry of Health of Iraq, Babil Health Directorate, Iraq. E-mail: ahmedaphrodite@gmail.com

Received on: 14-06-2019; Revised on: 18-07-2019; Accepted on: 20-08-2019

thrombin, and reduced activated protein C (APC)/ thrombin ratio in induced sputum[9,10] the relation between systemic inflammation and low lung functions were ill-defined. The exact explanation behind this association is unidentified but may be important for a number of causes;

1. Unrecognized lung illness may cause systemic inflammatory response with harmful effects on other aspects of well-being
2. A non-respiratory diseases may lead to chronic systemic inflammation and this may hasten lung function deterioration
3. Coexisting elements, such as smoking, sinusitis, and obesity, may influence on both systemic inflammation and lung function parameters.

Since systemic inflammation is implicated in the pathogenesis of cardiovascular diseases, the association may also help to explanation the association between low lung function and cardiovascular mortality.[11-15]

Plasma fibrinogen is manufactured in the liver and released into blood circulation.[16] It is a glycoprotein and it is an essential coagulation factor; furthermore, it plays an important role as an acute-phase reactant protein. Raised levels of fibrinogen have been described to be linked with a risk of inflammatory diseases.[17,18] The level of plasma fibrinogen might associate with disease activity and exacerbation hazards.[19-23] For that reason, it is acceptable that low-grade chronic systemic inflammation conversely disturbs lung parenchyma, although the exact mechanism by which this may happen is unidentified. Many new studies refer to increase evidence of coagulation activation in the asthmatic bronchial tree post allergen challenges test.[24,25]

In latest researches, a relationship between plasma fibrinogen level and other inflammatory biomarkers and cardiac disease has appeared.[12] Numerous studies have revealed that increased levels of plasma fibrinogen are accompanying later with the progression of atherosclerotic vascular changes such as cerebrovascular diseases, peripheral artery disease, and coronary heart disease.[26] All these illnesses were accompanying with low lung function test.[27] Current evidence shows that coagulation activity in the bronchial tree of asthmatic patients can exacerbate inflammation and airways hyperresponsiveness to certain stimuli.[28] Patients with severe uncontrolled asthma can be associated with increased fibrin production in alveolar space and these findings were established by heavy fibrin deposition in distal bronchial tree and alveolar space of died asthmatic victim.[29] Furthermore, earlier studies have shown that coagulation and fibrinolysis-related proteins may be involved in pathophysiology of asthma.[30] In recent times, it was described that precipitation of fibrin and aberrations in fibrinolytic and coagulation pathways in the terminal bronchioles of the lung considerably participate in bronchial tree hyperresponsiveness and remodeling in patients with severe asthma.[28] The current study was aimed to assess the role of plasma fibrinogen as inflammatory biomarker in asthmatic patients.

PATIENTS AND METHODS

Setting of the Study

This study was carried out on patients attended to respiratory clinic in Merjan Teaching Hospital in Babylon Province. These patients were diagnosed using spirometer and level of asthma control, according to GINA guideline.

Study Design

A case–control study was carried out on 50 patients with asthma and 40 healthy control.

Study Population

This study includes 90 individuals. These subjects were divided into two groups: The first group includes 50 asthmatic patients and the second group includes 40 apparently healthy individuals (control group).

Data Collection

The inclusion and exclusion criteria for this study are as follows:

Inclusion criteria

The participants in the present study were asthmatic patient group and apparently healthy control group, those who were accepted to participate in the current study.

Exclusion criteria

Any subjects suffered from the following were excluded from the study:

Lack of patient cooperation, known coagulation disorders, patients under treatment, using warfarin or having tumor, any chronic and acute illness, and smoker >10 pack years.

Study Instruments

Questionnaire

The sociodemographic characteristics composed of age, height, weight, gender, FEV1%, and medical history. Moreover, the questionnaire form (ACT™) was filed for each subject by direct interview.

Anthropometric measurement

The participant's age, sex, family history, ACT™ (ACT™)© 2002, 2004 QualityMetric, and incorporated. All asthmatic patients were diagnosed according to the criteria of GINA on the basis of suggested sign and symptom, spirometry, and radiological test,

while the height and weight of the participants were measured by measuring tape and electronic balance, respectively. The calculation of body mass index (BMI) was measured by dividing the weight (in kg) on the square of height (in m) BMI = kg/m^2.

Samples Collection

Samples were collected, during the period from December 2018 to February 2019, from the visitors of respiratory clinic in Merjan Medical City; verbal consent agreement from all subjects was obtained before the collection of samples.

3 ml of venous blood sample was aspirated by 5 ml disposable syringe, then the blood was kept in sodium citrate tube for plasma separation. The human hemostat fibrinogen kit was used to assess fibrinogen level of plasma for 2 h from blood sampling.

Statistical Analysis

Numerical variables were expressed as mean ± standard deviation (SD). Student's *t*-test was used to determine the difference in means between control and asthma groups for numerical variables using SPSS version 20 software (SPSS Inc.). In statistical analysis, the level of significant (*P*-value) was <0.05.

RESULTS

A total of 50 patients (70% females and 30% male) with asthma and 40 healthy controls (50% females and 50% male) were studied, as shown in Figure 1.

The mean (±SD) age of patients and controls was 40.32 ± 10.01 and 35.5 ± 10.3 years old, respectively. Demographics of the patients control are presented in Table 1.

The study shows significant changes between patients and control group parameters (FEV1, FEV1/FVC, fibrinogen level, and ACT), as shown in Table 2.

Furthermore, the study shows a significant inverse correlation between fibrinogen level and FEV1 in patients group, as shown in Figure 2.

Furthermore, the study shows a significant negative correlation between the level of plasma fibrinogen and FEV1/FVC in patients group, as shown in Figure 3.

Furthermore, the study reveals a significant negative correlation between level of plasma fibrinogen and ACT in patients group, as shown in Figure 4.

DISCUSSION

The biomarkers play a role in the evaluation of disease status and it is a zone of growing importance. Numerous validated multidimensional measures for asthma control assessment are now obtainable.[31] The association between coagulation and inflammation has been well established in diseases characterized by systemic inflammatory such as acute infections of respiratory tract, hemorrhagic viral infections, and sepsis.[32,33] At sites of tissue injury, fibrin is characteristically formed, also it can be made at any pulmonary system part, after epithelial damage, fibrin generation is required for normal healing of bronchial tree epithelium.[34] Asthmatic patients with poor control level can be associated with increased production of fibrin in intra-alveolar area, as revealed by huge fibrin precipitation in the terminal bronchioles of victim who died from a severe asthma bout that is refractory to anti-asthmatic drugs.[28] Mouse studies demonstrated that there was great role for

Table 1: Demographics of patients with asthma and controls

Parameters	Mean±standard deviation	
	Patients	Control
Age	40.32±10.10	35.5±10.3
Body mass index	28.64±6.1	27.89±6.2

Table 2: Patients and control group parameters

Parameters	Mean±standard deviation		*P*-value
	Patients	Control	
FEV1	76.93±22.4	92.8±7.5	<0.001
FEV1/FVC	65±4.38	85.39±5.1	<0.001
Fibrinogen	477.41±160.41	406.36±23.6	<0.007
ACT	14.4±4.68	25±0.00	<0.001

FEV1: Forced expiratory volume in 1 s, ACT: Asthma control test

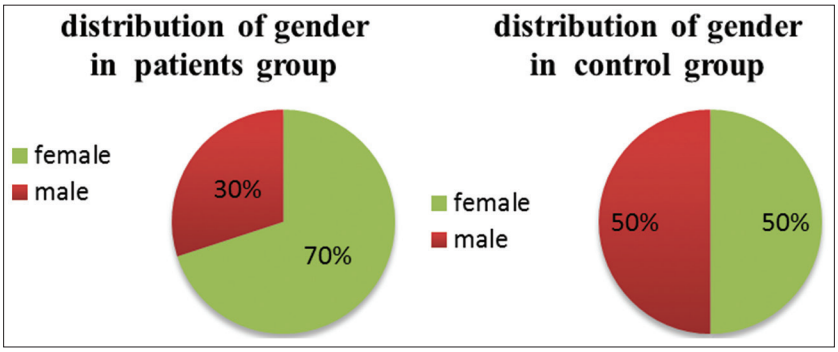

Figure 1: Distribution of gender in patients and control groups

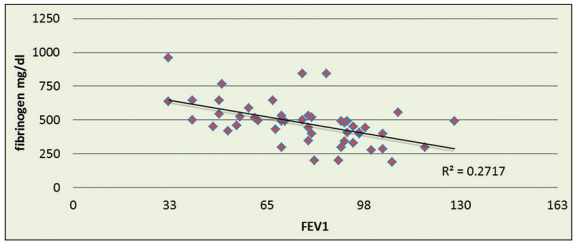

Figure 2: Correlation between plasma fibrinogen level and forced expiratory volume in 1 s in asthmatic patients

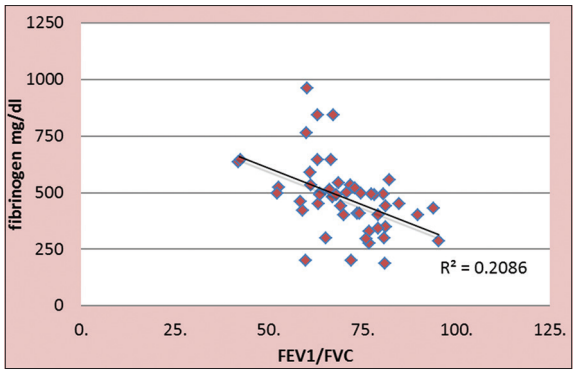

Figure 3: Correlation between plasma fibrinogen level and forced expiratory volume in 1 s/forced vital capacity in asthmatic patients

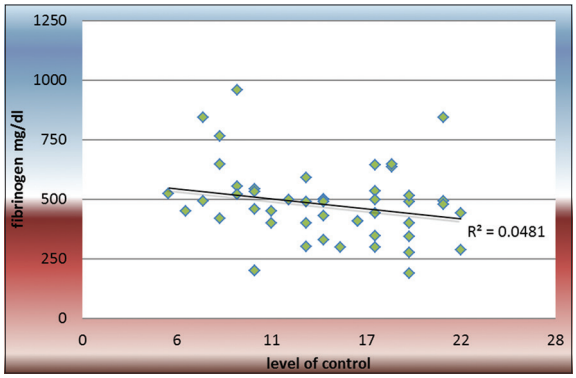

Figure 4: The correlation between plasma fibrinogen and level of control in asthmatic patients

activation of coagulation cascade in the lungs for asthma pathogenesis. When they exposed mice to inhaled fibrinogen, then after thrombin resulted in amplified hyper-responsiveness of bronchial airways.[12] All of above obviously indicate that raised level of fibrin in the bronchial tree can result in a lung function pattern that is specific for asthma.[35] We hypothesized that in the course of exacerbation of asthma, systemic, and bronchial tree inflammations raised, fibrinogen is one of the important clotting factors and good inflammatory marker, there is a well-established relationship between it and atherosclerotic disease.[36] Meanwhile a suppressed lung function parameters are also linked with atherosclerotic disease.[37] It is a reasonable that long-lasting, slowly growing systemic inflammation negatively affects lung parenchyma.[38-40] However, in Iraq no preceding data were available to link lung function test and plasma level of fibrinogen. High level of plasma fibrinogen, in turn, resulted in an augmented drop in parameters lung functions, Fogarty *et al*. found that higher levels of plasma fibrinogen in patients with more than 50 years of age and severe obstructive lung pattern than the controls.[41] Gan *et al*. revealed that high ranks of inflammatory biomarkers for example plasma fibrinogen and C-reactive protein were autonomously accompanying with low-level FEV1.[42] The stimulation of coagulation in pulmonary inflammatory diseases that are possibly triggered by extravasation of plasma proteins into the alveolar cavity, in addition to crucial mediators of coagulation that can be present in the lung tissue, comprising TF that recruits coagulation and thrombin, which play an important role in transforming fibrinogen to fibrin.[43] Hence, initially, physiologically required fibrin formation for regular wound restoration, started by TF-bearing cells, may broadcast into extravasated plasma, producing large and physiologically unwanted fibrin that might result in bronchial tree hyperresponsiveness, airways narrowing, formation of mucus plug, and fibrosis.[28,44,45]

Worth mentioning, a modern study has shown that asthmatic patients display evidence of a reduced function of the PC in pulmonary system. In bronchoalveolar lavage of persons with mild allergic asthma, the APC level reduced 4 h after a bronchial challenge test and was significantly lesser than healthy individuals.[25] Furthermore, provocation challenge test in mild asthmatic patients amplified the levels of soluble form of thrombomodulin and expression on dendritic cells in bronchoalveolar lavage.[25,46] In the current study, ACT score was found to reflect lung function and inflammation and these greatly concomitant with a Greek asthmatic population study.[47]

CONCLUSIONS

The results of this study indicated increased plasma fibrinogen concentration in asthma compared to the control group. This increasing correlates positively with severity of asthma and thus can be considered as biomarker in predicting status.

REFERENCES

1. Lambrecht BN, Hammad H. Asthma and coagulation. N Engl J Med 2013;369:1964-6.
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, *et al.* Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008;31:143-78.
3. Chhabra SK. Clinical application of spirometry in asthma: Why, when and how often? Lung India 2015;32:635-7.
4. Health NI of. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NHLBI/WHO Work Shop Rep; 1995.
5. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, *et al.* Interpretative strategies for lung function

tests. Eur Respir J 2005;26:948-68.
6. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.
7. Vestbo J, Rennard S. Chronic obstructive pulmonary disease biomarker (s) for disease activity needed-urgently. Am Thorac Soc 2010;182:863-4.
8. Matthay MA, Clements JA. Coagulation-dependent mechanisms and asthma. J Clin Invest 2004;114:20-3.
9. Kanazawa H, Yoshikawa T. Up-regulation of thrombin activity induced by vascular endothelial growth factor in asthmatic airways. Chest 2007;132:1169-74.
10. Hataji O, Taguchi O, Gabazza EC, Yuda H, Fujimoto H, Suzuki K, *et al.* Activation of protein C pathway in the airways. Lung 2002;180:47-59.
11. Littleton SW. Impact of obesity on respiratory function. Respirology 2012;17:43-9.
12. Thyagarajan B, Jacobs DR, Apostol GG, Smith LJ, Lewis CE, Williams OD, *et al.* Plasma fibrinogen and lung function: The CARDIA study. Int J Epidemiol 2006;35:1001-8.
13. Williams MJ, Williams SM, Milne BJ, Hancox RJ, Poulton R. Association between C-reactive protein, metabolic cardiovascular risk factors, obesity and oral contraceptive use in young adults. Int J Obes Relat Metab Disord 2004;28:998-1003.
14. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: Meta-analyses of prospective studies. JAMA 1998;279:1477-82.
15. Agusti A, Soriano JB. COPD as a systemic disease. COPD 2008;5:133-8.
16. Johnston SL, Pattemore PK, Sanderson G, Smith S, Campbell MJ, Josephs LK, *et al.* The relationship between upper respiratory infections and hospital admissions for asthma: A time-trend analysis. Am J Respir Crit Care Med 1996;154:654-60.
17. Vandenplas O, Malo JL. Definitions and types of work-related asthma: A nosological approach. Eur Respir J 2003;21:706-12.
18. Østergaard PA. Non-IgE-mediated asthma in children. Acta Pædiatr 1985;74:713-9.
19. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum igE levels and skin-test reactivity to allergens. N Engl J Med 1989;320:271-7.
20. Tollerud DJ, O'Connor GT, Sparrow D, Weiss ST. Asthma, hay fever, and phlegm production associated with distinct patterns of allergy skin test reactivity, eosinophilia, and serum igE levels. The normative aging study. Am Rev Respir Dis 1991;144:776-81.
21. Duvoix A, Dickens J, Haq I, Mannino D, Miller B, Tal-Singer R, *et al.* Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease. Thorax 2013;68:670-6.
22. Valvi D, Mannino DM, Müllerova H, Tal-Singer R. Fibrinogen, chronic obstructive pulmonary disease (COPD) and outcomes in two united states cohorts. Int J Chron Obstruct Pulmon Dis 2012;7:173-82.
23. Dahl M, Tybjaerg-Hansen A, Vestbo J, Lange P, Nordestgaard BG. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164:1008 11.
24. Kemona-Chetnik I, Bodzenta-Lukaszyk A, Kucharewicz I, Rogalewska AM. Tissue factor and tissue factor pathway inhibitor during specific bronchial challenge in allergic asthma patients. Przegl Lek 2005;62:98-101.
25. Schouten M, van DE Pol MA, Levi M, van der Poll T, van der Zee JS. Early activation of coagulation after allergen challenge in patients with allergic asthma. J Thromb Haemost 2009;7:1592-4.
26. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. The Framingham study. JAMA 1987;258:1183-6.
27. Gunnell D, Whitley E, Upton MN, McConnachie A, Smith GD, Watt GC, *et al.* Associations of height, leg length, and lung function with cardiovascular risk factors in the midspan family study. J Epidemiol Community Health 2003;57:141-6.
28. Wagers SS, Norton RJ, Rinaldi LM, Bates JH, Sobel BE, Irvin CG, *et al.* Extravascular fibrin, plasminogen activator, plasminogen activator inhibitors, and airway hyperresponsiveness. J Clin Invest 2004;114:104-11.
29. Schuliga M. The inflammatory actions of coagulant and fibrinolytic proteases in disease. Mediators Inflamm 2015;2015:437695.
30. Shinagawa K, Martin JA, Ploplis VA, Castellino FJ. Coagulation factor xa modulates airway remodeling in a murine model of asthma. Am J Respir Crit Care Med 2007;175:136-43.
31. Fuhlbrigge AL. Asthma severity and asthma control: Symptoms, pulmonary function, and inflammatory markers. Curr Opin Pulm Med 2004;10:1-6.
32. Chuansumrit A, Chaiyaratana W. Hemostatic derangement in dengue hemorrhagic fever. Thromb Res 2014;133:10-6.
33. van Wissen M, Keller TT, van Gorp EC, Gerdes VE, Meijers JC, van Doornum GJ, *et al.* Acute respiratory tract infection leads to procoagulant changes in human subjects. J Thromb Haemost 2011;9:1432-4.
34. Perrio MJ, Ewen D, Trevethick MA, Salmon GP, Shute JK. Fibrin formation by wounded bronchial epithelial cell layers *in vitro* is essential for normal epithelial repair and independent of plasma proteins. Clin Exp Allergy 2007;37:1688-700.
35. de Boer JD, Majoor CJ, van 't Veer C, Bel EH, van der Poll T. Asthma and coagulation. Blood 2012;119:3236-44.
36. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, *et al.* C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med 2012;367:1310-20.
37. Zureik M, Benetos A, Neukirch C, Courbon D, Bean K, Thomas F, *et al.* Reduced pulmonary function is associated with central arterial stiffness in men. Am J Respir Crit Care Med 2001;164:2181-5.
38. Jousilahti P, Salomaa V, Hakala K, Rasi V, Vahtera E, Palosuo T, *et al.* The association of sensitive systemic inflammation markers with bronchial asthma. Ann Allergy Asthma Immunol 2002;89:381-5.
39. Jain A, Gupta HL, Narayan S. Hyperfibrinogenemia in patients of diabetes mellitus in relation to glycemic control and urinary albumin excretion rate. J Assoc Physicians India 2001;49:227-30.
40. Bruno G, Cavallo-Perin P, Bargero G, Borra M, D'Errico N, Macchia G, *et al.* Hyperfibrinogenemia and metabolic syndrome in Type 2 diabetes: A population-based study. Diabetes Metab Res Rev 2001;17:124-30.
41. Fogarty AW, Jones S, Britton JR, Lewis SA, McKeever TM. Systemic inflammation and decline in lung function in a general population: A prospective study. Thorax 2007;62:515-20.
42. Gan WQ, Man SF, Sin DD. The interactions between cigarette smoking and reduced lung function on systemic inflammation. Chest 2005;127:558-64.
43. Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med 2010;38:S26-34.
44. Chambers RC. Procoagulant signalling mechanisms in lung inflammation and fibrosis: Novel opportunities for pharmacological intervention? Br J Pharmacol 2008;153 Suppl 1:S367-78.
45. Ma Z, Paek D, Oh CK. Plasminogen activator inhibitor-1 and asthma: Role in the pathogenesis and molecular regulation. Clin Exp Allergy 2009;39:1136-44.
46. Bratke K, Lommatzsch M, Julius P, Kuepper M, Kleine HD, Luttmann W, *et al.* Dendritic cell subsets in human bronchoalveolar lavage fluid after segmental allergen challenge. Thorax 2007;62:168-75.
47. Papakosta D, Latsios D, Manika K, Porpodis K, Kontakioti E, Gioulekas D, *et al.* Asthma control test is correlated to FEV1 and nitric oxide in Greek asthmatic patients: Influence of treatment. J Asthma 2011;48:901-6.

Source of support: Nil; Conflict of interest: None Declared