Value of Serum ECP and IgE in Differentiation between Asthma and COPD

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ABSTRACT. The significance of eosinophilic inflammation in asthma is well established, while its role in COPD is still under investigation, a proportion of patients with COPD exhibited some degree of sputum eosinophilia. It is debatable whether eosinophilia in COPD is related to concomitant features of asthma. The aim of this study was to evaluate the role of serum ECP and total IgE in differentiation between asthma and COPD in both stable condition and in exacerbations. The study conducted on 59 patients, 17 patients with COPD (10 with acute exacerbation and 7 with stable COPD) and 22 patients with asthma (10 patients with acute exacerbation and 12 with stable asthma). 20 healthy subjects were included as control. All patients were subjected to: *thorough history taking and clinical examination, chest x-ray to exclude other underlying pathology, ECG, and Spirometry*. COPD staging was done according to Gold study (2001), and estimation of serum ECP and total IgE was done for all subjects. There was significantly higher level of serum ECP and total IgE in stable COPD, acute COPD exacerbation, stable asthma and acute asthma exacerbation when compared to control, also level of ECP was significantly higher in stable asthma group than acute asthma exacerbation in contrast to serum level of Total IgE which was higher in acute asthma exacerbation group than stable asthma. There was no significant difference between serum ECP among acute versus stable COPD. There was significantly higher level of serum ECP and Total IgE in total asthma group than total COPD group. Also, there was higher level of serum ECP and Total IgE in stable asthma than stable COPD and higher level of serum Total IgE in acute asthma exacerbation than acute COPD exacerbation. Meanwhile, there was no significant difference between acute COPD exacerbation and acute asthma exacerbation in serum level of ECP. No correlation was found between serum ECP and FEV1, FEV1/FVC among asthma and COPD patients. *In Conclusion:* eosinophil share in airway inflammation and acute exacerbation of COPD. Asthma like components of COPD can be explained by increased serum Total IgE and ECP, also this could explain the variability and heterogeneity of COPD. ECP and Total IgE cannot differentiate between acute COPD exacerbation and acute asthma exacerbation but may be a differentiating point in stable state.
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INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are both characterized by airway inflammation. Studies using bronchoalveolar lavage (BAL), bronchial biopsy or more recently induced sputum have shown that the main cellular markers of intralumnal airway inflammation are eosinophils in asthma, and neutrophils in COPD. Moreover, good correlations have been found between eosinophils and airway hyper responsiveness in asthma, as well as between neutrophils and airway obstruction in COPD. However, there is some debate about the number and possible significance of eosinophils in the airways of patients with COPD ***(Sin and others, 2006)***. Subjects with COPD had higher percentage of sputum, eosinophil cationic protein (ECP) and bronchoalveolar lavage (BAL) fluid eosinophils. Sputum concentrations of ECP per eosinophil were not higher denoting that these eosinophil do not seem to be activated and the increases number of eosinophil are propably due to recruitment as a result of ongoing inflammation ***(Jindal 2006)***.

AIM OF THE WORK

This study was carried out at Thoracic Medicine Department Mansoura University Hospital. The study compromised 20 healthy control and 39 asthmatic and COPD patients. The patients were classified to the following subgroups; 10 patients with acute exacerbations of COPD, 10 patients with stable COPD, 7 patients with acute asthma exacerbation, 12 patients with stable asthma.

All patients were subjected to the following:

- Thorough history taking and clinical examination
- Chest x-ray to exclude other underlying pulmonary lesion
- ECG

- Spirometry
- COPD staging was done according to Gold study ***(Gold, 2001)***: All COPD cases were stage VI with type II respiratory failure and core pulmonale.
- Acute exacerbation of COPD was known by exaggeration of symptoms: dyspnea and increase or change in sputum production ***(Jenkins and others, 2005)***.
- Sample collection, 3 ml of venous blood sample were withdrawn into plain tubes and non haemolyzed sera were separated and kept frozen at -20^0C till analysis of ECP using chemiluminescent enzyme immunometric assay by Immulite Automated Analyzer supplied by diagnostic product corporation (USA) Reimert and Paulsen (1993). This procedure has sensitivity measuring 2µg/L of ECP. Serum immunoglobulin E was measured by ELISA (Enzyme immunoassay for quantitative determination og immunoglobulin E in human sera). The medics Total IgE quantitative test is solid phase enzyme linked immunosorbent assay ELISA based on the sandwich principle. Using the mean absorbance value for each sample determine corresponding concentration of Total IgE in IU/ml from the standard curve.

Statistical analysis: In normally distributed variables student's I Test was used for comparison between groups. In non-parametric variables Mann-Whitney test was used for comparison between groups.

RESULTS

Table (1): This table shows the age and sex distribution among studied subjects the mean age of control subjects was 36.8 years with range between 30 – 45 years and they were 10 males and 10 females with negative history of smoking and normal ECG findings. In total COPD group the mean age was 58.69 with range between 50 – 66 years and they were 15 males and 2 females with positive history of smoking and manifestation of pulmonary hypertension, right ventricular hypertrophy (RVH) in ECG. The mean age among asthma group was 40.9 years with range between 23 – 56 years with negative history of smoking and normal ECG findings.

Table (2): This table shows, the FEV1% and FEV1/FVC% of predicted among studied groups. There was significant lower FEV1% of predicted and FEV1/FVC% between studied cases and control subjects (P<0.001). There was significant lower FEV1% of predicted and FEV1/FVC% in acute COPD exacerbation versus acute asthma exacerbation (P<0.001). There was significant lower FEV1% of predicted and FEV1/FVC% in stable COPD versus stable asthma group (P<0.001). There was lower FEV1% of predicted and FEV1/FVC% in acute asthma group, but this was of no statistical significance. There was no significant difference between acute and stable COPD in FEV1% of predicted and FEV1/FVC%.

Table (3): This table shows the serum level of ECP in acute asthma exacerbation, stable asthma and control. There was significant higher serum ECP among studied asthma cases when compared to control subjects (P<0.001) and in the same time there was significant higher serum EGP among stable asthma when compared to acute asthma exacerbation group.

Table (4): This table shows correlation between ECP and FEV1% of predicted, FEV1/FVC% in total asthma group. There was no correlation found between serum ECP and FEV1% of predicted and FEV1/FVC% among studied subjects.

Table (5): This table shows correlation between ECP and FEV1% of predicted, FEV1/FVC% in total COPD group. There was no correlation found between serum BCP and FEV1% of predicted and FEV1/FVC% among studied subjects.

Table (6): This table shows the serum levels of ECP in acute COPD exacerbation, stable COPD and control. There was significant higher serum ECP in studied COPD cases when compared to control subjects (P<0.001), meanwhile there was no significant difference between serum ECP among acute versus stable COPD.

Table (7): This table shows the serum level of Total IgE in acute asthma exacerbation, stable asthma and control. There was significant higher serum Total IgE in asthma cases when compared to control (P<0.001). Also, there was significant higher serum Total IgE in studied acute asthma exacerbation cases when compared to stable asthma.

Table (8): This table shows the serum level of IgE in acute COPD exacerbation, stable COPD and control. There was significant higher serum Total IgE in acute and stable COPD when compared to control (P<0.001). Also, there was no significant difference in serum Total IgE between stable and acute COPD exacerbation in studied cases.

Table (9): This stable shows the comparison between serum ECP and Total IgE among total COPD and total asthma groups. There was significant higher serum ECP and Total IgE among total asthma group when compared to total COPD group.

Table (10): This table shows comparison between serum ECP and Total IgE in studied cases of acute COPD exacerbation and acute asthma exacerbation. There was no significant difference between serum ECP in acute COPD exacerbation versus acute asthma exacerbation groups (P=0.3), but there was significant higher serum Total IgE in acute asthma exacerbation when compared to acute COPD exacerbation (P=0.04).

Table (11): This table shows comparison between serum ECP and Total IgE in studied cases of stable COPD and stable asthma. There was significant higher serum ECP in stable asthma when compared to stable COPD (P<0.001) and in the same time there was significant higher serum Total IgE in stable asthma than stable COPD (P=0.01).

Table (1): Demographic and clinical characteristics of patients

Item	control (n=20)	total COPD (n=17)	asthma (n=22)
Age			
Mean	36.8	58.69	40.9
SD	±4.49	±4.01	±3.94
Range	30 – 45	50 – 66	23 – 56
Sex			
Male	10	15	8
Female	10	2	14
Duration (years)			
Mean		18.88	38
SD		5	5.26
Range		10 – 26	5 – 28
Smoking history	-ve in all	+ve in all	-ve in all
ECG (P-pulmonale & RVH configuration	-ve in all	+ve in all	-ve in all

Table (2): FEV1% and FFV1/FVC% of predicted among cases and control

Item	acute COPD exacerbation	stable COPD	acute asthma exacerbation	stable asthma	control	P value
FEV1% of pred						
Mean	52.18	58.58	60.91	76.83	89.50	<0.003
SD	±6.24	±9.61	±1.98	±6.02	±1.50	
	P1<0.001	P2<0.001	P3=0.07	P4=0.1		
FEV1/FVC%						
Mean	56.81	61.74	74.0	76.76	85.6	<0.001
SD	±3.21	±8.42	±2.73	±4.92	±2.01	
	P1<0.001	P2<0.001	P3=0.2	P4=0.2		

P1: acute asthma exacerbation vs acute COPD exacerbation P2: stable asthma vs stable COPD
P3: acute asthma exacerbation vs stable asthma P4: acute COPD exacerbation vs stable COPD

Table (3): serum level of ECP in acute asthma exacerbation, stable asthma and control

	ECP median (Range)	P value
acute asthma exacerbation	30.9 (7.9 – 189)	P1<0.001***
Stable asthma	81.2 (30.6 – 131)	P2<0.001***
Control	6.85 (2.2 – 13.8)	P3<0.001***

P1: acute COPD exacerbation vs stable COPD P3: stable COPD vs control
P2: acute COPD exacerbation vs control

Table (4): Correlation between ECP and FEV1, FEV1/FVC among asthma patients

	ECP	
	r	**P**
FEV1% of predicted	-0.271	0.223
FEV1/FVC	-0.042	0.853

Table (5): Correlation between ECP and FEV1, FEV1/FVC among COPD patients

	ECP	
	r	**P**
FEV1% of predicted	0.412	0.100
FEV1/FVC	0.293	0.254

Table (6): Level of ECP in acute COPD exacerbation, stable COPD and control

	ECP Median (Range)	**P value**
acute COPD exacerbation	24.7 (10.7 – 73.8)	P1=-0.53
stable COPD	21.2 (5.2 – 69.8)	P2<0.001***
Control	6.85 (2.2 – 13.8)	P3<0.001***

P1: acute COPD exacerbation vs stable COPD P3: stable COPD vs control
P2: acute COPD exacerbation vs control

Table (7): Level of Total IgE in acute asthma exacerbation, stable asthma and control

	Total IgE Median (Range)	**P value**
acute asthma exacerbation	445.75 (65.7 – 920)	P1<0.001***
stable asthma	132 (65 – 310)	P2<0.001***
Control	21.35 (6.2 – 80.2)	P3<0.001***

P1: acute COPD exacerbation P3: stable COPD vs control
P2: acute COPD exacerbation vs control

Table (8): Serum level of Total IgE in acute COPD exacerbation, stable COPD and control

	Total IgE Median (Range)	**P value**
acute COPD exacerbation	106.5 (37 – 211)	P1=0.23
stable COPD	76 (50 – 138)	P2<0.001***
Control	21.35 (6.2 – 80.2)	P3-0.025*

P1: acute COPD exacerbation vs stable COPD P3: stable COPD vs control
P2: acute COPD exacerbation vs control

Table (9): Comparison between serum ECP and Total IgE among total COPD and Total asthma

Item	**Total COPD Median (Range)**	**Total Asthma Median (Range)**	**Mann-Whitney**
ECP	234 (5.2 – 73.8)	61.6 (7.9 – 189)	P<0.001
Total IgE	94.5 (37 – 211)	169.5 (65 – 920)	P<0.001

Table (10): Comparison between ECP and Total IgE in studied cases of acute COPD exacerbation and acute asthma exacerbation

	acute COPD exacerbation median (Range)	acute asthma exacerbation median (Range)	P Value
ECP	24.7 (10.7 – 73.8)	30.95 (7.9 – 189)	P=0.35
Total IgE	106.5 (37 – 211)	445.75 (65.7 – 920)	P=0.043"

Table (11): Comparison between ECP and Total IgE in studied cases of stable COPD and stable asthma

	stable COPD median (Range)	stable asthma median (Range)	P Value
ECP	21.2 (5.2 – 69.8)	51.2 (30.6 – 131)	P<0.001
Total IgE	76 (50 – 138)	132 (65 – 310)	P=0.011*

DISCUSSION

The significance of eosinophilic inflammation in asthma is well established while its role in COPD is still under investigations ***(Jenkins and others, 2005)***. A proportion of patients with COPD exhibited some degree of sputum eosinophilia***(Jindal,2006)***. It is debatable whether eosinophilia in COPD is related to concomitant features of asthma ***(Papi and others, 2000)***. Clinical studies showed that assessment of eosinophilic inflammation can be measured systematically in serum by estimation of eosinophil derived inflammatory mediators such as eosinophil cationic protein (ECP) ***(Barnes, 1996)***. The aim of this study was to evaluate the role of serum ECP and Total IgE in differentiation between asthma and COPD in both stable condition and in exacerbations. Mean FEV1% of predicted among stable and acute COPD exacerbation cases were 58.58 and 52.18 respectively, ECG showed P pulmonale and RVH configuration. All COPD cases were severe degree, according to Gold study ***(Gold, 2001)***, acute exacerbation of COPD was noted by exaggeration of symptoms of dyspnea and increase or change in sputum production.

ECP in asthma

There was significant higher ECP serum level in stable asthma, acute asthma exacerbation when compared to control (81.2, 30.9, 6.85 µg/L respectively) and this was in agreement with ***Tang and Chen, 2001*** who found significant higher ECP serum level in stable and acute asthma exacerbation when compared to normal control subjects, and ***Kokuludag and others, 2002*** who found significant higher ECP serum level in acute asthma exacerbation when compared to control and this high level persist up to 7th day of the attack. Also in agreement with ***Salem and Hanna,2001*** who found higher significant level of ECP in acute asthma exacerbation attacks when compared to control group and in stable condition after 4 months when compared to normal control.

Literatures are divided as regard to value of serum ECP in monitoring the disease activity in asthma, there are many works that proved serum ECP as a viable marker of disease activity ***(Niimi and others, 1997; Blay and others, 1998; Prehn and others, 1998)***, while others proved it is not correlated to clinical or spirometric parameters of the disease ***(Mahajan et al., 2008 and Motojima et al., 1995)***. In our study, there was significant higher level of ECP in stable asthma when compared to acute asthma exacerbation. This can be explained according to ***Noguchi and others, 2003***, who studied the ECP gene and found polymorphism in ECP gene leading to variance in baseline serum ECP levels and found that serum ECP levels were not elevated in some patients with asthma even when they are symptomatic. Also, ***Tang and Chen, 2001*** found considerable overlap among patients with acute asthma exacerbation and those with stable asthma and stated that this overlap in the majority of patients limit the utility of this test in determining acute versus stable asthma. Also our results could be explained according to ***Ronchi and others, 1997*** who stated that although serum ECP levels appear to be useful indicator of disease, they do not accurately correspond with clinical or functional indices of asthma severity in chronic stable patients. No correlation was found between ECP and FEV1, FEV1/FVC in total asthma group and this in agreement with ***Kunkel and Ryden, 1999*** who found lack of relationship between serum ECP and bronchial hyper-responsiveness to cold dry air and anti histamine and ***Gruber and others, 1999***, who found no correlation between serum ECP and bronchial hyper-responsiveness to histamine.

ECP in COPD

There was significant higher level of serum, ECP in stable and acute COPD exacerbation when compared to control (21.2, 24.7, 6.85µ/L respectively) and these in agreement with ***Fiorini and others, 2000***, who found significant high level of serum ECP in both stable and acute COPD exacerbation when compared to healthy subjects.

There was no significant difference between serum level of ECP in acute COPD exacerbation when compared to stable COPD, also there was no correlation found between ECP and FEV1, FEV1/FVC in total COPD group and this could be explained according to ***Dahlen and others, 2001***, who found no change of serum BCP before and after treatment of COPD exacerbation in patients with severe COPD but not in mild or moderate COPD.

There was significant higher level of ECP in total asthma group (61.6µg/L) than total COPD group (23.4µg/L) and this was agreement with ***Motojima and others, 1995***, who found significant higher concentration of serum ECP in asthma than COPD patients and healthy subjects and ***Sin and others, 2006***, who found that eosinophilic inflammation more intense in asthma than in COPD.

There was no significant difference between serum level of ECP in acute asthma exacerbation versus acute COPD exacerbation group and this in agreement with ***Gursel and others, 1997)***, who found no significant difference in serum ECP level between patients with asthma attack and acute exacerbation of COPD. Also, the eosinophilic inflammation, not neutrophilic inflammation, in the airway is involved in the reversible part of the airflow obstruction in response to glucocorticoids in patients with pulmonary emphysema. This finding was found in this study indicated similarity of airway inflammation between asthma and COPD and this may limit the utility of this test to differentiate between exacerbation of COPD ***(Sears and others, 1991)***. There was significant higher level of serum ECP in stable asthma versus stable COPD and this in agreement with ***Motojima and others, 1995; Sin and others, 2006***.

Total IgE in asthma and COPD

There was significant higher serum Total IgE in asthma cases when compared to control (P<0.001). Also, there was significant higher serum Total IgE in studied acute asthma exacerbation cases when compared to stable asthma, this in agreement with ***Sear and others, 1991***, who found that there is a strong relationship between serum Total IgE, clinical asthma and airways hyperresponsiveness (AHR). ***Robinson and others, 2002*** stated that well-controlled asthmatic individuals will experience at times sudden apparently unexplained life threatening exacerbation of asthma that is unlikely to occur secondary to inhaled allergens. This is mediated by Total IgE mediated hypersensitivity reaction. This type I hypersensitivity reaction results from degradation of mast cells and eosinophils which carry high affinity receptors for Total IgE called FCERI receptors. There was significant higher serum Total IgE in stable and acute COPD exacerbation when compared to control (P<0.001). There was no significant difference in serum Total IgE between stable and acute COPD exacerbation in studied cases. ***Mahajan and others, 2008*** have found significant higher level of serum Total IgE in patients with COPD than control and this difference is related to smoking history and inversely related to pulmonary function. ***Chavannes and others, 2006*** found that serum Total IgE levels of COPD patients correlated with the smoking history where also found in bronchial lavage of those with patients increase of cell count of neutrophil, eosinophil, IL-8, myeloperoxidase (MPO) and ECP, he also stated that recruited neutrophils and eosinophils were activated and they release increased amount of inflammatory mediators capable of damaging the bronchial tissue. Also ***Robinson and others, 2002*** found that Total IgE has another type of receptors called low affinity Total IgE receptors (FCERTT) which is present on surface of many other cells such as epithelial cells, macrophages and even in alveolar macrophage and natural killer cells. Binding of Total IgE to FCERII receptor on the surface of these cells has been though capable of mediating many cytokines and cytotoxic effect of inflammatory cells and this may explain the elevated Total IgE and ECP in acute COPD exacerbation cases, hyper reactivity and asthma like component of COPD. There was significant higher level of serum Total IgE in total asthma group when compared to total COPD groups (169.5 IU/L and 94.5 IU/L respectively), this in agreement with ***Mahajan and others, 2008*** who found higher serum Total IgE concentrations in asthma than COPD and in elder patients of asthma this difference is still present.

Conclusion

Eosinophil share in airway inflammation and acute exacerbations of COPD, Asthma like components of COPD can be explained by increased serum Total IgE and ECP, also this could explain the variability and heterogeneity of COPD. ECP and Total IgE cannot differentiate between acute COPD exacerbation and acute asthma exacerbation but may be a differentiating point in stable state.

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