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Serum interleukin-1β as a marker for differentiation of asthma and chronic obstructive pulmonary disease

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are diseases of airway inflammation with clinical and physiological similarities, making their differentiation difficult. Airway inflammatory changes are associated with systemic changes. However, no serum marker is known for their differentiation. Therefore, serum interleukin (IL)-1β levels were determined. Out of a total of 1023 patients screened, we included in the study ten patients each with atopic asthma, non-atopic asthma and COPD and ten healthy subjects. Skin prick tests with 14 inhalant allergens were performed on each patient. Blood was collected in the symptomatic and asymptomatic phases of the diseases and serum IL-1β and IgE levels were determined. Our results showed that in the symptomatic phase in asthmatics, serum IL-1β levels were higher ($P<0.05$) than in patients with COPD. Serum IgE levels were higher ($P<0.05$) in atopic asthmatics than in non-atopic asthmatics and in COPD patients. We conclude that serum IL-1β level determination during the symptomatic phase of the diseases may help to differentiate asthmatics from patients with COPD. Serum IgE levels may differentiate atopic asthmatics from non-atopic asthmatics and COPD patients.

Keywords: *Diagnostic techniques, respiratory tract diseases, cytokines*

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are characterized by airway inflammation. The two conditions are distinct but their clinical features overlap in terms of reversibility, remodelling process, pathogenesis, patterns of inflammatory mediators and cytokines, and it is often difficult to differentiate, clinically diagnose and classify the two disorders (Jeffery 2001, Jindal 2006).

Serum levels of various cytokines and other markers have been evaluated in many studies on bronchial asthma and COPD. In bronchial asthma, markers such as interleukin (IL)-2, IL-4, IL-10, serum low-affinity Fc ε receptor II (sFcεRII), interferon (IFN)-γ, IgE, serum IL receptor 2 (sIL-2R) and intercellular adhesion

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molecule (sICAM)-1 have been reported but none of them are sensitive enough to determine the type, activity and severity of the inflammatory process in the asthmatic airways (Kral et al. 1997, Subratty & Hooloman 1998, Ceyhan et al. 2004). IL-5 is a marker of disease activity and treatment efficacy in bronchial asthma, but its serum levels are a poor indicator of disease activity in acute asthma (Huang et al. 2005). Therefore, monitoring serum IL-5 concentration is of limited value. Similarly, plasma levels of IL-6, IL-10, IL-12, IL-13, IL-17 and IL-18, have been reported to be higher in allergic asthmatics than in normal control subjects (Wong et al. 2001). As the differences are not statistically significant, they may not serve as systemic markers of bronchial asthma.

In COPD, sIL-2R antagonist (sIL-2Ra), tumour necrosis factor (TNF)-α, IL-4, IL-6, IL-8 and C-reactive protein (CRP) have been studied (Malo et al. 2002, Stankiewicz et al. 2002). Further, IL-1β is upregulated in the bronchial mucosa and its release increases in cultures of monocytes in COPD (DiStefano et al. 1994, Stankiewicz et al. 2002). However, none of these could be used as a serum marker for COPD.

It is known that IL-1β is expressed and released by mononuclear cells after stimulation of FcεRII by IgE immune complexes (Kips & Pauwels 1996) and serum IgE levels increase in asthma and in smokers (Sears et al. 1991, Burrows 1995, Motegi & Kida 1999). As smoking is one of the most important risk factors for COPD (Jindal 2006), it may be speculated that in these diseases, IL-1β expression may be induced in monocytes due to raised IgE levels, which may lead to their increased release in blood. Moreover, the levels may presumably be higher in the symptomatic phase than in the asymptomatic phase. Although, pulmonary inflammation is known to be associated with systemic inflammation (Hurst et al. 2006), none of the serum cytokines studied so far is helpful in the differential diagnosis of asthma and COPD. Therefore in the present study, we measured the serum IL-1β and IgE levels to (1) determine their levels in the symptomatic and asymptomatic phases of the diseases and (2) to evaluate whether or not their levels could be helpful as markers to differentiate between asthma and COPD.

Materials and methods

Study design

The study was conducted on patients with asthma and COPD diagnosed as per the NHLBI/WHO (NIH 1997) and ATS guidelines (Pauwels et al. 2001). A detailed history of the disease was recorded and various tests such as X-ray chest, pulmonary function test (PFT), skin prick test (SPT), etc. were performed. Blood samples were collected from each patient during the symptomatic and asymptomatic phases of their diseases after treatment. This was followed by determination of serum IL-1β and IgE levels by enzyme-linked immunosorbent assay (ELISA). Statistical analysis of the data was performed using 'Prism' software. A p-value <0.05 was considered to be significant. The study was approved by the Institutional Ethics Committee. Informed written consent was obtained from each patient.

Chemicals

IL-1β Duo-Set ELISA kits were purchased from R&D Systems Inc. (Minneapolis, MN, USA). IgE ELISA kits were purchased from Omega Diagnostics Kit (Alloa, Scotland, UK). Bovine serum albumin and tetramethylbenzidine were purchased from the Sigma Chemical Co., St Louis, MO, USA. Hydrogen peroxide, sodium nitrite and Tween-20 were obtained from Sisco Research Laboratories Pvt. Ltd. (Mumbai, India). All other chemicals used were of analytical grade and procured from Qualigens Fine Chemicals (Mumbai, India).

Patient selection

Patients suffering from asthma or COPD of either sex, age ranging between 16 and 65 years, attending the outpatients department of the Clinical Research Centre, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi were included in the study. The diagnosis of bronchial asthma and COPD was made as per NHLBI/WHO (NIH 1997) and ATS guidelines (Pauwels et al. 2001), respectively. Patients associated with a history of any other pulmonary and systemic disease; pregnant and breastfeeding females; patients on long-term antihistamines; and patients detected positive for parasitic infestation, which might effect the serum IgE levels, were excluded.

A total of 1023 patients were screened for inclusion in the study, of which 386 were suffering from asthma and 102 from COPD. Among the asthmatics, 81 cases were freshly diagnosed, out of which 24 were positive for a stool test (for parasitic ova and cyst), seven did not show any significant change in PFT and 21 declined to participate in the study. Therefore, 29 asthmatic patients were selected. Of these, 17 had a positive SPT but only ten patients who fulfilled the criteria for atopic asthmatics were included in the study. Out of the remaining 12 patients, ten patients who tested negative for the SPT, fulfilled the criteria for non-atopic asthmatics and gave written consent were selected. Similarly, out of 102 patients with COPD, 45 were freshly diagnosed cases, of which 28 were positive for the stool test, 15 attended for the SPT and two opted out. Of these, ten patients who fulfilled the criteria for COPD and gave written consent were included in the study.

The details of patients' clinical history of disease are provided in Table I.

Patients with bronchial asthma. The diagnosis of bronchial asthma (NIH 1997) was made on the basis of history of recurrent episodes of cough, dyspnea and wheezing, general physical examination, signs and symptoms, and spirometric evaluation of pulmonary function using a spirometer (Morgan Transfer test model C; P.K. Morgan Ltd, Kent, UK). Spirometry included assessment of forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC%, and a test for reversible airway obstruction, i.e. an increase in FEV_1 or FVC by more than 12% and 200 ml, after administration of 200 μg of salbutamol through a metered dose inhaler. Routine blood investigations, chest skiagrams, a stool test and a SPT (Kausar et al. 2007) with 14 allergen extracts (Table II) were also performed on all the patients. The asthmatics were further subdivided into atopic (Johansson et al. 2004) and non-atopic asthmatics.

Table I. History of disease in the study patients.

Age (years)	Sex M/F	Smoker PY/D	FEV_1 (% predicted)	Medication
Atopic asthma				
17	F	No	56	Inh Sal, Bec
16	F	No	35	Inh Sal, Bec, oral Predn, Ctz
30	F	No	69	Inh Sal, Bec, oral Ctz
32	F	No	29	Inh Sal, Bec, oral Predn, Ctz
50	F	No	47	Inh Sal, Bec, oral Fex
60	M	No	41	Inh Sal, Bec, oral Predn ,Fex
31	M	No	35	Inh Sal, Bec, oral Predn, Fex
16	M	No	62	Inh Sal, Bec, oral Ctz
50	M	No	43	Inh Sal, Bec, oral Sal
40	M	No	57	Inh Sal, Bec
Non-atopic asthma				
30	F	No	18	Inh Sal, Bec, oral Predn ,Fex
34	F	No	72	Inh Sal, Bec, oral Predn ,Fex
27	F	No	44	Inh Sal, Bec
35	F	No	42	Inh Sal, Bec
44	F	No	77	Inh Sal, Bec
31	F	No	54	Inh Sal, Bec, oral Fex
30	M	No	62	Inh Sal, Bec, oral Fex
16	M	No	71	Inh Sal, Bec, oral Fex
16	M	No	57	Inh Sal, Bec
42	M	No	54	Inh Sal, Bec
COPD				
60	M	15/35	36	Inh Sal, Bec, oral Fex
55	M	20/35	20	Inh Sal, Bec, oral Predn, Sal
63	M	20/30	62	Inh Sal, oral Sal, Fex
56	M	20/10	61	Inh Sal, oral Sal
55	M	12/25	49	Inh Sal, Bec, oral Sal
60	M	15/30	46	Inh Sal, Bec, oral Predn, Sal
62	M	25/35	22	Inh Sal, oral Sal
59	M	20/35	66	Inh Sal, Bec, oral Sal
60	M	25/40	41	Inh Sal, Bec, oral Sal
49	M	20/20	58	Inh Sal, Bec, oral Predn, Sal

COPD, chronic obstructive pulmonary disease; M/F, male/female; PY/D, no. of pack years/duration of smoking (years); Inh, inhaler; Sal, salbutamol; Bec, beclomethasone dipropionate; Predn, prednisolone; Ctz, cetirizine; Fex, fexofenadine.

Atopic asthmatics – Patients showing a family history of allergy and a positive SPT to one or more of 14 allergen extracts were classified as atopic asthmatics (Johansson et al. 2004). Their age ranged between 16 and 60 years (mean $\pm$ SD, 34.20 ± 4.93).

Non-atopic asthmatics – Patients with no family history of allergy and showing a uniformly negative SPT response to all the 14 allergen extracts were classified as non-atopic asthmatics. Their age ranged between 16 and 44 years (mean $\pm$ SD, 30.54 ± 9.31).

Patients with COPD. This group consisted of ten patients. The diagnosis of COPD (Pauwels et al. 2001) was established on the basis of a history of smoking, a cough with expectoration for at least 2 years in the past, accompanied by progressive dyspnea on exertion. The diagnosis was confirmed by spirometry, in which the post-bronchodilator FEV_1 was $<80\%$ of the predicted value along with an FEV_1/FVC

Table II. Allergen extract used.

No.	Common name	Zoological/botanical name
1	Cockroach male	*Periplaneta americana*
2	Cockroach female	*Periplaneta americana*
3	Housefly	*Musca domestica*
4	House Dust Mite	*Dermatophagoides pteronyssinus*
5	Butterfly	*Danais chrysippus*
6	Moth	*Bombyx mori*
7	Mosquito	*Anopheles stephensi*
8	Aspergillus	*Aspergillus tamarii*
9	Wilayati keekar	*Prosopis juliflora*
10	Doob grass	*Cynodon dactylon*
11	Chaulai	*Chenopodium album*
12	House dust	–
13	Rice dust	–
14	Wheat dust	–

of $<70\%$, which suggested the presence of an airflow limitation that is not fully reversible. Their age ranged between 49 and 63 years (mean $\pm$ SD, 57.90 ± 4.17).

Healthy subjects

Ten healthy non-smoker volunteers of either sex, aged 16–59 years (mean $\pm$ SD, 36.90 ± 16.57) with no personal or family history of any respiratory or systemic disease constituted the control group.

Determination of serum levels of IL-1β and IgE

Blood (5.0 ml) was collected from each subject by venipuncture. Patients' samples were collected in both the symptomatic and asymptomatic phases. Serum was separated and stored frozen in aliquots (0.5 ml) at -80°C until analysed. IL-1β and IgE were measured by ELISA using Duo-Set kits of R&D Systems, USA and Omega Diagnostic Kit, UK, respectively. Samples were run in duplicate. IL-1β and IgE levels were calculated using a standard plot and expressed as pg ml^{-1} (IL-1β) and IU ml^{-1} (IgE) of serum.

Statistical analysis

'Prism' software was used for analysing the data for one-way ANOVA, Dunnet's multiple comparison test, mean $\pm$ SD (or SEM, wherever applicable) and receptor operator characteristics (ROC) curve. A p-value <0.05 was considered to be significant.

Results

Serum IL-1β levels

Serum IL-1β levels of the control subjects, and asthmatic (atopic and non-atopic) and COPD patients in symptomatic and asymptomatic phases are shown in Figure 1. The

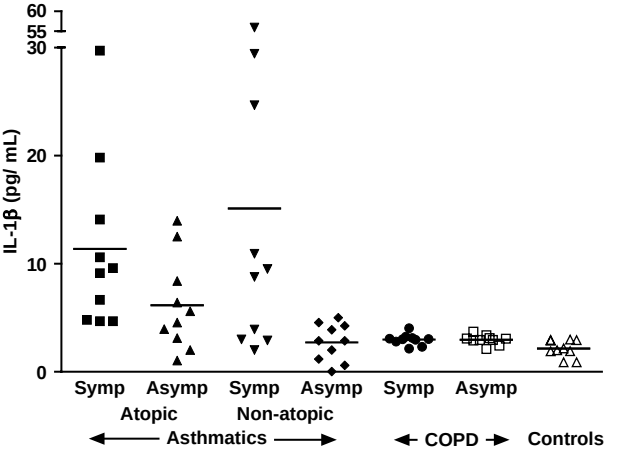

Figure 1. Serum interleukin (IL)-1β levels of atopic, non-atopic asthmatics and chronic obstructive pulmonary disease (COPD) patients in symptomatic and asymptomatic phases.

IL-1β levels of paired samples from both atopic and non-atopic asthmatics in symptomatic and asymptomatic phases showed a decreasing trend in the asymptomatic condition, while in COPD, there was no such change (Figure 2). The values (mean $\pm$ SEM) of IL-1β are given in Table III. In the control group, the IL-1β level was 2.15 ± 0.26 pg ml^{-1} (mean $\pm$ SEM), which ranged between 0.87 and 2.98 pg ml^{-1}. The ANOVA showed a significant difference in serum IL-1β levels in the various groups ($p < 0.0005$). The IL-1β levels were significantly raised in atopic asthmatics ($p < 0.05$) and non-atopic asthmatics ($p < 0.01$) in the symptomatic phase in comparison with the COPD patients (in both symptomatic and asymptomatic phases) and healthy subjects. In the symptomatic phase of non-atopic asthmatics, the IL-1β levels were significantly higher than in COPD patients of both symptomatic ($p < 0.05$) and asymptomatic ($p < 0.01$) phases. In the asymptomatic phase of atopic asthmatics, the IL-1β levels were significantly higher than in COPD patients in both the phases ($p < 0.05$). When IL-1β values of atopic and non-atopic asthmatics in the symptomatic phase were taken together, they were significantly raised in comparison with their asymptomatic phase. However, serum IL-1β levels in asymptomatic asthmatics were not significantly different from patients with COPD (both in symptomatic and asymptomatic phases) and healthy subjects. Moreover, there was no significant difference in IL-1β levels of COPD patients in the symptomatic phase in comparison with their asymptomatic phase and healthy subjects.

The ROC curve of IL-1β levels of asthmatics in a symptomatic condition (values of both atopics and non-atopics taken as one group) versus COPD patients (Figure 3A), shows the area to be 0.94 ± 0.05 ($p < 0.0002$), which is highly significant. The analysis showed that at a cut-off value of < 4.35 pg ml^{-1} of serum IL-1β, the sensitivity is 100% and the specificity is 85%. The ROC curves of atopic asthmatics versus COPD patients, at a cut-off value of < 4.35 pg ml^{-1} had a sensitivity and specificity of 100%, while in the case of non-atopic asthmatics versus COPD patients at a cut-off value of < 3.975 pg ml^{-1} the sensitivity and specificity was 90% (Figure 3B,C).

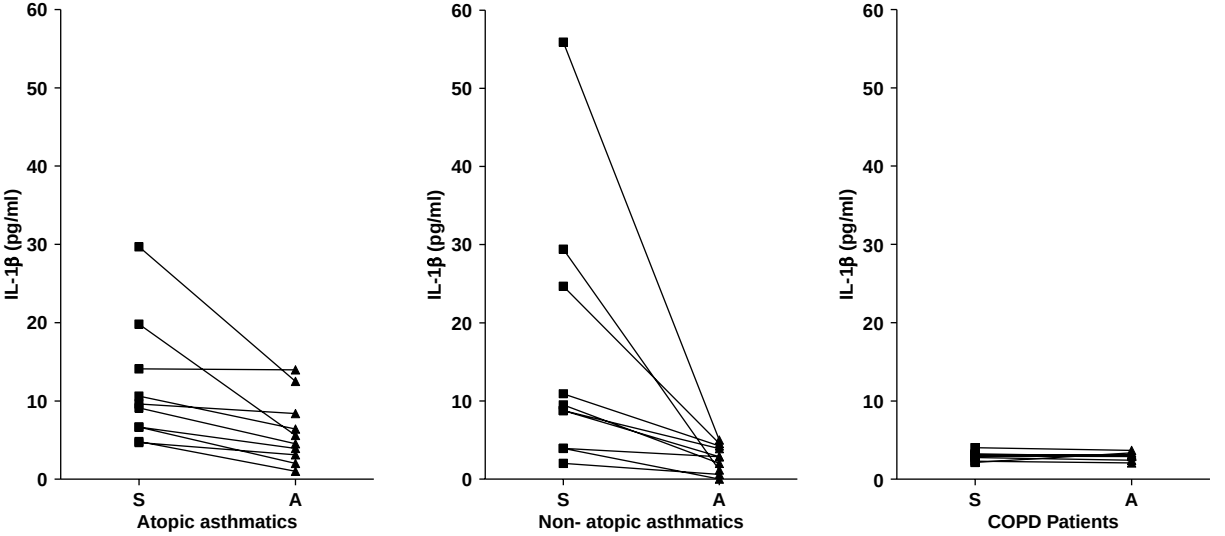

Figure 2. Serum interleukin (IL)-1β levels of paired samples of (A) atopic asthmatics, (B) non-atopic asthmatics and (C) chronic obstructive pulmonary disease (COPD) patients in symptomatic (S) and asymptomatic (A) phases.

Table III. Serum interleukin (IL)-1β and IgE levels (mean ± SEM) of atopic asthmatic, non-atopic asthmatic and chronic obstructive pulmonary disease (COPD) patients.

		Atopic asthma ($n=10$)		Non-atopic asthma ($n=10$)		COPD ($n=10$)	
	Healthy subjects ($n=10$)	Symptomatic phase	Asymptomatic phase	Symptomatic phase	Asymptomatic phase	Symptomatic phase	Asymptomatic phase
IL-1β (pg ml^{-1})	2.15 ± 0.26 (0.87–2.98)	11.57 ± 2.57 *†§(4.68–29.70)	6.15 ± 1.36 (1.04 –13.98)	15.78 ± 5.28 **††§§(2.02–55.92)	2.72 ± 0.55 (0.01–5.01)	2.97 ± 0.16 (2.14–4.03)	2.96 ± 0.14 (2.11–3.71)
IgE (IU ml^{-1})	52.20 ± 7.03 (23–77)	743 ± 100.60 **††§§(300–1150)	602 ± 93.2 **††§§(185–1050)	60.4 ± 9.49 (25–105)	52.5 ± 7.04 (24–90)	108.8 ± 7.97 (75–155)	103.8 ± 7.10 (66–125)

Data in parentheses are ranges. $^{\star}p<0.05$, $^{\star\star}p<0.01$ in comparison with healthy subjects; $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.01$ in comparison with COPD patients in the symptomatic phase; $^{\S}p<0.05$, $^{\S\S}p<0.01$ in comparison with COPD patients in the asymptomatic phase.

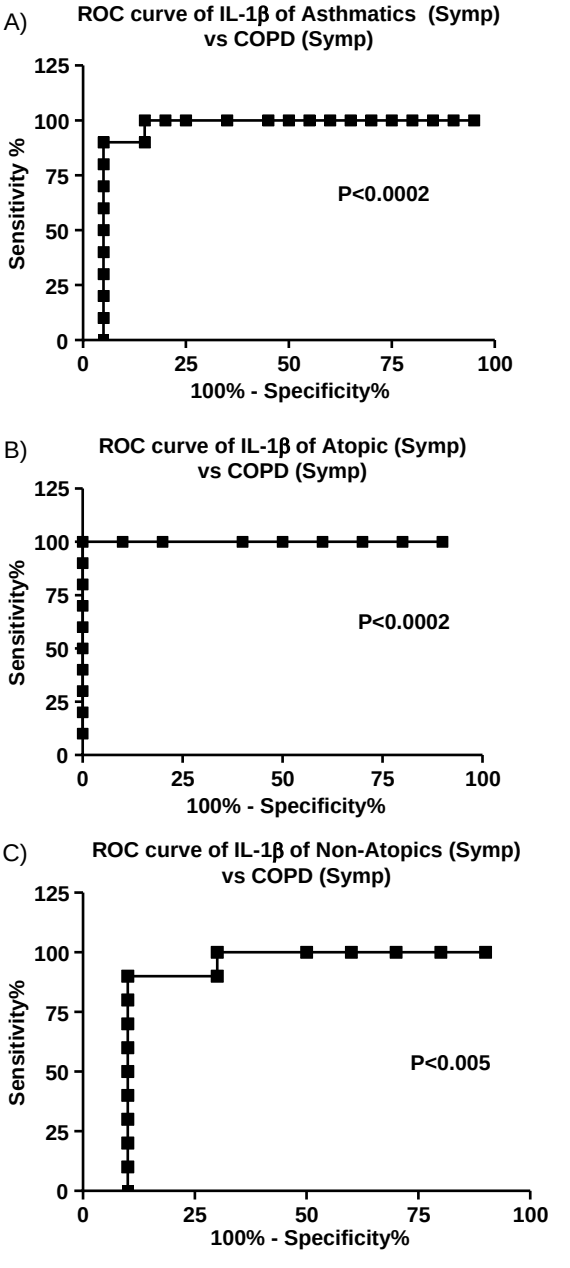

Figure 3. ROC curve of interleukin (IL)-1β levels of asthmatics and chronic obstructive pulmonary disease (COPD) patients in a symptomatic condition. (A) Atopic and non-atopic asthmatics vs COPD patients, (B) atopic asthmatics vs COPD patients and (C) non-atopic asthmatics vs COPD patients.

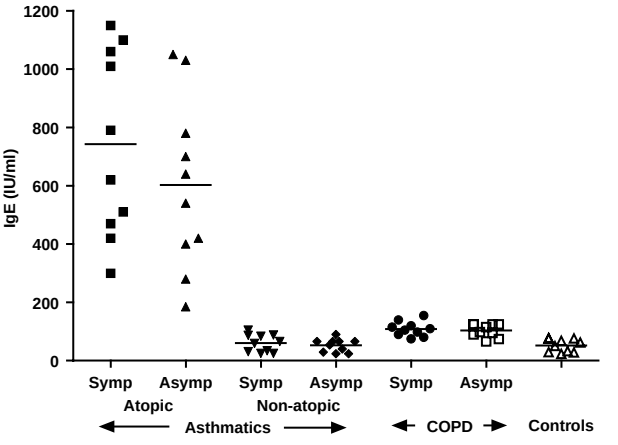

Figure 4. Serum IgE levels of atopic and non-atopic asthmatics and chronic obstructive pulmonary disease (COPD) patients in the symptomatic and asymptomatic phases.

Serum IgE levels

The serum IgE levels of all the groups are given in Figure 4. The IgE levels of paired samples of atopic asthmatics in the symptomatic and asymptomatic phases showed a decreasing trend, while in non-atopic asthmatics and COPD patients, the change was negligible (Figure 5). The values for IgE levels (mean $\pm$ SEM) are given in Table III. The ANOVA was significant ($p<0.0001$). In the control group, the total serum IgE level was 52.20 ± 7.03 IU ml^{-1} (mean $\pm$ SEM), which ranged between 23 and 77 IU ml^{-1}. Serum IgE levels of atopic asthmatics in the symptomatic and asymptomatic phases were significantly raised ($p<0.01$) compared with the symptomatic and asymptomatic phases of non-atopic asthmatics, COPD patients and healthy subjects. In non-atopic asthmatics and COPD patients, no significant difference in the levels of serum IgE was observed in comparison with the controls. All the atopic patients showed a positive SPT response to at least one of the 14 test allergen extracts.

The IgE values of the atopic asthmatics were significantly higher than those of the non-atopic asthmatics and COPD patients. Therefore, the IgE values in the symptomatic and asymptomatic phases of atopic asthmatics were taken as one group and similarly, they were taken together for the non-atopic asthmatics and COPD patients for the ROC curve analysis. The ROC curves of atopic versus non-atopic asthmatics and of atopic asthmatics versus COPD patients are given in Figure 6A and B showing the sensitivity and specificity to be 100% ($p<0.0001$) for both the curves with cut-off values of <145.0 and <170.0, respectively.

Discussion

Asthma and COPD are diseases of airway inflammation with overlapping features. Airway reversibility, i.e. increase in FEV_1 by more than 15% of baseline value, is diagnostic for asthma but several COPD patients also show significant reversibility. Similarly patients with moderate or severe persistent asthma may also have an irreversible component of airflow limitation (Celli et al. 2004). The differential diagnosis has to depend on a history of smoking, clinical assessment and signs and

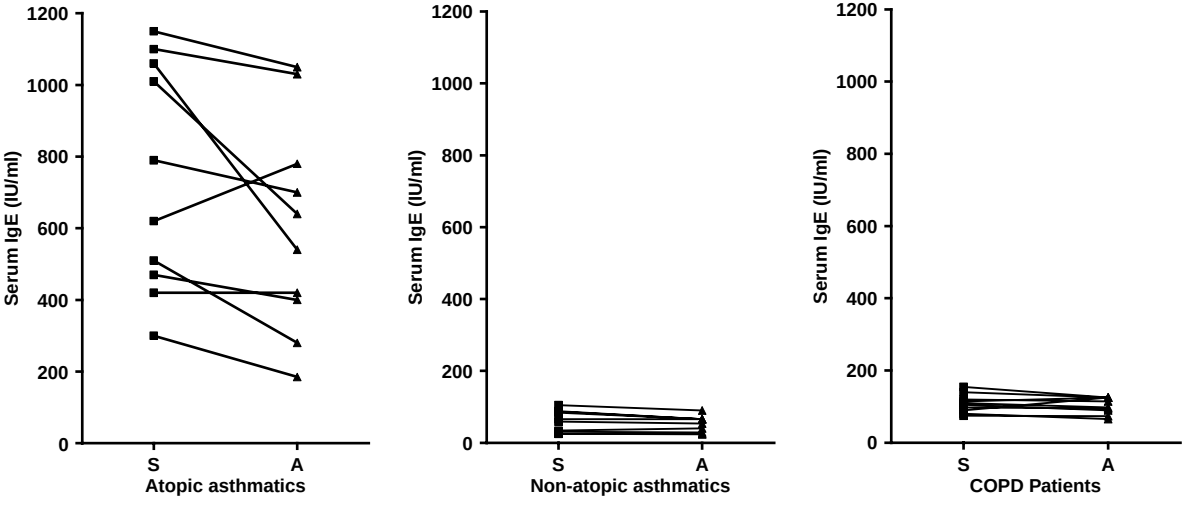

Figure 5. Serum IgE levels of paired samples of (A) atopic asthmatics, (B) non-atopic asthmatics and (C) chronic obstructive pulmonary disease (COPD) patients in symptomatic (S) and asymptomatic (A) phases.

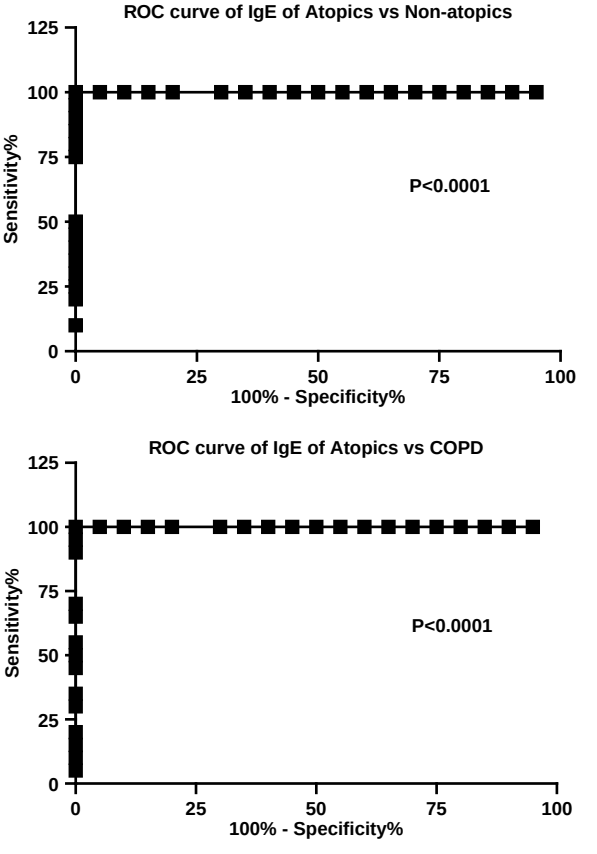

Figure 6. ROC curve of IgE levels of (A) atopic asthmatics vs non-atopic asthmatics, and (B) atopic asthmatics vs chronic obstructive pulmonary disease (COPD) patients.

symptoms of the disease. In asthma and COPD, where it is difficult to resolve and diagnose the disease, the biochemical parameters could be helpful, but are not yet defined. Thus, with the aim of developing some biochemical parameters, we measured the serum levels of IL-1β and IgE in patients with asthma and COPD in the symptomatic and asymptomatic phases of the conditions, as proinflammatory cytokines such as IL-1β and TNF-α (Broide et al. 1992, Mossalayi et al. 1994) are released from monocytes and macrophages (Jenson et al. 1992) in response to IgE molecules, which are known to have a role in the pathogenesis of both the diseases (Ricci & Rossi 1990). This may help in the differential diagnosis of these diseases.

In the present study, the IL-1β levels of the controls ranged between 0.87 and 2.98 pg ml^{-1}, which are comparable to the values reported by Subratty & Hooloman (1998). In symptomatic asthmatics, the levels were higher than in asymptomatic asthmatics, COPD patients and healthy subjects. The ROC curve for IL-1β levels of asthmatics and COPD patients in the symptomatic phase shows an area of 0.94 ± 0.05 ($p < 0.0002$), which is highly significant. At a cut-off value of < 4.35 pg ml^{-1} of serum IL-1β, the sensitivity is 100% and the specificity is 85%. If the cut-off value is lowered to 3.58 pg ml^{-1}, which is closer to the COPD range, the sensitivity reduces to 90%

but the specificity increases to 95%. At this level, there will be an overlap of 6.66% between asthmatics and COPD patients in their symptomatic phases. Therefore, by assaying serum IL-1β levels in the symptomatic phase, we can differentiate between asthmatics and COPD patients. The IL-1β levels of patients with COPD did not differ significantly from those of healthy subjects. Moreover, there was no significant difference in the levels of IL-1β in the symptomatic and asymptomatic phases of COPD patients. However, in their asymptomatic phase, the IL-1β levels in asthmatics were not significantly different compared with those of the patients with COPD and healthy subjects. In asthmatics, the increased levels of IL-1β may be due to its increased expression in bronchial tissue (Humbert et al. 1996) and in bronchoalveolar lavage fluid, which is higher in symptomatic asthmatics than in asymptomatic asthmatics (Ackerman et al. 1994, Mossalayi et al. 1994).

IgE molecules are known to have a role in the pathogenesis of both the diseases (Ricci & Rossi 1990, Dow et al. 1992). In our study, we observed a significant increase in serum IgE levels of atopic asthmatics in comparison with non-atopic asthmatics, COPD patients and healthy subjects. The serum IgE levels of healthy controls ranged between 23 and 77 IU ml^{-1}, which are comparable to those reported by Ackerman et al. (1994) and De Jong et al. (1997). The ROC curve of IgE in atopic and non-atopic asthmatics showed the area to be 1 ($p<0.0001$). It showed that at a cut-off value of 145 IU ml^{-1} of IgE, the sensitivity and specificity were 100%, which was higher than the upper limit of non-atopic asthmatics even in the symptomatic phase and far below the lower limit of atopic asthmatics in the asymptomatic phase. Thus, based on the serum IgE levels, atopic asthmatics can be differentiated from non-atopic asthmatics. Similarly, the ROC of IgE of atopic asthmatics and COPD patients gives an area of 1 ($p<0.0001$) and at a cut-off value of 170 IU ml^{-1}, the sensitivity and specificity is 100%, making it a significant parameter for differentiating between atopic asthma and COPD in both symptomatic and asymptomatic phases. The serum IgE levels of non-atopic asthmatics and COPD patients were not significantly different from healthy subjects, although there was a slight increase, suggesting some local production of IgE in the bronchial mucosa (Horwitz & Busse 1995). There was no significant difference in IgE levels between non-atopic asthmatics and COPD patients.

These findings indicate that on the basis of the serum levels of IL-1β, asthma (both atopic and non-atopic) can be differentiated from COPD during the symptomatic phase. On the other hand, differentiation between atopic and non-atopic asthma can be done on the basis of the SPT and serum IgE levels (cut-off value of 145 IU ml^{-1}). Further, in patients with the signs and symptoms of airway obstruction, if serum IL-1β and IgE levels are ≤ 4.35 pg ml^{-1} and ≤ 170 IU ml^{-1}, respectively, the diagnosis is in favour of COPD.

The differential diagnosis of bronchial asthma and COPD is usually made on the basis of clinical history, physical examination and the PFT. However, in some cases, these parameters fail to establish conclusively the diagnosis of these diseases. It may be emphasized that in our study, in the symptomatic phase serum IL-1β levels in asthmatics (atopic and non-atopic) were found to be significantly higher than those in patients with COPD. We conclude that the determination of serum IL-1β levels may help in differentiating these two diseases distinctly.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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