

Effect of Smoking on Atopic Predisposition and Sensitisation to Allergens

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ABSTRACT

Background. Previous studies elsewhere have shown higher serum immunoglobulin E (IgE) levels in smokers and an association between smoking and sensitisation to allergens. Such information is not available for Indian population. Hence, the present study was carried out to evaluate the effect of smoking on atopic predisposition and sensitisation to aeroallergens.

Methods. A total of 70 subjects were included in the present study comprising of 25 smokers, 22 reformed smokers and 23 non-smokers. Absolute eosinophil count (AEC), serum total IgE levels and skin prick test (SPT) against common aeroallergens were performed in all the subjects along with breath carbon monoxide (CO) levels and pulmonary function tests.

Results. Smokers showed significantly higher serum total IgE levels (328.80 ± 161.82 IU / mL) as compared to reformed smokers (177.27 ± 86.47 IU / mL) and non-smokers (29.56 ± 9.75 IU / mL). A number of subjects among smokers and reformed smokers elicited positive SPT reactions to various allergen extracts. Non-smokers did not show any significant positive skin reaction. The AECs were slightly higher in smokers (350 ± 1145.61 / mm³) as compared to reformed smokers (305 ± 146.33 / mm³). Breath CO was considerably higher (greater than three times) in smokers than reformed smokers. However, reformed smokers showed greater airways obstruction than smokers. The former also had higher Brinkman index (646.81 ± 392.32) as compared to the latter (448.36 ± 279.86).

Conclusions. Smokers had significantly higher IgE serum levels than reformed smokers and non-smokers. Smoking seems to induce an atopic orientation and allergen sensitisation in individuals. [*Indian J Chest Dis Allied Sci* 2008; 50: 329-333]

Key words: Smokers, Atopy, Allergens, Serum total IgE, Skin prick test, Pulmonary function test.

INTRODUCTION

There are 1.1 billion tobacco smokers aged 15 years and above worldwide representing one-third of the entire population.¹ Several factors, including age, sex and atopic status have been reported to influence levels of serum IgE.² Studies have shown higher total serum IgE levels in smokers,³⁻⁸ though there are also contrary reports.⁹⁻¹³ An association has been observed between elevated total IgE levels and increased annual forced expiratory volume in one second (FEV₁) loss in old smokers with airway symptoms.⁵ Smoking was found to be a risk factor for increasing bronchial responsiveness and decreasing lung function.¹⁴ Maternal smoking in utero and later has been found to be significantly related to lifetime wheezing and asthma.¹⁵ It is assumed that both active and passive smoking may facilitate the development of atopy,¹⁶ even if a negative association between SPT reactivity and cigarette smoking is demonstrated.¹⁷⁻¹⁹ Smoking

has also been reported to decrease the activity of natural killer cells and induce T-cell unresponsiveness, i.e., failure to respond to antigens or mitogens.^{20,21}

Previous studies have shown a lower prevalence of sensitisation to common aeroallergens among current smokers than in never smokers.^{4,22,23} However, another study showed that association between smoking and sensitisation varies with the allergen.³ In some studies the relationship between SPT reactivity and total serum IgE levels was strong.^{19, 24} On the other hand, there are studies that show that SPT reactivity does not correlate with total serum IgE levels.²⁵ Thus, both determinations are required in order to get a complete and precise evaluation of the immunologic status.

The prevalence of smoking in India is about 28.5% in men and 2.1% in women.²⁶ The prevalence rate varies from region to region from a lowest of 13.9% in Punjab to the highest of 49.4% in Mizoram.²⁷

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Knowledge about IgE titres and sensitisation with aeroallergens in smokers is lacking in our country. The present study was aimed to monitor total serum IgE levels in smokers, reformed smokers and non-smokers and correlate it with respiratory symptoms, lung function and skin reactivity with extracts of common aeroallergens. Brinkman index was also worked out for smokers and reformed smokers; and analysed with pulmonary obstruction and sensitisation to allergens.

MATERIAL AND METHODS

Study Subjects

The subjects included individuals visiting the outpatient Department or Tobacco Cessation Clinic, Vallabhbhai Patel Chest Institute, Delhi. Seventy subjects were included in the present study, comprising of 25 current smokers, 22 reformed smokers and 23 non-smokers, during the year 2004. Informed consent was taken from each subject for participation in the study. The study protocol was approved by the Human Ethics Committee of the Institute.

Inclusion Criteria

Both *bidi* and cigarette smokers, aged 18 to 68 years, from both the sexes were included in the study in three groups, namely, smokers, reformed smokers and non-smokers. One *bidi* was considered equal to one cigarette. Smokers had a Brinkman index greater than 100, obtained by multiplying the number of cigarettes per day by the duration of the smoking in years.¹⁰ Reformed smokers were defined as those who had quit smoking at least for the last one month.¹² Non-smokers were never smokers, taken as control subjects.

Exclusion Criteria

Subjects with a history of asthma, allergic rhinitis, eczema/urticaria, anaphylactic reaction, unstable cardiac or renal condition and pregnant or lactating females were not included in the study. Subjects with stool positive for helminthic ova/cyst were also excluded from the study.

Study Design

Details of smoking history and respiratory symptoms, such as persistent cough, sputum, wheezing and shortness of breath, were recorded. Routine microscopic examination of stool for the presence of ova and cyst was also done. Haemoglobin, total leukocyte counts, differential leukocyte counts, erythrocyte sedimentation rate, absolute eosinophil counts were determined. Carbon monoxide concentration of expired air was recorded by a portable CO monitor (Mini - smokerlyzer, Bedfont,

England). Spirometry (Maximal expiratory flow volume loops) was performed on an automated apparatus [Transfer test model 'C', (P.K. Morgan, England)]. Forced vital capacity (FVC), FEV₁, FEV₁ as percentage of forced vital capacity (FEV₁/FVC%) and forced mid-expiratory flow (FEF_{25-75%}) were measured using American Thoracic Society criteria.²⁸ Pulmonary obstruction was graded²⁹ as per GOLD 2003.

Serum Total IgE Levels

Venous blood sample was obtained from each subject and sera separated for IgE estimation. Serum total IgE levels were determined by enzyme linked immunosorbent assay (ELISA) using Pathozyne kit following manufacturer's instruction. A standard curve was constructed by plotting the absorbance values of standards against their concentration. The absorbance value for each sample was used to determine the corresponding concentration of IgE in IU/mL from the standard curve. The minimum detectable concentration of IgE by Pathozyne IgE kit is estimated to be 5.0 IU/mL.

Skin Prick Tests

The subjects were skin prick tested³⁰ with common aeroallergen, viz. Pollens (Grasses) *Cynodon dactylon*, *Pennisetum typhoides*; (Weeds and cultigens) *Amaranthus spinosus*, *Artemisia scoparia*, *Brassica campestris*, *Ricinus communis*; (Trees) *Holoptelea integrifolia*, *Prosopis juliflora*, (Fungi) *Aspergillus fumigatus*, *Alternaria alternata* and (Insects) *Periplaneta americana*, *Clilex quinquefasciatus*. The allergen extracts for skin test were obtained from Antigen Laboratory, Institute of Genomics and Integrative Biology (CSIR), Delhi. The SPT reactions were graded³⁰ based on the wheal size of positive control, i.e., 5 mg/mL histamine diphosphate. Glycerinated phosphate buffer saline (50%) was used as negative control. Skin reactions with ≥ 3 mm wheal were considered as marked positive ($\geq 2^+$) SPT reactions [1+ skin reaction=1-2.5 mm wheal (negative), 2+ skin reaction ≥ 3 mm wheal (positive), 3+ skin reaction=6 mm wheal or more with 1-2 pseudopodia (positive), 4+ skin reaction > 6 mm wheal with multiple pseudopodia (positive)].

Statistical Analysis

Statistical analysis of the data was done using statistical computer software (SPSS). Correlations were computed using Pearson's correlation coefficient. The serum IgE levels, AEC, breath CO levels, total leucocyte counts and spirometric values were compared in the three groups using one way analysis of variance (ANOVA) followed by Post Hoc Bonferroni multiple comparison test. The significance of SPT reactivity was compared in three groups using Chi square test. The level of significance was set at 5% in all evaluations.

RESULTS

The baseline characteristics of the subjects are presented in table 1. The Brinkman index for reformed smokers was higher (646.81 ± 392.32) than smokers (448.36 ± 279.86). All the subjects in smokers and reformed smokers group were males. There were 18 males and five females in the non-smoker group. Among smokers, 12 were *bidi* smokers and 13 were cigarette smokers, whereas reformed smokers group contained 17 *bidi* and five cigarette smokers. None of the subjects had a family history of atopy and asthma. Non-smokers did not present with any respiratory complaints or other disease. Among smokers, 20 (80%) were suffering with breathlessness and 12 (48%) with cough. All the reformed smokers suffered with breathlessness but 21 had associated cough. About one-fourth of smokers (6/25) had rhonchi whereas it was demonstrated in about two-thirds (18/25) in reformed smokers. The reformed smokers had lower weight (53.72 ± 11.04) than the smokers (67.24 ± 11.11) and non-smokers (62.39 ± 14.46). They were not suffering from any other disease, which could alter the allergic response in these subjects.

Serum IgE levels were highest in smokers followed

Table 1. Baseline characteristics of subjects in the three groups

Characteristic	Smokers (n=25)	Reformed smokers (n=22)	Non-smokers (n=23)
Age (yrs)	47.80 $\pm$ 14.33	56.50 $\pm$ 6.53	42.91 $\pm$ 10.21
Height (m)	1.67 $\pm$ 0.08	1.63 $\pm$ 0.06	1.63 $\pm$ 0.09
Weight (kg)	67.24 $\pm$ 11.11	53.72 $\pm$ 11.04	62.39 $\pm$ 14.46
Brinkman index	448.36 $\pm$ 279.86	646.81 $\pm$ 392.32	Not applicable

Data presented as mean $\pm$ SD

Table 2. Total serum IgE levels, absolute eosinophil counts and breath 'CO' levels (mean $\pm$ SD) in the three groups

Variables	Smokers (n=25)	Reformed smokers (n=22)	Non-smokers (n=23)	F-ratio (ANOVA)	P-value
IgE (IU / mL)	328.80 $\pm$ 161.82 ^a	177.27 $\pm$ 86.47 ^b	29.56 $\pm$ 9.75 ^c	45.67	<0.0001
AEC (/ mm ³)	350 $\pm$ 145.61 ^a	305 $\pm$ 146.53 ^b	197 $\pm$ 58.24 ^c	9.46	<0.0001
Breath CO (ppm)	15 $\pm$ 3.94 ^a	4.18 $\pm$ 1.33 ^b	1.73 $\pm$ 0.62 ^c	192.13	<0.0001

a, b, c in superscript indicates significance of difference

IgE=immunoglobulin E; CO=carbon monoxide; ANOVA=analysis of variance;

AEC=absolute eosinophil count; SD=standard deviation

Table 3. Skin Prick Test (SPT) to different aerollergens in subjects belonging to three groups

Allergen Extracts	Marked Positive Skin Test Reactions (2+ to 4+)				Mild Skin Reactions (1+)	
	Smokers (n=25)		Reformed Smokers (n=22)		Non-smokers (n=23)	
	Number	%	Number	%	Number	%
Grass pollen	3	12	2	9.09	1	4.34
Weeds and cultigen pollen	3	12	5	22.27	–	
Tree pollen	6	24	6	27.27	–	
Fungi	1	4	1	4.54	–	
Insects*	15	60	7	31.81	3	13.04

Smokers SPT positivity to insect allergens was more compared to reformed smokers and non-smokers ($p \leq 0.01$)

by reformed smokers and lowest in non-smokers (Table 2). The average serum total IgE level in smokers ranged from 100 to 870 IU / mL, while in reformed smokers, it was from 80 to 350 IU / mL and in non-smokers from 20 to 50 IU / mL. The difference was statistically significant in all the groups ($p < 0.0001$). Similarly the AECs were highest among smokers followed by reformed smokers and lowest in non-smokers. The difference was statistically significant between smokers and non-smokers ($p < 0.0001$) and between reformed smokers and non-smokers ($p = 0.015$), but not between smokers and reformed smokers ($p = 0.647$). The breath CO level was also the highest among smokers followed by reformed-smokers and lowest in non-smokers. The difference in all the three groups was statistically significant ($p < 0.0001$ smokers vs reformed smokers, $p < 0.0001$ smokers vs non-smokers, $p = 0.005$ reformed smokers vs non smokers).

Smokers elicited maximum markedly positive SPT reactions with allergen extracts followed by reformed smokers. The non-smokers exhibited only mild reactions to few extracts (Table 3). The difference in skin reactions was statistically significant in all the three groups ($p \leq 0.01$). Smokers demonstrated positive skin reactions with insect extracts (15/25), followed by tree pollen (6/25), weeds and grasses in three each out of the 25 subjects tested. Reformed smokers showed positive SPTs with insects extracts (7/22), followed by tree pollen extracts (6/22) and weeds (5/22). Non-smokers showed mild skin reactions with insect extracts in 3/23 and with grass allergen in one subject. There was no statistically significant association between serum IgE levels and skin reactivity in any of the three groups.

The correlation between serum IgE levels and FEV₁%, serum IgE levels and AEC and between serum IgE levels and Brinkman index were not

Table 4. Analysis of pulmonary function test values in all three groups of subjects (mean±SD)

Group (subjects)	FVC% Predicted	FEV ₁ % Predicted	FEV ₁ /FVC% Predicted	FEF ₂₅₋₇₅ % Predicted	FEF _{max} % Predicted
Smokers (n=25)	85.24±19.43	72.64±21.42	84.12±14.50	53.72±1.05	74.92±28.22
Reformed smokers (n=22)	74.81±21.70	49.80±20.17	63.50±15.22	20.40±13.93	42.95±23.88
Non-smokers (n=23)	92.56±8.16	93.00±8.23	99.08±5.75	96.08±26.48	106.17±14.46
F-ratio (ANOVA)	5.85	33.37	45.12	50.95	40.61
p-value	<0.005	<0.0001	<0.0001	<0.0001	<0.0001

FVC=forced vital capacity; FEV₁=forced expiratory volume in first second; FEV₁/FVC%=ratio of forced expiratory volume in first second to forced vital capacity; FEF_{max}=maximal forced expiratory flow rate; FEF₂₅₋₇₅%=forced mid expiratory flow rate; SD=standard deviation; ANOVA=analysis of variance

statistically significant in any of the groups. The pulmonary function test was normal in all non-smokers (control group). However, smokers and reformed smokers showed airway obstruction (Table 4). Comparison of spirometric values demonstrated statistically significant difference in all the three groups with the lowest mean FEV₁% in reformed smokers. The difference in FEV₁/FVC% predicted was also statistically significant.

DISCUSSION

Earlier studies showed raised serum total IgE levels in smokers.³⁻⁸ Elevated IgE levels indicate an increased probability of Type I hypersensitivity. In the present study, smokers demonstrated higher serum IgE levels than non-smokers. Reformed smokers had lower serum IgE levels than smokers but considerably higher than non-smokers. The serum IgE levels were not related to the amount smoked as revealed by the Brinkman index. Vollmer *et al*³¹ also observed that IgE was not related to either amount smoked or pack-years in smokers, whereas Omenaas *et al*⁴ reported that smoking and pack-years were independent predictors of total IgE levels.

It has been recorded that cigarette smoke increases mucosal permeability allowing easier and greater access of allergens to subepithelial lymphoid tissue. The mucosal theory of atopy proposes that increased permeability to antigenic material may enhance atopy.³² Thus, smoking may be stated to induce predisposition to atopy. Evidence is accumulating that elevated levels of serum IgE may play a role in the pathogenesis of chronic airflow obstruction. The studies^{31,33} on total serum IgE levels in smokers have shown a relationship between IgE levels and the rate of decline of FEV₁. In the present study, serum IgE levels and FEV₁% predicted did not show significant correlation. This was in contrast to the other studies.^{5,31} This disparity may be because in earlier studies patients with atopic history were not excluded.

Burrows *et al*³⁴ reported that smokers despite higher serum IgE showed a lower rate of sensitisation as determined by skin reactivity to common aeroallergens than non-smokers. It was suggested that the excess IgE related to smoking is qualitatively different than that observed in subjects reacting to aeroallergens. This may not be important

in the pathogenesis of upper respiratory tract disease, but may play a role in the development of some lower respiratory tract disorders. However, Freidhoff *et al*¹³ showed a negative relationship between smoking and skin test responsiveness that may reflect a tendency for allergic subjects to avoid the irritative effects of smoking.

In the present study, the difference in markedly positive skin reactions to allergen extracts was statistically significant ($p \leq 0.01$) between smokers and non-smokers. More subjects showed SPT positive reactions among smokers than reformed smokers. Insect extracts demonstrated marked positive SPTs in many smokers as well as in some reformed smokers. Non-smokers did not show positive skin reactions (2+ to 4+), however 1+ reactions were there with insect and grass pollen extracts in some subjects. Our findings were in contrast to most other studies,^{4,22,23} which showed lower sensitisation to aeroallergens in smokers than non-smokers.

According to Jarvis *et al*,³ current smokers are at an increased risk of sensitisation to house-dust mite allergen than non-smokers, but were at a decreased risk of sensitisation to grass and cat allergens. Exclusion of those with symptoms suggestive of asthma strengthened the association of smoking with sensitisation to house-dust mite allergen. It appears that the association between smoking and sensitisation to aeroallergens varies from allergen to allergen. The sensitisation to antigens tested varied with smoking status and the antigens involved were different in the present study.

In the present study, the AECs were higher in smokers than reformed smokers and non-smokers with a significant difference between the groups. Schneider *et al*³⁵ also concluded that the higher AECs were associated with greater smoking intensity. The reformed smokers had more severe airway obstruction than smokers in our study. This may be due to the greater amount of previous smoking in reformed smokers, as evident by the Brinkman index.

The limitation of the present study was that the number of subjects included was small. Besides, the age difference in the three groups was statistically significant. These were because of the stringent criteria followed for the selection of the subjects.

In conclusion, smokers have significantly raised serum IgE levels and increased skin reactivity to

allergens as compared to reformed smokers and non-smokers. Smoking seems to induce an atopic orientation and allergen sensitisation.

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