SİGARA İÇEN VE İÇMEYEN KOAH'LI KADINLARDA ATOPİ VE DİĞER RİSK FAKTÖRLERİNİN DEĞERLENDİRİLMESİ

EVALUATION OF ATOPY AND OTHER RISK FACTORS FOR SMOKER AND NON-SMOKER WOMEN WITH CHRONIC OBSTRUCTIVE LUNG DISEASE

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Keywords: Atopy, COPD, Dutch hypothesis, risk factors, smoking, women

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ÖZ

Amaç: *Kronik obstrüktif akciğer hastalığı (KOAH) ilerleyici ve kısmen geri dönüşlü hava yolu obstrüksiyonu ile karakterize bir hastalıktır. Etiyolojide en önemli risk faktörü sigara olmakla birlikte diğer pek risk faktörü bulunmaktadır. Çalışmamızın amacı sigara içen ya da içmeyen KOAH tanılı kadın olgularda atopy ve risk diğer risk faktörlerini incelemektir.*

Gereç ve Yöntem: *Çalışmaya KOAH nedeniyle takip edilen veya yeni tanı alan 96 kadın hasta dahil edildi. Sigara içmeyenler grup I (n=42), içenler grup II (n=54) olarak kabul edildi.*

Bulgular: *Grup I'in yaş ortalaması grup II'den daha yüksekti (64.5±10.7 ve 58.4±9.5; p=0.04). Grup I ve II arasında kişisel atopik hastalık öyküsü, aspirin/analjezik intoleransı, deri prik testi pozitifliği, kan eozinofil yüzdesi, serum total IgE ve α1-AT düzeyleri açısından fark yoktu. Bronş hiperreaktivitesi oranı grup I ve grup II için sırasıyla %85.7 ve %75.9 idi (p>0.05). Grup I'nin ortalama mutlak FEV1 değerinin grup II'den daha düşük (1.2±0.4 ve 1.4±0.5L; p=0.015) olduğu saptandı. Tüm hastalarda serum total IgE (ln IgE) düzeyi yükseldikçe beklenen FEV1 düzeyinde düşme izlendi. Ancak grup I ve II'ye tek tek bakıldığında benzer eğilim izlenmekle birlikte aralarında istatistiksel olarak anlamlı fark yoktu.*

ABSTRACT

Aim: *Chronic obstructive pulmonary disease (COPD) is mainly characterized by progressive and not fully reversible airflow limitation. Cigarette smoking is the main cause of COPD and there are many other known risk factors. The aim of our study was to investigate the presence of atopy and other risk factors for smoker and non-smoker women with COPD.*

Material and Methods*: Ninety six women who have been followed up or newly diagnosed as COPD were enrolled to this survey for a period of 14 months. Nonsmokers were accepted as group I (n=42) and smokers as group II, (n=54).*

Results: *Mean ages were higher in group I than group II (64.5±10.7 vs 58.4±9.5, p=0.04). No significant differences were detected between group I and II in personal atopy history, aspirin/analgesic intolerance, skin prick test positivity, blood eosinophils percentage, serum total IgE and α1-antityripsin levels. Bronchial hyperreactivity rate was %85.7 in group I and %75.9 in group II (p>0.05). The mean FEV1 value was lower in group I compared to that of group II (1.2±0.4 vs.1.4±0.5L; p=0.015). Elevated serum total IgE (ln IgE) level was correlated with FEV1 decline in all patients; but there was no correlation when groups I and II were analyzed separately. COPD patients were analyzed separately.*

Sonuç: *KOAH'lı kadın hastalarda IgE düzeyi ile tanımlanan atopi ile solunum fonksiyon testi arasında ilişki saptanırken, sigara içen ve içmeyenler arasında benzer bir ilişki izlenmemiştir. Hastalardaki bronş hiperreaktivitesi öyküsünün ve serum total IgE düzeyi ile FEV1 arasındaki korelasyonun Dutch hipotezini destekler bir bulgu olabileceği düşünülmüştür.*

Conclusion: *Atopy was related to pulmonary function tests in women with COPD, but there was no similar relationship between smokers and non-smokers groups. We think that bronchial hyperreactivity rate and relation between increase in serum total IgE and decline of FEV1 might support Dutch hypothesis.*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is mainly characterized by progressive and not fully reversible airflow limitation which is expected to be the third leading cause of death worldwide in 2020 (1). Cigarette smoking is the main cause of COPD and other known risk factors for the development of COPD include air pollution, occupational exposure, biomass exposure and genetic factors such as alpha1-antitrypsin deficiency and cystic fibrosis (2). Although cigarette smoking seems to be the main risk factor for COPD development, biomass (wood, dung and crop residues) exposure has still an important place among risk factors for women in Turkey.

Atopy is a genetic tendency to develop specific immunoglobulin E (IgE) for common environmental allergens. It is defined as skin test positivity to aeroallergens and/or elevations in total/specific IgE levels (3) Some previous studies showed a relationship between atopy and decline in lung function among current smokers (4). Otherwise, it has been reported that atopy is a possible risk factor for developing COPD (5,6). The present prospective study was designed to assess atopy and possible other risk factors for smoker and non-smoker women with chronic obstructive lung disease.

MATERIALS AND METHODS

Ninety-six women (61.0±10.4, range 40-83 yrs.) who have been followed up or newly diagnosed as COPD (Chronic bronchitis, emphysema and small airway disease) were enrolled to this survey for a period of 14 months. The diagnosis of COPD was made according to the patient's history, physical and radiological examination with pulmonary function tests (PFT's). A questionnaire including questions about was filled-in by the same physician. Skin prick tests (SPT's) and PFT's (Mır Spirolab, Holland) were performed. Blood was drawn for total eosinophil number, total IgE and alpha-1 antityripsin (□-1 antitrypsin) levels.

Atopy was assessed by SPT's as a positive reaction to any one of the allergens. Positive reaction was defined at least ≥3mm in mean diameter. Fifteen standard antigen solutions of common aeroallergens (dermatophagoides pteronyssinus, phleum pratense, olea europaea, artemisia vulgaris, parietaria officinalis, corylus avellana, betula verrucosa, cockroach, blatella, cat, dog, horse, cladosporium herbarum, aspergillus fumigatus and alternaria alternata) obtained from ALK (Denmark) were used in the tests. Familial atopy was defined as having asthma, allergic rhinitis and atopic dermatitis in first-degree relatives. The study protocol approved by the local ethical committee (LUT 05/106-24).

Statistical analysis was carried out using SPSS package version 20. Descriptive data were presented as mean and (SD), and median (range), when there was not a normal distribution. Chi square testing and t-test were used for categorical and continuous factors, respectively. IgE had a skewed distribution and so it was log-transformed. Correlation analysis was performed to assess the relation between IgE and FEV1. Statistical significance was considered as $p<0.05$.

RESULTS

The baseline characteristics of 96 women are showed in Table 1. The mean age of all 96 patients was 61.0±10.4. Sixty-six (68.8%) patients were passive smoker. Nonsmokers were accepted as group I (n=42) and smokers as group II (n=54). Demographic characteristics of the both groups are summarized in Table 2. Patients in-group I were older and time of living in rural area was longer compared to group II. Livestock farming rate was higher in-group I compared to that of group II. Symptom duration was longer in non-smokers than smokers; but comparison of the diagnosis time showed no statistically significant difference.

Majority of the patients were stage B (54.8%) and stage C (21.4 %) in group I and stage A (18.5%) and stage B (50%) in group II according to the Global Initiative of Chronic Obstructive Lung Disease (GOLD) criteria (2). The self reported doctor diagnosed atopy history rates were similar between two groups (Table 3). But, familial atopy history was present in 11.9% of group I and 42.6% in group II (p=0.001). There were no differences in self reported bronchial hyper responsiveness and aspirin/analgesic intolerance history. SPT's results was shown in figure 1.

Table 1. Demographic, clinical, spirometric and laboratory findings of study population (n=96)

Variables	**Results**
Age, years range	61±10.4 (40-83)
Smoking history	
Passive smoker, n %	66 (68.8)
Current smoker, n %	52 (54.2)
Former smoker, n %	2 (2.1)
Biomass exposure, n %	55 (57.3)
Comorbidities, n %	58 (60.4)
Hypertension	37 (38.5)
Diabetes mellitus	16 (16.7)
Others	5 (5.2)
FEV1, L/min	1.32±0.49, (0.40-2.73)
FEV1 predicted	61.5±19.7, (12-118)
FVC, L/min	1.91±0.60, (0.52-3.53)
FVC predicted	66.1±19.5, (20-120)
FEV1/FVC	69.1±0.8, (40-70)
COPD stage, n %	
A	15 (15.6)
B	50 (52.1)
C	15 (15.6)
D	9 (9.4)
Total serum IgE, mean±SD (Range)	143.4±47.5 (1.1-1128)
Positive skin prick test result, n (%)	11 (11.5)
α -1 antitrypsin (mean±SD, mg/ml), Range	209.2±49.7 (2-326)
Eosinophil % ±SD, Range	2.5±1.8 (0-11.6)
Bronchial hyper responsiveness, n (%)	77 (80.2)

Table 2. Demographic characteristics of two groups.

	Group 1 (n: 42)	Group 2 (n: 54)	P value
Age, yr.	64.5±10.7	58.4±9.5	0.04
No education, n (%)	25 (59.5)	8 (14.8)	<0.001
Income±SD, dolar	4345±1703	7577±5553	<0.001
Smoking history			
Smoking, pack-years, (range)	-	36.8±17.5 (14-80)	
Passive smokers, n (%)	33 (78.6)	33 (61.1)	NS
Current smokers, n (%)	-	52 (97.9)	
Former smokers, n (%)	-	2 (2.1)	
Biomass exposure, n (%)	36 (85.8)	19 (35.2)	<0.001
Rural area of residence, n (%)	42 (100)	33 (61.1)	<0.001
Rural area of residence, year (mean±SD)	41.7±18.1	12.7±16	<0.001
Pulmonary tuberculosis history, n (%)	4(9.5)	1 (1.9)	>0.05
Pneumonia history, n(%)	22(52.4)	18(33.3)	>0.05
Agricultural chemical, n(%)	8(19)	1(1.9)	0.004
Livestock farming n (%)	30(71.4)	20(37)	0.001
RADS history, n(%)	5(11.9)	22(40.7)	0.002
Comorbidities			NS
Hypertension, n (%)	13 (30.9)	24 (44.4)	
Diabetes mellites, n (%)	7 (16.6)	9 (16.6)	
Others, n (%)*	26 (52.5)	32 (39)	
Symptoms, yr	9.8±7.0	6.6±4.9	p=0.009
Diagnosis time, yr	5.2±4.9	4.2±4.7	NS

*: Coronary arterial disease, thyroid disease, anemia, etc.
NS:Non-significant, RADS:Reactive airway dysfunction syndrome

Table 3. Atopy characteristics in groups. NS:Non-significant

	Group 1 (n:42)	Group 2 (n:54)	p value
Atopy history, n (%)	15 (35.7)	17 (31.5)	NS
Atopy history, n (%)			NS
Asthma	8 (19)	9 (16.7)	
Allergic rhinitis	6 (14.3)	5 (9.3)	
Atopic dermatitis	1 (2.4)	3 (5.6)	
Familial atopy, n (%)	5 (11.9)	23 (42.6)	0.001
Familial atopic diseases, n (%)			0.029
Asthma	4 (9.5)	15 (27.8)	
Allergic rhinitis	2 (4.8)	6 (11.1)	
Atopic dermatitis	0 (0)	0 (0)	
Bronchial hyper responsiveness, n (%)	36 (85.7)	41 (75.9)	NS
Aspirin/analgesic intolerance, n (%)	2 (4.8)	8 (14.8)	NS

Mean FEV1 value was lower in group I compared to group II (1.2±0.4 L versus 1.4±0.5 L respectively; p=0.015). FEV1/FVC ratio, α-1 antitrypsin level and total eosinophil number were investigated; no statistically significant differences were detected (Table 4). SPT's results are shown in figure 1. Comparison of the mean ln IgE in the two groups showed no significant differences (4.3±1.3 vs. 3.9±1.4; Table 4). Elevated serum IgE (ln IgE) level was correlated with FEV1 decline in all patients; but there was no correlation when groups I and II were analyzed separately.

DISCUSSION

This study was performed to evaluate atopy and other possible risk factors for smoker and non-smoker women with COPD. This is the first study to investigate atopy in smoker and nonsmoker women with COPD. Elevated serum IgE (ln IgE) level was correlated with FEV1 decline in all patients; but there was no correlation when smoker and nonsmoker groups were analyzed separately.

In the respiratory disease study, atopy is defined by positivity of skin prick tests and/or elevated serum IgE levels (7). Some studies reported a relation between atopy, COPD and chronic bronchitis (8,9). A recent study showed that atopy was not associated with accelerated decline in lung function but with increased incidence and prevalence of respiratory symptoms (6). They showed that the prevalence of atopy is higher in males and younger patients. In our study we investigated only women with COPD and did not determine high prevalence of atopy in young patients. These results might be different because their study population is larger than ours.

Some epidemiological studies showed that SPT's positive patients had lower FEV1 and higher respiratory symptoms (10). In our study SPT's positivity was, 9.5% in nonsmokers, 10% in smokers and 10% of the total patients, but there was no relation between SPT's positivity and FEV1 decline and also, this result was similar when the groups were analyzed separetely. In Nerves' study, atopic patients had more severe COPD (less reduction in absolute FEV1) and had greater reversibility of airflow obstruction (10). In our study, we evaluated only women with COPD which differ from the Nerves' and Fattahi's studies. We showed that elevated serum IgE level was correlated with FEV1 decline in women with COPD.

Table 4. PFT's and laboratory findings in groups.

	Group 1 (n:42)	Group 2 (n:54)	p value
Mean FEV1±SD, L	1.2±0.4	1.4±0.5	0.015
Mean predicted FEV1±SD, %	57.2±17.2	64.9±21.2	0.058
Mean FVC±SD,L	1.8±0.6	2.2±0.9	0.03
Mean predicted FVC±SD, %	62±17.6	69.4±20.5	NS
FEV1/FVC±SD	66.6±2.6	63.6±1.1	NS
Mean ln IgE±SD	4.3±1.3	3.9±1.4	NS
Eosinophil % ±SD	2.7±2.2	2.4±1.5	NS
α-1 antitrypsin ±SD, mg/ml	201.2±52.8	215.7±46.6	NS
SPT's positivity, n (%)	4 (9.5)	7 (13)	NS

FEV1:Forced expiratory volume in 1 second, FVC: Forced vital capacity, lnIgE: logarithm of IgE level, SPT:Skin prick test.

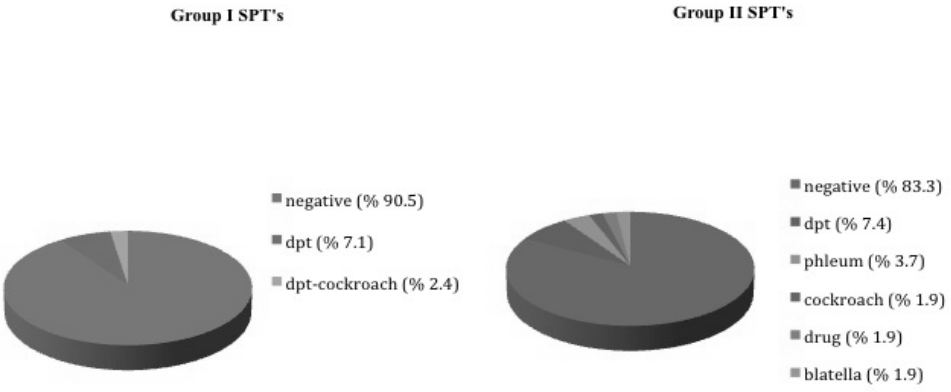

Figure 1. SPT's positivity in non-smoker (Group I) and smoker (Group II) groups. dpt: Dermatophagoides pteronyssinus, Phleum: Phleum pratense

The mean age of our study participants was 61.0±10.4 years, which is similar to the ones in other study (11). As was mentioned in the GOLD report, advanced age is a risk factor for COPD (2). In our cases as well, age might be a risk factor particularly for the nonsmoking group. It was determined that smokers are younger than nonsmokers. This could be explained by the smokers' starting smoking at adolescent ages and the females' being affected from smoking more than males due to anatomically narrower airways (9,12). In the present study group, all of the nonsmoking females have been living in rural areas and 85.8% expressed biomass exposure. Besides, the rate of livestock farming was significantly higher in this group than the other group. The study determined that organic dusts in the droppings enhance the risk of chronic bronchitis and COPD by leading to airway irritation and inflammation (13). Although the present study corroborates earlier findings, the fact that the amount of airborne particles of these substances has not been measured is a limitation of the present study. In brief, although biomass exposure is the primary cause of COPD in nonsmoking females, exposure to second-hand smoke and livestock farming could make a contribution.

The earlier study has demonstrated that insecticides cause various airway diseases primarily chronic bronchitis and decrease the respiratory function tests (14). Pesticides and insecticides are metabolized more rapidly in smokers due to the activation of liver enzymes and thus their toxic effect decreases. That is to say, toxic effect due to pesticides and insecticides is higher in nonsmokers. (15,16). Therefore, it is thought that pesticides and insecticides as well as biomass exposure contribute to the development of COPD in nonsmokers. However, it is impossible to make a comment about the kind of these substances since the patients have not been questioned about the content of the pesticides and insecticides they have been using.

Low socioeconomic status is an important risk factor for COPD (2). Although its effect is unclear, low socioeconomic status appears to be associated with poor nutrition, infections, and indoor and outdoor air pollution (2). In the present study, socioeconomic status of nonsmoking group was statistically lower than that of the smokers. Low socioeconomic status was considered to be a risk factor for COPD in such females.

The most significant genetic risk factor for the development of COPD is α -1 antitrypsin deficiency. In the present patient group, α -1 antitrypsin deficiency was not determined in either groups.

In GOLD, which is the most widely used guideline for COPD, it was stated that viral and

bacterial lower respiratory tract infections might play a role in the pathogenesis and progression of the disease (2,17). It was determined that history of pneumonia or bronchitis particularly in infancy contributes to the reduced FEV1 and FVC in adulthood by means of influencing lung maturation (18). Again, it was determined that pneumonia in the first two years of life may be associated with reduced pulmonary functions and various respiratory symptoms in the adulthood by causing bronchial hyperreactivity (18,19). Therefore, we questioned the patients for the history of pneumonia and tuberculosis. However, we found no difference between the groups in terms of presence of either diseases. Despite the consideration that infections lead to bronchial hyperreactivity, many patients in the present study with no history of pneumonia described bronchial hyperreactivity. Pulmonary function tests may be impaired in the subjects that have tuberculosis (20); however, evidences on the development of COPD are weak. In the present patient group, the number of patients that had had tuberculosis was limited with no statistical significance determined between the groups.

History of asthma is considered as a potential risk factor for COPD (2). Tucson Epidemiological Study of Airway Obstructive Disease stated 12-fold higher risk of COPD in asthmatic adults (21). Some studies determined the bronchial hyperreactivity as a risk factor for COPD as well as for decreased pulmonary functions in mild COPD cases (22,23). Zanini et al. determined bronchial hyperreactivity in 41.4% of COPD group (24). It has been observed that bronchial hyperreactivity is associated with rapid FEV1 reduction in COPD (25). In the present patient group, we as well questioned our patients in terms of previous diagnosis of asthma and bronchial hyperreactivity. The prevalence of bronchial hyperreactivity was higher in the nonsmoking group even though it was not statistically significant. For this reason, results of pulmonary function tests might be lower in this group as compared to the smoking group. However, the diagnosis of asthma and bronchial hyperreactivity has been made based on the patients' self-report without performing bronchial provocation test.

Reactive Airway Dysfunction Syndrome (RADS) is a picture that results from acute exposure to high-dose corrosive substances such as bleach or muriatic acid, gasses, and smokes leading to coughing, shortness of breath and squeezing sensation in the chest (26). The study reported that there may be chronic respiratory symptoms after the diagnosis of RADS (27). While planning the present study, we as well estimated that history of RADS may contribute to the development of COPD. Whilst there was no difference between the groups in terms of the rate and amount of bleach or muriatic acid use, history of RADS was more prevalent in the smoker group. There was no statistically significant difference between groups for seeking medical help following exposure to corrosive substances and duration of healing. Unfavorable effects on the respiratory tract after acute exposure to corrosive substances may be associated with additive interaction between cigarette and these substances. However, it is not possible to say that there is no similar interaction in biomass exposure because of the limited patient number. Moreover, absence of respiratory symptoms before exposure is important in the diagnosis of RADS. In the present study, the patients have not been questioned for this aspect and the diagnosis of RADS was made based on the patients' self-statements.

There was no difference between the groups in terms of time to diagnosis, but symptom duration (9.8±7.0 and 6.6±4.9, respectively). In a study, symptom duration was found to be 7.3±1.5 years in the nonsmoking group, of which 83% were females (28). In the present study, whilst duration was similar for the whole group, it was longer for the nonsmoking group. The difference might have arisen from patient selection because biomass exposure was considered as the primary cause of COPD among nonsmoking patients in the present

study, whereas biomass exposure was not in the forefront in the other one (28). Advanced age of the nonsmoking group may be the cause of longer symptom duration. However, shorter symptom duration in the smoking group might have arisen from not considering the symptoms such as coughing, sputum and shortness of breath as the signs of disease.

In 1961, Orie et al. suggested that asthma, chronic bronchitis and emphysema are the different clinical manifestations of a single disease (chronic non-specific lung disease) (29). This hypothesis, which was called as 'Dutch hypothesis' after 1969, defends that asthma and bronchitis develop due to interaction between personal and environmental factors. Atopy and bronchial hyperreactivity are present in both asthma and bronchitis (2,12). It was considered that contact with allergens, infections and exposure to various irritating substances, as well as age, gender, personal atopy and history of bronchial hyperreactivity, manipulate clinical presentation. A study published in 1988 suggested that Dutch hypothesis is rather appropriate for female COPD patients of advanced age (30). The relation between history of bronchial hyperreactivity, serum total IgE level and FEV1 in the participants of the present study appears to support the Dutch hypothesis.

The fact that the evaluation of data has been based on personal statements such as history of pneumonia, family history of asthma, pesticide and insecticide use and history of having RADS is among the limitations of the present study. In addition, bronchial provocation tests for bronchial hyperreactivity could not be performed because of hospital-related impossibilities. Further studies could be planned with increased number of cases to reduce statistical errors.

CONCLUSION

The present study determined that biomass exposure may be the most significant factor in nonsmoking female COPD patients and these are usually the patients living in the rural area with low income and education status. Moreover, absolute FEV1 and FVC values are lower in nonsmoking female COPD patients as compared to the smoking group. In female patients with COPD, expected FEV1 value decreases as serum total IgE level increases. However, this relationship has not gained significance when smoking and nonsmoking groups were evaluated individually. Further studies with larger patient groups may be beneficial.

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