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Original article

Influence of cigarette smoking on allergic rhinitis: a comparative study on smokers and non-smokers

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Summary. It has been described that exposure to tobacco smoke causes worsening of allergic rhinitis symptoms. Otherwise, some studies have demonstrated a negative association between cigarette smoke and allergic rhinitis (AR). Given this inconsistency, this study evaluated the quality of life and immuno-inflammatory parameters in current smokers and nonsmokers suffering from AR. A comparative cross-sectional study was conducted in patients who presented symptoms of AR. Patients were categorized into two groups: current smokers and non-smokers based on salivary cotinine measurements. Primary outcomes were the levels of immuno-inflammatory biomarkers (IgE, IL-4, IL-5, IL-13, IL-17, and IL-33) in serum and nasal lavage and the quality of life assessed by the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ). Secondary outcomes included salivary cotinine levels, and pulmonary function parameters, such as forced vital capacity (FVC), forced expiratory volume in 1s (FEV_1), and FEV_1/FVC ratio. Twenty-two patients per group were included in the analysis, with no significant difference regarding demographic characteristics. Statistically significant higher values in salivary cotinine levels ($p<0.001$) and lower lung function FEV_1 ($p=0.044$) and FEV_1/FVC ($p=0.047$) were found in smokers than in nonsmokers. Only serum IL-33 was significantly different in the 2 groups ($p<0.001$): smokers had higher values compared to non-smokers. There were no significant differences in MiniRQLQ parameters. Although cigarette smoking was not associated with more severe symptoms, smoking could be associated with increased risk of developing airway remodeling and decreased lung function in AR patients, thus appropriate treatment should be prescribed if smoke avoidance is unfeasible. (www.actabiomedica.it)

Key words: cigarette smoking, allergic rhinitis, quality of life

Introduction

Allergic rhinitis (AR) is a common and chronic IgE-mediated respiratory inflammatory disease, AR affects between 10 and 25% of the worldwide general population (1).

Although AR has different degrees of severity, it impairs quality of life (QoL), sleep, daily activities, and school or work performance (2). It is frequently ignored, misdiagnosed, and mistreated, which not only is detrimental to health but also has societal costs (3). The clinical expression of AR has been reported in relation to environmental allergen exposure in genetically predisposed individuals (4).

Environmental factors, such as exposure to indoor and outdoor air pollution, changed lifestyle, bacterial/viral infections, geographic variations, socioeconomic conditions, and infant feeding, are frequently quoted as adjuvant factors for allergic sensitization and clinical expression variability (5). Indoor air pollution includes

the combustion products of biomass for domestic energy (6), the endotoxins, a component of the cell wall of gram-negative bacteria, which is a potent pro-inflammatory agent commonly found in house dust (7), and the cigarette smoke exposure which can be divided into primary smoking exposure and secondary 'passive' or 'second-hand' smoking exposure (8, 9).

Previous studies have provided conflicting results regarding the potential correlation between tobacco smoke and AR. A study on 155 adolescents demonstrated a significantly higher prevalence of AR in current smokers compared to nonsmokers and an even greater difference in passive smokers as opposed to nonsmokers (10). Conversely, a cross-sectional study found a higher prevalence of allergic nasal symptoms in nonsmokers, in contrast, an increased prevalence of nasal congestion and chronic rhinitis no-AR correlated was associated with a positive smoking history (11). Moreover, in a cross-sectional study in adult patients with AR, symptoms severity and quality of life in smokers were not significantly different from non-smokers (12). Previous studies have documented a significant difference of goblet cell density and thickening of the nasal mucosa epithelium in smokers compared to nonsmokers, with a significant increase of neutrophils and T-helper 2 (Th2) lymphocyte subsets (13), as well as in total and specific IgE levels that were significantly higher in smokers compared with nonsmokers (14).

On the contrary, another study found that exposure to tobacco smoke caused a decrease in cytokines involved in IgE-mediated mechanisms (IL-4, IL-5, IL-13, IL-25), suggesting that smokers could have less expression of allergy than non-smokers (15).

Given the little consensus regarding the current evidence, the aim of the study was to evaluate the quality of life, nasal function, and immuno-inflammatory parameters in current smokers and nonsmokers suffering from AR.

Materials and Methods

A comparative cross-sectional study was conducted at the Otolaryngology Unit of the Santa Marta e Santa Venera Hospital in Acireale, Catania, Italy, between 2018 and 2019 in smokers and nonsmokers who presented symptoms of AR.

Investigations were performed according to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects. The study design was approved by the local ethics committee. All subjects were informed about the procedures and aims of the study and provided written informed consent.

Inclusion criteria were: adulthood, both genders, and presence of AR symptoms.

Patients were excluded if they had AR diagnosed less than a year, who were receiving nasal or systemic corticosteroids in the 3 months before the examination, who took antihistamines longer than 15 continuous days in the last 30 days, or who received allergen immunotherapy in the last 3 years. Patients with a history of respiratory tract infections in the last 4 weeks were also excluded.

The diagnostic criteria used for AR were those defined by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (16), in combination with positive skin test reactions to suspected allergens, according to a procedure previously described (17).

Status of current smoking was assessed measuring the salivary cotinine levels. Cotinine is a biomarker of nicotine exposure and can be measured in blood, urine, and saliva; in all three matrices, it has a half-life of approximately 17 h, allowing time for detection of recent nicotine exposure (18). Salivary cotinine was biochemically analyzed using Enzyme-Linked ImmunoSorbent Assay (ELISA) kit from Salimetrics, USA according to a procedure previously described (19). Cotinine value of 15 ng/ml was used as the cut-point, as recommended by the Society for Nicotine and Tobacco Research (20). Patients were categorized into two groups as current smokers if reporting a value > 15 ng/ml of salivary cotinine and nonsmokers if lower than that value.

The primary outcome of the study was the difference between current smokers and nonsmokers patients regarding the levels of immuno-inflammatory biomarkers in serum and nasal lavage, and the quality of life parameters assessed using the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) (21). Nasal lavage was performed inserting 5 ml of sterile isotonic saline into each nostril with a slightly

reclined position of the head during occlusion of the soft palate and aspirated subsequently from each nasal cavity three times before the sample was collected. Samples were centrifuged at 1200 × g for 10 min at 4°C and supernatants were extracted and aliquoted in 0.5 mL and stored at -80°C for subsequent measurement. To obtain serum, venous blood was collected into EDTA containing vials and centrifuged at 1200 × g for 10 min at 4 °C. All samples were stored at -80°C until cytokine analysis.

Levels of IgE, IL-4, IL-5, IL-13, IL-17, and IL-33 in nasal lavages were determined using Multiplex assays (FlowCytomix, eBioscience) according to the manufacturer's instructions. Levels of IgE, IL-4, IL-5, IL-13, IL-17 and IL-33 in serum were assessed by enzyme-linked immunosorbent assay (ELISA) using commercially available assays.

Secondary outcomes included differences in salivary cotinine levels, inhalant allergens sensitivity, and pulmonary function. This last has been evaluated by using a dry spirometer (MasterscreensBody, Viasys, Hoechberg, Germany) and performed according to the ATS recommendations (22). The best values of FEV_1, FVC, FEV_1/FVC were taken for the study analysis.

Statistical analysis

Data were analyzed by using the Statistical Package for Social Sciences program (SPSS for Windows 20.0 Chicago, USA). Groups were compared using the Student t test for normally distributed quantitative data. Data not showing normal distribution were analyzed using the Mann-Whitney U-test. Results were presented as frequency, mean ± standard deviation and median (min-max). Values of $p<0.05$ were considered significant.

Results

Of the 49 patients invited to participate, 44 patients (89.8%), who met the inclusion and exclusion criteria, agreed to participate, 22 current smokers (cases) and 22 non-smokers (controls). The two groups were similar in relation to age, gender, duration of AR disease, and types of sensitization to allergens (Table 1).

In nasal lavages, only IgE, IL-4, IL-17, and IL-33 levels could be detected, but no significant differences were found between the two study groups. Otherwise,

Table 1. Demographic characteristics of study participants with diagnosed AR

Characteristics	Current smokers N=22	Non-smokers N=22	p-value
Age, (years)			
Mean ± SD	36.4 ± 11.3	32.5 ± 10.4	0.102
Median	38	36	-
Range	20-64	19-62	-
Gender, n (%)			
Male	13 (59.1)	11 (50)	0.484
Female	9 (40.9)	11 (50)	
Duration of AR, (years)			
Mean ± SD	5.3 ± 1.8	4.8 ± 1.4	0.357
Median	3	3	-
Range	1-6	1-7	-
Types of sensitization to allergens, n (%)			
Monosensitized	7 (31.8)	9 (40.9)	0.305
Polysensitized	15 (68.2)	13 (59.1)	

AR: Allergic Rhinitis; SD: standard deviation
*$p < 0.05$

levels of IgE, IL-4, IL-5, IL-13, IL-17, and IL-3 were detectable in the serum of all patients, but only IL-33 levels were significantly higher in current smoker patients compared with non-smokers (586.8±23.7 pg/mL vs. 203.1±21.4 pg/mL, respectively, p<0.001) (Table 2).

Current smoker patients presented a significantly higher concentration of cotinine in saliva than non-smokers (285.7±52.3 ng/mL vs. 1.9±0.6 ng/mL, respectively, p<0.001). In current smoker group, a significantly lower FEV_1 (p=0.044) and FEV_1/FVC ratio (p=0.047) were found when compared to non-smokers values. However, no differences were observed between the two study groups regarding FVC values. The overall mean score for MiniRQLQ showed no significant differences between the two study groups (p=0.386) (Table 3).

Discussion

Nowadays, it is clear that the severity of allergic airway diseases, such as AR and asthma, is a consequence of the interaction between genes and the environment (23,24).

Cigarette smoke is probably the most common environmental factor that has been associated with

Table 2. Nasal and serum immuno-inflammatory markers in study patient groups

Characteristics	Current smokers N=22	Non-smokers N=22	p-value
Nasal immuno-inflammatory biomarkers, mean ± SD			
IgE, (kU/L)	3.9 ± 0.7	4.6 ± 0.5	0.318
IL-4, (pg/mL)	14.3 ± 2.1	13.7 ± 1.9	0.287
IL-5, (pg/mL)	No detected	No detected	/
IL-13, (pg/mL)	No detected	No detected	/
IL-17, (pg/mL)	29.2 ± 3.2	33.2 ± 3.6	0.347
IL-33, (pg/mL)	85.7 ± 14.8	105.1 ± 13.7	0.092
Serum immuno-inflammatory biomarkers, mean ± SD			
IgE, (kU/L)	189.4 ± 32.7	197.6 ± 31.5	0.288
IL-4, (pg/mL)	34.2 ± 16.3	24.3 ± 12.2	0.402
IL-5, (pg/mL)	0.5 ± 0.3	0.4 ± 0.2	0.721
IL-13, (pg/mL)	0.6 ± 0.1	0.5 ± 0.1	0.074
IL-17, (pg/mL)	0.5 ± 0.2	0.6 ± 0.2	0.619
IL-33, (pg/mL)	586.8 ± 23.7	203.1 ± 21.4	< 0.001*

pg/mL: picogram/milliliter; kU/L: Kilo unit/Liter; SD: standard deviation
*p < 0.05

Table 3. Salivary cotinine levels, pulmonary function outcomes, and MiniRQLQ overall in study patient groups

Characteristics	Current smokers N=22	Non-smokers N=22	p-value
Salivary cotinine levels (ng/mL), mean ± SD	285.7 ± 52.3	1.9 ± 0.6	< 0.001*
Pulmonary function outcomes, mean ± SD			
FEV_1 (L)	2.2 ± 0.8	3.3 ± 0.8	0.044*
FVC (L)	3.1 ± 0.9	3.6 ± 0.8	0.175
FEV_1/FVC	70.8 ± 4.8	89.4 ± 9.7	0.047*
MiniRQLQ overall, mean ± SD	1.48 ± 0.29	1.51 ± 0.22	0.386

ng/mL: nanogram/milliliter; FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; L: Liter; MiniRQLQ: Mini Rhinoconjunctivitis Quality of Life Questionnaire; SD: standard deviation
*p < 0.05

various airway diseases, including rhinosinusitis, bronchitis, and pneumonia in children (25-27). However, previous population-based studies have provided conflicting information regarding the potential correlation between tobacco smoke and AR. A study recruiting 200 patients demonstrated that both past and current SHS exposure were significant risk factor for AR (28). Contrariwise, other studies showed a negative association between cigarette smoke and AR (11).

In the present cross-sectional study, we examined the impact of cigarette smoking on immuno-inflammatory parameters and quality of life in current smokers and nonsmokers suffering from AR. Immuno-inflammatory biomarkers were measured on nasal lavage fluid and serum because it was an easy and non-invasive method for detecting and characterizing biochemical alterations associated with allergic inflammation (29, 8).

This study showed that current smoker AR patients had no worsening in both quality of life and immuno-inflammatory parameters, compared to non-smokers. These findings were in contrast to a previous study where cigarette smoke exposure resulted in a noticeable increase in nasal levels of IL-4, IL-5, and IL-13 causing a shift to a Th2-dominated local cytokine milieu and supposing an enhancement of allergic response (30).

Other works supported the notion that cigarette smoke is an adjuvant factor for AR showing an association between smoke and increased serum IgE and skin test reactivity, presumably because of heightened histamine release (30, 31). However, other studies, including the present, did not report any association (32).

Although the similarity between current smokers and non-smokers found in our investigation is striking, there nevertheless are other aspects of divergence, such as the serum level of the cytokine IL-33 and lung function. There are recent studies reporting the involvement of IL-33 in Th2-mediated inflammatory responses in allergic diseases, such as asthma, atopic dermatitis, and AR (33). Moreover, the elevated level of this cytokine was correlated with the severity of rhinitis symptoms, suggesting a role in the pathophysiology of this disorder (34). IL-33 may be released by epithelial cells during injury or necrosis caused by exogenous triggers, such as mechanical trauma, viruses, smoke, airborne allergens, or endogenous triggers, suggesting that IL-33 may act as an endogenous danger signal; thus, it has been termed an "alarmin" (34, 35).

Our study confirmed these findings, emphasized by much more higher serum IL-33 levels in smokers compared to non-smokers. Moreover, this study also present data that further support the concept of the role of IL-33 as a promoter of airway remodeling by acting on lung fibroblasts (36). This assumption arises mainly from the fact that, in our study, current smokers had impaired lung function, provided by low values of FEV_1 and FEV_1/FVC ratio, typical markers for bronchial obstruction.

In addition, increasing cotinine levels in smokers have been shown to be associated, as in our study, with worse pulmonary function test results in a dose-dependent manner (37).

There are some limitations to this study. First, regarding the failure to identify all cytokines chosen as the object of the study despite we performed all procedures (serum and nasal lavage collections) according to previously described techniques. This issue could be due to the limited half-life of the cytokines or patients not completely symptomatic at the time of the examination.

Another limitation to this study is the inability to prove the airway remodeling from a histological point of view; bronchial mucosa biopsy specimens should be obtained to corroborate this assertion

This study shows no differences in quality of life and immuno-inflammatory parameters between current smokers and non-smokers suffering from AR, suggesting that the effect of cigarette smoke exposure may have a distinct mechanism of action in allergic disease. Indeed, there is evidence of an increased signal alarm (IL-33) in smokers, which results in harmful consequences, such as decreased lung function, and its inexorable progression if the consumption of tobacco is maintained. The observed findings reinforce the need for any existing preventive action, on the avoidance of tobacco use. However, it is well known that smoke avoidance is frequently infeasible, thus there is the need to prescribe appropriate treatments able to reduce the smoke damage on respiratory airways. As tobacco smoke induces a chronic depend-

ence, prolonged pharmacological therapy could be adequately integrated with nutraceuticals. In this regard, bromelain is an effective and safe anti-inflammatory agent, particularly indicated in upper airways disorders (38).

In conclusion, tobacco smoke may significantly affect airways in patients with AR; consequently, careful evaluation and management of smokers should be performed.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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