Lower Airway Inflammation in Nonasthmatic Allergic Rhinitis Patients

Non-Astmatik Allerjik Rinitli Hastalarda Alt Hava Yolu İnflamasyonu

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ABSTRACT Objective: Allergic rhinitis and asthma have been considered as a single airway disease sharing a common pathophysiological mechanism of airway inflammation. We aimed to investigate the lower airway inflammation in allergic rhinitis patients without asthma. **Material and Methods:** Forty patients who referred to our tertiary care hospital's otorhinolaryngology clinic and diagnosed as moderate/severe persistent allergic rhinitis according to ARIA criteria were included in the study. After evaluation for the eligibility for the study, a nasal smear was taken, and rhinomanometry was performed to measure the nasal obstruction on visit 1. Twenty-four hours later from the visit 1, pulmonary functions including bronchial hyperactivity (BHR) were measured on visit 2. Twenty-four hours later from the visit 2, sputum induction was performed, and cell distribution of the sputums was evaluated. **Results:** Mean age of the 17 male and 23 female patients was 37 ± 11. Nasal smear eosinophilia was studied in 36 of the patients and found positive in 36%. Nasal obstruction was demonstrated in 68% of the patients by rhinomanometry. BHR was positive in 30% of the participants. There was not any statistical significant relationship between nasal eosinophilia and nasal obstruction severity, BHR and induced sputum eosinophilia ($p > 0.05$). Among the induced sputums which were of good quality to be evaluated, 7.5% had an eosinophil ratio of 2%. Any relationship between induced sputum eosinophil percentages and FEV1, FEV1/FVC, nasal obstruction severity was not observed ($p > 0.05$). However, BHR was found to be significantly related with FEV1/FVC ratio which was >70% through the whole study population ($r = 0.392$ $p = 0.012$). **Conclusion:** We could not demonstrate the expected relationship between nasal and lower airway inflammation markers in our study group of allergic rhinitis patients. This may be due to the small number of study population and strict exclusion of asthmatic patients as well as particularly the difficulties in standardization of the induced sputum technique.

Key Words: Rhinitis, allergic, perennial; sputum; inflammation mediators

ÖZET Amaç: Allerjik rinit ve astım, hava yollarının inflamasyonu ile karakterize ve ortak bir patofizyolojik mekanizmayı paylaşan hava yolu hastalıkları olarak kabul edilmektedir. Çalışmamızda, daha önce astım tanısı almamış olan alerjik rinitli hastalarda alt solunum yolu inflamasyonunu araştırmayı amaçladık. **Gereç ve Yöntemler:** Üçüncü basamak bir sağlık kurumu olan hastanemizin kulak burun boğaz kliniğine başvuran ve ARIA kriterlerine göre orta/ağır persistan alerjik rinit tanısı olan kırk hasta çalışmaya alındı. Çalışma için uygunluğu bakımından gözden geçirildikten sonra, nazal smear alındı ve ilk vizittte nasal obstrüksiyonu ölçmek için rinomanometri yapıldı. İlk vizitten yirmi dört saat sonraki ikinci vizitte bronşiyal hiperaktivite (BHR) dahil olmak üzere akciğer fonksiyonları ölçüldü. İkinci vizitten yirmi dört saat sonra, balgam indüksiyonu yapıldı ve balgamda hücre dağılımı araştırıldı. **Bulgular:** On yedi erkek ve 23 kadın hastanın yaş ortalaması 37 ± 11 idi. Otuz altı hastada nazal smearde eozinofili değerlendirilebildi ve %36'sında pozitif bulundu. Rinomanometride nazal obstrüksiyon hastaların %68'inde gösterildi. Katılımcıların %30'unda BHR pozitif bulundu. Nazal eozinofili ile nazal obstrüksiyonun şiddeti ve ayrıca BHR ile indükte balgamda eozinofili arasında istatistiksel olarak anlamlı bir ilişki yoktu ($p > 0.05$). Değerlendirme açısından iyi kalitede olan indükte balgam örneklerinin %7.5'inde %2'lik eozinofil oranı vardı. İndükte balgam örneklerindeki eozinofil yüzdeleri ve FEV1, FEV1/FVC ve nazal obstrüksiyon şiddeti arasında herhangi bir ilişki görülmedi ($p > 0.05$). Ancak, BHR tüm çalışma grubunda % 70'in üzerinde olan FEV1/FVC oranı ile ile anlamlı şekilde ilişkili idi ($r = 0.392$ $p = 0.012$). **Sonuç:** Allerjik rinitli hastalardan oluşan çalışma grubumuzda nazal ve alt solunum yolu inflamasyon belirteçleri arasında beklenen ilişkinin gösterilmesi mümkün olamamıştır. Bu da, çalışma grubumuzdaki hasta sayısının azlığı yanında astımlı olan hastaların katı şekilde çalışma dışı bırakılması ve de özellikle indükte balgam tekniğinin standardizasyonundaki zorluklardan kaynaklanabilir.

Anahtar Kelimeler: Rinit, allerjik, yıl boyu; balgam; inflamasyon mediatörleri

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Allergic rhinitis (AR) is a disorder of the nose resulting from IgE-mediated inflammation induced by the nasal mucosal allergen exposure. Three major symptoms of AR are mucous discharge, sneezing, and nasal obstruction.[1] AR and asthma are usually comorbid diseases and AR is a major risk factor for asthma.[2] The influence of AR on lower airways has been investigated widely. Inspiration of unfiltered and unconditioned air, nasobronchial neural interactions and direct irritation of nasal secretions on lower airways have been suggested as possible mechanisms for nasal and bronchial interaction. However, it seems that the impaired nasal functions have a little effect on lower airways.[3-6] The most important link between the lung and the nose is systemic inflammation upon mediators and inflammatory cells of bone marrow, and both upper and lower airways are affected by respiratory inflammation bidirectionally.[7,8] The patterns of inflammation are very likely to be similar in AR and asthma.[7] An inflammatory infiltration of eosinophils, mast cells, T lymphocytes and similar T-helper (Th) lymphocyte cytokines including interleukin-5 (IL-5) are present in both AR and asthma.[1]

Airway inflammation is considered as the major cause of asthma as well as other airway diseases,[9] however traditionally the diagnosis and management of asthma depend on clinical and pulmonary functional parameters.[1] Pulmonary functions measured in terms of the forced expiratory volume in 1 second (FEV_1) do not reflect the airway inflammation. Even in asymptomatic patients with normal pulmonary functions, airway inflammation can be demonstrated.[10] In clinical practice, assessment of airway inflammation is difficult. There are several methods for evaluating inflammation in both upper and lower airways. Nasal cytology examinations can be performed by nasal swabs for upper airways.[11] Induced sputum is a simple, safe, valid and noninvasive technique for the assessment of inflammation in lower airways. This method gives an opportunity to measure cellular and molecular indices of airway inflammation in sputum.[12]

The magnitude of the respiratory inflammation differs according to the disease severity. In clinical practice, AR severity can be evaluated by symptom scores. In addition, some objective methods for measuring nasal patency have been suggested. One of them is rhinomanometry which gives information about the extent of nasal obstruction although it has a limited reproducibility.[13]

Bronchial reactivity to methacholine or histamine can be detected in many patients with AR, especially during the pollen season.[14] This response is independent of the presence of asthma symptoms[5] although the magnitude of hyperreactivity differs between asthmatics and patients with rhinitis.[6]

It is an important preventive function for public health to detect the individuals at risk however not developed overt clinical disease yet. There may be a window period of opportunity for prevention of the inflammatory changes associated with the asthmatic symptoms in AR patients. AR patients do have an increased risk of developing asthma; however asthma may be underdiagnosed in this population. In our study, we aimed to evaluate the possible early lower airway inflammation in AR, which may predict the development of asthma before asthma phenotype presents.

MATERIAL AND METHODS

We recruited 40 consecutive patients referred to our Ear Nose Throat (ENT) outpatient clinic between August 2008 and June 2009, who were diagnosed as moderate/severe persistent allergic rhinitis (PAR). Definition of moderate/severe persistent AR was done according to Allergic Rhinitis and its Impact on Asthma (ARIA) criteria such as; the presence of one or more of the items including sleep disturbances, impairment of daily activities, leisure and/or sport, impairment of school or work and troublesome symptoms for more than four days a week in more than four consecutive weeks.[6] All patients had similar documented clinical histories of moderate or severe PAR and positive skin prick tests with at least one member of the Dermatophagoides spp. None of the patients were tested or treated for AR previously. The nasal congestion was found to be due to the bilateral inferior turbinate hypertrophy via nasal endoscopic examination. Patients underwent a detailed examination by a pul-

monologist, and those who were previously diagnosed with asthma and had symptoms consistent with asthma or laboratory findings associated with asthma recognized in the run-in period were excluded. Other exclusion criteria were smoking history, associated co-morbidities such as chronic obstructive pulmonary disease, bronchiectasis, urticaria, previous sino-nasal or turbinate surgery, severe nasal septal deviation, nasal valve insufficiency and concomitant sino-nasal disorders including rhinosinusitis.

The study was approved by the instuitional human-research review board and all patients provided written informed consents. Patients were evaluated for the eligibility for the study in a two-week run-in period, and the ones meeting the inclusion criteria were asked to attend the visit 1. After obtaining the informed consent, on the visit 1, nasal smear was obtained and active anterior rhinomanometry was performed. Twenty-four hours after from the visit 1, pulmonary function tests including bronchial hyperactivity (BHR) were done on the visit 2. Finally, 24 hours after the visit 2, sputum induction was performed on visit 3. Patients attended the laboratory on three different days, but at the same time interval between 9 am and 11 am.

NASAL SMEAR PROCESSING

Patients were asked to rinse their noses before obtaining the nasal smear. Single-use probes were applied to inferior turbinate. Samples were disseminated on the slides and treated with 95% alcohol solution for at least one minute. Hematoxylin eosin stained samples were examined with x100 magnificence under the light microscope and presence of eosinophils was evaluated. The presence of eosinophils was regarded as eosinophilia.

RHINOMANOMETRY

Active anterior rhinomanometry measurements were performed using SRE2000 (Rhinomanometrics A/S, Lynge, Denmark). All measurements were done in the non-decongested state. An experienced ENT specialist carried out each measurement in a standard fashion as described previously.[13] The 150 Pa reference pressured "R" value obtained from active anterior rhinomanometry curves was determined by 2.6 version of Rhinoscan programme and total nasal resistance was evaluated. A cut off value of >0.4 Pa $cm^{-3}s^{-1}$ was regarded as presence of nasal obstruction.

PULMONARY FUNCTION TESTS (PFT)

PFT was performed with Jaeger Master Screen Pneumo (Spirolab II®) spirometry device. The best test among the three consecutive tests was taken into consideration. FEV_1, forced vital capacity (FVC), FEV_1/FVC were measured according to American Thoracic Society (ATS) criteria.[15]

METHACHOLINE CHALLENGE

Bronchial challenge was always performed between 9 am and 10 am according to 2 minute breath test for methacholin standard protocol described in the ATS guidelines.[16] After three reproducible FEV_1 measurements, doubled concentrations of methacholine 0.0625-0.125-0.25-0.50-1-4-8-16 mg/ml were inhaled through a nebulizer and spirometry was performed. The dose provoking a FEV_1 decrease by 20% or more from basal measurements was accepted as PD20, provocative dose. A PD20 value below or equal to 8 mg/ml was regarded as bronchial hyperreactivity (BHR) positivity.

SPUTUM INDUCTION

After pretreatment with a short acting beta-2 agonist, sputum was induced by the inhalation of hypertonic saline solution (3%) generated by a nebulizer (Pari Master, Pari Respiratory Equipment Inc., Richmond, VA, USA), with an output of 0,5 ml/min and a particle size of less than 5 μm aerodynamic mass median diameter. Patients inhaled the nebulized saline for up to 20 minutes through a mouthpiece. Ten minutes after the beginning of the nebulization and every five minutes thereafter, patients were encouraged to cough and expectorate sputum into a sterile petri dish. Three flow volume curves were performed before and after each inhalation and induction of the sputum was stopped if the best FEV_1 dropped 15% from the baseline or any symptoms occurred. Nebulization was stopped before 20 minutes if sufficient and good quality sputum was obtained earlier.

SPUTUM PROCESSING

Samples were processed within 3 hours. The method of sputum examination described by Popov et al was used with some modifications.[17,18] Sputum was disseminated in the petri dish and all opaque or dense portions seemed different from saliva were collected using the selection plug method. Then the sample was placed into an Eppendorf tube and weight of the sample was measured. The amount of dithiothreitol (DTT; Sigma) having double weight of the sample was freshly prepared by distilled water with a dilution of 1:10, and was added. The mixture was mechanically stirred with the aspiration of the sputum in and out of a pipette about 20 times. Afterwards, the sample was placed in a shaker at 24°C for 15 minutes to achieve complete homogenization. The suspension was further diluted with phosphate buffered solution (PBS) to a volume equal to the sputum plus DTT to stop the effect of DTT, and centrifuged at 2000 rpm for 5 minutes. The supernatant was aspirated and the cell pellets were resuspended with Roswell Park Memorial Institute (RPMI) media to achieve a concentration of 10/L. One drop was put in each cytocentrifuge cube and cytocentrifuged at 600 rpm for 10 minutes. The cytospins were stained with Giemsa. Differential cell counts were measured by scanning slides starting at the top left corner in an undulating manner from top to bottom using high power (x100) magnification. Two hundred non-squamous cells were counted and the results were expressed as percentages of total non-squamous cell counts.

STATISTICAL ANALYSIS

Data were analyzed by SPSS 15.0 package program. Inflammatory cell counts in sputum were shown as the percentage of total non-squamous cell counts and they were expressed as mean, median, standard deviation, minimum and maximum values and interquartile range. Parameters were analyzed after an initial evaluation for normal distribution in the study population. Correlations between the data obtained by acoustic rhinomanometry and BHR, nasal smear and induced sputum eosinophilia were tested using Spearman's rank correlation tests. Categorical data as BHR positivity, nasal obstruction and nasal smear eosinophilia presence were analyzed with Chi square test. A, p-value <0.05 was considered to indicate statistical significance.

RESULTS

Among 60 patients who were evaluated for the eligibility of the study, 40 patients met the inclusion criteria. Demographic features and characteristics of the 17 male and 23 female patients are shown in Table 1.

Thirteen (36%) of the patients out of 36 had eosinophils in their nasal smear.

Mean values of nasal rhinomanometric measurements were 1 ± 0.7 Pa $cm^{-3}s^{-1}$. Nasal obstruction was regarded positive over 0.4 Pa $cm^{-3}s^{-1}$. Twenty-seven (68%) of the patients were found to have nasal obstruction.

Five patients had a FEV_1<80%, whereas all the participants have FEV_1/FVC ratio greater than 70%. Bronchial hyperreactivity was positive in 12

TABLE 1: Characteristics of the study population.

	Mean ± SD	Median (25th to 75th percentiles)	Minimum	Maximum
Age	37 ± 11	38 (27-46)	20	58
FEV_1 (%)	98 ± 13	99 (88-110)	70	117
FEV_1 (lt)	3 ± 1	3 (3-4)	2	5
FEV_1/FVC (%)	81 ± 7	81 (76-87)	70	100
Rhinomanometry	1 ± 0.7	0.7±(0.5-1)	0.3	3.2

FEV_1: Forced expiratory volume in 1 second. FVC: Forced vital capacity.

SD: Standart deviation.

(30%) of the patients. Five patients (12.5%) had a methacholine challenge positivity at 8 mg/ml, four (10%) at 4 mg/ml and three (7.5%) at 1 mg/ml. BHR was found weakly correlated with the FEV_1/FVC ratios (r= 0.392 p= 0.012).

Sputum induction was well tolerated in all of the patients; however 27 of the sputums were of good quality to evaluate. Mean percentage of the eosinophils were less than other cell types like neutrophils, lymphocytes and macrophages (Figure 1). Eosinophils were not determined in the sputums of 23 of the patients while only two had 1% and the other two had 2% eosinophilia, respectively. Induced sputum cell distribution among the study population is shown in Table 2.

There was not any correlation with nasal smear eosinophilia and sputum eosinophilia, FEV_1 (%), FEV_1/FVC and nasal obstruction in terms of rhinomanometry.Presence bronchial hyperreactivity was not found to be related with either nasal obstruction (p= 0.412) or nasal eosinophilia (p= 0.548) presence in addition, BHR severity did not have an effect on these results. Any significant relationship was not observed between induced sputum eosinophilia and FEV_1 (%), FEV_1/FVC, nasal obstruction severity and methacholine challenge positivity.

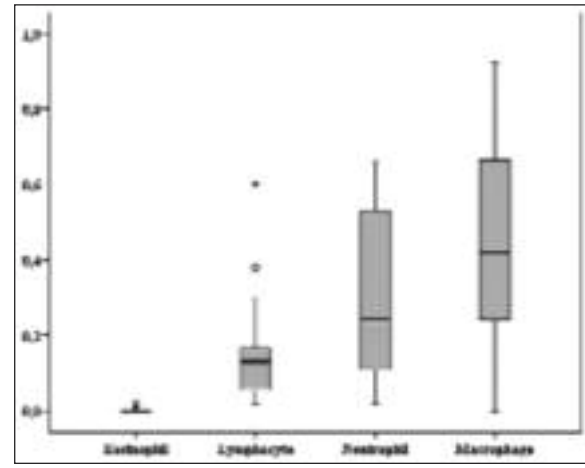

FIGURE 1: Induced sputum cell distrubution of the study population according to mean percentage.

DISCUSSION

Nasal and bronchial mucosa have similar features and though there are some pathophysioloical differences between rhinitis and asthma, the concept of "one airway one disease" has been accepted widely over the past several years.[19] More than 80% of asthmatics have rhinitis and 10-40% of patients with rhinitis have asthma.[1] Evaluation for asthma is highly recommended in patients with persistent AR. It is not clear whether the presence of AR predicts the development of asthma or AR causes asthma.[6] There are not many studies investigating the association of rhinitis and asthma throughout the country, in Turkey.[20]

Several biomarkers that can be obtained by invasive or non invasive sampling methods have been suggested for the evaluation of AR and asthma. Nasal lavage techniques, nasal brushings and nasal biopsies are some methods for sampling upper airway inflammation. They are relatively easy to be performed and have reproducibility. Lower airways can be sampled by brochoscopic procedures, exhaled breath and induced sputum. Brochoscopy is an invasive method, induced sputum is non invasive, but it needs well-organized centers. Generally, one biomarker may reflect only one aspect of the disease, so it is recommended to sample multiple clinically relevant markers whenever possible.[21] In our study, we investigated some markers in

TABLE 2: Differential cell counts in the induced sputums of the study population.

	Mean ± SD	Median (25th to 75th percentiles)	Minimum	Maximum
Eosinophils%	0.2 ± 0.5	0 (0-0)	0	2
Neutrophils%.	30 ± 22	24 (10-54)	2	66
Lymphocytes	15 ± 13	13 (5-17)	2	60
Macrophages	43 ± 24	42 (22-68)	0	92

SD: Standart deviation.

AR which may predict asthma and reflect respiratory inflammation for both AR and asthma.

It has been reported that healthy individuals have less than 5% eosinophils in their nasal lavage.[22] Eosinophils are the major inflammatory cells in asthma and a number of studies investigated sputum eosinophilia as a marker of lower airway inflammation and evaluation of asthma control.[23] However, there is not much information about the importance of inflammatory cells in nasal secretions on the assessment of lower airway inflammation. Amorim et al colleagues found that nasal lavage fluid was a good predictor of sputum eosinophilia in a group of asthmatic patients, and they concluded that nasal fluid lavage examination might be useful in determining airway inflammation in asthmatic patients.[24] We performed nasal smear examination which partially differed from the nasal lavage technique in our study, and we were not able to show any relation between nasal and induced sputum eosinophilia. This may be explained by the characteristics of our study population, which included only non-asthmatic AR patients. Based on the European Respiratory Society (ERS) International Guidelines[25] a normal upper value of eosinophils can be accepted as 3% or 2.5% and with the cut value of 2.5% for eosinophils in induced sputum, we did not determine sputum eosinophilia at all, whereas 20% of the patients had nasal smear eosinophilia. Studies on nasal smear suggest that an eosinophil percentage higher than 5-10% may be regarded as nasal eosinophilia.[26] Nasal smear eosinophilia was reported approximately in 40-70%[27,28] in AR patients, and the low eosinophilia rate in our study may be due to some technical aspects. Significant positive relationships were also reported among nasal eosinophil infiltration, nasal airflow and FEV_1 in a group of patients with PAR and asthma.[29] We also did not find any relation between nasal smear eosinophilia and pulmonary functions in terms of FEV_1, FEV_1/FVC and BHR.

It has been suggested that on the basis of T helper type 2 (Th2) cells, nasal inflammation leads to nasal and bronchial structural and functional impairment including both nasal and bronchial airflow.[30] One of the objective methods for the assessment of nasal obstruction and airflow is rhinomanometry which is a technique that measures nasal pressure flow relationship during normal breathing. In individuals without signs of nasal disease mean total resistance has been reported to be around 0.23 Pa $cm^{-3}s^{-1}$, ranging between 0.15 and 0.39 Pa $cm^{-3}s^{-1}$.[31] Upper limit of the normal range for total nasal resistance to airflow can be accepted as 0.3 Pa $cm^{-3}s^{-1}$.[32] Nasal airflow was shown to be associated with FEV_1,[33] as well as with nasal eosinophilia in cytological examination.[34] In our study, although the mean value of rhinomanometric measurements revealed nasal obstruction, we did not observe any significant correlation with FEV_1, FEV_1/FVC and BHR.

Upper and lower airways not only have anatomical integrity, but also show functional complementarities. Patients with persistent AR show bronchial hyperreactivity more than the ones with intermittent AR.[6] The BHR positivity rate has been reported between 53.5% and 82.2% in a group of seasonal and persistent AR patients, respectively.[35] In another study, BHR was present in 32.4% of the persistent rhinitic subjects.[36] Similarly, BHR was positive in 30% of our patients with PAR, however it was positive at 8 mg/ml in 12.5% of the study population. It has been suggested that AR patients with BHR, had different dsypnea perceptions and this might be related to the development of asthma symptoms.[37] In our study, we strictly excluded the patients with asthma symptoms or asthma diagnosis. Although some of our patients had BHR, they did not have symptoms related to asthma. The magnitude of bronchial reactivity may change from AR to asthma.[6] In our study, the magnitude of the BHR was high in only 5% of the patients; most of the patients had methacholine challenge positivity around the cut off limit. There have been studies reporting asymptomatic bronchial involvement and reduced FEV_1, FEF25-75 and positive BHR in AR patients. They demonstrated that the degree of the reactivity also correlated with FEV_1 and FEF25-75. It was suggested that significant number of rhinitis patients might have an asymptomatic bronchial inflammation and bronchial inflammation was related to the severity of BHR.[38,39] In our study, we also found

BHR and FEV_1/FVC ratios significantly correlated but only five patients had low FEV_1 values while all had normal FEV_1/FVC ratios. BHR was not so severe in our study population, and this may explain why we did not find a relation between BHR and other parameters which we investigated in our study like nasal smear, rhinomanometry and induced sputum.

There are studies that investigated the effects of AR on bronchial mucosa in non-asthmatic patients that reported a slight increase in basement membrane size and a moderate eosinophilic inflammation.[40] Induced sputum technique is a noninvasive method that may enable better assessment of severity of airway diseases, disease control and may discriminate the phenotypes of patients showing specific biological markers.[12] It may be used to monitor airway inflammation, although it is not a standard procedure currently. Eosinophilic airway inflammation is one of the most important issues in the pathogenesis of asthma. A number of studies on non-asthmatic AR subjects have demonstrated increased number of induced sputum eosinophils[41,42] while some others failed to show a significant difference in induced sputum eosinophil percentages of seasonal AR patients and healthy controls.[43,44] Median and interquartile range of eosinophil and neutrophil percentages in induced sputums of healthy controls have been reported around 0.5-1.1% and 24.1-26.8 5, respectively.[45] We found these values similar to healthy controls, as 0-0% and 24-44% for eosinophil and neutrophils respectively. We were not able to determine the expected increase in eosinophils rates in induced sputum of our patients, and this may be due to low positivity rates of BHR as well as methodological and study protocol differences. Dixonet al. did not show any correlation between lung functions and cellular compositions of induced sputum, and they explained this by the small number of their study population. However, they defined a trend of fewer eosinophils and neutrophils in patients with low lung functions while in some other studies it was reported that induced sputum eosinophilia was well correlated with low lung function.[46,47] We also could not show any correlation between induced sputum cell compositions and lung functions. Some studies showed a correlation between BHR and eosinophilic inflammation[48] although some did not.[49]

CONCLUSION

There are many questions that have to be highlighted in allergic diseases such as is AR, which may be a predictor of future asthma development . Long term prospective follow-up studies are required to determine whether and when there may be a 'window of opportunity' for prevention of the structural and inflammatory changes associated with the asthma phenotype in allergic rhinitis patients.

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