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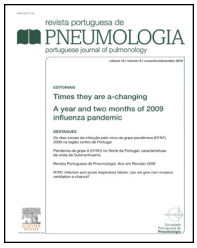

ORIGINAL ARTICLE

Evaluation of vascular endothelial growth factor-A and Endostatin levels in induced sputum and relationship to bronchial hyperreactivity in patients with persistent allergic rhinitis monosensitized to house dust☆

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Vascular remodeling

Summary
Background: Studies about the pathogenesis of bronchial hyperreactivity (BHR) in patients with persistent allergic rhinitis (PAR) and its relationship with lower airway remodeling are extremely limited.
Objective: This study evaluated bronchial vascular remodeling via the measurement of angiogenic factor, vascular endothelial growth factor-A (VEGF-A), and anti-angiogenic factor, Endostatin, and evaluated their relationship with BHR in patients with PAR.
Methods: The study group consisted of 30 patients with PAR monosensitized to house dust mites and 14 non-allergic healthy controls. All subjects underwent induced sputum and methacholine (M) bronchial provocation tests. VEGF-A and Endostatin levels were measured by ELISA in induced sputum supernatants.
Results: The percentages of eosinophils in induced sputum were significantly increased in patients with PAR compared with healthy controls. There were no significant differences between patients with PAR and healthy controls in terms of levels of VEGF (37.9 pg/ml, min–max: 5–373 pg/ml vs. 24.9, min–max: 8–67 pg/ml, $p = 0.8$ respectively), Endostatin

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(532.5 pg/ml, min–max: 150–2125 pg/ml vs. 644, min–max: 223–1123 pg/ml, $p = 0.2$ respectively) and VEGF/Endostatin ratio (0.057 vs. 0.045, $p = 0.8$ respectively). In addition, there were no significant differences between patients who are BHR positive ($n = 8$), or negative to M ($n = 22$) in terms of levels of VEGF, Endostatin and VEGF/Endostatin ratio and no correlations among value of PD20 to M and levels of VEGF, Endostatin and VEGF/Endostatin ratio.
Conclusion: We conclude that VEGF-A and Endostatin did not differ between patients with PAR and healthy controls regardless of BHR to M.

Introduction

The presence of inflammation and airway *remodeling* are cornerstones in the pathogenesis of asthma.[1,2] Angiogenesis has recently attracted considerable attention as a component of airway *remodeling* in bronchial asthma. One of the key molecules for angiogenesis is VEGF; it is widely expressed within many highly vascularized organs including the lungs and is a potent inducer of endothelial cell growth.[3] Vascular *remodeling* and increased expression of associated growth factors such as VEGF are well-recognized features of asthma.[4,5] Endostatin is a strong endogenous inhibitor of angiogenesis and is produced by various types of cells.[6] Endostatin specifically inhibits endothelial cell growth and migration and directly antagonizes the biological effects of VEGF.[7] The vascular component of *remodeling* is regulated by a balance between *angiogenic* and *anti-angiogenic* factors. However, there are no data regarding the balance of major *angiogenic* and *anti-angiogenic* factors in the lower airways of patients with allergic rhinitis (AR) without concomitant asthma.

AR, which is particularly associated with bronchial hyperreactivity (BHR), is considered as a risk factor for asthma development.[8,9] The mechanism of BHR in AR is not fully understood and it is not known whether the BHR in asthma and AR have the same pathophysiologies. Studies on the pathogenesis of BHR in patients with AR and its relationship with lower airway *remodeling* are extremely limited.[10–13] In our first trial, we evaluated bronchial vascular *remodeling and its* relationship with BHR via measurement of VEGF-A and Endostatin levels in allergic rhinitis patients monosensitized to pollen.[10] In the present study, bronchial vascular *remodeling* parameters and their relationship with BHR were evaluated by measuring the same *angiogenic/anti-angiogenic* factors in patients with persistent allergic rhinitis (PAR).

Methods

Subjects

Inclusion criteria for patients with rhinitis were as follows: (1) a history of persistent rhinitis without cough, wheezing, or shortness of breath during natural exposure, (2) positive skin test to house dust mites only, (3) baseline forced expiratory volume in 1 second (FEV_1) greater than 80% of predicted value. Pulmonary function tests, Bronchial Provocation Test (BPT) to methacholine (M) and induced sputum were performed. All subjects denied any past or present symptoms suggestive of asthma including intermittent dyspnea, wheezing, or a recurrent cough, and any respiratory infection during the month preceding this study. Control subjects had normal spirometry and airway responsiveness to M ($PC_{20} > 16$ mg/ml), had negative skin prick test to common inhalant allergens, no history of rhinitis, no current or past symptoms suggesting asthma, and no respiratory infection during the month before enrollment. Patients and controls were all nonsmokers and were free of all systemic diseases and malignancies. None had eczema or history of nasal polyposis. None of the patients had previously been treated with immunotherapy. All patients discontinued their medications (nasal steroid and oral antihistamine) at least 1 week before M BPT, but they were allowed to use nasal antihistamine spray if necessary. Patients were classified according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.[14] The study was approved by Ankara University Medical School's Ethics Committee (Decision No: 152-4759).

Evaluation of atopy

Skin prick tests were performed by using a common panel, including *D. pteronyssinus*, *D. farinae*, grass, tree, and weed pollens, cat, dog, *Alternaria*, *Cladosporium*, and cockroach allergen extracts (Allergopharma, Stockholm, Sweden). The positive and negative controls used were histamine (10 mg/mL) and phenolated glycerol saline, respectively. A mean wheal diameter of 3 mm or greater than that obtained with the control solution was considered positive.

Pulmonary function tests and nonspecific bronchial provocation test

Pulmonary function tests (Flowhandy Zan 100 USB, Germany) were performed before sputum induction to determine baseline FEV_1. BPT using M was performed between 8:30 and 10:30 AM according to the method described by Cockcroft et al.[15] After inhalation of physiologic saline, patients inhaled doubling concentrations of M