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ORIGINAL ARTICLE

Plasma paraoxonase, oxidative status level, and their relationship with asthma control test in children with asthma☆

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Abstract
Background: Assessment of asthma with a control test has been suggested as a relevant approach in recent years. However, no biomarker of systemic inflammation has been included in the assessment of asthma control.
Objective: To evaluate plasma paraoxonase (PON1), total oxidant status (TOS), and total antioxidant status (TAS) levels in children with asthma according to the disease control, and the performance in the identification of uncontrolled patients.
Methods: Stable asthmatic children ($n = 85$) and healthy controls ($n = 55$) were recruited for this study. Blood samples were collected for plasma PON1, TOS, and TAS measurements. Any contributing factors that may affect plasma PON1, TAS, and TOS levels were excluded from both groups. The diagnostic potential of these measures was evaluated using receiver operating characteristic (ROC) analysis.
Results: Comparing the asthmatic children with the control group, plasma TAS and TOS levels were significantly higher (TAS; 6.9 ± 2.1, 1.05 ± 0.32, $P < 0.001$, and TOS; 12.5 ± 3.4, 5.5 ± 3.8, $P < 0.001$, respectively) and PON1 level was significantly lower (156.5 ± 55, 298.6 ± 87.6, respectively, $P < 0.001$) in the asthmatic group than controls. In ROC analysis, PON1 presented an AUC 0.679 and TOS presented an AUC 0.645 for the identification of uncontrolled asthma, respectively. Asthma Control Test (ACT) presented an AUC of 0.972 for the identification of uncontrolled asthma.
Conclusion: PON1 and TOS levels may be systemic markers of uncontrolled asthma in children. Combined use of these two biomarkers with asthma control test may identify patients with uncontrolled asthma in children.

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Introduction

Although the large surface area and high exposure to atmospheric oxygen increase the lungs' susceptibility to oxidative injury, these organs are equipped with strong defences to counteract the oxidative insult (e.g. asthma is a chronic inflammatory lung disease that is worsened by increased oxidative stress).[1,2] Increased levels of reactive oxygen species (ROS) such as hydroxyl radicals, superoxides and peroxides can lead to increased airway reactivity and secretions, and increased vascular permeability, which collectively augment the existing inflammation that is a hallmark of asthma.[3,4] The mechanisms responsible for both remodelling and the inflammation are incompletely understood, but some clinical studies indicate that inflammation is related to disease severity.[5,6] Despite longstanding use, the classification of severity is no longer recommended except in newly diagnosed patients; instead, the assessment of asthma control tests is reported as a relevant approach according to recent guidelines.[7] Ideally, asthma control tests should include not only patient-reported clinical manifestations of the inflammatory process, but also laboratory markers that indicate inflammation and pathophysiological features of the disease as well. Subclinical inflammation may precede actual clinical impairment so that conventional measures may be insufficient to detect the inflammatory component of adverse health effects. Therefore, there is a need for objective evaluation of asthma symptoms and control, suggesting a possible role for biomarkers of airway inflammation. Unfortunately, objective measurement cannot be performed due to its prohibitive cost and the unavailability of confirmed markers or measures that definitively indicate inflammation.

Oxidised low-density lipoprotein (Ox-LDL) is a parameter closely associated with atherosclerosis. It is also suggested to be involved in the aetiology of many other diseases (e.g. chronic inflammatory diseases of the airways and includes other Chronic Obstructive Pulmonary Disease (COPD) diseases).[8,9] Leukotrienes, known to be involved in asthma pathogenesis, are synthesised from arachidonic acid (AA) through the action of lipoxygenase.[10] Because the leukotriene pathway is stimulated by ROS upon exposure to AA, a relationship may exist between LDL formation and the development of Asthma.[11] Paraoxanase (PON1) is another component, which is known to retard the oxidation of LDL by preventing the generation of lipid peroxides.[12] Serum PON1 is synthesised mainly by the liver that circulates serum in association with high-density lipoprotein (HDL).[13] Additionally, it contributes to detoxification of organophosphorous compounds, including the pesticide paraoxon.[14] In this study, aside from the members of lipid and lipoprotein profile, PON1 enzyme activities were determined in children with asthma because of their close association with lipoprotein metabolism as well as their antioxidant property.[15] The aim of this study was to evaluate plasma PON1, total oxidant status (TOS), and total antioxidant status (TAS) levels in atopic asthmatic children and to investigate the correlation with the atopy, level of disease control and the frequency of attacks.

Methods

Subjects and study design

We conducted a prospective case control study among 85 children diagnosed with stable mild-to-moderate atopic asthma from the authors' Paediatric Allergy-Pulmonology outpatient clinic and who were enrolled consecutively between October 2009 and December 2010. The diagnosis and severity of asthma were defined according to GINA[16] guidelines. Children were defined as asthmatic according to the following criteria: (a) recurrent episodes of at least one symptom of asthma, including cough, wheezing, breathlessness, and chest tightness; (b) an improvement of at least 12% in baseline forced expiratory volume in one second (FEV_1) after bronchodilator use; (c) a total serum Ig E level of over 52 IU/mL determined by direct chemiluminescence, and a positive skin test for at least one allergen. Informed consent was given by the family of the patients.

Eighty-five subjects, aged 7–14 years, with stable asthma who had been attending the Paediatric Allergy Unit of Medical Faculty of Bezmialem Vakif University were recruited for this case-control study. Exacerbation of asthma was defined as episodes of progressive increase in shortness of breath, cough, chest tightness, or combination of these symptoms. After selecting the group, age, gender, duration of asthma, lung function tests, the frequency of attacks per year, daytime symptoms, the need for rescue treatment, and the medication used were all recorded. A family history of atopy was considered positive if atopy was present in parents and/or siblings (bronchial asthma, allergic rhinitis, atopic dermatitis). The patients also underwent skin-prick tests. If a wheal response of $\geq$3 mm in diameter developed after 15 min to one or more of the allergens in the presence of both negative (0.9% saline) and positive (histamine acid phosphate) controls, the test was considered as a positive response. Patients with clinical signs of asthma who had a positive skin prick test results were included in the atopic asthma groups. Exclusion criteria for the patient group were as follows: any infection or asthma exacerbation within the previous four weeks; the use of antihistaminic, oral or parenteral steroid within the previous four weeks; any allergic co-morbidity such as allergic rhinitis, and atopic dermatitis; and any systemic disease such as acute or chronic liver disease, etc. The control group consisted of 55 age-matched healthy children (6–14 years). Healthy children were chosen from those referred to the paediatric out-patient clinic for routine pre-op check-ups for their elective surgery (inguinal hernia, tonsillectomy, etc.). Control patients were evaluated with regard to chronic and/or severe infections, autoimmune disorders, and familial and personal history of atopy, and also by laboratory tests. Children were included in the control group if they had no personal and familial history of atopy and no signs of atopic disorder, and if they were negative for skin prick test. As smoking effects oxidative status, patients came from non-smoking households, and the control group was also selected from non-smoking households. Patients taking antioxidant drugs, vitamins, diuretics, hormone replacement therapy and those who smoked were also excluded from study. Blood samples were collected from