

## Asymmetric dimethylarginine levels in allergic rhinitis and nasal polyposis

Mehmet TOSUN<sup>1\*</sup>, Tayfun APUHAN<sup>2</sup>

<sup>1</sup>Department of Medical Biochemistry, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey

<sup>2</sup>Department of Otorhinolaryngology, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey

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**Aim:** Asymmetric dimethylarginine (ADMA) is the major endogenous inhibitor of nitric oxide synthase. We aimed to investigate the ADMA levels in allergic rhinitis (AR) and nasal polyposis (NP).

**Materials and methods:** A total of 29 AR patients, 21 NP patients, and 30 healthy subjects to be used as a control group were enrolled in the study. ADMA was measured in the AR, NP, and control groups with enzyme-linked immunosorbent assay. Any patients or control subjects with coronary artery disease, renal failure, diabetes mellitus, or hypertension were excluded from the study.

**Results:** The mean ADMA serum concentration was  $0.52 \pm 0.08$   $\mu\text{mol/L}$  in the AR group,  $0.62 \pm 0.10$   $\mu\text{mol/L}$  in the NP group, and  $0.67 \pm 0.09$   $\mu\text{mol/L}$  in the control group. The ADMA serum concentration in the AR group was significantly lower than in the control group ( $P < 0.001$ ). Considered together, the NP and AR groups had ADMA levels that were significantly lower than in the control group ( $P < 0.001$ ).

**Conclusion:** In the present study, lower ADMA levels were found in the AR and NP groups.

**Key words:** Asymmetric dimethylarginine, allergic rhinitis, nasal polyposis

### 1. Introduction

Allergic rhinitis (AR), encountered particularly in industrialized countries, is increasing in prevalence and is an important health problem affecting the quality of life for affected people (1). Immunoglobulin E-mediated inflammatory response plays an important role in the formation of AR. This inflammatory response is triggered by various allergens in the nasal mucosa. Various mediators such as chemokines and cytokines released from eosinophils, basophils, T cells, and mast cells play a role in this formation. This local inflammation may trigger systemic inflammation (2).

Nasal polyposis (NP) is a chronic inflammatory disease of the nasal mucosa and upper respiratory tract (3). The etiology and pathogenesis of NP are still unclear, but it is seen in a variety of disease states such as infection, allergy, asthma, and aspirin hypersensitivity (4,5).

Nitric oxide (NO) has various roles in the upper airway physiology. NO is an endogenous free radical gas mediator of fundamental importance in the regulation of vascular tone, host defense, inflammation, coagulation, and neurotransmission (6). In addition to these, it has been reported that NO may be used as a marker in the diagnosis of esophageal cancer (7). NO has been measured

in the upper respiratory tract and tends to be elevated in inflammatory disorders such as AR (8,9). Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NOS) (10). ADMA may play a role in inflammatory airway diseases such as asthma (11). ADMA has been shown to affect airway physiology and collagen formation in the airways of mice by altering the L-arginine metabolizing pathways (12). ADMA levels were also found to be increased in human asthma lung and sputum samples (13). However, the similar pathogenic features of NP and ADMA are not yet known.

In the present study, we aimed to compare ADMA levels in patients with AR and NP who did not have any cardiovascular risk markers like diabetes, hypertension, coronary artery disease, or renal disease to the ADMA levels in control subjects without AR or NP.

### 2. Materials and methods

#### 2.1. Study population

The total study population consisted of 81 subjects: 29 of them were patients with AR, 21 of them were patients with NP, and 30 of them were healthy controls. All patients were informed about the study, and informed consent was obtained. The study was approved by the

\* Correspondence: mehmet\_tosun@yahoo.com

Ethics Committee of Abant İzzet Baysal University. Patients and control subjects were selected to participate in the study from the otorhinolaryngology outpatient clinics at our hospital. A whole physical examination was performed, and a thorough clinical history was taken from each patient. AR diagnosis was made mainly by clinical history. NP was diagnosed mainly by nasal examination with a lighted instrument or, rarely, with the aid of nasal endoscopy or paranasal computerized tomography. Subjects in the control group were selected from persons without a history of nasal disease or allergies. Any patients or control subjects with diabetes, hypertension, coronary artery disease, or renal disease were excluded from the study.

## 2.2. Laboratory analysis

Venous blood samples were obtained from each participant in the morning following a 12-h fasting period. Blood samples were centrifuged 30 min after collection at  $2750 \times g$  for 10 min, and the supernatant plasma was then transferred into polypropylene tubes at  $-80^\circ\text{C}$  until the assays were determined. The plasma levels of ADMA were measured by the enzyme-linked immunosorbent assay (ELISA) method. Plasma ADMA levels were determined using a commercial ELISA kit (Immundiagnostik AG, Bensheim, Germany).

Other biochemical parameters such as fasting glucose, lipid profile, renal function tests, hepatic function tests, and complete blood counts were analyzed with standard laboratory methods using commercially available kits.

## 2.3. Statistical analysis

SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical calculations. Data are shown as mean  $\pm$  standard deviation or median for continuous variables and frequencies and percentages for categorical variables. Comparisons between the groups were performed using one-way ANOVA for the continuous variables and the Kruskal–Wallis test for the categorical variables. Subgroup analysis was made using Student's t-test.  $P < 0.05$  was considered statistically significant.

## 3. Results

There were 29 patients in the AR group, 21 patients in the NP group, and 30 healthy subjects in the control group. The mean ages of the groups were  $37.3 \pm 12.5$  years,  $42.2 \pm 12.1$  years, and  $35.9 \pm 14.4$  years, respectively. The mean ages were similar among groups ( $P = 0.354$ ). The mean ADMA serum concentration was  $0.52 \pm 0.08$   $\mu\text{mol/L}$  in the AR group,  $0.62 \pm 0.10$   $\mu\text{mol/L}$  in the NP group, and  $0.67 \pm 0.09$   $\mu\text{mol/L}$  in the control group. The ADMA serum concentration was significantly higher in the NP group than in the AR group ( $P = 0.001$ ). ADMA serum concentration was significantly lower in the AR group than in the control group ( $P < 0.001$ ). ADMA serum

concentrations were lower in the NP group than in the control group, but this trend did not reach statistical significance ( $P = 0.069$ ). When the NP and AR groups were considered together, the ADMA levels were significantly lower than in the control group ( $P < 0.001$ ). The Figure shows the groups' ADMA serum levels.

## 4. Discussion

ADMA is a NOS inhibitor. Human neuronal NOS (nNOS), inducible (iNOS), and endothelial (eNOS) are types of NOS. The relationship between the increase in ADMA levels and endothelial dysfunction has been established clearly. ADMA level has also been found to be influential in diabetes mellitus, chronic renal failure, metabolic syndrome, and Behçet's disease (14–16).

AR is an allergic reaction, expressed as inflammation in the nasal mucosa. Studies have reported that increased oxidant stress and antioxidant mechanism deficiencies may play a role in the pathophysiology of AR (17,18). In several studies, it has been reported that there is a high level of NOS associated with AR. This condition may be connected to a low or normal level of ADMA. High levels of iNOS have been found in AR patients, but eNOS levels were not found to be significantly different in AR patients (19,20). Similarly, Chiba et al. found higher levels of iNOS in their experimental study. They found no significant difference in the levels of eNOS and nNOS. They reported that excess iNOS may have a role in the pathophysiology of AR (21). The low ADMA levels that we found in the AR group support the description of this relationship. Li et al. supported this view by reporting increased iNOS and nNOS in AR patients (22).

Increased levels of NOS in AR patients may also suggest increased NO levels. In several studies, as expected, NO was higher in patients with AR than in the control group (23,24). Ciprandi et al. reported that the amount of NO directly increases with exposure to allergens (25). ADMA

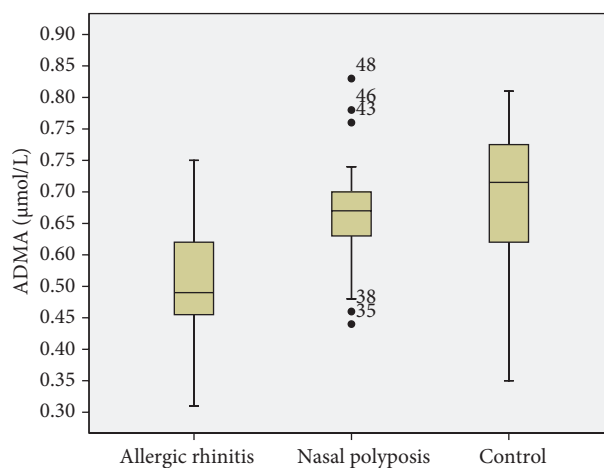


Figure. The study groups' ADMA serum levels.

levels in our AR patient group were significantly lower than in the control group. ADMA levels may be associated with the pathophysiology of AR and also may be related to allergic conditions.

Allergic processes may play an important role in the formation of NP. An increase in oxidative stress and deficient antioxidant mechanisms may also play a role in the pathophysiology of NP (26,27). Several studies have reported increased NOS levels in NP patients (28,29). We also found lower ADMA values in the NP group than in the control group, but there was no statistically significant difference. This may be due to the limited number of patients in the NP group.

Yoshimura et al. reported that NOS and NO may trigger some allergic-based diseases (30). The relationship between the phagocytic myeloperoxidase system and NO has been established clearly. However, increases in cases

of allergic mechanisms have not been clearly confirmed. In both the NP and AR groups, ADMA levels were significantly lower than in the control group. There may be a relationship between decreased ADMA levels and increased NOS and NO levels.

The present study is the first investigation of the relationship between ADMA levels and the allergy-based diseases AR and NP. Based on our results, increased NOS and NO levels in allergic states may indicate a possible relationship with ADMA. However, to more clearly confirm the relationship between ADMA and NOS and NO in these allergic diseases, more studies are needed.

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