

# Nasal nitric oxide and its metabolites as potential biomarkers for the diagnosis and follow-up of allergic rhinitis

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## Abstract

**Objective:** This study was conducted to investigate nasal nitric oxide (nNO) and its metabolites nasal nitrite-nitrate (nNOx) in patients with allergic rhinitis (AR), the effects of two different drugs (oral antihistamine and intranasal steroid) on nNOx and the presence of a correlation between nNOx and clinical parameters.

**Methods:** Sixty patients with active symptoms of perennial AR and 25 healthy adults as a control group were enrolled. The patients were randomized into two groups. Half of the patients received fexofenadine 1x120 mg/day orally, and the other half received triamcinolone acetonide 1x2 puff/day intranasally for one month. The amount of nNOx in nasal lavage fluid was measured by using a commercially available kit and the photometric endpoint determination method.

**Results:** Pre-treatment levels of NOx in the nasal lavage fluids (1.92±1.20 mg/l) of patients with AR were found to be significantly higher when compared with nasal lavage fluid NOx levels of healthy adults (1.38±0.78 mg/l) (p=0.04). The post-treatment nNOx level (1.52±0.85 mg/l) was significantly lower when compared with the pre-treatment value (p=0.028).

**Conclusion:** Nasal nitric oxide metabolites were shown to be good biomarkers for AR, and that oral fexofenadine significantly decreased nNOx levels.

**Keywords:** Allergic rhinitis, nitric oxide, nitrite, nitrate, nasal lavage, fexofenadine, triamcinolone acetonide, nasal steroid, antihistaminic.

## Özet: Alerjik rinitin tanı ve izleminde potansiyel biyolojik belirteçler olarak nazal nitrik oksit ve metabolitleri

**Amaç:** Bu çalışma alerjik riniti (AR) olan hastalarda nazal nitrik oksiti (nNO) ve metabolitleri nazal nitrit-nitratı (nNOx), iki farklı ilacın (oral antihistamin ve intranasal steroid) nNOx üzerine etkilerini ve nNOx ile klinik parametreler arasındaki korelasyonun varlığını araştırmak için yürütülmüştür.

**Yöntem:** Çalışmaya aktif perenniyal AR semptomları olan 60 hasta ve kontrol grubu olarak 25 sağlıklı erişkin katıldı. Hastalar iki gruba randomize edildi. Bir ay devam etmek üzere hastaların yarısı günde bir kez oral yoldan 120 mg fexofenadin aldı. Diğer yarısı burun içine günde bir kez 2 doz triamsinolon asetonid püskürttü. Nazal lavaj sıvısında nNOx'un miktarı piyasada bulunan ticari bir kit ve fotometrik son nokta belirleme yöntemi kullanılarak ölçüldü.

**Bulgular:** Alerjik rinit hastalarının nazal lavaj sıvısındaki tedavi öncesi NOx değerleri (1.92±1.20 mg/l), sağlıklı erişkinlerin NOx düzeylerine (1.38±0.78 mg/l) kıyasla anlamlı derecede daha yüksek saptandı (p=0.04). Tedavi sonrası nNOx düzeyi (1.52±0.85 mg/l) tedavi öncesi değere göre anlamlı derecede daha düşüktü (p=0.028).

**Sonuç:** Nazal nitrik oksit metabolitlerinin AR'nin iyi biyolojik belirteçleri olduğu ve oral fexofenadinin nNOx düzeylerini anlamlı derecede azalttığı gösterilmiştir.

**Anahtar sözcükler:** Alerjik rinit, nitrik oksit, nitrit, nitrat, nazal lavaj, fexofenadin, triamsinolon asetonit, nazal steroid, antihistaminik.

Allergic rhinitis (AR) is a chronic inflammatory and IgE-dependent disease of the upper respiratory tract, especially involving nasal mucosa. Various mediators, cells, and the

interaction between vascular structures and glands are responsible for the development of the clinical picture.<sup>[1]</sup> Nitric oxide (NO) was first described in 1982 by two inves-

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tigators, Ignarro and Palmer, as a substance regulating vasodilation, which is produced and released from endothelium.<sup>[2,3]</sup> In light of these developments, Nijkamp et al. suggested that NO was a novel mediator that plays a role in the complex pathogenesis of AR.<sup>[4]</sup> In later years, it has been shown to be a very important autacoid that plays a role in inflammation and autoimmunity.<sup>[5,6]</sup>

Nitric oxide is a free radical and quite reactive. It may freely diffuse in a liquid environment, may easily pass through cell membranes, and combines with other free radicals in a few seconds. It rapidly transforms into nitrite and nitrate in biological systems. Nitrite and nitrate are good parameters of endogenous NO production.<sup>[7]</sup> NO is synthesized from L-arginine by the nitric oxide synthase (NOS) enzyme, which has three different isoforms: endothelial NOS, neuronal NOS, and inducible NOS. Inducible NOS is produced in many cells, especially immune system cells, and it is induced by infection products, bacterial endotoxins, exotoxins, some inflammatory mediators, and some cytokines.<sup>[5]</sup> NO has been shown to play a role in immune response and inflammation in the body. Moreover, increased nasal NO (nNO) levels have been shown in viral upper respiratory tract infection (URTI)<sup>[8]</sup> and asthma.<sup>[9]</sup>

There are quite a few studies about exhaled NO (FeNO) in asthma but few studies about nasal NO in AR. At present, the effects of intranasal steroids and oral antihistaminic drugs on nNO are not well known. We conducted this study to investigate the nNO levels in patients with AR, the presence of a correlation between nNO levels and clinical parameters, and also the effects of fexofenadine oral antihistaminic and triamcinolone acetonide intranasal steroid on NOx.

## Materials and Methods

The study was approved by the Ethics Committee of Karadeniz Technical University Medical Faculty (approval number 2002/34). Volunteer consent forms and written permission were taken from participants.

### Design and participants

The study enrolled 60 adult patients with AR (according to the ARIA 2008 guideline criteria) and positive skin prick testing who were admitted to the otorhinolaryngology outpatient clinic of Karadeniz Technical University Medical Faculty with active complaints and 25 healthy adults as a control group. The patient and control groups were composed of individuals who were non-smokers, non-asthma-

tic, had no history of URTI for the last ten days, and received no medical treatment for AR for the last three weeks.

The patients were randomly assigned to corticosteroid or antihistamine treatment groups according to the referral order; a group of 30 patients received oral antihistamine treatment (fexofenadine 1×120 mg/day) for one month, while the other group of 30 patients received local steroid spray treatment (triamcinolone 1×2 puff/day) for one month. During the study, six patients from Group I (antihistaminic group) and ten patients from Group II (local corticosteroid group) were excluded from the study due to patients' non-compliance and the study was completed with a patient group including 44 individuals. In the patient group, the age distribution was 14–67 years (24 females, 20 males), and the mean age was 31±11.5 years, while the age distribution of the control group was 17–50 years (14 females, 11 males) and the mean age was 29.5±9.8 years.

### Outcome parameters

In all patients, pre- and post-treatment symptoms (nasal stuffiness, nasal discharge, nasal itching, sneezing, postnasal drainage, watery eyes, itching in the eyes) were recorded and physical examination findings (color of mucosa, edema in concha, nasal discharge, oropharyngeal inflammation) were evaluated and scored (0: absent, 1: mild, 2: moderate, 3: severe).<sup>[10,11]</sup> Routine laboratory examinations (complete blood count, the percentage of eosinophils in the blood), the percentage of eosinophils in nasal smear, total and specific IgE levels were assessed in all patients enrolled in the study. The SPT were performed according to the European guidelines using a test kit (Allergopharma, Merck, Reinberck, Germany) comprising fifteen aeroallergens: house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), pollens (grass mix, cereal mix, weed mix, mold mix, feather mix, acacia, ash, elder, linden, and sorrel), and animal dander (cat, dog, and rabbit epithelia).<sup>[12]</sup>

### Method of nasal lavage

Nasal lavage fluids were obtained from all patients and the control group by using 0.9% NaCl, prewarmed to 37°C and Naclerio's classic nasal lavage technique to examine nNOx levels.<sup>[13]</sup> Each patient remained in a sitting position, extended their neck gently backward to 30° from the horizontal, such that the nasal cavity was pointing upward, and instilled fluid would not be lost anteriorly because of gravity.<sup>[14]</sup> The posterior loss was limited by having subjects close their soft palate, hold their breath during the

**Table 1.** Pre- and post-treatment patient group and control group values for symptom scores, physical examination scores, and percentages of eosinophils in the nasal smear.

	Pre-treatment	Post-treatment	Control group
Symptom score	13.73±4.38	6.34±4.13*	2.36±1.60
Physical examination score	5.55±1.70	3.39±1.70 <sup>†</sup>	1.40±0.96
Eosinophil % in nasal smear	5.86±13.25 <sup>§</sup>	1.14±3.332 <sup>‡</sup>	0.20±0.58

\*,<sup>†</sup>Significantly lower than pretreatment scores (p=0.001, p=0.001); <sup>‡</sup>Significantly lower than pretreatment values (p=0.0002). <sup>§</sup>Significantly higher than control group values (p=0.001).

period of nasal lavage retention, and hold their mouth slightly open. The volume instilled within each nostril was 5.0 mL, and the fluid was left within the nasal cavity for 10 seconds.<sup>[14]</sup> The subject then leaned forward and expelled the fluid from the nostrils by gently exhaling into a container that had been washed with clean, distilled water. Fluid collected from both nasal cavities was transferred into a plastic tube resistant to -70°C and sent to a biochemistry research laboratory swiftly.

At the end of the one-month treatment period, all patients were interviewed for their complaints and examined, results were scored, routine laboratory examinations were repeated, and nasal lavage fluids were collected similarly. Nitrite and nitrate determination in nasal lavage fluid was performed by the photometric endpoint determination method using a Nitrite/Nitrate kit (Roche, Product No. 11746081001; Sigma-Aldrich Merck, Merck KGaA, Darmstadt, Germany).

### Statistical analysis

All data were presented as “mean ± standard deviation” at the end of the study. The Mann-Whitney U test was used in the comparison of nonparametric data of patient and control groups, the student’s t-test was used in the compar-

ison of parametric data, and the same tests were used in between-group comparisons of patients receiving antihistamine and corticosteroid treatment. Nonparametric pre- and post-treatment values of the patient group were compared by using the Wilcoxon matched test, and the paired t-test was used for comparison of parametric values. A value of p<0.05 was accepted as a significant difference in between-group comparisons.

### Results

In the AR patient group, post-treatment symptom and physical examination scores were found to be significantly lower when compared with pre-treatment scores (Table 1).

There was no significant difference between antihistaminic and corticosteroid groups regarding pre-treatment symptoms, physical examination scores, values of blood and nasal smear eosinophil percentages and total IgE levels (Table 2). No significant difference was detected between the two groups about these parameters after treatment.

The results showed that pre-treatment levels of NOx in the nasal lavage fluids (1.92±1.20 mg/l) of patients with AR were significantly higher when compared with nasal lavage

**Table 2.** Values of antihistaminic and steroid groups for pre- and post-treatment symptom and physical examination scores, eosinophil ratio in blood and nasal smear, and total IgE levels in blood.

	Antihistaminic group		Corticosteroid group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Symptom score	13.75±4.95	6.25±4.72	13.70±3.73	6.45±3.39
Physical examination scores	5.67±1.66	3.50±1.77	5.40±1.79	3.25±1.74
Eosinophil % in blood	3.00±1.59	3.53±4.79	3.17±2.35	3.00±1.96
Eosinophil % in nasal smear	9.96±15.84	1.17±3.87	4.55±9.50	1.10±2.62
Total IgE in blood	212.53±256.54	179.46±218.6	174.62±222.92	155.25±174.49

fluid NOx levels of healthy adults ( $1.38 \pm 0.78$  mg/l) ( $p=0.04$ ). The post-treatment nNOx levels ( $1.52 \pm 0.85$  mg/l) were significantly lower when compared with the pre-treatment values ( $p=0.028$ ).

Also, the pre-treatment nitrate levels in the nasal lavage fluids of the patients with AR were found to be higher when compared with nasal lavage fluid nitrate levels of the control group (Fig. 1).

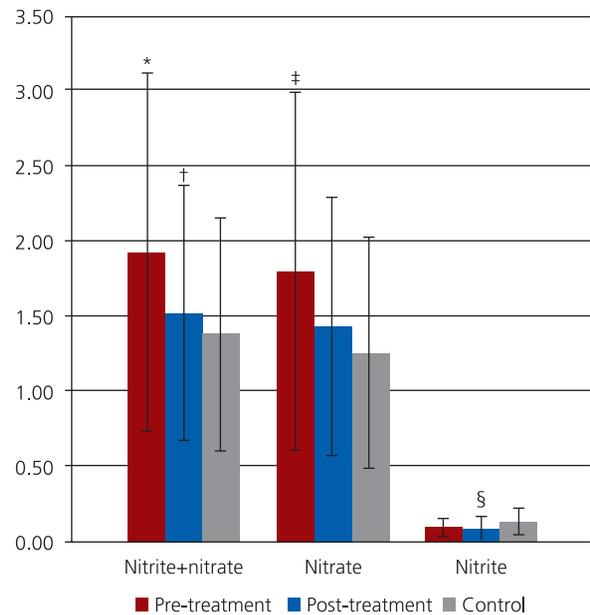
In the study, pre- and post-treatment values of two different patient groups receiving an intranasal corticosteroid and an oral antihistamine were compared (Table 3). Although there was no statistically significant difference between the steroid and the antihistamine groups regarding NOx level ( $p=0.053$ ) before the treatment, a significant difference was observed between two groups in the post-treatment period ( $p=0.016$ ).

This study revealed that both the clinical parameters and NO metabolite levels decreased after the treatment, but there was no direct correlation between these values and the NO metabolite levels ( $r=0.013$ ,  $p=0.9$ ).

### Discussion

This study showed the increase in nasal NOx, marker of endogenous nasal NO production in patients with AR. Nasal NO levels may be measured by direct or indirect methods. The chemiluminescence technique is a direct method measuring the NO level in the exhaled air. It requires a special gas analyzer and equipment. The indirect method measures NO metabolites in nasal lavage. In this study, the indirect method was used to measure nasal NO levels; nitrite and nitrate metabolites were measured in nasal lavage fluid.

Patients with active symptoms and a positive SPT test who had no medical treatment for AR during the last three weeks were enrolled to our study, whereas patients who



**Fig. 1.** \*Significantly different from controls ( $p=0.04$ ); †Significantly different from pre-treatment ( $p=0.028$ ); ‡Significantly different from control group ( $p=0.02$ ); §Significantly different from pre-treatment ( $p=0.033$ ).

were smokers, asthmatic, or had acute or chronic rhinosinusitis and a history of URTI during the last ten days were excluded. Previous studies have shown that smoking decreased nasal NO levels.<sup>[14,15]</sup> Low levels of NO were also detected in patients with severe nasal obstruction and inflammation.<sup>[16-18]</sup>

The association of asthma with AR is well known, and it is also well known that AR is a risk factor for asthma.<sup>[19]</sup> About 30% of patients with perennial AR have asthmatic symptoms. Rhinitis is present in 75% of patients with allergic asthma. In some of the studies showing high nasal NO levels in asthma, asymptomatic patients without active AR signs were not excluded and were enrolled in the studies.

**Table 3.** Pre- and post-treatment nitrite, nitrate, and nitrite+nitrate values of antihistaminic and steroid groups.

	Antihistaminic group		Corticosteroid group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Nitrite	0.07±0.037	0.06±0.04	0.12±0.07	0.11±0.10
Nitrate	1.73±1.30	1.14±0.70*	1.89±1.07	1.76±0.90*
Nitrite + nitrate	1.81±1.30	1.24±0.70†	2.04±1.082	1.85±0.91†

\*Significant difference between post-treatment values of both groups ( $p=0.012$ ); †Significant difference between post-treatment values of both groups ( $p=0.016$ ).

Ciprandi et al. assessed FeNO in the exhaled air of three groups of patients with AR, asthma, and AR together with asthma. The FeNO level was found to be higher in the AR group compared to the control group. The FeNO levels of asthmatic patients were higher than those of patients with AR, whereas the highest level was detected in the patient group with asthma together with AR.<sup>[20]</sup> In our study, none of the AR patients enrolled had concomitant allergic asthma. Patients with a history or diagnosis of asthma were excluded from the study.

Suojalehto et al. revealed that nNO was elevated in AR when compared to the controls, and an inverse correlation existed between the nNO level and sinus ostial obstruction. In nonallergic rhinitis, the level of nNO was similar to that of the controls. They also revealed that a high nNO level might be a useful marker of eosinophilic inflammation in the nasal cavity and indicate the absence of marked sinus ostial obstruction.<sup>[21]</sup> In the study by Gupta et al., both nNO in nasal aspiration fluid and FeNO levels were assessed by a chemiluminescence analyzer. The nNO levels of patients with asthma were not higher than the control group's levels, whereas nNO levels of the patients with AR were higher when compared with the patients with asthma and the control group. Similarly, the highest nNO level was detected in the patients with both asthma and AR.<sup>[22]</sup> These two studies revealed that the nNO level might be used to detect the inflammatory process in AR patients and FeNO levels in asthmatic patients.

Exhaled NO is used as a surrogate of eosinophilic airway inflammation in asthma. Most of the NO production in the airways originates from the nasal region. The main production of nNO is located within the mucosal epithelium of the paranasal sinuses. The level of nNO is influenced by the presence of marked sinus ostial obstruction by several airway diseases as rhinosinusitis and nasal polyps.<sup>[23]</sup>

In our study, a statistically significant difference was detected between pre- and post-treatment in terms of total nitrite+nitrate levels in nasal lavage. Following the treatment, nitrite+nitrate levels reached the level of the control group, and the pre-treatment difference disappeared.

Although a marked decrease in nitrate levels was detected after treatment, the difference was not found to be statistically significant ( $p=0.06$ ). However, it is interesting to note that the  $p$ -value was very close to the limit for statistical significance.

In the light of these results, NO metabolites may be assessed separately as nitrite and nitrate. Nitrate, as a NO

metabolite, may be accepted as a better indicator of AR, which is an inflammatory process. The nitrite level was detected to be very low as compared with the nitrate level. This may be due to the reaction between nitrite and hemoglobin, a very effective inactivator found in the blood that causes the transformation of nitrite to nitrate.

In our study, we also compared post-treatment nitrate and nitrite+nitrate levels of the oral antihistaminic group and the local corticosteroid group. Although there was no significant difference between the two groups regarding the levels (nitrate and NOx) in the pre-treatment period, the post-treatment nitrate and NOx of the antihistaminic group were found to be significantly lower when compared with the local corticosteroid group. These results brought up the question of whether oral antihistaminics might be more effective than local corticosteroid in suppressing nasal NO production or not. This situation might also be due to the use of a local form of corticosteroid. However, no statistically significant difference was observed between two groups regarding post-treatment symptoms and physical examination findings.

H1-antihistamines are widely used in the treatment of AR, and second-generation H1-antihistamines prevent and relieve the sneezing, itching, rhinorrhea, and nasal congestion that characterize the early and late responses to allergen.<sup>[24]</sup> In a study comparing nasal H1-antihistamine and nasal glucocorticoid in patients with allergic and non-allergic rhinitis, azelastine was as effective as triamcinolone in improving nasal symptoms, sleep symptoms and quality of life.<sup>[25]</sup>

In a randomized, double-blind and place-controlled study by Bautista et al., it was shown that nNO levels significantly decreased following oral levocetirizine use.<sup>[26]</sup> Our results are also supported by the study of Asano et al. which showed a significant decrease in nNO levels due to fexofenadine. It was also shown that fexofenadine suppressed NO production in nasal fibroblasts in vitro and in lung tissue of rats in vivo.<sup>[27]</sup>

Takeno et al. showed that increased nasal NO levels in AR patients were caused by increased levels of the iNOS isoenzyme form.<sup>[28]</sup> Kawamoto et al. compared iNOS levels of various nasal tissues of patients with AR and the control group. In the group with AR, significant staining was shown in subepithelial tissue, deposited inflammatory cells, endothelial cells, and glandular tissue for iNOS. In the control group, staining was less prominent in epithelial surface and submucosal glandular tissue

Studies have shown that the measurement of FeNO levels have come into use in the diagnosis and follow-up of asthmatic patients, but it requires additional studies for its standardization.<sup>[29-31]</sup>

## Conclusion

The levels of nasal NO metabolites significantly increase in AR patients, it might be possible to use nNO and its metabolites as biomarkers in the diagnosis and follow-up of patients with AR, but further studies are required on this issue.

**Conflict of Interest:** No conflicts declared.

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