

Serum levels of stress hormones in Albanian patients with allergic rhinitis

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Background: The integration of the immune and endocrine systems through a network of signaling molecules—including cytokines and hormones—produces a consequent modulatory effect on immune function. In this study we aimed to comparatively evaluate the serum concentrations of dehydroepiandrosterone sulfate (DHEA-S) and cortisol in patients with allergic rhinitis and healthy control subjects.

Methods: Morning fasting blood samples were obtained from 96 participants, including 66 patients with allergic rhinitis (mean age, 28 ± 10.7 years; range, 11–59 years) and 30 healthy control subjects (mean age, 32.4 ± 11.1 years; range, 14–57 years). Total immunoglobulin E (IgE), DHEA-S, and cortisol concentrations were measured by radioimmunoassay.

Results: Female patients with allergic rhinitis exhibited lower DHEA-S levels than male patients and control subjects ($p < 0.001$). Although no intergroup differences were observed in the morning:evening cortisol ratio, the DHEA-S:cortisol ratio was the highest among female patients with allergic rhinitis (1:11). Total IgE levels were significantly higher among patients of both sexes ($p < 0.05$) than among

the control subjects. There was a positive correlation between body mass index and age among all groups of participants (male and female patients: $r = 0.6$ and 0.7 , respectively; male and female controls: $r = 0.6$ and 0.4 , respectively) and a negative correlation between DHEA-S level and age among females (patients and controls: $r = -0.4$ and -0.5 , respectively) and healthy male subjects ($r = -0.7$).

Conclusion: In this study, female patients with allergic rhinitis exhibited significantly lower DHEA-S levels than their healthy counterparts and male patients. These results should be confirmed in a larger group of participants.
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Key Words:

allergies; rhinitis; total immunoglobulin E; cortisol; dehydroepiandrosterone sulfate; sex; body mass index; age; radioimmunoassay

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Dehydroepiandrosterone (DHEA), a hormone produced by the adrenal glands, is used by the body for producing male and female sex hormones, namely androgens, and estrogens. The concentration of DHEA peaks at the age of about 25 years and declines steadily with age.¹

Elevated levels of DHEA and its sulfated analog DHEA sulfate (DHEA-S) are associated with prolonged physical

stress, female hirsutism, and type II diabetes; in contrast, decreased levels of these hormones are associated with a variety of medical conditions, including immune system disorders.^{1–4} As a consequence of the interaction between the immune and endocrine systems through a network of signaling molecules—including cytokines and hormones—sex steroids can influence the function and development of the immune system.^{5,6} This leads to a dual immune response, with women exhibiting higher immunoglobulin (Ig) levels and an increased humoral immune response to a variety of antigens compared with men.^{7,8} Accordingly, data from several studies on animal and human models have demonstrated a modulator effect of DHEA-S on immune function,^{9–13} revealing that DHEA-S levels are associated with the production of type I cytokines (interferon- γ and interleukin-2)^{14,15}; these cytokines could also modulate the development of allergic reactions because they can affect the balance between type 1 and 2 helper T (Th1/Th2) cells, IgE synthesis, and eosinophil proliferation.^{9,16,17} In

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addition, it is well known that DHEA-S and cortisol act as shock absorbers and that DHEA-S helps neutralize the immunosuppressant effect of cortisol, thereby improving resistance to diseases. Consequently, there have been several hypotheses explaining the relatively low circulating DHEA-S levels in patients, some suggesting that, during chronic inflammatory response or severe stress conditions, a hormonal shift may occur in adrenal steroid production in the direction of increased synthesis of cortisol relative to DHEA-S, which is probably necessary for achieving adequate cortisol levels at the expense of adrenal androgens.^{18–20}

The behavior of DHEA-S and cortisol in the serum of allergy patients is under investigation. Therefore, in the present study, we comparatively evaluated the serum concentrations of DHEA-S and cortisol in patients with allergic rhinitis and healthy control subjects.

Patients and methods

Study participants

This study included 66 patients diagnosed with allergic rhinitis by a doctor and 30 volunteers without rhinitis. The patients included in this study were consecutive patients who presented to the allergy outpatient service of University Clinical Center (UCC) of Prishtina. They were recruited on a voluntary basis after evaluation for allergy symptoms and diagnosis of allergic rhinitis. Written informed consent was obtained from all participants included in this study. Patients with other allergic disorders, including asthma/eczema with rhinitis, were excluded, as were patients with rhinitis or healthy subjects who were taking or had taken (within the previous 3 months) systemic/local steroids or any other medication that could possibly interfere with hormone metabolism. Each subject was given a study questionnaire on demographic data (including age and sex), family history of atopy, respiratory symptoms, and smoking habits. The subjects were measured for height and weight using a stadiometer and an electronic scale, respectively. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2) and classified as low ($<18.5 \text{ kg}/\text{m}^2$), normal ($18.5\text{--}24.9 \text{ kg}/\text{m}^2$), overweight ($25\text{--}29.9 \text{ kg}/\text{m}^2$), or obese ($\geq 30 \text{ kg}/\text{m}^2$), in accordance with the guidelines of the World Health Organization, United States Preventive Services Task Force, and International Obesity Task Force.

The control subjects were healthy volunteers who were selected if their answers indicated that they did not have or never had symptoms of respiratory allergies (coughing, sneezing, itching, and nasal discharge). The mean ages ($\pm$ standard deviation [SD]) of the patients and control subjects included in this study were 28.5 ± 10.7 years (range, 11–59 years) and 32.4 ± 11.1 years (range, 14–57 years), respectively, and the male:female ratio was 40:56. The protocol for this research project was approved by the ethics committee of the Faculty of Medicine, University of Prishtina.

Investigations

Blood sampling

Venous blood (2 mL) was collected between 8:00 and 9:00 AM for measurement of total IgE, DHEA-S, and morning serum cortisol levels, and between 6:00 and 8:00 PM on the same day for measurement of evening cortisol levels. Blood from female subjects was collected on the third day of their menstrual cycle. The blood samples were allowed to clot at room temperature, after which serum was separated by centrifugation at 1200g for 10 minutes and stored at -80°C . The serum samples were thawed at room temperature before measurement. Cortisol and DHEA-S levels were measured by radioimmunoassay at the endocrinology laboratory of the Institute of Physiology, UCC of Prishtina, using products from Immunotech Beckman Coulter (France). According to the manufacturer's suggestion, the expected normal ranges for morning and evening cortisol levels were 260–720 and 50–350 nmol/L, respectively. The expected normal ranges for DHEA-S level were 0.81–9.0 women and 3.6–11.9 $\mu\text{mol}/\text{L}$ for men. The normal range for total IgE level was 1.0–183.0 IU/mL.

Skin-prick test

All participants were subjected to a skin-prick test for aeroallergens using Test Kit G (Allergopharma, Reinbeck, Germany), with histamine (1 mg/mL) and saline as the positive and negative controls, respectively. The evaluated allergenic extracts included 4 groups of allergens: pollen from sources such as grasses (grasses/cereals, grasses, and rye), trees (alder, hazel, birch, and beech), and weeds (mugwort and English plantain); dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*); animal epithelia (cat, dog, golden hamster, and guinea pig); and molds (*Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium notatum*, and *Alternaria tenuis*). Each allergenic extract was placed on the volar surface of the forearm and introduced into the epidermis at a 1-mm depth using a separate sterile lancet each time. The diameters of the allergen-induced skin wheals were recorded 15 minutes later, and the skin-prick test was considered positive for an allergen if the corresponding diameter was $>3 \text{ mm}$. All patients in this study were allergic to at least 1 allergenic extract, and some of the subjects from the control group also exhibited positive reaction.

Statistical analysis

All statistical analyses were performed using InStat 3 software. The data are presented as median and range or mean and SD. Differences between the patient and control groups were analyzed by the Dunn multiple comparison test, Mann-Whitney *U* test, Kruskal–Wallis variance analysis, 1-way analysis of variance, or *t* test. $p < 0.05$ was considered significant. The relationship between variables was examined by Pearson correlation analysis.

TABLE 1. Participant characteristics subdivided according to the history of allergic rhinitis

Parameters	Control group (n = 30)	Rhinitis group (n = 66)	p value
Age (years), mean $\pm$ SD			
Total	32.4 $\pm$ 11.1	28.5 $\pm$ 10.7	0.10
F	32.1 $\pm$ 10.8	30.9 $\pm$ 10.4	0.67
M	33.5 $\pm$ 13.2	26.1 $\pm$ 10.6	0.25
BMI (kg/m ²), median (range)			
F	24.0 (16.7-36.2)	23.0 (15.8-32.8)	0.54
M	25 (23.4-29.4)	23.4 (10.0-31.5)	0.028 ^a
Total IgE level (IU/mL), median (range)			
F	22.2 (2.3-174.5)	68.6 (4.9-354)	0.012 ^a
M	16.9 (1.5-93.2)	83.9 (4.4-350)	0.029 ^a
DHEA-S (μ mol/L), median (range)			
F	6.6 (3.0-16.0)	5.3 (0.65-13.5)	0.002 ^b
M	6.4 (4.2-9.6)	6.2 (1.2-17.0)	0.437
Morning cortisol level (nmol/L), median (range)			
F	478.55 (62.3-1062.0)	488.5 (36.5-1400.0)	0.174
M	464.5 (245.0-820.0)	520 (205.0-1150.0)	0.281
Evening cortisol level (nmol/L), median (range)			
F	199 (25.0-464.0)	213 (24.0-1400.0)	0.904
M	139 (78.0-357.7)	191 (71.0-970.0)	0.475

^aStatistically significant at $p < 0.05$.

^bStatistically significant at $p < 0.001$.

BMI = body mass index (normal, 18.5-24.9 kg/m²; overweight, 25-29.9 kg/m²; obese, >30 kg/m²); DHEA-S = dehydroepiandrosterone sulfate; F = female; IgE = immunoglobulin E; M = male; SD = standard deviation.

Results

A total of 96 subjects participated in this study. Of these, 66 were patients who presented to the outpatient allergy service at UCC Prishtina with symptoms of allergy (such as coughing, sneezing, itching, and nasal discharge), whereas 30 were healthy volunteers (chiefly medical staff) who reported no history of the aforementioned allergy symptoms or diseases. The mean age of the patient group (32.4 $\pm$ 11.1 years) was slightly higher than that of the control group (28.5 $\pm$ 10.7 years), because the male patients with allergic rhinitis were younger than their healthy counterparts (Table 1). All patients with allergic rhinitis reacted positively to at least 1 aeroallergen; however, 74.2% of the patients reacted positively to house dust mites, 48.5% to grasses, 28.8% to weeds, 24.2% to trees, 9.1% to animal epithelia, and only 1.5% to molds. Among the healthy participants, 30% reacted positively to the skin-prick test, whereas 55.6% of these participants reacted positively to grasses, 44.4% reacted almost equally to all other allergens except animal epithelia, to which none of the healthy participants reacted positively. There was no significant difference in median BMI between the patient and control

groups or even between the sexes; however, the median BMI showed the men in the control group to be overweight (Table 1). Nevertheless, the BMI values of 34.4% and 41.1% of women and men with allergic rhinitis and 37.5% and 66.7% of healthy women and men, respectively, were over their corresponding normal ranges for BMI (Table 2).

With regard to hormone concentrations, women with allergic rhinitis exhibited lower serum DHEA-S levels than those in the control group ($p = 0.0023$). Also, when the control group was divided into 2 subgroups comprising participants with positive or negative reaction to aeroallergens, there was a significant difference in serum DHEA-S level between women with rhinitis and those in atopic group ($p = 0.0021$). There were no significant differences in cortisol levels among the study groups (Table 1). In addition, there was no significant difference in morning:evening cortisol ratio among the study groups; however, the morning DHEA-S: cortisol ratio was the highest among women with allergic rhinitis (Table 3). Patients of both sexes exhibited higher levels of total IgE than the control subjects (Table 1). Moreover, there was a positive correlation between BMI and age among all groups of

TABLE 2. Comparison of BMI between patients with allergic rhinitis and control subjects according to sex*

	Rhinitis group (n = 66)	Control group (n = 30)
Females		
N	32	24
Median (range), kg/m ²	23.0 (15.8-32.8)	24.0 (16.7-36.2)
Normal ^a	21 (65.6)	15 (62.5)
Overweight ^a	9 (28.1)	8 (33.3)
Obese ^a	2 (6.3)	1 (4.2)
Males		
N	34	6
Median (range), kg/m ²	23.4 (10.0-31.5)	25 (23.4-29.4)
Normal ^a	20 (58.8)	2 (33.3)
Overweight ^a	13 (38.2)	4 (66.7)
Obese ^a	1 (2.9)	—

*Data expressed as number of subjects (%).

BMI = body mass index (normal, 18.5-24.9 kg/m²; overweight, 25-29.9 kg/m²; obese, >30 kg/m²).

participants, albeit with varying strengths of relationship (Fig. 1). In addition, there was a negative correlation between DHEA-S level and age among females (patients, $r = -0.4$; controls, $r = -0.5$) and healthy male subjects ($r = -0.7$); however, no such correlation was observed among male patients (Fig. 2). Finally, there was no correlation between BMI and DHEA-S level among female subjects of the patient and control groups or between total IgE and DHEA-S level among any of the study groups.

TABLE 3. Comparison of cortisol:DHEA-S ratios between patients with allergic rhinitis and control subjects

	Rhinitis group		Control group	
	F	M	F	M
Morning cortisol level (nmol/L), mean	524	586	462	475
Evening cortisol level (nmol/L), mean	259	286	204	160
Morning:evening cortisol ratio	2:1	2:1	2:1	3:1
DHEA-S level (nmol/L), mean	5700	8894	7300	6500
Morning cortisol:DHEA-S ratio	1:11 (0.09)	1:15 (0.06)	1:16 (0.06)	1:14 (0.07)

DHEA-S = dehydroepiandrosterone sulfate; F = female; M = male.

Discussion

Apart from their roles as precursors for synthesis of sex hormones, DHEA and its sulfated analog DHEA-S are involved in modulation of immune responses such as allergic inflammation and autoimmune reactions,²⁰ representing pivotal upregulators of Th1 immune response due to interleukin-2 production and IgE synthesis.^{16,21} However, there are conflicting data about DHEA-S levels in allergy patients, with some studies reporting no statistically significant differences between patients with allergic rhinitis and healthy nonatopic subjects²² and others reporting lower serum DHEA-S concentrations among men than among women or vice versa.^{16,23} The present findings point to significantly lower levels of DHEA-S among women with allergic rhinitis than among their healthy counterparts and men with the same disease. However, these differences could not be linked to older age, considering that DHEA-S concentrations are at their highest during the third decade of life and the fact that the mean ages of women in the patient and control groups in this study were comparable (32.1 ± 10.8 years and 30.9 ± 10.4 years, respectively).²⁵ Also, it should be noted there was a much higher level of DHEA-S seen in atopic asymptomatic women (median, 8.0 μ mol/L; range, 4.3–16.0 μ mol/L) who reported no previous symptoms of allergic disease. In this regard, we can speculate that this group of atopic women lack the allergic symptoms precisely because of the protective role of the DHEA-S hormone. Therefore, our results are consistent with those of other studies reporting that decreased DHEA-S production is associated with Th2-cytokine production, mast-cell degranulation, and thrombin-activated platelet aggregation,²⁴ all of which can be downregulated through several therapeutic methods that employ DHEA-S to treat asthma and allergic rhinitis.^{26–36}

In our study, the nonsignificant differences observed in DHEA-S concentration between men in the patient and control groups may have been due the small number of men in the latter group. Although several studies have shown a correlation between allergy and stress markers, the results have often been contradictory or ambiguous. Considering that DHEA-S and cortisol levels are inversely proportional to each other and that DHEA-S helps neutralize the immunosuppressant effect of cortisol, the ratio between the two should be taken into consideration when reporting their biological impact on the body.³⁷ Our results reveal that morning and evening cortisol levels were higher among patients of both sexes than among the control subjects, although these differences were not statistically significant. These results could be explained by the fact that high cortisol levels are linked to chronic stress, but the morning:evening cortisol ratios remained similar in all participant groups.

Hence, we speculate that low DHEA-S levels in female patients may be responsible for a deficiency in the protective function of androgens, which suggests that DHEA-S may predispose a person to developing allergic rhinitis rather

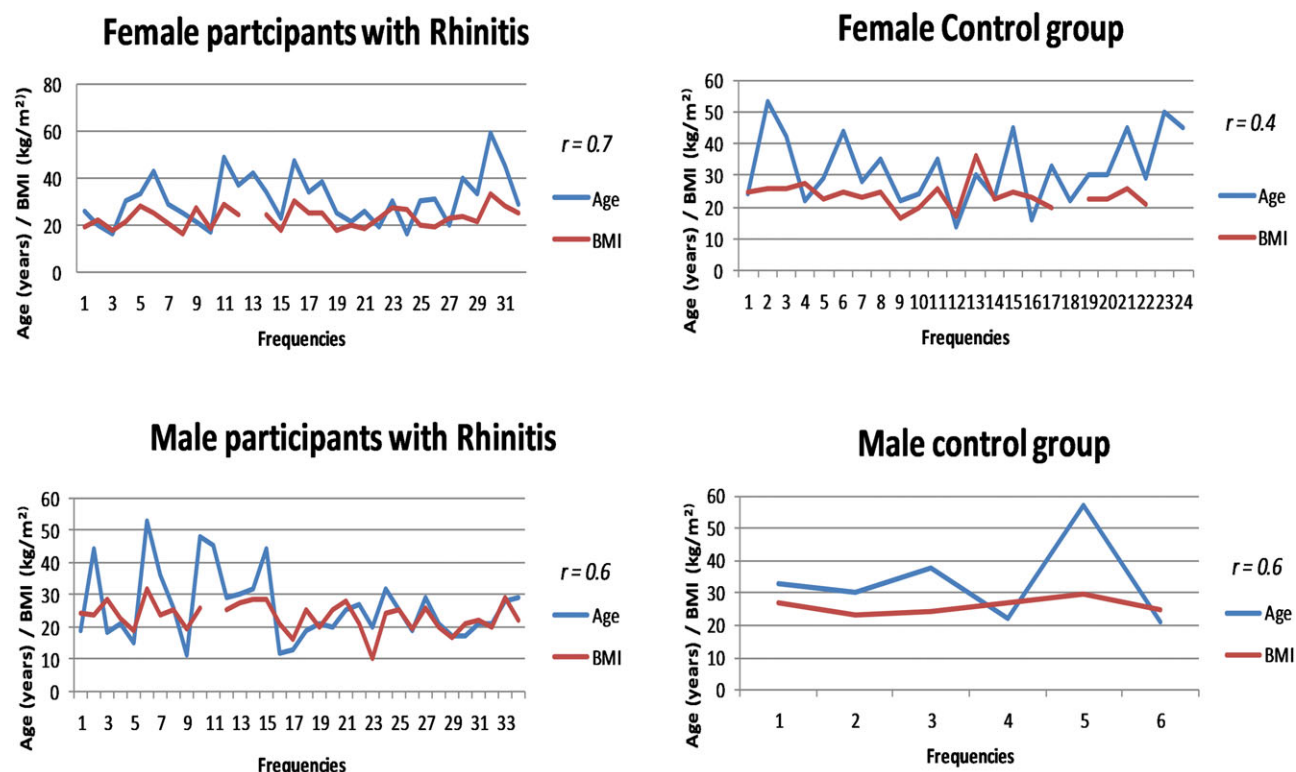


FIGURE 1. Strong positive correlation between age and BMI in patients with allergic rhinitis and control subjects. BMI = body mass index.

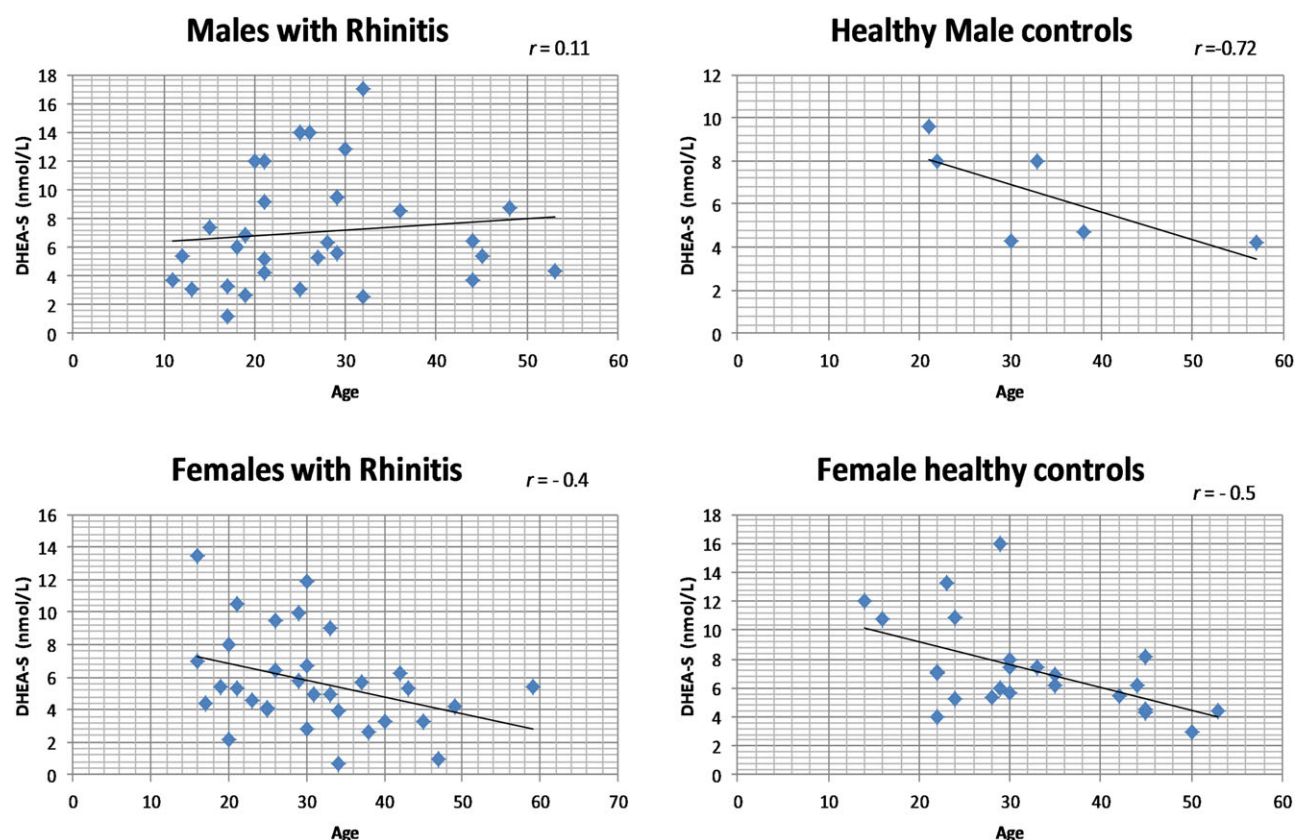


FIGURE 2. Moderate to strong negative correlation between age and DHEA-S in patients with allergic rhinitis and control subjects. DHEA-S = dehydroepiandrosterone sulfate.

than directly influence the severity of the inflammatory reaction in subjects predisposed to allergic rhinitis. However, the nonvariability of DHEA-S levels between male patients and control subjects in this study reminded us that the most important anti-inflammatory androgen in males is testosterone and not DHEA-S.

Conclusion

We have demonstrated that women with allergic rhinitis have significantly lower DHEA-S levels and higher cortisol:DHEA-S ratios than their healthy counterparts and male patients with the same disease. Therefore, DHEA-S replacement therapy could be ideal for treatment of

allergic rhinitis in women but not in men, unless otherwise suggested, probably done by another research group, with a larger men's control group. Although prospective analyses are needed to help untangle the direction of causality, the present results suggest that cortisol:DHEA-S ratio is worthy of further study in the context of allergic rhinitis. 

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