



ORIGINAL ARTICLE

Prolactin and Dehydroepiandrosterone Sulfate: Are They Related to the Severity of Chronic Urticaria?

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Background and Aims. Elevated prolactin and reduced dehydroepiandrosterone sulfate (DHEA-S) levels are associated with autoimmune diseases. A limited number of studies have investigated these hormones in chronic urticaria (CU). The autologous serum skin test (ASST) reaction has also been linked to autoimmune diseases, and a positive reaction is usually associated with a more severe disease. We aimed to compare serum prolactin and DHEA-S levels between female CU patients with positive and negative ASST reactions and healthy controls.

Methods. The study included 30 female CU patients with a positive ASST reaction, 30 female CU patients with a negative ASST reaction, and 30 healthy female controls. All identifiable causes of urticaria were excluded. Serum prolactin and DHEA-S levels were measured in all subjects.

Results. Prolactin was significantly higher among ASST positive patients than among ASST negative patients and controls but did not differ between ASST negative patients or controls. Higher prolactin levels were associated with increasing disease severity among ASST positive patients. DHEA-S levels did not differ between ASST positive or negative patients but were significantly lower among both patient subgroups than controls. DHEA-S levels did not differ according to the severity of disease among either of the patient subgroups. DHEA-S levels did not correlate with prolactin among any group.

Conclusion. We demonstrate for the first time a possible role for prolactin in ASST-positive CU patients and its association with disease severity. We recommend larger prospective studies to assess changes in prolactin and DHEA-S levels after complete disease remission. © 2012 IMSS. Published by Elsevier Inc.

Key Words: Autoimmune disease, Autologous serum skin test, Chronic urticaria, Dehydroepiandrosterone sulfate, Prolactin.

Introduction

Chronic urticaria (CU) is defined as the occurrence of daily, or almost daily, wheals and itching with or without angioedema for at least 6 weeks (1). It is characterized by the activation of autoimmune and inflammatory

processes (2). Up to 45% of patients with CU exhibit auto-reactivity characterized by an immediate wheal and flare response to an intradermal injection of autologous serum (autologous serum skin test, ASST) (3). A positive ASST reaction has been associated with various autoimmune diseases including rheumatoid arthritis (RA) (4), autoimmune thyroiditis, celiac disease (5), type 1 diabetes, and Graves' disease (6) and with markers of autoimmunity such as antinuclear antibodies, rheumatoid factor, and anti-thyroid antibodies (7).

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Prolactin is a peptide hormone secreted by lactotroph cells in the anterior pituitary gland. In addition to its well-known lactogenic and mammatrophic functions, prolactin is a common mediator of the neuroendocrine-immune network (8). Its immunostimulatory effects may be mediated by inhibition of apoptosis and increased antibody production (9). Elevated prolactin levels have been associated with various autoimmune diseases and have been observed in patients with systemic lupus erythematosus (SLE), RA, multiple sclerosis and Sjögren's syndrome (10).

Dehydroepiandrosterone (DHEA) and its sulfated metabolite (DHEA-S) are the major androgens secreted by the adrenal glands and are precursors for synthesis of androgens and estrogens (11). Circulating DHEA and DHEA-S possess anti-inflammatory, anti-proliferative and immunomodulatory properties and have been shown to decrease in various chronic inflammatory and immune-mediated diseases. Their deficiency has been observed among patients with SLE, RA, autoimmune thyroiditis and other immune inflammatory disorders (12–14).

Only very limited information is available on the status of these hormones in patients with CU. In the present study we aimed to evaluate serum concentrations of prolactin and DHEA-S among 30 female patients with CU and a positive ASST reaction as compared to 30 female patients with CU and a negative ASST reaction and 30 healthy female controls.

Materials and Methods

The current case-control study was conducted from April 2011–December 2011 and included 30 female patients with CU and a positive ASST reaction (mean age 30.1 ± 6.7 years) and 30 female patients with CU and a negative ASST reaction (mean age 28.7 ± 7.4 years). All patients were recruited from the Allergy and Clinical Immunology outpatient clinic at Ain Shams University Hospital and were symptomatic at the time of their enrollment. CU was diagnosed based on the appearance of continuous or recurrent hives with or without angioedema for more than 6 weeks (15). In all patients, identifiable causes of urticaria were previously excluded by history, clinical examination and appropriate investigations. These investigations included a complete and differential blood cell count, erythrocyte sedimentation rate, C-reactive protein, tests for infectious diseases and hepatitis virus markers, skin prick test for allergy, antinuclear antibodies, C3, C4, thyroid hormones (free T3, free T4, thyroid-stimulating hormone) and thyroid antibodies, including anti-thyroglobulin and anti-thyroid peroxidase antibodies (16). Further exclusion criteria were physical urticaria, subjects who had been on systemic steroid therapy within 6 months prior to recruitment, subjects who had been receiving antihistamines or any other therapies for urticaria within 10 days before recruitment, pregnant or lactating

females, and females with any past history of contraception. Disease duration was comparable between both groups [median (interquartile range): 6 (3,9) years among ASST-positive patients and 6 (3,7) years among ASST-negative patients, $p = 0.736$]. In addition, the study also included 30 apparently healthy female controls who were not pregnant or lactating and who had negative ASST reactions (mean age 29.1 ± 7.5 years). None of the controls had received any medications for at least 4 weeks before recruitment. A written informed consent was obtained from all study participants prior to conducting the study, and the study was approved by the Research Ethics Committee of Ain Shams University.

Grading of Disease Severity

This was assessed according to the number of wheals present at the time when blood samples were collected, as follows: 1–10 small (<3 cm in diameter) wheals = grade 1 (slight); 10–50 small wheals or 1–10 large wheals = grade 2 (moderate); > 50 small wheals or > 10 large wheals = grade 3 (severe); virtually covered with wheals = grade 4 (very severe) (17).

Autologous Serum Skin Test Procedure

ASST was performed for all patients with chronic urticaria and for all healthy controls according to the method by Sabroe et al. A positive test was defined as a serum-induced wheal response with a diameter of 1.5 mm or more than that of the saline-induced response (18).

Hormonal Assays

Morning fasting blood samples were obtained from all patients and controls for measurement of serum prolactin and DHEA-S levels. Prolactin concentrations in serum were measured by a microplate immunoassay (Monobind Inc., Lake Forest, CA) according to the manufacturer's instructions. According to this kit, normal prolactin levels in serum among healthy adult females were 1.2–19.5 ng/mL. DHEA-S levels in serum were measured by enzyme immunoassay (DIAsource ImmunoAssays SA, Nivelles, Belgium) according to the manufacturer's instructions. According to this kit, normal DHEA-S levels in serum among healthy adult females <50 years of age were 0.40–2.17 µg/mL.

Statistical Analysis

Data analysis was performed using the SPSS program, v.12. Data were expressed as mean $\pm$ standard deviation (SD) for parametric data and as median and interquartile range (IQR) for nonparametric data, respectively. Parametric data were analyzed using one-way analysis of variance (ANOVA) for the comparison of three groups. Nonparametric data were analyzed using the Mann-Whitney U and

Kruskal-Wallis tests to compare two and three groups, respectively. Chi-square test was used to compare categorical data. To assess the strength of the relationship between prolactin and DHEA-S levels and other quantitative variables, Spearman's correlation coefficient was performed; p value <0.05 was considered significant.

Results

The present study was conducted on 30 female patients with CU and a positive ASST reaction, 30 female patients with CU and a negative ASST reaction and 30 apparently healthy females as a control group. All three groups were of comparable age with no significant differences between them ($p = 0.761$). As shown in Table 1, ASST-positive patients showed a significantly greater degree of disease severity than ASST-negative patients.

Prolactin

Comparison of prolactin levels across the three study groups revealed a highly significant difference ($p = 0.001$). Prolactin was significantly higher among ASST-positive patients as compared to ASST-negative patients and controls. However, there was no significant difference in prolactin levels between ASST-negative patients and controls (Figure 1). We compared prolactin levels according to disease severity among ASST-positive and ASST-negative patients separately. Among ASST-positive patients only, there was a highly significant difference in prolactin levels across the three grades of severity ($p = 0.007$). Prolactin levels in this group were significantly higher among those with a severity score of 3 as compared to those with severity scores of 1 and 2 (Figure 2). On the other hand, prolactin levels did not differ significantly according to disease severity among patients with CU and a negative ASST reaction (Figure 3).

Dehydroepiandrosterone Sulfate (DHEA-S)

Comparison of levels of DHEA-S across the three study groups revealed a highly significant difference ($p < 0.001$). DHEA-S was significantly higher among controls than among CU patients with a positive or negative ASST reaction. However, DHEA-S levels did not differ

Table 1. Comparison of disease severity between ASST positive and ASST negative patients with CU

Severity, n (%)	ASST +ve	ASST -ve	p
1	2 (6.7)	12 (40)	0.003*
2	14 (46.7)	13 (43.3)	
3	14 (46.7)	5 (16.7)	

ASST, autologous serum skin test.

*Significant.

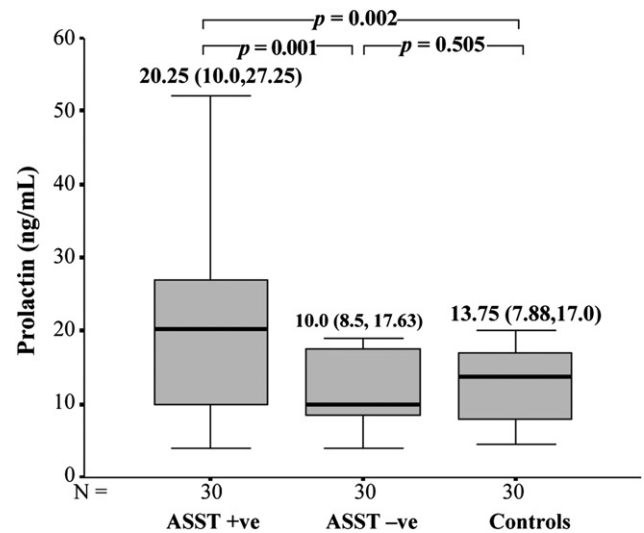


Figure 1. Comparison of prolactin levels among the three study groups. All values are presented as median (interquartile range). ASST, autologous serum skin test.

significantly between ASST positive and ASST negative patients (Figure 4). DHEA-S levels did not differ significantly according to the severity of disease among either of the two patient groups (Table 2).

Correlation between Prolactin and DHEA-S Levels

Prolactin levels did not correlate significantly with DHEA-S levels among any of the three study groups ($r = -0.049$, $p = 0.798$; $r = 0.174$, $p = 0.358$; $r = -0.299$, $p = 0.108$ for ASST-positive patients, ASST-negative patients, and controls, respectively).

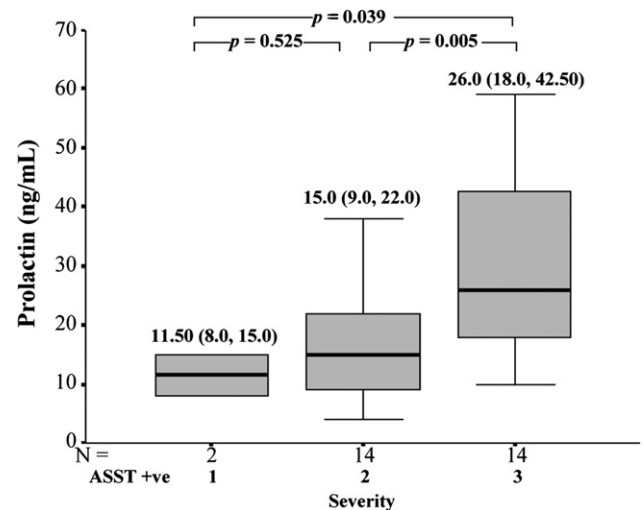


Figure 2. Comparison of prolactin levels according to disease severity among chronic urticaria (CU) patients with a positive ASST. All values are presented as median (interquartile range). ASST, autologous serum skin test.

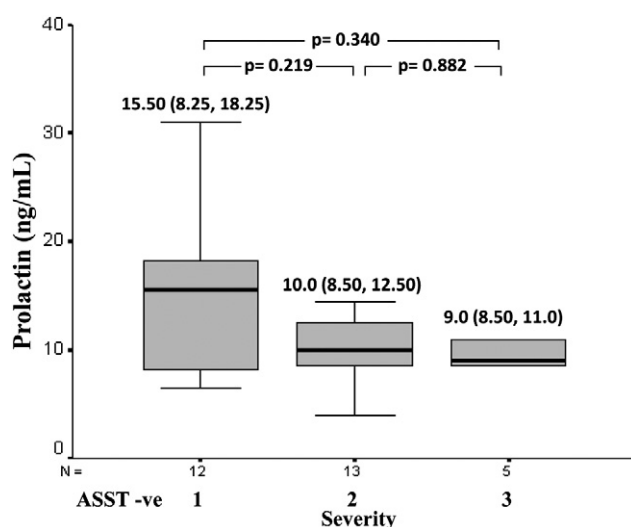


Figure 3. Comparison of prolactin levels according to disease severity among CU patients with a negative ASST. All values are presented as median (interquartile range). ASST, autologous serum skin test.

Discussion

Chronic urticaria is characterized by the activation of autoimmune and inflammatory processes (2). The ASST is a widely used test for detection of autoreactivity in patients with CU *in vivo*. A positive ASST reaction has been associated with various autoimmune diseases (4–6). In the present study we demonstrate for the first time a significant elevation of prolactin among CU patients with a positive ASST reaction in comparison to CU patients with a negative ASST reaction and healthy controls. To our knowledge, only one single study has previously investigated the relationship between prolactin and CU (19). In that study, the authors observed a nonstatistically significant elevation of

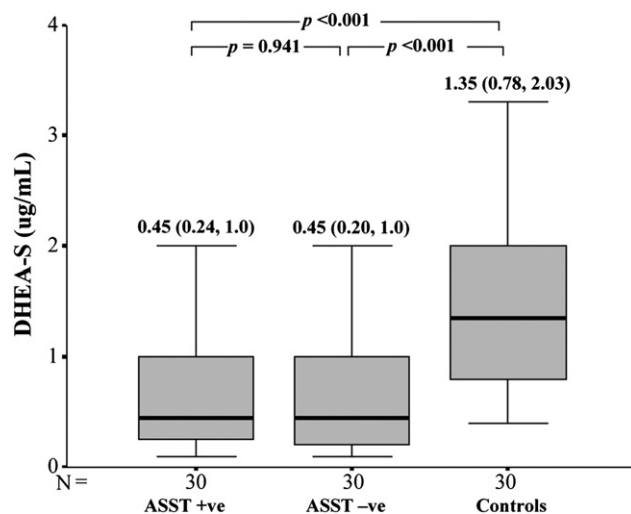


Figure 4. Comparison of DHEA-S levels among the three study groups. All values are presented as median (interquartile range). ASST, autologous serum skin test; DHEA-S; dehydroepiandrosterone sulfate.

Table 2. Associations of DHEA-S levels with disease severity among ASST positive and ASST negative patients with CU

Severity	DHEA-S (μg/mL)	
	ASST +ve	ASST -ve
1	1.15 (0.30, 2.0)	0.40 (0.20, 1.0)
2	0.40 (0.10, 0.69)	0.25 (0.23, 0.83)
3	0.80 (0.24, 1.13)	1.0 (0.35, 4.25)
P	0.300	0.279

ASST, autologous serum skin test; DHEA-S, dehydroepiandrosterone sulfate; CU, chronic urticaria.

All values are presented as median (interquartile range).

prolactin levels among ASST-positive patients as compared to ASST-negative patients and controls.

There has been growing interest in the association of prolactin hormone with autoimmune diseases. Elevated levels have been observed among patients with SLE (20–40%), RA (6–40%), systemic sclerosis (13–59%), and Sjögren syndrome (16–46%), as well as among those with organ-specific autoimmune diseases as Graves' disease, Hashimoto's thyroiditis, type 1 diabetes mellitus, and celiac disease (20). Prolactin is a peptide hormone secreted by the anterior pituitary gland under hypothalamic inhibition, via dopamine. Apart from being secreted by the anterior pituitary gland, prolactin is also secreted by extrapituitary sites including the immune cells, and its receptors have been found in many cell types including monocytes and lymphocytes (21), suggesting a role for prolactin in the innate and adaptive immune response. Prolactin regulates the maturation of CD4⁺ CD8⁺ thymocytes to CD4⁺ CD8⁺ T-cells, enhancing pro-B cell generation. It stimulates a decrease in apoptosis of transitional B cells, aiding in the development of autoimmunity. It may also contribute to increased autoreactivity by enhancing immunoglobulin production (9). Our findings of elevated prolactin levels among CU patients with a positive ASST reaction therefore support and highlight the important role of prolactin in autoreactivity and autoimmunity. Moreover, we report the novel finding that prolactin levels were significantly and positively associated with the grade of disease severity among ASST-positive CU patients. In the same context, prolactin has also been demonstrated to be related to the severity or activity of disease in other autoimmune diseases including SLE (22,23) and RA (24). A few controlled experimental trials with dopaminergic agonists such as bromocriptine, which selectively inhibits pituitary prolactin secretion, have been conducted on SLE patients and have shown a reduction in disease activity. Smaller trials have also shown encouraging results in patients with RA (20). Accordingly, our present findings of a significant role for prolactin in ASST-positive chronic urticaria may pave the way for possible therapeutic clinical trials with dopamine agonists in the future.

Patients with a positive ASST reaction in our study showed a significantly higher disease severity than those with a negative ASST reaction. Similarly, the majority of studies demonstrated that ASST-positive patients had a more severe disease than ASST-negative patients (25). Sabroe et al. reported that patients with autoantibodies had more severe urticaria than patients without autoantibodies; they had higher urticaria scores, a more widespread distribution of urticaria, more itching, and a greater incidence of systemic symptoms (26). Several other investigators have also reported a more severe disease among ASST-positive CU patients (5,27,28).

In the present study, serum concentrations of DHEA-S in patients with CU were significantly lower than those of healthy controls. A similar decline in serum concentrations of this hormone in patients with CU has been reported in a limited number of studies. Kasperska-Zajac et al. were the first to report the presence of a significantly lower serum concentration of DHEA-S among female patients with CU as compared to healthy controls (29). Subsequently, the same authors confirmed this finding among other studies (19,30,31). The finding of low DHEA-S levels among patients with active CU may be explained by several suggested hypotheses. The first hypothesis is that DHEA-S possesses immunomodulatory effects (32) as evidenced by its ability to promote a shift in Th1/Th2 balance toward Th1-dominant immunity, downregulating the Th2 response and thus suppressing the allergic inflammation (33,34). Another hypothesis is that DHEA-S has shown a potential direct effect on vascular inflammation and an ability to directly inhibit the inflammatory process (35), and chronic urticaria is characterized by the presence of activated endothelial cells due to inflammatory mediator and cytokine actions (36). A third hypothesis is a suggestion that low DHEA-S levels may be a phenomenon secondary to psychological disturbances induced by CU. This hypothesis could be supported by the findings of a recent study showing that serum DHEA-S levels in patients with CU correlated negatively with levels of anxiety and depression (37). Concerning this point, it has been proposed that in patients with chronic inflammatory diseases, a shift in steroid synthesis by the adrenal gland occurs, raising cortisol levels at the expense of DHEA and DHEA-S (38).

In the present study there was no significant difference in DHEA-S levels between ASST-positive and ASST-negative patients, confirming the findings of previous studies (19,29,37). Our observation that DHEA-S reduction was not dependent on the ASST status suggests that this phenomenon may not be related to the autoimmune/not autoimmune pathogenesis of the disease. Our findings that DHEA-S levels were not associated with the severity of CU also do not support the hypothesis of CU stress-induced DHEA-S reductions. It is possible that the role of DHEA-S in CU may be related to its potential direct inhibitory effect on vascular inflammation. Nonetheless, the exact role

of DHEA-S in CU still remains unclear and warrants further studies.

A possible role for prolactin in DHEA secretion and vice versa has been suggested, and a tendency for an inverse correlation between prolactin and DHEA-S concentrations in immune-mediated disorders has been observed (39). However, lack of any significant correlation between serum DHEA-S and prolactin levels in our study may signify that the reduction of serum DHEA-S concentrations in CU may occur irrespective of changes in prolactin secretion (19).

In summary, the present study reports for the first time significantly higher levels of prolactin in serum among ASST-positive CU patients, which were significantly associated with increasing grades of disease severity. In addition, the study confirms the low DHEA-S levels observed among patients with CU, which did not differ significantly according to their ASST status. We recommend further large-scale prospective studies to investigate changes in these hormone levels after complete remission of the disease. Understanding the changes in the hormonal environment in CU may lead to the development of new therapeutic modalities.

Conflict of Interest

The authors declare that no funding or grant was received for the study, and that they have no conflict of interest, financial or personal relationship related to the study.

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