Investigation of dermatology life quality index and serum prolactin and serum dehydroepiandrosterone sulphate levels in patients with chronic urticaria

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Summary

Background: **Chronic urticaria (CU) is known to be one of the most disturbing diseases which significantly affect the quality of life. Prolactin (PRL) and DHEA-S (dehydroepiandrosterone sulfate) are stress-associated hormones in chronic urticaria.**

Objective: **In the present study, we measured DHEA-S and prolactin levels of CU patients, compared them with healthy subjects and evaluated the association between disease status and serum levels.**

Methods: **Plasma DHEA-S and serum PRL concentrations were measured in 48 CU patients and 31 healthy subjects. CU activity was assessed with the use of the symptom scores recommended with EAACI/GALEN/EDF guidelines. All the patients participating in this study were evaluated by means of Dermatology Life Quality Index (DLQI). With respect to DLQI and clinical activity scores, plasma DHEA-S and serum prolactin levels were compared.**

Results: **Median plasma concentration of DHEA-S was significantly lower in CU patients as compared with healthy subjects ($p = 0.026$). DHEA-S levels of females were significantly lower than males ($p = 0.001$). Mean PRL values of the patients were higher than the controls, but not statistically significant ($p = 0.619$) and there was a statistically signifcant inverse correlation with DHEA-S levels ($p = 0.04$, $r = -0.298$). There was a significant correlation between DLQI and clinical disease activity ($p < 0.001$, $r = 0.748$).**

Conclusions: **The exact relation of hormones to CU pathogenesis remains to be determined by further clinical studies. In addition, therapies aiming to increase DHEA-S and decrease PRL may be subject to trial in CU.** ***(Asian Pac J Allergy Immunol 2014;32:293-9)***

Keywords: *Chronic urticaria, dehydroepiandrosterone-sulphate, life quality index, prolactin, clinical disease activity*

Introduction

Chronic urticaria is characterised by itchy wheals and is a disturbing disease for researchers with unknown causes, mechanisms and mediators.[1] Dysfunction of the neuroendocrine-immune system due to stress may play a role in the pathogenesis of urticaria.[2]

It has been demonstrated that relative deficiency of dehydroepiandrosterone sulphate (DHEA-S) is associated with various inflammatory and immune-mediated diseases, as well as stressful disorders,[3-5] including chronic urticaria.[6,7] It has been shown that both prolactin (PRL) and DHEA-S hormones have multiple immunomodulatory effects.[5,8] Besides, levels of these hormones in the blood circulation have been shown to be inversely related to the course of some immune-inflammatory diseases.[9] Dehydroepiandrosterone and its sulphate derivative (DHEA-S) are regulated by nervous system. It also has a regulatory role in immune homeostasis. In short, it is known to act as a regulatory element of neuroimmunomodulation.[10] Reduced levels of DHEA-S have also been noted in individuals with mental disorders, including depression [11–13] and anxiety.[14] Brozoza et al confirmed in a study the clinical observations indicating that CU patients suffer from psychological distress. The correlations presented may support the hypothesis that the decrease in DHEA-S levels observed in CU patients can be a secondary phenomenon resulting from

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psychological distress.[15] DHEA-S aids in stress management of the organism.[16]

Staubach et al.[17] reported negative influence of psychiatric comorbidity on overall quality of life, emotions, the physical symptoms, and functioning. Lennox et al demonstrated that the Dermatology Life Quality Index (DLQI) is a valid, safe and clinically applicable test in assessment of life quality related to urticaria.[18]

This study was designed to assess life quality in patients suffering from CU and determine its association with DHEA-S and prolactin levels.

Methods

Patients

Forty-eight Caucasian CU patients (29 females and 19 males); median age 32.13±9.21 (range 18–55) and 31 Caucasian healthy controls (20 females, 11 males) with median age is 33.87±10.48 (range 20-68) were included in the study. All other identified causes of urticaria had been excluded following appropriate investigations.

Patients with CU were divided into two subgroups according to the results of the autologous skin serum test (ASST). This test was performed in accordance with the method by Sabroe *et al* .[19] Negative ASST was found in 37 patients and 11 patients had a positive reaction. All controls responded negatively to ASST. The administration of anti-histaminic drugs was interrupted about 1 week before the study. None of the patients included in the study had any other drug administration history until 6 weeks to the study. None of the subjects were taking any medication affecting the levels of the hormones measured. All participants gave written, informed consent, and the study was approved by the University Ethics Committee.

Assessment of urticaria activity scores

Urticaria activity score (UAS) was calculated in accordance with guidelines of EAACI/GA2LEN/ EDF[20]. The number of wheals and intensity of pruritus was used to estimate UAS on the day of blood sampling. Grading of number of wheals was made as follows: Zero for no wheals, 1 for 1–20 wheals, 2 for 21–50 wheals and 3 for more than 50 wheals. Pruritus intensity was graded as: 0 for no pruritus, 1 for mild, 2 for moderate and 3 for severe pruritus. UAS (daily total of 0-6) was graded as mild if 0–2, moderate if 3-4 and severe if 5-6. Our study comprised 13 patients with mild CU, 18 patients with moderate CU, and 17 patients with severe CU.

Blood sampling and DHEA-S and prolactin assay

Between 8:00 and 10:00 a.m. the blood of all patients was taken and stored at –80°C until they were studied. Serum samples were gradually brought to room temperature and concentrations of these hormones were measured by automated electrochemiluminescence immunoassay (ECLIA). DHEAS immulate 2000 (Siemens, USA) and prolactin cobas e 601 immunologic tests (Roche Diagnostics, Germany) were used.

Assay of DLQI

All the patients were asked DLQI questions during the initial examination. The DLQI is composed of 10 items listed under six subsections: Symptoms and Feelings (items 1 and 2), Daily Activities (items 3 and 4), Leisure (items 5 and 6), Work and School (item 7), Personal Relationships (items 8 and 9) and Treatment (item 10). Every item has four choices: ‘not at all’, ‘a little’, ‘a lot’ and ‘very much’ which are scored as 0, 1, 2 and 3 respectively. Adding the scores of the ten questions yields the DLQI score which varies between 0 and 30. A total DLQI 0-1 indicates no impairment in quality of life, 2-5 mild impairment, 6-10 moderate impairment, 11-20 severe impairment and 21-30 very severe impairment.[21] We used the official Turkish version downloaded from www.dermatology.org.uk. The number of patients with mild impairment, moderate impairment, severe impairment and very severe impairment was 5, 9, 25 and 9, respectively.

Statistical analyses

Data were delivered as medians and ranges, and comparisons between groups were performed by Mann–Whitney’s and binary logistic regression. The Kruskal–Wallis variance analysis was used for screening differences between the groups. Correlation was analysed by the Spearman test and correlation coeffiecients were compared using Fisher’s r-to-z transformation. P-values below 0.05 were considered significant.

Results

Median plasma concentration of DHEA-S was significantly lower in CU patients as compared with healthy subjects (Figure 1), (p = 0.026). Median plasma concentration of PRL was not significantly different in CU patients as compared with healthy subjects (Table 1) (p = 0.619). DHEA-S and PRL was statistically correlated (p = 0.04, r = -0.298). Plasma concentration of DHEA-S in female CU patients compared with male was significantly

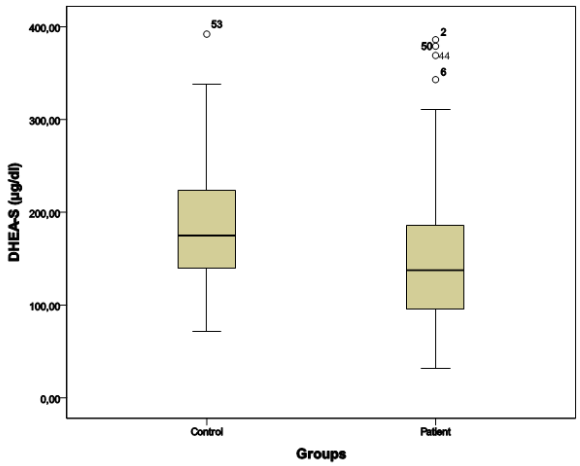

Figure 1. Serum concentrations of DHEA-S in CU patients and in healthy controls. Boxes represent median value.

lower. (p = 0.001) Plasma concentration of PRL in female CU patients compared with male was significantly higher (p = 0.012) (Table 2).

There was no significant correlation between UAS and DHEAS or PRL (p = 0.338, p = 0.746, respectively). ASST positive patients had significantly higher UAS compared to ASST negative patients (p = 0.015). There were no significant differences in plasma DHEA-S concentrations between the CU patients with mild, moderate, and severe symptoms (median: 145.0 µg/dl, 156.0 µg/dl, 110.5 µg/dl, respectively). DHEA-S levels were not statistically different between CU groups with mild and moderate UAS, mild and severe UAS and moderate and severe UAS (p = 0.446, p = 0.933, p = 0.137, respectively). There were no significant differences in plasma PRL concentrations between the CU patients with mild, moderate, and severe symptoms (median: 8.38 ng/ml, 11.50 ng/ml, 9.29 ng/ml, respectively). PRL levels were not statistically different between CU groups with mild and moderate UAS, mild and severe UAS and moderate and severe UAS (p = 0.162, p = 0.421, p = 0.486, respectively). DHEAS levels were inversely correlated with age when the whole study population was taken into consideration (r = -0.331, p = 0.003) whereas PRL was not correlated (p = 0.151). Correlation coefficients DHEAS with age of the patient and control groups were r = -0.281 and -0.526, respectively (p = 0.053 and 0.002, respectively). Fisher's r-to-z transformation yielded a z value of 1.23 (p = 0.22).

Table 1. Comparison of median serum concentrations of DHEA-S and PRL in CU patients and in healthy controls.

	CU patients (n=48)	healthy controls (n=31)	*P value*
DHEA-S (µg/dl)	137.50 (31.40-386.00)	175.00 (71.40-392.00)	0.026
PRL (ng/ml)	9.26 (4.02-50.93)	8.88 (3.28-38.62)	0.619

DHEA-S: Dehydroepiandrosterone sulfate; CU: Chronic urticaria; PRL: Prolactin; n: Number of subjects.

There was no statistically significant correlation of DLQI scores with DHEA-S or PRL (p = 0.470, p = 0.876, respectively). There was a statistically significant correlation between UAS and DLQI (p < 0.001, r = 0.748).

DHEA-S and PRL levels of the patients with ASST positivity and negativity were not significantly different (p = 0.759, p = 0.873, respectively).

Discussion

Lower DHEA-S and higher PRL concentrations were detected in patients with CU in this study. In addition, these differences were more evident in female patients, compared with males. Decline in concentration of dehydroepiandrosterone (DHEA) is a phenomenon accompanying many inflammatory and immune disorders.[9] Reduced levels of DHEA are evident in many inflammatory and immune mediated diseases.

DHEA-S deficiency is known to be a permanent characteristic of autoimmune diseases, which is also helpful in understanding the aetiology and pathophysiology of such as systemic lupus eryhtematosus and rheumatoid arthritis.[5,22,23] It is questionable whether lack of DHEA-S is the cause or result of the disease. In some studies, clinical recovery was observed following the oral application of DHEA.[23,24] Previous studies demonstrated decrease in serum DHEA-S levels in patients with CU.[6,7,8,22] In 2006, in his first study, Kasperka et al studied only females with CU and their DHEA-S levels were detected to be significantly decreased.[6] In 2007, in a study carried out on 18 female patients, DHEA-S levels were detected to be significantly decreased.[7] Later, in a study on males, DHEA-S levels of both symptomatic and non-symptomatic patients were detected to be significantly decreased.[8] In studies carried out on both males and females,

Table 2. Comparison of median serum concentrations of DHEA-S and PRL in female and male patients with CU.

	Female (n=29)	Male (n=19)	*P value*
DHEAS (µg/dl)	107.00 (31.40-215.00)	196.00 (40.70-386.00)	0.001
PRL (ng/ml)	11.58 (5.36-36.46)	6.66 (4.02-50.93)	0.012

DHEA-S: Dehydroepiandrosterone sulfate; CU: Chronic urticaria; PRL: Prolactin; n: Number of subjects.

levels of DHEA-S were found to be decreased regardless of gender.[25] Decreased DHEA-S may be a secondary result of psychological distress caused by CU.[25]

DHEA-S was shown to decrease with age for both sexes, with the mean significantly higher in males.[26] The DHEA-S versus age graph of our study population is in confirmation with this study (Figure 2). Prolactin, on the other hand, was shown to decline with age in females but increases with age in males.[27] Although our patient and control populations were age and gender-matched, there was a wide range in age. Due to these reasons, binary logistic regression was performed. DHEAS levels between patients and controls were significant (p = 0.017) (Table 3) whereas PRL levels were not significantly different (p = 0.987). Previous studies have reported a relationship between clinical disease status and DHEA-S. Symptomatic patients with active CU had lower DHEA-S concentrations compared to patients in remission and healthy controls.[25] In the present study, a relationship between DHEA-S and disease activity was not found. The lack of patients in remission in might constitute a reason for this. Urticaria may be associated with diseases or conditions characterized by sex hormonal changes such as menstrual cycle, pregnancy, menopause, and hormonal contraceptives or hormone replacement therapy.[28] In agreement with this, in the present study, the number of females afflicted by CU are higher than males. Despite this, the roles of endogenous and exogenous sex hormones and estrogen mimetics in the pathogenesis of the disease are poorly understood.[28] The agreement of various studies on the presence of lower DHEA-S levels in patients with CU should prompt further investigation a possible relationship between these hormones and CU.

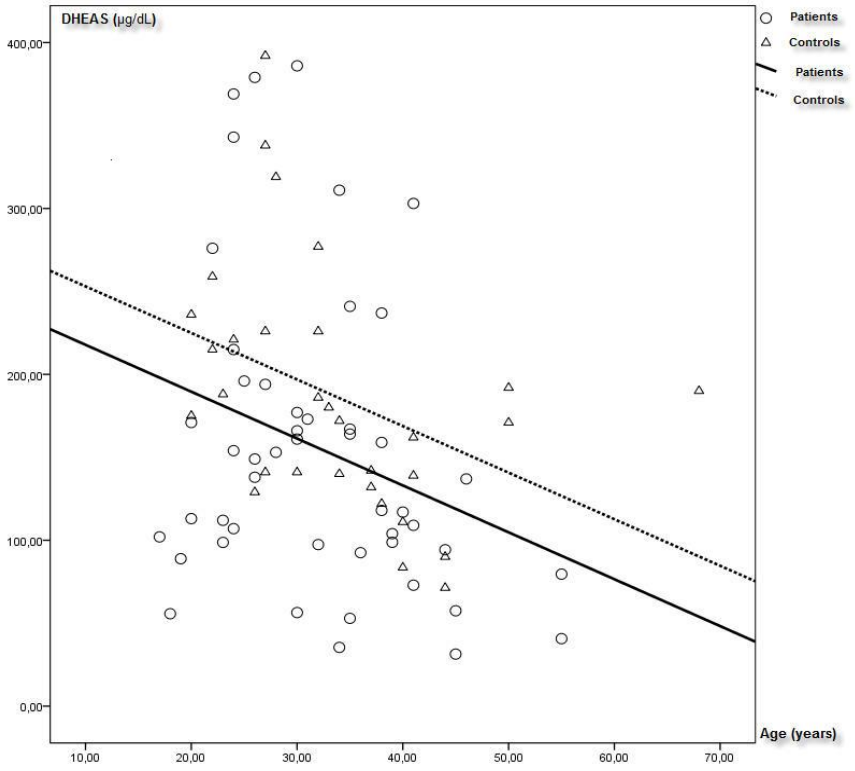

Figure 2. Graphic comparison of DHEA-S levels versus age in the patient and control groups.

Table 3. Binary logistic regression analysis of data

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	age	-.046	.028	2.650	1	.104	.955
	sex(1)	-1.040	.637	2.666	1	.102	.353
	DHEAS	-.009	.004	5.666	1	.017	.991
	Constant	4.126	1.607	6.592	1	.010	61.938

a. Variable(s) entered on step 1: age, sex, DHEAS.

ASST is extensively used in clinical practice and positive ASST suggests the autoimmune basis of the disease.[19] Previous studies have shown that decreased DHEA-S levels are not correlated with ASST results.[29] No association was determined between DHEA-S levels and ASST + and – groups in our study.

As to PRL, its relation with immune and endocrine diseases has also been investigated.[9] Hyperprolactinemia has been demonstrated in the active phase of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, celiac disease, thyroid disease and type 1 diabetes mellitus.[9] There is an inverse correlation between DHEA-S and PRL in immunemediated diseases[10] and this correlation has been demonstrated in the peripheral blood of patients with some non-organ specific and some organ-specific autoimmune diseases. [6,9] In a study considering the role of PRL on the secretion of DHEA-S and vice versa, high PRL and low DHEA-S levels have been detected in patients with systemic sclerosis. [10] In the light of this result, the correlation of the two hormones have been evaluated and a tendency was recognized, although not significant.[22] Increased PRL accompanied low DHEA-S in our study as well, and was statistically significant.

The impact of CU clinical symptoms on patients' quality of life (QoL) is often underestimated, with few reports in literature. The Dermatology Life Quality Index (DLQI) was the first construct for assessing the quality of life specifically related to dermatology, developed by Finlay and Khan in 1994.[21] The DLQI was translated into Turkish and validated by *Öztürkcan* et al.[30] Skin diseases may affect the daily lives of individuals and their psychological and social relationships.[31] Although there are numerous studies investigating the impact of other dermatologic diseases on quality of life and psychiatric comorbidity, there are only a limited number of studies investigating psychological problems in patients with urticaria. It has been shown that quality of life is significantly affected by urticaria.[18] Disease activity scores were positively correlated with DLQI scores in our study.

Stress, hormones and inflammatory or immune stimuli may be secondary factors influencing decrease in the circulating DHEA-S. In particular, stress is supposed to be a factor affecting DHEA-S concentration.[6] We did not detect any correlation between the life quality index and DHEA-S levels in our patients. This was also true for serum PRL concentration and DLQI.

Urticaria symptoms, such as pruritus and uncomfortable lesions, can appear as a considerable source of physical and psychological distress.[32] In addition, Baiardini et al. reported a severe impairment of quality of life in CU patients.[33] Many studies investigated the quality of life of chronic urticaria patients by DLQI and many other tests. DLQI studies revealed deterioration in questions related to symptoms, feelings, and school and business life of chronic urticaria patients. The leisure times and daily activities were impacted to a lesser degree.[34,35] Leisure time and daily activities were the least affected questions in our study as well. CU negatively affected the quality of life and especially caused deterioration in sleeping habits and mental health.[32,36] Compatible with scores in the literature, Karadag et al found that the highest scores were for symptoms and feelings.[31] In our patient group, scores related to symptoms and feelings were highest. 64% of the patients replied "very severe" to the first question and 34% gave the same response to the second question. The life quality of our patients was not correlated with DHEAS levels. UAS had a significant effect on the quality of life of CU patients. There was no association between degree of UAS and levels of DHEA-S and PRL. In the literature, serum DHEAS levels have been shown to be lower in patients with higher levels of anxiety and depression. Moreover, the correlations may support the hypothesis that the decline in DHEA-S observed in CU patients can be a secondary phenomenon, resulting from psychological distress.[15]

Conclusions

CU is an upsetting disease causing significant impairment in the life quality of patients. As UAS increases, quality of life decreases proportionately. The exact relation of hormones to the disease remain

to be determined by further clinical studies. In addition, therapies aiming to increase DHEA-S and decrease PRL may be subject to trial in CU.

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