

Research Article

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Evaluation of serum 25-hydroxyvitamin D levels and cortisol/dehydroepiandrosterone sulfate ratio in chronic spontaneous urticaria

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Abstract

Background: Various studies have reported different results for cortisol, dehydroepiandrosterone sulfate (DHEA-S) and 25-hydroxyvitamin D (25(OH)D) levels in patients with chronic spontaneous urticaria (CSU) and these were not sufficient for explaining the underlying reasons.

Objectives: To evaluate the levels of cortisol, DHEA-S and 25(OH)D in patients with CSU and to investigate the relationships between these parameters.

Methods: Fifty patients who had diagnosed with CSU and 30 healthy controls were enrolled into the study. Stress levels of CSU and control groups were determined by perceived stress scale (PSS-14). The activity of urticaria of the patients was also determined by urticaria activity score (UAS7). Serum DHEA-S, cortisol and 25(OH)D levels of the participants were measured and compared.

Results: DHEA-S and 25(OH)D levels of CSU patients were lower than the control group ($p < 0.001$ and $p < 0.001$, respectively) while stress level and cortisol/DHEA-S ratio were higher ($p < 0.001$ and $p = 0.003$, respectively).

Conclusions: Lower 25(OH)D levels and higher cortisol/DHEA-S ratio in CSU patients who have higher stress level indicate that the level of 25(OH)D seems to be associated with steroidogenesis and thus 25(OH)D levels may decrease secondarily in CSU.

Keywords: 25-hydroxyvitamin D; chronic urticaria; cortisol; dehydroepiandrosterone sulfate; stress.

Introduction

Chronic spontaneous urticaria (CSU) is a common skin disease that is defined as the recurrence of weals, angioedema or both for more than six weeks due to known or unknown causes [1]. Urticaria is a mast cell-mediated disease, but these diverse signals that lead to mast cell activation have not been clearly revealed. Mediators and cytokines such as histamine and platelet-activating factor released by the mast cell as a result of stimulation lead to urticaria lesions by sensory nerve activation, vasodilation, and plasma extravasation [1]. Systemic inflammatory findings are also accompanied by local cutaneous infiltrate during the attack period so that C-reactive protein (CRP) and IL-6 increase have been observed [2, 3].

The diagnosis of CSU is completely clinical so far [4]. However, objective tools are needed to monitor CSU activity and the effectiveness of treatment. Recently, some publications suggest that blood parameters may be potential biomarkers associated with CSU. In a recent review, strong evidence was found for significant differences between patients with CSU and healthy controls in blood levels of some parameters including dehydroepiandrosterone sulfate (DHEA-S) and vitamin D [4].

Although it has been documented that psychological stress triggers and/or exacerbates CSU [1], stress is another factor affecting cortisol and DHEA-S levels [5]. Some studies have reported that DHEA-S levels are lower in patients with CSU, nevertheless, cortisol levels are variable [6–9]. Furthermore, it has been shown that vitamin D levels of patients with CSU are lower than controls [10].

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The first aim of this study was to evaluate the levels of cortisol, DHEA-S and 25-hydroxyvitamin D (25(OH)D) levels in patients with CSU as various studies have reported different results which were not sufficient for explaining the underlying reasons. Therefore, the second aim was to investigate the relationships between these parameters, stress, and the activity of urticaria.

Materials and methods

Cases

Fifty patients who admitted to Okmeydani Training and Research Hospital Dermatology Urticaria Clinic and diagnosed as CSU between April 2017 and June 2017 formed the patient group and 30 healthy volunteers who formed the control group were included in the study. Fasting blood of all patients and control subjects were collected between 08:00–10:00 am in the morning.

All participants were between 18 and 64 years old and have not taken any vitamin D supplementation within the last six months. CSU patients who were enrolled into the study were taking antihistamine treatment alone. Subjects who had acute or episodic urticaria and who were on continuous corticosteroid or immunosuppressive treatment or regular non-steroid anti-inflammatory drugs were not included into the study.

After anamnesis and physical examinations, all CSU patients completed urticaria activity score (UAS7) which was used in the diagnosis and follow-up of urticaria [11]. Also, they completed the perceived stress scale (PSS-14) [12] to measure the stress levels of the patients. PSS-14 was also given to the control group to measure their stress levels.

Written informed consent from all participants was obtained and ethical approval with the number 616 was obtained from Okmeydani Training and Research Hospital Ethics Committee.

Biochemical parameters and laboratory analyses

Serum DHEA-S and cortisol levels were measured in the Cobas e602 analyzer (Roche Diagnostics, Mannheim, Germany) using DHEA-S and Cortisol kits (Roche Diagnostics, Mannheim, Germany) while serum 25(OH)D levels of the subjects were measured in Zivak Tandemgold Triple-Quadrupole LC-MS/MS analyzer (Zivak Technologies, Istanbul, Turkey) using the 25-hydroxy vitamin D2-D3 Serum LC-MS/MS APCI Assay Kit (Zivak Technologies, Istanbul, Turkey). Inter-assay coefficient of variations (CV) of DHEA-S, cortisol and 25(OH)D measurements were ≤ 2.7 , ≤ 2.8 and $\leq 2.8\%$, respectively.

Statistical analysis

The normality of the distributions was assessed by Kolmogorov Smirnov test when the sample number was more than 50 and by Shapiro-Wilk test when the sample number was less than 50. For the parameters which were not normally distributed, square root conversion was performed for 25(OH)D, and logarithmic conversion was performed for the DHEA-S and cortisol/DHEA-S ratio to obtain normal distribution and then the parameters were analyzed. However,

the results of the converted parameters were given as the values before the conversion so that they would be more understandable and suitable for clinical practice.

In descriptive statistics, normally distributed parameters were given as mean \pm standard deviation. Student-t test was used comparing quantitative data between patient and control groups while chi-square test was used for the comparison of qualitative data. Analysis of covariance (ANCOVA) test was used to adjust the effect of age and gender. Marginal mean \pm standard error values were estimated after adjustment for age and gender. Kruskal-Wallis test was used to compare the urticaria activity scores between CSU patients and control group, and Mann-Whitney U test was used to compare the post-hoc analysis between the groups. Spearman correlation test was used to evaluate the dual and multiple correlations between all parameters. All statistical analyses were performed using SPSS 17 (SPSS Inc., Chicago, Illinois, USA) software program. Statistical significance was taken as p-value < 0.05 .

Results

CSU patients have lower DHEA-S and 25(OH)D levels

While DHEA-S and 25(OH)D levels of CSU patients were lower than control group, PSS-14 scores and cortisol/DHEA-S ratio were higher ($p < 0.001$, $p < 0.001$, $p = 0.001$ and $p = 0.003$, respectively). Age and gender distributions of CSU and control groups were found to be significantly different than each other ($p = 0.03$ and $p = 0.02$, respectively).

The mean duration of urticaria in the CSU patients was 13.5 (8.0–29.5) months. There was no significant difference in cortisol levels between CSU and control groups ($p = 0.26$) (Table 1).

Differences between CSU and control groups are not due to age and gender differences

After the adjustment for age and gender, the same differences in biochemical parameters remained significant between CSU and control groups (Table 2).

DHEA-S and 25(OH)D levels do not change according to urticaria activity

DHEA-S levels of the control group were higher than well-controlled urticaria, mild urticaria, moderate urticaria and severe urticaria groups ($p = 0.025$, $p = 0.005$, $p = 0.049$ and $p < 0.001$, respectively). There were no significant differences between the urticaria groups in terms of DHEA-S levels ($p > 0.05$ for each) (Figure 1A).

Table 1: Comparison of descriptive and biochemical parameters of CSU and control groups.

	CSU, n=50	Control, n=30	p-Value
Age	40.3 ± 9.9	35.5 ± 9.1	0.03
Gender, M/F ^a	11/39	14/16	0.02
PSS-14	30.3 ± 7.7	23.2 ± 7.3	<0.001
Cortisol, µg/dL	11.3 ± 3.8	12.2 ± 3.3	0.26
DHEA-S, µg/dL	166.6 ± 103.3	283.0 ± 141.8	<0.001
Cortisol/DHEA-S	0.10 ± 0.10	0.05 ± 0.04	0.003
25(OH)D, ng/mL	12.1 ± 7.0	20.4 ± 6.5	<0.001

^aMale/female ratio: p-value was obtained using chi-square test. CSU, chronic spontaneous urticaria; PSS-14, perceived stress scale-14; DHEA-S, dehydroepiandrosterone sulfate.

Table 2: Estimated marginal mean ± standard error values of biochemical parameters adjusted for age and gender.

	CSU, n=50	Control, n=30	p-Value
PSS-14	29.6 ± 1.3	23.2 ± 1.4	0.001
Cortisol, µg/dL	11.3 ± 0.6	12.4 ± 0.7	0.28
DHEA-S, µg/dL	194.7 ^a ± 18.3	271.9 ^a ± 20.1	0.008
Cortisol/DHEA-S	0.09 ^a ± 0.01	0.06 ^a ± 0.01	0.03
25(OH)D, ng/mL	13.2 ^b ± 1.1	20.9 ^b ± 1.3	<0.001

^aLog-transformed values, ^bSquare root transformed values. p-values were obtained by ANCOVA for comparisons among CSU and controls. Values were adjusted for the following covariates: age, gender. CSU, chronic spontaneous urticaria; PSS-14, perceived stress scale-14; DHEA-S, dehydroepiandrosterone sulfate.

25(OH)D levels of the control group were higher than well-controlled urticaria, mild urticaria, moderate urticaria and severe urticaria groups ($p=0.006$, $p<0.001$, $p=0.007$ and $p=0.001$, respectively). There were no significant differences between the urticaria groups having regard to 25(OH)D levels ($p>0.05$ for each) (Figure 1B).

The correlations between 25(OH)D levels and cortisol levels, cortisol/DHEA-S ratio in the control group are replaced by the correlation between 25(OH)D and DHEA-S levels in the CSU group

In the control group, there were significant positive correlations between the 25(OH)D levels, and cortisol levels and cortisol/DHEA-S ratio ($r=0.60$, $p<0.001$ and $r=0.38$, $p=0.041$, respectively) (Figure 2A). In the CSU group, there was a significant positive correlation between the 25(OH)D levels and DHEA-S levels ($r=0.30$, $p=0.03$) (Figure 2B). There were no significant correlations between other parameters ($p>0.05$ for each).

Discussion

It is well known that stress plays an important etiological role in many somatic and mental diseases. In dermatology, the relationship between psychological factors and dermatological diseases has been observed since a few decades [13]. Stress and similar factors have been shown to cause urticarial blistering and exacerbation [14].

In our study, we measured the perceived stress levels of all participants and determined that, the stress levels of CSU patients were higher than the control group. Other studies also show that CSU is frequently associated with emotional stress/anxiety and/or depression [15, 16]. Staubach et al. [17] have reported that psychological comorbidities can exacerbate urticaria and at the same time, urticaria can induce psychological comorbidities.

There is evidence that may explain the mechanisms for the role of stress in urticaria. It has been shown that stress is associated with the onset of disease by activation of the sympathetic and adrenomedullary system and hypothalamic-pituitary-adrenal (HPA) axis [18]. In acute stressed conditions, both adrenocortical and medullary systems are activated, leading to increased secretion of cortisol and catecholamines. However, chronic stress decreases cortisol secretion by suppressing the response level of the HPA axis and increases secretion of inflammatory cytokines, typically reversed by cortisol [19, 20]. Thus, chronic stress can cause some inflammatory diseases, such as chronic urticaria, which have been shown to have degranulation of mast cells and possibly basophils and increased mediator release.

From this point of view; in chronic inflammatory response [21] and under severe stress conditions [22], it has been suggested that there may be a hormonal shift in the direction of cortisol rather than DHEA-S in the production of adrenal steroids, at the expense of adrenal androgens, probably to achieve the required cortisol levels [21]. It has even been discussed that similar changes in steroidogenesis may be occurring in chronic urticarial inflammation [23]. Higher cortisol/DHEA-S ratio in CSU patients compared to the control group, in our study, strongly supports the hypothesis that the above mentioned hormonal shift in steroidogenesis may also occur in CSU patients.

In our study, the cortisol levels were not significantly different between CSU and control. Brzoza et al. [24] have not found any difference between patients with CSU and control subjects in terms of basal cortisol levels. Dyke et al. [9] have reported that basal cortisol levels tended to be high in patients with chronic urticaria, but this difference was

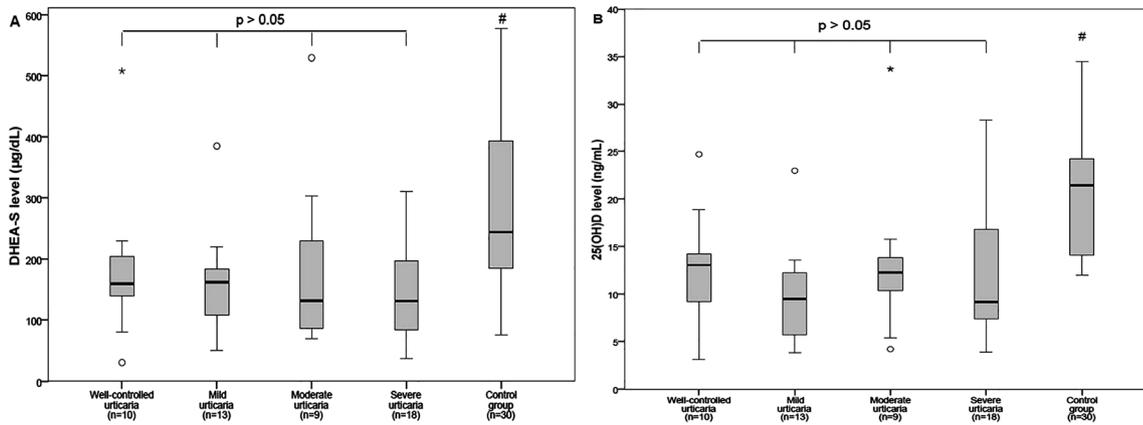


Figure 1: DHEA-S and 25(OH)D levels of CSU patients and controls. (A) Differences in DHEA-S levels. (B) Differences in 25(OH)D levels. # Levels of control group were significantly higher than the other groups.

not statistically significant. In a recent study by Varghese et al. [8], it has been found that cortisol levels of chronic urticaria patients were significantly lower than control subjects. They have stated a significant negative correlation between urticaria duration, urticaria severity and stress levels and serum cortisol levels [8]. However, we did not find a correlation between serum cortisol levels and urticaria duration or activity.

Many theories are trying to explain how an individual’s normally functioning HPA axis turns into stress-induced HPA axis dysfunction (presenting as hypercortisolism, hypocortisolism or some form of diurnal dysrhythmia) [25]. Most of these models follow Selye’s General Adaptation Syndrome [26]. Selye’s General Adaptation Syndrome suggests that acute or chronic stressors will eventually transform the HPA axis from an over-responsive system to an

under-responsive or non-responsive system (popular terms suggest that it will cause adrenal “fatigue/exhaustion”) [27]. In this case, it is thought that the ratio of cortisol production to DHEA/DHEA-S is important in determining how HPA axis functions in an individual [26]. While most of the time HPA axis dysfunction of patients is not distinguishable with basal cortisol levels, it can be noticed by the cortisol/DHEA ratio [26].

In this study, we found that the cortisol/DHEA-S ratio of CSU patients were significantly higher than the subjects in the control group. These results show that patients with CSU have HPA axis dysfunction, which we do not know whether this condition is temporary or not. In the literature, we did not run across a study examining the cortisol/DHEA-S ratio of urticaria patients. However, it should be considered that the levels of cortisol response in patients with CSU may vary

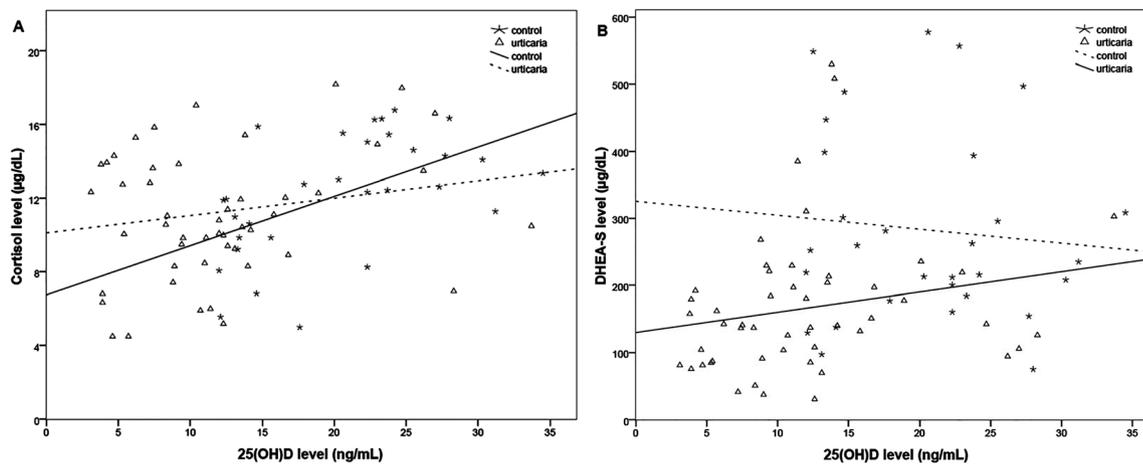


Figure 2: Correlations between cortisol, DHEA-S and 25(OH)D levels in CSU and controls. (A) Correlation between cortisol and 25(OH)D levels. (B) Correlation between DHEA-S and 25(OH)D levels. Continuous lines show the significant correlations.

between individuals depending on the duration of urticaria, active/inactive periods of urticaria, chronic stress duration and levels. The levels of cortisol and DHEA-S in our CSU patients suggest that most of the patients may be in General Adaptation Syndrome stage II that cortisol levels begin to decrease to normal levels and the DHEA-S levels gradually decrease [26]. This situation may explain the differences between the previously published studies [8, 9, 24] and our study with regard to cortisol levels in patients with chronic urticaria. In fact, these different results for basal cortisol levels of CSU patients suggest that cortisol levels change secondary to CSU (due to chronic stress and/or chronic inflammation) rather than being involved in the pathogenesis of CSU, similar to DHEA-S.

When 25(OH)D levels were evaluated, we found that 25(OH)D levels of CSU patients were lower than control group. In recent years, many researchers have shown interest to 25(OH)D levels in chronic urticaria and in studies conducted in different populations, it has been shown that levels of 25(OH)D in patients with CSU are lower than those in the control group [10, 28–34]. While some of the studies have found a correlation between urticaria activity score (UAS) and 25(OH)D levels [10, 28, 32], some have not found any association [29, 30, 34]. Similarly, some of these studies have documented a relationship between urticaria duration and 25(OH)D levels [10, 31] and some say the exact opposite [29, 30, 33, 34]. In our study, we did not find a correlation between 25(OH)D levels and urticaria activity or duration of patients with CSU. For chronic urticaria, it has been suggested that low levels of 25(OH)D may be a secondary response to different stimuli, including inflammation, and therefore it may not be contributing to the pathogenesis of the disease in any way [29]. In the literature, we did not run across a study which has shown that 25(OH)D levels were low before the onset of the disease or a study that has investigated the 25(OH)D levels other than active periods (in remission periods), similar to DHEA-S levels. We think that following up 25(OH)D levels in CSU patients for longer periods may be useful in clarifying whether this process is primary or secondary.

In our study, while there were positive correlations between the cortisol levels, cortisol/DHEA-S ratios and 25(OH)D levels in controls, there was no correlation in CSU patients. However, in CSU patients, there was a correlation between DHEA-S which was decreased compared to the control group and 25(OH)D levels. This situation suggests that a change in 25(OH)D levels may be associated with HPA axis dysfunction. A possible hypothesis that can explain this relationship is the fact that the HPA axis activated in favor of cortisol in CSU patients may also affect vitamin D synthesis.

We have some limitations such as age and gender differences between CSU patients and the controls but we showed that age and gender were not confounding factors as the same findings were found after the adjustment for age and gender.

Conclusions

Due to high levels of stress in CSU patients, a higher ratio of cortisol/DHEA-S which would support the finding of the shift from DHEA-S synthesis to cortisol synthesis in adrenal steroidogenesis suggests that low DHEA-S levels in CSU patients are secondary to the adaptation or dysfunction in HPA axis. Also, lower serum 25(OH)D levels in CSU group compared to control group and correlations of 25(OH)D levels with DHEA-S levels and cortisol/DHEA-S ratio show that 25(OH)D levels may be associated with HPA axis and steroidogenesis, thus 25(OH)D levels may decrease secondarily in CSU. Further studies in larger patient groups, following up the levels of cortisol, DHEA-S, 25(OH)D and cortisol/DHEA-S ratio as HPA axis activity of CSU patients in active and remission periods are needed to clarify these findings.

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Informed consent: Informed consent was obtained from all individuals included in this study.

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