

Original Article

Is dehydroepiandrosterone sulphate involved in the pathogenesis of chronic idiopathic urticaria?

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Abstract

B **ackground:** Recently, particular consideration is given to the role of hormonal factors that seem to contribute substantially to the course and activity of chronic urticaria.

Aim of Work: To assess a possible change in the serum levels of dehydroepiandrosterone sulphate (DHEAS) in patients with chronic idiopathic urticaria (CIU).

Subjects and Methods: Forty three consecutive patients (8 males and 35 females) with CIU were included in this study together with 50 age and sex matched healthy controls. Urticaria activity score (UAS) was estimated in

every patient and serum levels of DHEAS was measured for patients and controls.

Results: Serum DHEAS levels were significantly lower in CIU patients compared to controls ($p \leq 0.001$). Those significantly lower levels were found in both male and female patients in comparison to their control group. There was significant inverse correlation between DHEAS levels and UAS ($r = -0.38$, $P = 0.013$).

Conclusion: Decreased DHEAS in CIU suggest a possible role of this hormone in pathophysiology of CIU. Further studies on the potential use of exogenous dehydroepiandrosterone (DHEA) for treatment or reducing CIU are recommended.

Key words: Chronic idiopathic urticaria (CIU), Dehydroepiandrosterone sulphate (DHEAS).

Introduction

Chronic urticaria is defined as recurrence of wheals with or without angioedema for more than 6 weeks⁽¹⁾. Chronic idiopathic urticaria (CIU) represents a special challenge. Its pathogenesis has not yet been fully elucidated and, despite a detailed history and extensive laboratory investigations, it is not usually possible to indicate any probable cause of urticaria^(2,3). Where there is evidence of histamine-releasing autoantibodies, the patient has chronic autoimmune urticaria but where there is no evidence of functional autoantibodies the patient has CIU⁽³⁾.

Dehydroepiandrosterone (DHEA) and its sulphated metabolite, (DHEAS) are the major androgens secreted by the adrenal glands. Those very abundant hormones are converted into testosterone and estrogen in systemic circulation⁽⁴⁾. It has been well-documented that DHEA and its metabolites have anti-inflammatory, anti-proliferative and certain immune regulating properties and have shown immunological effects both in vitro and in vivo in experimental animals and humans^(5,6). Furthermore, a decline in serum level of DHEA is associated with aging and loss of several aspects of immunity and health⁽⁶⁾. DHEA and its metabolite DHEAS has been linked, usually controversially, to many diseases, including malignancies⁽⁷⁾, systemic lupus erythematosus and other immune inflammatory disorders⁽⁸⁾, including atopic eczema and asthma⁽⁹⁾.

Only few studies are available regarding DHEAS concentration in chronic urticaria^(10,11,12). In this study we assess a possible change in the level of serum DHEAS in patients with CIU in comparison to age and sex matched healthy controls aiming to find a possible correlation between CIU and change in DHEAS level.

Subjects and Methods

A total of 43 consecutive patients (8 males

and 35 females) with age ranged from 17 - 55 years (mean 35.3 ± 11.6) with CIU defined as recurrent wheal lasting less than 24 hours and occurring at least twice a week for more than 6 weeks was recruited from Dermatology out-patient clinic of the University hospital of Mansoura. Female patients included 28 premenopausal and 7 post-menopausal patients. All patients had active disease at the time of the study. None of them had received any systemic steroid or immunosuppressive drug for at least 4 weeks preceding the study. Furthermore, patients were instructed to stop antihistamines at least 3 days before the blood sampling. Potential causes for urticaria were evaluated by a detailed history, physical examination and laboratory tests as shown in Table (1) modified after Schnyder et al⁽¹³⁾. Urticarial patients with suspected etiological factor or had abnormal investigation were excluded from the study. Patients with positive autologous serum skin test (ASST) were also excluded. The ASST was performed according to the method described by Sabroe et al⁽¹⁴⁾. Clinical evaluation of urticaria activity was estimated by the first investigator, using Breneman scale score⁽¹⁵⁾. A 4-grade scale was used for describing the number of lesions, the average size of lesions, the duration of lesions, the frequency of episodes and the intensity of pruritus. The number of wheals was classified as follow: 0 = no wheals; 1 = 1-10 wheals; 2 = 11-20 wheals; 3 = >20 wheals. The average size of lesions was categorized as follow : 0 = no wheals; 1 = <1.25 cm; 2 = 1.25-2.5 cm; 3 = >2.5 cm. Average duration of lesions: 0 = no symptoms; 1 = up to 4 h; 2 = >4-12 h; 3 = >12 h. The frequency of lesions was scored as follow: 0 = no wheals; 1 = lesions appearing one time a week; 2 = 2-3 times a week; 3 = >3 times a week. Intensity of pruritus: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Therefore, the urticaria activity score (UAS) ranged from 0-15.

Fifty (12 males and 38 females) age, sex and body mass index (BMI) matched healthy non atopic subjects served as control group. They were recruited from medical and paramedical

personnel from our hospital. None of patients nor controls were smoker, pregnant, lactating or on hormonal contraception. All patients gave informed consent to participate in the study and investigations.

Blood samples

Morning blood samples (9:00 AM) were obtained from all patients and controls. Serum DHEAS was assayed by solid phase competitive chemiluminescent enzyme immunoassay using Immulite analyzer supplied by Siemens, Los Angeles, CA 90045-6900, USA.

Statistical analysis

Data were processed using SPSS software (version 11.0; SPSS Inc., Chicago, IL, USA). Qualitative variables were presented as number and percent. Chi square was used for comparison between groups. Quantitative variables were presented as mean \pm SD and t-test was used for comparison between groups. Pearson's correlation coefficient was used to calculate correlation between variables, $P \leq 0.05$ was considered to be statistically significant.

Results

The mean age of studied patients were 31.1 ± 9.8 , 51.3 ± 3.2 and 36 ± 10.2 years for pre, post-menopausal females and males respectively. The duration of chronic urticaria in studied patients ranged from 5 months- 28 years, mean was 37.9 ± 64.4 months. Among the studied patients, UAS ranged from 7-15 (mean 10.8 ± 2.4). The mean of UAS among pre-menopausal, post-menopausal females and males were 10.9 ± 2.6 , 10.6 ± 1.4 & 10.9 ± 2.8 , respectively. Regarding serum DHEAS levels, there were significantly lower levels of DHEAS in CIU patients versus controls ($p \leq 0.001$) (Table 2). The significantly lower DHEAS levels were found in both male and female patients in comparison to control

group. The decrease of DHEAS levels were more significant in pre-menopausal than the post-menopausal female patients in comparison to their control group ($P \leq 0.001$, 0.002 respectively) (Table 2). DHEAS levels inversely correlated with the duration of chronic urticaria, but without statistical significance ($r = -0.18$, $P = 0.26$). We found significant inverse correlation between DHEAS levels and UAS ($r = -0.38$, $P = 0.013$), data not shown in tables.

Discussion

Our results showed that serum concentrations of DHEAS in patients with CIU are lower than those of normal controls. A similar decline of serum concentration of this hormone in patients with CIU has been reported⁽¹⁰⁻¹²⁾. This finding raises the possibility that either normal DHEAS level might protect against CIU or CIU could induce reduction in the levels of DHEAS. There are several lines of evidence to suggest that DHEAS might protect against CIU. Firstly, DHEAS has been found to have immunomodulatory properties⁽¹⁶⁾. DHEAS suppresses the spontaneous elevation of both serum IgE and IL-6 levels in atopic dermatitis model NC/Nga mice⁽¹⁷⁾. Furthermore, DHEA appears to be able to down regulate the production of Th2 cytokines⁽¹⁶⁾. Secondly, the concentration of serum DHEAS was low in active CIU in the study of Kaserska-Zajac et al⁽¹⁸⁾. During remission of CIU, DHEAS concentration elevated in the same patients to level comparable of healthy control. However, an unresolved question is whether restored serum DHEAS concentration results in improved clinical status in urticaria or vice versa⁽¹⁸⁾. Thirdly, the decrease of serum levels of DHEAS is typical for chronic inflammation⁽¹⁹⁾. In general, DHEAS is able to directly inhibit the inflammatory process and show a potential direct effect of DHEAS on vascular inflammation⁽²⁰⁾. In chronic urticaria, there are activated endothelial cells due to action of inflammatory mediator and cytokines⁽²¹⁾. Fourthly, DHEAS was

successfully used to prevent attack of hereditary angioneurotic edema⁽²²⁾. This effect may be due to inhibition of both the spontaneous and immune activation of the classical complement pathway⁽²³⁾. Complement 5a has been shown to augment IgG-dependent histamine release from basophiles in chronic urticaria⁽²⁴⁾. Lastly, apart from direct immunomodulating effect, DHEA and DHEAS can be converted into other hormones including estrogen and testosterone. It has been found that estrogen and testosterone play an important function in peripheral target tissue and mast cells⁽²⁵⁾. The possibility that CIU could induce reduction in the levels of DHEAS comes from the following observations: (i) a decline in DHEAS is observed in patients with chronic urticaria associated with psychological distress, the authors suggested that low DHEAS level might be a phenomenon secondary to psychological disturbances⁽²⁶⁾. Furthermore, psychiatric morbidity (such as depression and anxiety) is high among CIU patients and is detrimental to their quality of life^(27,28). On the other hand, stress is one of the most prominent trigger of symptom onset in chronic urticaria⁽²⁹⁾.

In this study, there was significant inverse correlation between DHEAS levels and UAS ($r=-0.38$, $P=0.013$). This finding may strengthen the

possibility that the decline of DHEAS levels may be involved in pathogenesis of CIU. However, in the study of Kaserska-Zajac et al⁽¹⁰⁾, they didn't find significant correlation between DHEAS levels and UAS in 34 female patients with CIU. The discrepancy between results may be due to larger number⁽⁴³⁾ of patients in our study in comparison to their study.

In chronic urticaria, beside the autoimmune pathogenesis, recent findings stress on the role of activation of the coagulation cascade even in patients with positive ASST. Activation of coagulation cascade resulting in thrombin production. Thrombin is a serine protease which may play a key role in urticaria⁽¹⁾. A possible role of lower circulating DHEAS in CIU pathogenesis among studied patients may be through its effect on coagulation and fibrinolysis as DHEA decreases platelet aggregation and plasminogen activator inhibitor⁽³⁰⁾.

In conclusion, decrease DHEAS in CIU suggest a possible role of this hormone in pathophysiology of CIU but the underlying mechanisms remain unknown. Further studies on the potential use of exogenous DHEA for treatment or reducing CIU are recommended.

Table (1): History, examination, physical test, investigation done to recruit patients with CIU⁽¹³⁾.

1-History regarding influencing factors
Food additive
Infection
Bacterial (UTI, sinusitis, dental infection, H. pylori infection)
Viral (hepatitis B, C & HIV)
Parasitic infestation.
Drugs (aspirin, NSAID, penicillin, ACEI, codeine & alcohol)
Stressful life event
Metal pin in femur
History of atopic disease
2-Physical factors observed by the patient
Physical exercise
Delayed pressure (> 4 hours)
Cold/ heat
Exposure to sunlight
3-Examination for systemic diseases (thyroid & collagen diseases)
4- Test done by doctor
Dermographism
Autologous serum skin test (ASST) ¹⁴
5- Laboratory investigations
Full blood count & white cell differential
Urine & stool examination
ESR
Screening for hepatitis B & C infection
TSH
ANA
IgE
Anti-H. pylori Ig G antibody

This table was modified after Schnyder et al⁽¹³⁾ with permission from the corresponding author.

Table (2): Demographic, clinical and laboratory findings of CIU patients versus controls.

	Total Patients (n = 43)		Controls (n = 50)		Significant Test
Age	35.3	± 11.6	34.1	± 11.4	t=0.5, P=0.6
Sex					
Males	8	18.6%	12	24%	c2=0.4,P=0.5
females	35	81.4%	38	76%	
BMI	24.1	± 2.6	24.9	± 2.3	t=1.6, P=0.1
DHEAS(mg/dl)	160.3	± 63.7	236.5	± 86.3	T=4.8,P≤ 0.001
	Pre-menopausal patients (n = 28)		Pre-menopausal controls (n = 30)		Significant Test
Age	31.1	± 9.8	29.7	± 7.8	t=0.6, P=0.5
BMI	23.6	± 2.6	24.2	± 2.6	t=1.7, P=0.1
DHEAS(mg/dl)	159.4	± 42.5	244.5	± 63.5	t=5.95, P≤ 0.001
	Post-menopausal patients (n = 7)		Post-menopausal controls (n = 8)		Significant Test
Age	51.3	± 3.2	52.8	± 2.3	t=1, P=0.3
BMI	24.4	± 2.5	25.1	± 1.9	t=0.6, P=0.6
DHEAS(mg/dl)	72.9	± 8.5	98.2	± 15.7	t=3.9, P=0.002
	Male patients (n=8)		Male controls (n=12)		Significant Test
Age	36	± 10.2	32.7	± 10.4	t=0.7, P=0.5
BMI	26.6	± 1.9	25.4	± 1.6	t=1.9, P=0.5
DHEAS(mg/dl)	236.6	± 56.6	308.4	± 51.6	t=2.9, P=0.009

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