CIRCADIAN SERUM LEVELS OF DEHYDROEPIANDROSTERONE SULPHATE IN POSTMENOPAUSAL ASTHMATIC WOMEN BEFORE AND AFTER LONG-TERM HORMONE REPLACEMENT

B. Kos–Kudla, Z. Ostrowska*, B. Marek, N. Ciesielska-Kopacz**, M. Kudla***, D. Kajdaniuk, L. Siemidska, J. Strzelczyk

*Department of Pathophysiology and Endocrinology, *Department of Clinical Biochemistry, ** Clinic of Internal and Allergic Diseases, *** III Clinic of Obstetrics and Gynaecology. Silesian Medical University, Katowice, Poland*
E-mail: beatakos@ka.onet.pl

Objective. To assess mean 24-h serum concentrations of dehydroepianrosterone (DHEAS) in postmenopausal women with asthma before and after hormone replacement therapy (HRT).

Methods. Studies were performed in 55 asthmatic and 20 healthy postmenopausal women aged 48-60 before HRT and after 6 months of transdermal 17b-estradiol (E_2) and medroxyprogesterone acetate treatment (cyclical method). Serum DHEAS concentrations were assessed with the use of RIA method.

Results. In the group of postmenopausal asthmatic women treated with glucocorticoids the mean 24 h DHEAS serum levels were lower than in a similar group not treated with glucocorticoids and a control group of healthy postmenopausal women. However, in both groups of asthmatic women (e.g. glucocorticoid treated and untreated) a significant increase of mean daily DHEAS levels after 6 months of HRT was observed. The hormone concentrations did not change in control group.

Conclusions. Postmenopausal asthmatic women show diminished circadian dehydroepiandrosterone sulphate serum concentrations irrespective whether they were treated with glucocorticoids or not. However, after 6 months of hormonal replacement therapy in these groups increased levels of DHEA were found.

Key words: Dehydroepiandrosterone sulphate - Bronchial asthma - Hormone replacement therapy

The role of dehydroepiandrosterone sulphate (DHEAS) in pathogenesis of several diseases, particularly of immune ethiology, has been emphasized recently. Reduced androgen synthesis is thought to be a potential factor predisposing to occurrence of diseases of immunological ethiology. It can also be secondary to disturbances in the course of chronic diseases (Semple et al.1987; Hall et al. 1993). DHEAS, which is the primary androgen circulating in serum of postmenopausal women plays an immunomodulatory role (Hall et al. 1993; Ebeling and Koivisto 1994). Daynes et al. (1990) noticed that DHEAS enhance interleukin-2 synthesis with T-helper cells. Risdon et al. (1991) found that DHEAS inhibits T-killer cells differentiation. This hormone also inhibits the tumour necrosis factor production (Danenberg et al. 1992). The effect of stimulating immune system after DHEAS administration in postmenopausal women has been also described (Casson 1993). Its low concentrations indicate a short life and death caused by circulatory system diseases. Chronic disease, infection and stress can also accompany it. DHEA and DHEAS concentrations are lowered with age. DHEA positively influence lymphokines and antibody production disturbances related to the immune aging of an organism (Daynes et al. 1993; Weksler 1993). Women with higher DHEAS concentrations have higher mineral bone density (Nawata et al. 1995).

Our own clinical observations, confirmed by some reports from literature (Studd et al. 1989; Myers and Sherman 1994), indicate that the use of hormone replacement therapy in postmenopausal, asthmatic women can improve the clinical status of patients. This led us to develop a trial to determine the function of endocrine organs as well as to elucidate the question whether DHEAS concentrations can have both diagnostic and therapeutic meaning. Since a single estimation of homone level sometimes appears of limited diagnostic value, the circadian hormone concentration assays appear more suitable approach to measure endocrine organ function.

Thus, the purpose of this study was to measure and assess circadian DHEAS concentration in postmenopausal asthmatic women and after hormone replacement therapy.

Subjects and Methods

The study was performed in 55 asthmatic women with physiological menopause between the age of 48 to 60 (mean 52.93 ± 3.16), who were divided into following groups: Group I: 32 women using glucocorticoid drugs (GC) in inhalation form (Budesonide in mean doses 600-1600 mg/day); Group II: 23 women, not treated with GC; Group III (Control): 20 healthy postmenopausal women between the age of 49 to 58, who were not treated with any drugs except HRT. Women excluded from the study were: 1. more than 60 year old; 2. with a postmenopausal period lasting more than 5 years; 3. with neoplastic diseases, nephropathy and hepatopathy (e.g. cholecystolithiasis), heart diseases and angiopathy (e.g. chronic hypertensive disease, new or past arterial and venous thrombus episodes), metabolic (e.g. diabetes), hematologic, endocrine (which were not complications of asthma and glucocortico therapy) and gynecological (e.g. bleeding from genital tracts of an unknown reason, endometriosis) diseases; obese (BMI> 26 kg/m^2) or cigarette smokers.

The clinical status of all patients, as assessed by physical examination on the day of blood test for hormone assessment, was good and satisfactory. Contraindications to the use of HRT were not documented in any of the women. No steroid drugs, other than those mentioned above, antidepression medication or thyroid hormones were taken during the studies. The study was approved by the Ethical Committee of Silesian University.

Studies of circadian DHEAS concentrations were performed before HRT therapy and after six 28 days cycles of 17b-estradiol and medroxyprogesterone acetate therapy with the use of cyclic method. 17b-estradiol (using the product Estraderm TTS by Novartis or Systen by Cilag) was administered in a daily dose of 50 mg in transdermal patch twice a week (on Mondays and Thursdays) from 1st to 21st day of the cycle. Medroxyprogesterone acetate (Provera) was administrated orally from 11th to 22nd day of the cycle in a dose of 10 mg/day.

Circadian hormone concentration assessment after HRT was done between the 18th and 20th day of the sixth cycle. Venous blood for hormone assessment was collected every 3 hours during a day. DHEA-SO_4 concentrations in serum were assessed by RIA method with the use of DPC set (Diagnostic Products Corporation, Los Angeles, USA). The sensitivity of the method, defined as the smallest detectable concentration (detection limit for assays) was for DHEAS 1.1 mg/dl. The intraassay coefficient of variation was 7.4 %. The interassay coefficients of variation was 7.5 %.

Statistical evaluation. Wilcoxon matched pair test was used to determine the significance of mean values. Simple linear regression was noted in the study. All calculations were made with the use of Statistica program run on an IBM personal computer. The statistical analysis of the circadian rhythm was performed with the use cosinor test according to Halberg et al. (1967).

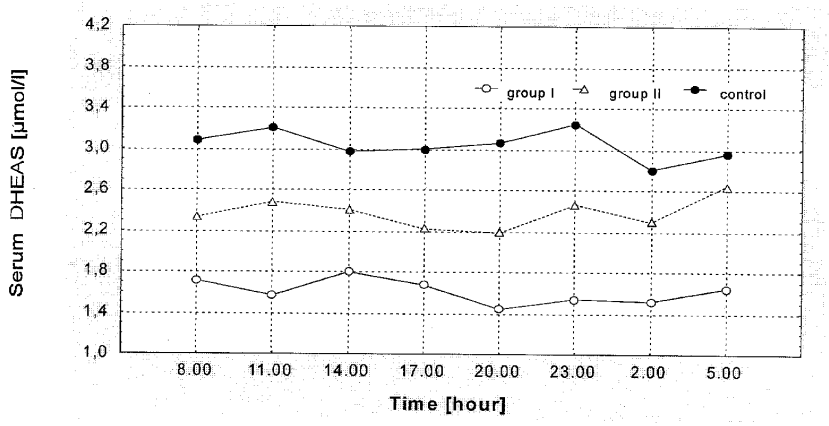
Results

Mean DHEAS concentrations in particular circadian clock times and parameters of daily rhythm

before and after HRT in the asthmatic women and in control group are presented in Fig. 1. We have not observe any circadian rhythm of DHEAS level. In all cases cosinor (p) was statistically unsignificant and therefore we did not analyse the amplitude values and rhythm of acrophase. Mesor values responding to mean 24 h DHEAS serum concentrations were, however, significantly lower in the Group I of asthmatic women as compared to Group II and Group III (Control) before and after HRT use (Fig. 2). In both

A. Before HRT

	GROUP	MESOR [µmol/l] /±SD/	AMPLITUDE [µmol/l] /±SD/	ACROPHASE [h, min] /±SD/	COSINE (p)
DHEAS	I	1,61 ± 0,75	0,11 ± 0,37	$11^h33' \pm 5^h49'$	NS
	II	2,38 ± 1,08	0,12 ± 0,52	$6^h38' \pm 5^h46'$	NS
	III	3,04 ± 0,96	0,04 ± 0,71	$14^h53' \pm 6^h37'$	NS



B. After HRT

	GROUP	MESOR [µmol/l] /±SD/	AMPLITUDE [µmol/l] /±SD/	ACROPHASE [h, min] /±SD/	COSINE (p)
DHEAS	I	2,11 ± 0,75	0,17 ± 0,53	$5^h29' \pm 6^h30'$	NS
	II	2,87 ± 0,81	0,08 ± 0,70	$16^h50' \pm 6^h29'$	NS
	III	3,44 ± 1,16	0,25 ± 0,51	$7^h24' \pm 4^h47'$	NS

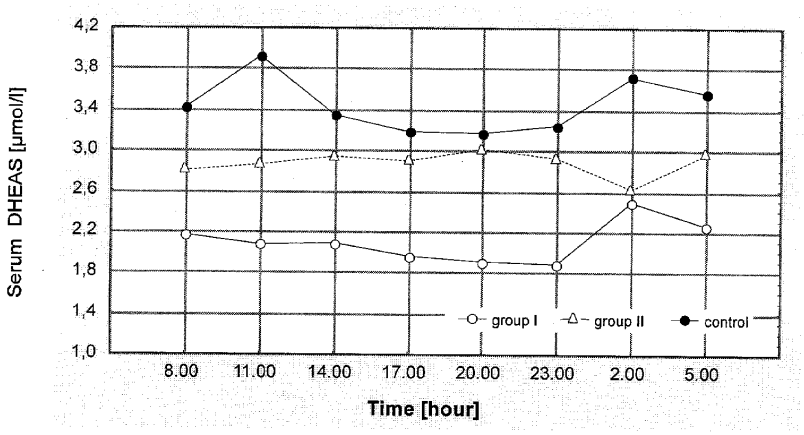


Fig. 1 Circadian oscillation of mean concentrations of dehydroepiandrosterone sulphate in serum and chronobiological parameters of daily rhythm in asthmatic patients treated with GC (Group I), not treated with GC (Group II) and in control (Group III)

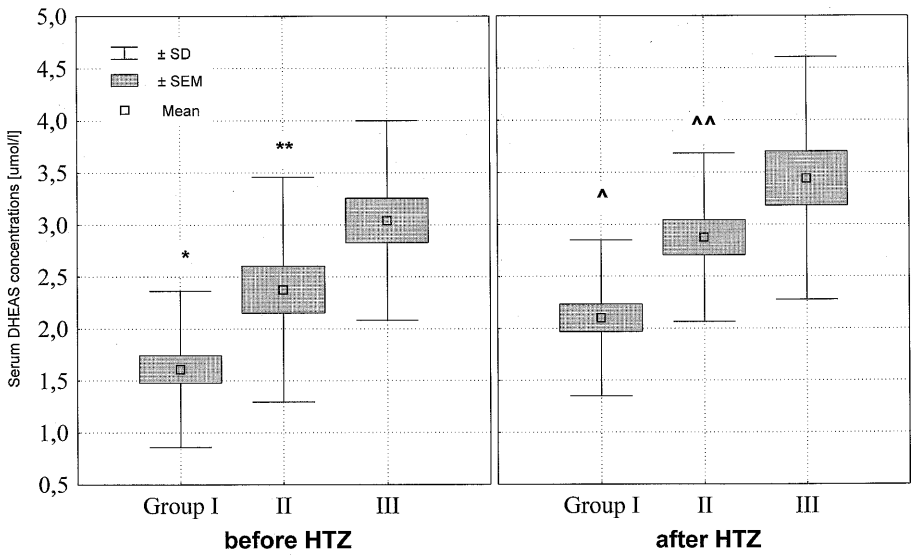


Fig. 2 Comparison of mean 24 h serum dehydroepiandrosterone sulphate (DHEAS) concentrations between particular groups in asthmatic patients treated with GC (Group I) and not treated with GC (Group II) and in control (Group III) before and after hormone replacement therapy (HRT).
*** - PL 0.05 Group I vs. Group III before HRT; ** - PL 0.05 Group I vs. Group II before HRT; ^ - PL 0.05 Group I vs. Group III after HRT; ^^ - PL 0.05 Group I vs. Group II after HRT**

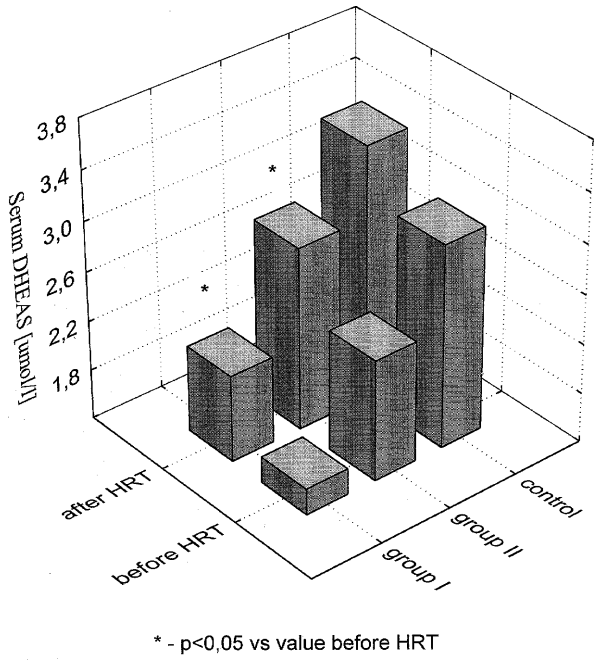


Fig. 3 Mean 24 h serum dehydroepiandrosterone sulphate concentrations before and after hormone replacement therapy (HRT) in asthmatic patients treated with GC (Group I) and not treated with GC (Group II) and in control Group (III)

groups of asthmatic women (I and II) a significant increase of mean daily DHEAS levels after HRT use was observed. The hormone concentrations did not change in control group (III) (Fig. 3).

Discussion

Different opinions on the existence of a daily rhythm of DHEAS secretion were presented in the litarerature. Most of them (Moltz and Schwartz 1986; Dolan and Carey 1989; Hall et al. 1993) suggested that any daily rhythm of DHEAS could not be detected. This was confirmed in our studies. In postmenopausal women daily DHEAS and its precursor DHEA concentrations decrease in comparison to menstruating women. This is explained by the decrease of enzymatic activity of 17,20-desmolase after menopause, which plays an essential role in biosynthesis of D^5 adrenal cortex androgens (Liu et al. 1990).

Our study showed a decrease of mean 24 h DHEAS serum concentrations in asthmatic women before HRT use in compared to the control group. However, this decrease was statistically significant only in the case of the patients using GC. Weinstain

et al. (1996) obtained similar results. They showed that DHEAS concentrations, assessed only in basic conditions in postmenopausal asthmatic women were significantly lower compared with healthy women.

Our results are in agreement with those by DUNN et al. (1984) who showed a lowering of DHEAS concentrations in about 40 % of asthmatic patients in relation to normal values. They suggested that numerous groups of patients with low DHEAS levels could have a potentially weakened adrenal reserve in range of GC production. However, diminished cortisol (F) production was not noted in any of those cases in which lower DHEAS concentration was observed. In patients with normal DHEAS secretion the disturbances in F secretion were also not shown. However, we cannot support the view that the decrease of DHEAS serum concentrations in asthmatic patients result only from a decrease of glucocorticoid function of adrenal cortex. The relationship of ovarial steroidogenesis in maintenance of adequate androgen concentrations in the serum of postmenopausal women must be also taken into consideration (SLUIJMER et al. 1995).

The use of other drugs necessary for asthma symptoms control, such as methylxantines or b-receptor agonist, which can decrease hormone concentrations in serum had also an influence on DHEAS secretion. In our studies the levels of mean 24 h DHEAS concentrations increased significantly after HRT, but they were still lower in patients treated with GC compared to those without GC treatment and to control group. We did not see an increase of DHEAS concentrations caused by HRT in healthy postmenopausal women like in other studies (CASTELO-BRANCO et al. 1995; SLOWINSKA-SRZEDNICKA et al. 1993).

In our previous studies we found that HRT diminishes the number of asthma exacerbations and quantity of used GC drugs (KOS-KUDLA et al. 1999, 2000). An increase of mesodaily DHEAS serum concentrations in asthmatic women treated with GC may depend on decreased use of GC during HRT and the diminished influence of pituitary-adrenal axis function (BARNES and PEDERSEN 1993). Lowering of GC doses during HRT use probably limited suppressory GC action on GnRH secretion and inhibitory influence on ovarium steroidogenesis of androgens (SEKAKURA et al. 1975).

However, the increase of DHEAS in patients not treated with GC is difficult to explain. An increase of DHEAS serum concentrations in asthmatic patients might show an essential clinical value because it may result in a lowering DHEAS concentrations before HRT. Low concentrations of this hormone are related to a weakening of immune system function. However its increase can positively influence lymphokines and antibody production disturbed by immunological aging of the organism and changes related to asthma (WEKSLER 1993, DAYNES et al. 1993). Perhaps the increased DHEAS serum concentrations influence improving course of this disease in postmenopausal women using HRT.

In conclusion, postmenopausal asthmatic women show diminished circadian serum concentrations of dehydroepiandrosterone sulphate. Hormonal replacement therapy in these women influence positively increased the levels of this hormone.

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Corresponding author Beata Kos-Kudla, M.D.
Department of Pathophysiology and Endocrinology
Silesian Medical University
Ul. Sobieskiego 9A/8, 41-800 Zabrze, Poland
Phone/Fax (0048) -32-2786126
E-mail: beatakos@ka.onet.pl