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Relationship Between Blood Pressure Variability and Serum Dehydroepiandrosterone Sulfate Levels

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Decreased diurnal blood pressure variability and low dehydroepiandrosterone sulfate (DHEAS) levels are important predictors of cardiovascular morbidity and mortality. The aim of the study was to determine the relationship between DHEAS levels and diurnal blood pressure variability in normotensive subjects and in patients with essential hypertension of both genders. An ambulatory blood pressure monitor (ABPM), Meditech O2 device and radioimmunoassay were used for ambulatory blood pressure monitoring and the determination of DHEAS levels, respectively. A close correlation ($P < .001$) was found between the diurnal indices and plasma DHEAS levels of the 387 subjects (86 normotensive and 301 hypertensive patients) participating in the study. Decreased plasma DHEAS levels were associated in both genders, and in both normotensive and hypertensive patients with significantly ($P < .001$) lower diurnal indices. There was a close correlation ($P < .001$) between the age-related decrease in plasma DHEAS levels and diurnal indices in both genders. Systolic and diastolic blood pressure variability changed parallel to plasma DHEAS levels in both genders, whether hypertension was present or not. Additional investigations are needed to find out whether reduced DHEAS levels play a role in decreased diurnal indices or whether both can be traced back to one and the same cause. Am J Hypertens 1998;11:532–538 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: **Ambulatory blood pressure monitoring, dehydroepiandrosterone sulfate, hypertension, diurnal blood pressure variability.**

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) offers clear benefits compared to so-called casual blood pressure (BP) measurements[1] because a series of readings helps the physician make diagnostic and therapeutic decisions.[2] With external stimuli and physical activity at a minimum, BP variability ranges between relatively narrow limits, including the 20% fall in BP during sleep.[3,4] Diurnal variation is lower in different types of hypertension but the cause of this phenomenon is unknown. The main androgen hormone produced in the adrenal cortex is dehydroepiandrosterone (DHEA), with its sulfate ester dehydroepiandrosterone sulfate (DHEAS). DHEA excretion changes parallel to diurnal cortisone excretion, whereas no similar change can be observed with DHEAS. Plasma DHEAS levels decrease with age in both healthy men and women (2% per year), reaching an average of 20% of the levels typical at the age of 25 years.[5,6] DHEAS levels show great variations at any age, and genetic differences may explain why normal levels are significantly lower in Japanese men than in American men.[7] It was reported more than 10 years

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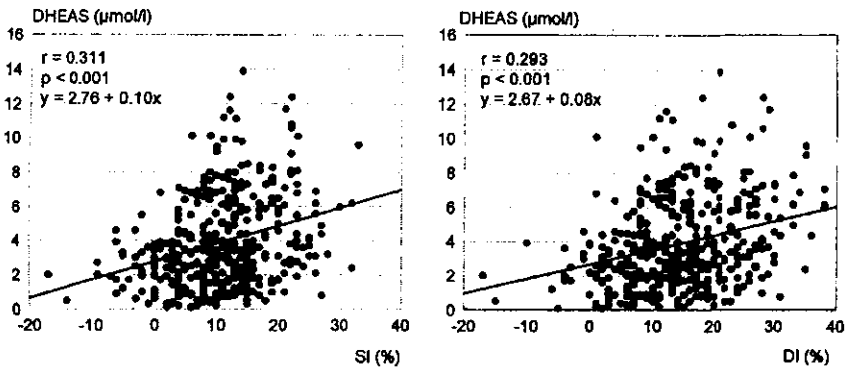

FIGURE 1. *Correlation between serum DHEAS levels and systolic and diastolic indices in the total population studied.*

ago that cardiovascular mortality increased with the reduction of serum DHEAS levels in men.[8] A similar correlation was found later between ischemic heart disease and plasma DHEAS levels in men.[9]

Our aim was to demonstrate a correlation between diurnal BP variability and actual serum DHEAS levels in normotensive subjects and in patients with untreated and treated hypertension. We studied the changes in serum DHEAS levels in women and men of different ages with normal and reduced diurnal indices.

MATERIALS AND METHODS

Normotensive subjects and patients were studied on an outpatient basis; at screening, the usual clinical methods were used to exclude hypertension of endocrine and renal origin. All subjects and patients gave their informed consent to the study.

The 24-h ambulatory BP monitor (Meditech-02 ABPM) was applied between 8:00 and 9:00 AM on the day of the study. According to the previously set program, BP and heart rate were measured every 20 min during the day and every 30 min at night. Daytime and nighttime were considered between 6:00 and 10:00 PM and between 10:00 PM and 6:00 AM, respectively. Thus, 60 to 70 readings were available for each course of measurement. The results were not accepted if technical failures exceeded 10% of the total number of BP measurements. Each patient kept a log of the events of the day, the times of drug intake, if any, and the times of getting up and going to bed. The patients whose average daily BP recorded by the 24-h BP measuring device and found to exceed 130/85 mm Hg were considered hypertensive.[10] The following formula was used to calculate the systolic diurnal index of normotensive patients and patients with clinically established hypertension:

$$\text{SI (\%)} = \frac{\text{mean of daytime systolic BP} - \text{mean of nighttime systolic BP}}{\text{mean of daytime systolic BP}} \times 100;$$

The diastolic index was calculated in a similar way. Blood samples were taken in the fasting state before starting 24-hour BP monitoring to determine serum DHEAS levels by the direct, nonextractive radioimmunoassay (RIA) technique developed in the endocrine laboratory of our department. A high-sensitivity, specific polyclonal antibody against the DHEA-3-hemisuccinate-BSA antigen was produced in rabbit tissue. This method is based on the tritium technique ([1,2,6,7,(3H)] DHEA; Amersham Radiochemical, Amersham, Buckinghamshire, England) and separation was made by dextran-animal charcoal suspension. The methods were confirmed by tests complying with international standards. Details have been provided in our earlier papers.[11] Linear regression analysis and paired *t* test were used for statistical calculations.

RESULTS

Results were evaluated by analyzing the data of a total of 387 (86 normotensive and 301 hypertensive) patients. As antihypertensive medication is known to have no effect on diurnal indices, no differentiation was made between hypertensive patients receiving the drug and nondrug treatments. A close correlation was found between serum DHEAS levels and either systolic ($r = 0.311$) or diastolic ($r = 0.293$) diurnal indices (SI and DI, respectively) ($P < .001$ for both) (Fig. 1). The separate analysis of normotensive and hypertensive patients also resulted in a significant correlation between serum DHEAS levels and both indices (SI and DI, $P < .001$ in hypertension as well as normotension, Figure 2A). There were significant correlations between serum DHEAS levels and systolic and diastolic indices in both untreated and treated hypertensive patients (Figure 2B).

Serum DHEAS levels were significantly higher in men than in women in both normotension (5.5 *v* 3.9 μmol/L, $P < .01$) and hypertension (4.8 *v* 3.1 μmol/L, $P < .001$). Hypertensive patients had lower DHEAS levels than normotensive subjects of the same gender.

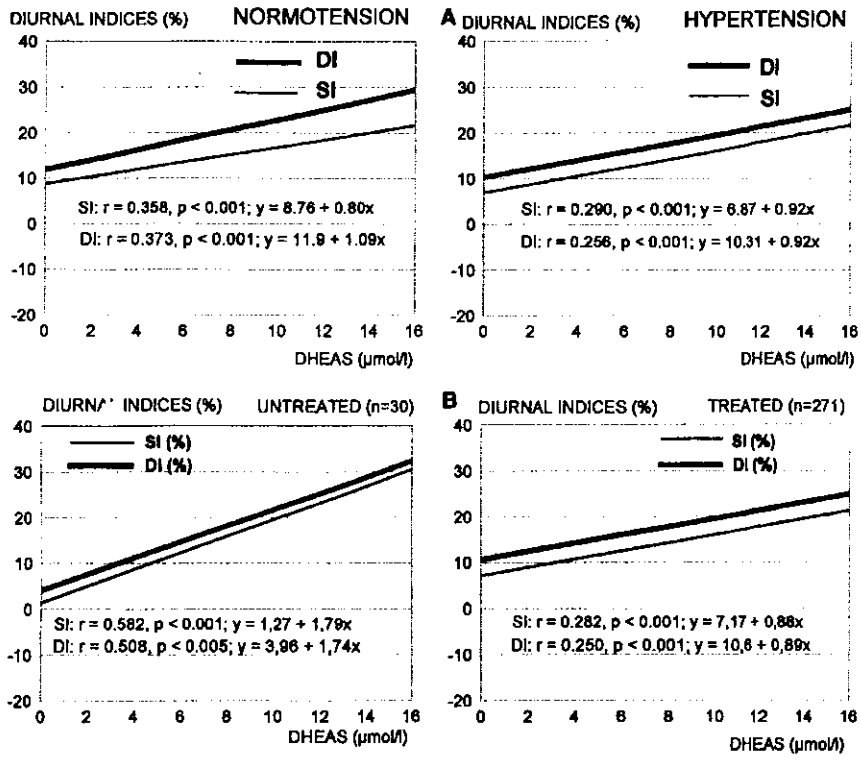

FIGURE 2. *(A) Correlation between serum DHEAS levels and systolic and diastolic indices in normotensive and hypertensive patients. (B) Correlation between serum DHEAS levels and systolic and diastolic indices in untreated and treated hypertensive patients.*

The systolic (9 *v* 12, $P < .02$) and diastolic (13 *v* 16, $P < .05$) indices of women were significantly lower in hypertension than in normotension, whereas men showed significant differences in the diastolic indices (14 *v* 18, $P < .02$). There were no significant differences in either DHEAS levels or in SI/DI values between treated and untreated hypertensive patients. We found significant differences in DHEAS levels and in diurnal indices between normotensive and hypertensive men and women (Table 1). We analyzed the treated and untreated patients separately according to the relation of serum DHEAS and in both groups the significant correlations were valid. We have not found differences in the serum DHEAS levels in different and combined antihypertensive treatments in women. They were significantly higher in hypertensive men treated in monotherapy with β-blockers or calcium channel blockers (Table 2).

Because there were both high and low values in normotension and hypertension, it seemed worth-

TABLE 1. SERUM DHEAS LEVELS AND SYSTOLIC AND DIASTOLIC INDICES OF NORMOTENSIVE AND HYPERTENSIVE PATIENTS

	Women			Men		
	N	DHEAS (µmol/L)	SI/DI (%)	N	DHEAS (µmol/L)	SI/DI (%)
Normotension	53	3.9 ± 2.3	12 ± 8.5/16 ± 8.0	33	5.5 ± 3.3*	13 ± 7.1/18 ± 9.0
Hypertension	196	3.1 ± 2.1	9† ± 8.0/13‡ ± 9.1	105	4.8 ± 2.8**	12 ± 7.6/14 ± 9.4§
Untreated	17	3.0 ± 1.9	8 ± 7.7/12 ± 8.5	13	4.9 ± 2.2	13 ± 6.2/15 ± 9.6
Treated	179	3.2 ± 2.1	10 ± 8.0/14 ± 9.0	92	4.8 ± 2.9	12 ± 8.0/15 ± 10.1

x ± *SD.*

* $P < .01$, *difference in DHEAS levels between normotensive men and women.*

† $P < .001$, *difference in DHEAS levels between hypertensive men and women.*

‡ $P < .02$, *difference in SI values between normotensive and hypertensive women.*

** $P < .05$, *difference in DI values between normotensive and hypertensive women.*

§ $P < .02$, *difference in DI values between normotensive and hypertensive men.*

TABLE 2. SERUM DHEAS IN NORMOTENSIVE SUBJECTS, AND IN UNTREATED AND TREATED HYPERTENSIVE PATIENTS, ACCORDING TO MOST FREQUENT ANTIHYPERTENSIVE TREATMENT

	Men			Women		
	N	DHEAS	Age	N	DHEAS	Age
Normotensive	33	5.5 ± 3.4	42 ± 18.9	53	3.9 ± 2.3	44 ± 14.6
Untreated hypertension	13	4.9 ± 2.2	56 ± 8.8	17	3.0 ± 1.9	54 ± 13.2
Treated hypertension	92	4.8 ± 2.9	54 ± 12.3	179	3.2 ± 2.1	56 ± 12.8
Most frequent therapy						
ACE	21	4.1 ± 2.6	58 ± 9.9	26	3.4 ± 1.9	52 ± 11.3
ACE-Bbl	7	3.7 ± 2.2	60 ± 8.5	9	2.4 ± 1.6	56 ± 10.4
ACE-Bbl-CaA	4	5.9 ± 3.4	55 ± 3.5	18	3.9 ± 2.5	54 ± 14.1
ACE-Bbl-CaA-DIU	2			9	1.9 ± 1.5	55 ± 9.2
ACE-Bbl-DIU	2			4	1.4 ± 1.4	58 ± 9.7
ACE-CaA	12	3.5 ± 2.1	58 ± 12.8	31	3.1 ± 2.4	59 ± 13.7
ACE-CaA-DIU	2			8	2.2 ± 1.5	65 ± 8.8
ACE-DIU	1			7	2.9 ± 2.6	60 ± 12.6
Bbl	6	7.8 ± 1.5*	34 ± 1.5	14	3.5 ± 2.7	53 ± 12.2
Bbl-CaA	2			12	4.1 ± 2.0	49 ± 16.7
Bbl-DIU	4	3.8 ± 1.9	62 ± 11.6	1		
CaA	9	7.0 ± 4.0*	55 ± 4.0	13	2.9 ± 2.0	51 ± 14.5
CaA-DIU	2			6	2.8 ± 1.1	63 ± 7.8
DIU	4	4.7 ± 2.5	56 ± 2.6	3		

** Significant difference (P < .005) in hypertensive men between those treated with β-blocker and ACE inhibitors.*

** Significant difference (P < .05) in hypertensive men between those treated with β-blocker and diuretics.*

** Significant difference (P < .05) in hypertensive men between those treated with calcium channel blockers and ACE inhibitors.*

ACE, angiotensin converting enzyme; Bbl, β-blocker, CaA, calcium antagonist; DIU, diuretic; DHEAS, dehydroepiandrosterone sulfate.

while to use a different approach in the analysis of the data. Subjects of both genders, whether normotensive or hypertensive, with an SI/DI index of less than 12/18, had significantly lower DHEAS levels than those whose indices exceeded 12/18 (Table 3). Serum DHEAS levels and diurnal indices were shown to decrease with age both in men and women (Fig. 3), and were found to change parallel with age in hypertensive patients as well as normotensive subjects (Fig. 4).

DHEAS levels showed a marked decrease between the ages of 45 and 50, accompanied by a delayed decrease in the indices in women and an immediate decrease in men. The correlation between plasma DHEAS levels and the SI/DI indices were therefore analyzed separately in men and women either

TABLE 3. SERUM DHEAS LEVELS OF NORMOTENSIVE AND HYPERTENSIVE PATIENTS AT NORMAL AND DECREASED DIURNAL INDICES

	Normotension			Hypertension		
	N	SI/DI (%)	DHEAS (μmol/L)	N	SI/DI (%)	DHEAS (μmol/L)
Women						
> 12/18	19	17 ± 3.6/24 ± 4.6	4.7 ± 2.3	47	19 ± 5.1/25 ± 4.6	3.6 ± 2.2
≤ 12/18	25	7 ± 4.9/10 ± 6.0*	3.0 ± 2.5	123	5 ± 5.6/8 ± 6.3	2.7† ± 1.9†
Men						
> 12/18	13	20 ± 3.4/27 ± 3.7	7.4 ± 3.5	33	21 ± 4.7/26 ± 5.7	5.1 ± 2.9
≤ 12/18	14	6 ± 3.1/10 ± 5.1	3.9‡ ± 2.5‡	59	6 ± 4.6/8 ± 5.2	3.5** ± 2.7**

x ± SD.

** P < .02, difference in DHEAS levels between normal and decreased diurnal indices in normotensive women.*

† P < .01, difference in DHEAS levels between mormal and decreased diurnal indices in hypertensive women.

‡ P < .001, difference in DHEAS levels between normal and decreased diurnal indices in normotensive men.

*** P < .01, difference in DHEAS levels between normal and decreased diurnal indices in hypertensive men.*

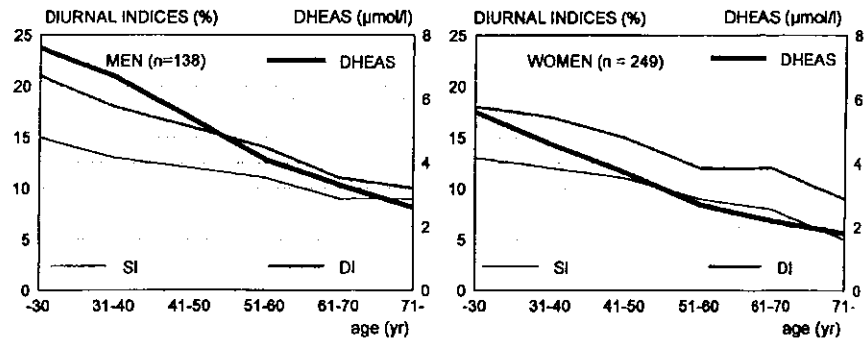

FIGURE 3. *Changes in serum DHEAS levels in men and women by function of age.*

younger or older than 45 years. Lower age-related DHEAS levels were associated with significantly lower diurnal indices in normotensive women (DI, 13 *v* 18, $P < .05$), in hypertensive women (SI, 8 *v* 13, $P < .001$; DI, 12 *v* 17, $P < .005$) and in normotensive men (SI, 10 *v* 15, $P < .05$; DI, 14 *v* 21, $P < .05$) (Table 4).

DISCUSSION

Many papers have been published recently on the changes in the circadian rhythm of BP as measured by ABPM in hypertension of various origins. By analyzing a large number of patients, diurnal indices were found to be 11/17% in normotension, 11/16% in essential hypertension, 3/6% in renal hypertension, and 4/6% in hypertension of endocrine origin.[12] Our study group also analyzed the diurnal BP variability of normotensive individuals, patients with essential and renal hypertension, and patients who underwent renal transplantation.[13,14] Several studies have confirmed the close correlation between reduced diurnal BP variability and end-organ impairment caused by hypertension. Reduced diurnal indices are known to correlate with enlarged left ventricular mass[15], increased 24-h albumin excretion,[16] alcohol consumption and bodyweight[17], and the development of cerebral lacunar infarctions indicating ischemic events in the brain[18].

The significance of DHEAS has raised considerable interest recently. According to a 19-year prospective follow-up study based on mortality statistics, lower serum DHEAS levels tend to be associated with increased cardiovascular mortality in men even when other confounding factors are considered[19]. It is widely known that plasma DHEAS levels decrease with age. Though the number of longitudinal surveys is few, several data suggest that higher DHEAS levels may indicate longevity[20,21]. Other authors, however, have found that high DHEAS levels increase the risk of myocardial infarction[22]. Some papers reported decreased hormone levels in hypertension, obesity, and conditions accompanied by hyperinsulinemia.[23,24]

We have not found any data in the literature on the age-dependent change in diurnal indices or on the correlation between DHEAS and diurnal indices. In our study, a close correlation was found between serum DHEAS levels and systolic or diastolic indices. Normal DHEAS values were accom-

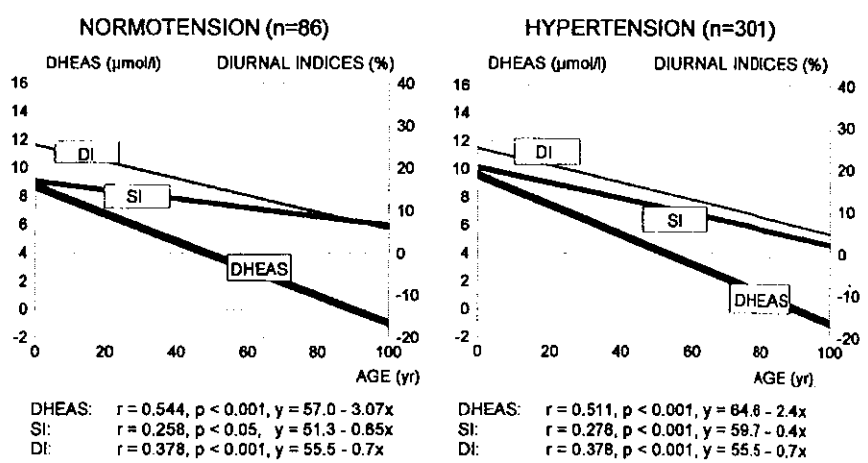

FIGURE 4. *Correlation between age and DHEAS levels and systolic and diastolic indices in normotensive and hypertensive subjects.*

TABLE 4. SERUM DHEAS LEVELS AND SI/DI VALUES OF NORMOTENSIVE AND HYPERTENSIVE PATIENTS OF DIFFERENT AGES

	Normotension			Hypertension		
	N	DHEAS (μmol/L)	SI/DI (%)	N	DHEAS (μmol/L)	SI/DI (%)
Women						
≤ 45	29	5.1 ± 2.3	13 ± 4.9/18 ± 7.1	41	5.4 ± 2.4	13 ± 6.4/17 ± 8.3
> 45	24	2.4 ± 1.5	10 ± 6.7/13* ± 8.3*	155	2.6 ± 1.6	8† ± 8.1/12‡ ± 9.0
Men						
≤ 45	18	6.9 ± 3.5	15 ± 6.9/21 ± 8.0	16	7.4 ± 3.3	13 ± 7.5/15 ± 10.4
> 45	15	3.8 ± 2.3	10** ± 6.7**/14§ ± 8.5§	89	4.2 ± 2.5	10 ± 7.3/13 ± 8.2

$x \pm SD$.

* $P < .05$, *difference between the diastolic indices of normotensive women of different ages.*

† $P < .001$, *difference between the systolic indices of hypertensive women of different ages.*

‡ $P < .005$, *difference between the diastolic indices of hypertensive women of different ages.*

** $P < .05$, *difference between the systolic indices of normotensive men of different ages.*

§ $P < .05$, *difference between the diastolic indices of normotensive men of different ages.*

panied by normal SI or DI values, whereas decreased hormone levels were accompanied by lower indices whether hypertension was present or not. Amlodipine, a calcium channel blocker, raises serum DHEAS, diminishes hyperinsulinemia, and decreases cortisol levels in obese hypertensive men[25]. We found elevated serum DHEAS in men who were treated in monotherapy with calcium channel blockers or with β-blockers.

The analysis of our data as a function of age showed diurnal indices to decrease in parallel with DHEAS levels. The different values for men and women as a function of age are explained mainly by hormonal changes. Hypertension occurs most frequently in middle-aged and older individuals. No difference was found in the DHEAS levels and SI or DI values between normotensive and hypertensive patients either in the group aged < 45 years or that aged > 45 years. Consequently, hypertension itself does not account for decreased diurnal indices. Reduced DHEAS values were found to be accompanied by low SI/DI indices in both normotensive and hypertensive patients. Therefore, an age-related decrease in DHEAS correlates to the progressive onset of cardiovascular diseases, and Barbagallo et al[26] found evidence of the direct vascular action of DHEAS, suggesting its modulating effects on intracellular calcium metabolism. DHEAS administration may provide substantial protection against the age-related decrease in DHEAS in the development of cardiovascular mortality. We are planning on analyzing its effect on diurnal variability. Further investigations are needed to find out whether reduced DHEAS levels play a role in decreased diurnal indices, or whether both can be traced back to one and the same cause.

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