Turkish Journal of Endocrinology and Metabolism, (1999) 2 : 71-75 **ORIGINAL ARTICLE**

The Association of Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate with Obesify, Waist-hip Ratio, and Insulin Resistance in Postmenopausal Women*

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Recent studies revealed that oral dehydroepiandrosterone (DHEA) reduced vveight gain in genetically obese mice without affecting their food inlake. We aimed to compare the associîation of DHEA and dehydroepiandrosterone sulfate (DHEAS) levels with obesity, tat distribution and insulin resistance in different groups of postmenopausal vvomen.

Thirty postmenopausal women were divided into age-matched three groups; Group-I: 10 obese vvomen vvith Type II diabetes mellitus, group-II: 10 obese women without diabetes, group III: (Controls); 10 nonobese and nondiabetic vvomen. Body mass index (BMI), waist-hip ratio (WHR), and insulin resistance (by hyperinsulinemic euglycemic clamp studies} were calculated in ali groups. Plasma DHEA and DHEAS levels were also measured.

Women in group-I and II had significantly higher WHR than control women, indicating central deposition of body fat (p=0.039, p=0.041 respectively). As expected, insulin resistance was most sîgnificant in obese and diabetic women (group-I). Follovvİng them obese but nondiabetic vvomen (group-II) had more insulin resistance than women without obesity and diabetes (group-III). DHEA and DHEAS levels of women vvith obesity and diabetes {group-I) were greater than those of group-II and group-III. Group-III had the lovvest DHEA and DHEAS levels in ali vvomen. DHEA and DHEAS vvere positively correlated with both BMI and WHR. However, glucose disposal rate was inversely and significantly correlated vvith DHEA and DHEAS levels.

These data do not support the hypothesis that DHEA ör DHEAS protect postmenopausal vvomen against diabetes and obesity. These findings suggest that increasing levels of DHEA and DHEAS may be associaîed vvith vveight gain, central obesity and reduced insulin sensitivity.

KEY VVORDS Dehydroepiandrosterone, dehydroepiandrosterone sulfate, obesity, waist-hip ratio, insulin resistance, postmenopausal women

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Introduction

Dehydroepiandrosterone (DHEA) unconjugated ör as its sulfate (DHEAS) is the majör secretory steroid product of the adrenal gland (1). DHEA is considered as a weak androgen, and its concentration has a greater diurinal variation than DHEAS. The secretion of DHEAS is stimulated by corticotrophin (ACTH), but responsiveness of DHEAS to stimulation decreases with advancing age and

the rnean concentration of DHEAS in serum is reduced progressively from a peak at age 25 to less than 20% of that peak before the age of 70(2). Despite the abundance of DHEA and DHEAS their physiological role has remained unclear.

Yen and his colleagues reveaied that oral DHEA reduced weight gain in genetically obese mice without affecting their food intake (3). Since then, an antiobesity effect of DHEA has been confirmed in many other studies of laboratory animals, which have also shown a variety of favorable metabolic effects including an antidiabetogenic effect (4). DHEA has been shown to reduce the hyperglycemia and hyperinsulinemia of diabetic ör obese mice (5,6).

Studies in humans, however, produced contradictory results. in a study of obese men, 1600 mg/day DHEA was adrninistered orally for 4 weeks but this protocol could not demonstrate any effect of DHEA on body fat ör fat distribution (7). in 6 obese postmenopausal wornen who were treated with DHEA for 28 days, peak insulin levels during a glucose tolerance test were found to be significantly higher than pretreatment values (8). However, there was no change İn body weight ör fat distribution.

After infusion of physiological doses of insulin, DHEA concentrations significantly increased in oophorectomized women but not in regularly menstruating obese women (9,10,11). Menopausal status may play an important role in determining how DHEA and DHEAS will affect obesity and insulin sensivity (9).

We aimed to investigate the association of DHEA and DHEAS levels with obesity, fat distribution and İnsulin resistance in three different groups of postmenopausal women: obese, diabetic and non-obese-nondiabetic.

Materials and Methods

We included 30 postmenopausal women aged between 50-65 years in the study. Demographic data, menopausal status, gynecological surgery, history of diabetes, and current use of selected medications were determined by a Standard questionnaire.

Women were considered to be postmenopausal if they had had no menses for l year, ör had had an oophorectomy.

Postmenopausal women were divided into three groups:

Group-I: 10 obese women with Type II diabetes mellitus (BMI>30 kg/m^2).

Group-II: 10 obese women without diabetes (BMI>30 kg/m^2).

Group III: (Controls); 10 nonobese and nondiabetic women (BMI<25 kg/m^2).

Body weight was measured with subjects wearing light clothes and no shoes. Body mass index (BMI) was calculated as kg/m^2. BMI was used to determine overall obesity according to the recommendations of the World Health Organization. Waist circumference was measured at the bending point and hip circumference at the widest part of the gluteal region. Waist-hip ratio (WHR) was calculated and used as a measure of central obesity, WHR values greater than 0.8 showed central obesity. Subjects in group-III were examined and tested for having diabetes mellitus by oral glucose tolerance test. Subjects who had no diabetes and no impaired glucose tolerance were included in the study.

Subjects using oral antidiabetic agents, insulin, ör estrogen replacement therapy were excluded to remove possible effects of therapy on DHEA and DHEAS levels. Subjects also were excluded if they had renal failure, liver ör lung diseases, heart failure, malignancy, anemia ör endocrine diseases other than diabetes.

Fasting plasma specimens wcre frozen at -70°C. After an average of 3 months, these specimens were fİrst thawed for DHEA and DHEAS rneasurements. Assays were performed by RIA (Diagnostic Products Corporation/USA kits) with Packard gamma counter. The intraassay and interassay coefficients of variation were less than 8% and 9%, respectively. Ali hormone measurements were analyzed within a single assay.

Hyperinsulinemic euglycemic clamp studies were performed according to previously described methods and lissue sensitivity to insulin was expressed

as the glucose disposal rate (M) (milligrams per kg/minute) (12). A catheter was inserted into an antecubital vein for infusion of insulin and glucose. A second catheter was inserted into a dorsal hand vein, which was kept in a heating device, for sampling of arterialized venous blood. Recombinant human regular insulin was infused via an Abbott(pump at a rate of 40 m U/m^2. Min for a total of 240 mİn. Serum glucose was maintaİned al eııglycemic levels by adjusting a variable infusion of 20% glucose based on the glucose values determined at 5 min intervals. Whole body glucose disposal rates were calculated by determining the rnean of data from the last 60 min of the study.

Results are reported as mean (SD. Comparisons between groups were made by Students' two tailed unpaired t test. P<0.05 was considered to be significant. Linear regression and correlation analysis were used for the calculation of correlation between parameters. For this purpose; r>0.20 and p<0.05 were considered to be significant. The negativity ör positivity of r showed the direction of correlation.

Results

Table l shows comparison of age, BMI, presence of diabetes mellitus, WHR, insulin sensitivity, and DHEA, and DHEAS levels in ali groups. The patients in ali three groups were age matched (p>0.05). BMI showed obesity in group-I and group-TI and no statistically significant difference was found between these groups (p=0.678). Group-Ill had a lower BMI value than the first two groups (p=0.000). Central obesity is more pronounced in the women of group I and II as compared with group III. (p-0.039, p=0.04l respectively). As expected, insulin resistance was most significant in obese and diabetic women (group-I). Followİng them, obese but nondiabetic women (group-II) had insulin resistance, where as subjects without obesity and diabetes did not have insulin resistance (group-III).

DHEA and DHEAS levels of women with obesity and diabetes (group-I) were greater than those of group-II and group-III. Women without obesity and diabetes (group-III) had the lowest DHEA and DHEAS levels.

Table 1. Comparisons of groups according to measured parameters.

Parameters	Group-I	Group-II	Group-III	P values
Age (year)	55.91±5.10	56.90±4.92	56.25±4.81	p_1>0.05 p_2>0.05 p_3>0.05
BMI (kg/m^2)	31.92±2.13	31.34±3.78	24.85±0.80	p_1=0.678 p_2=0.000 p_3=0.000
WHR	0.86±0.11	0.87±0.13	0.76±0.09	p_1=0.855 p_2=0.039 p_3=0.041
M (mg/kg.min)	3.62±0.46	4.53±0.83	6.76±0.75	p_1=0.007 p_2=0.000 p_3=0.000
DHEAS (µg/dl)	78.33±10.33	64.21±8.41	54.29±8.81	p_1=0.004 p_2=0.000 p_3=0.19
DHEA (ng/ml)	9.94±2.59	7.79±1.27	6.03±1.81	p_1=0.030 p_2=0.001 p_3=0.022

p_1: group-I vs group-II; p_2: group-I vs group-III; p_3: group-II vs group-III

M: glucose disposal rate

DHEA and DHEAS were positively correlated with both BMI and WHR. However, glucose disposal rate was inversely and significantly correlated with DHEA and DHEAS levels. Table 2 shows the correlatıon of DHEA and DHEAS with BMI, glucose disposal rate and WHR.

Table 2. The Correlation Of DHEA And DHEAS With BMI, Glucose Disposal Rate And WHR.

	DHEA (ng/ml)	DHEA-S (µg/dl)
BMI (kg/m^2)	r=0.818, p<0.001	r=0.904, p=0.02
M (mg/kg.min)	r=-0.962, p<0.001	r=-0.965, p<0.001
WHR	r=0.741, p=0.035	r=0.871, p=0.011

(r>0.20 and p<0.05 was considered significant.)

Discussion

Our results showed that postmenopausal women with high DHEA and DHEAS levels have significantly higher BMIs, WHRs and more insulin resistance than women with lower levels of these hormones. These fİndİngs are the reverse of what nıight have been predicted f rom animal studies. in animal studies, DHEAS was shown to have an antîobesity and antidiabetîc effect (5,6). These results are, however, concordant vvith a clinical trial in which DHEAS levels were found to be hîgher in obese postmenopausal women Ihan in postmenopausal women with lower BMI (9).

in vitro and in vivo data suggest that DHEA and DHEAS have eİther oestrogen ör androgen like effects, depending on sex hormone homeostasis (13). Also the DHEA metabolite 5-androstene-3(3, 17(3-diol (ADIOL) has both androgenic and oestrogenic effects in human rnyometrial tissue and in mammary cancer celi s (14). ADIOL is 500 times more potent as an inhibİtor of eostrogen binding than DHEA (15). in woınen 100% and in men approximately 60% of ADIOL is derİved fromDHEA(16).

in literatüre a hypothesis of Ebeling and Koivisto trİes to explain sonıe points of DHEA(S)'s physiological importance (1). in postmenopausal women DHEA administratîon is strongly androgenic, lowering sex hormone binding globulin (SHBG) and raising free testosterone (17). The role of DHEA and DHEAS in central obesity and insulin resistance can be explained by their dual actions as oestrogen ör as androgen.

in healthy individuals the site-specific regulation of lipoprotein lipase (LPL) activity plays an important part in the maintenance of normal body fat distribution(lS). Activation of the corticolrophin-releasing factor (CRH) cortisol (DHEA) axis increases the accurnulation of visceral fat, as seen in patients with Cushing's disease(19). Glucocorticoids increase LPL enzyme activity more in the visceral than in subcutaneous adipose tissue (18).

The androgenic effects of DHEA may have a role in fat distribution too. in postmenopausal women serum DHEAS concentrations correlate positively with trunk fat accurnulation whereas no such effect is seen in men (20,21). A shift in fat accumulation in women towards abdominal obesity can be an androgenic effect of DHEA (17). in healthy postmenopausal women androgen levels are inversely related to fasting plasma glucose concentrations and predictive of central adiposity 10-15 years later (22). Thus, an increased androgenic effect in women may contribute to abdominal obesity, leading to moderate hyperglycemia.

Ebeling and Koivisto suggest that high DHEA (S) levels, especially in oestrogen-deficient postmenopausal women, lead to a vicious circle: greater androgenic effect —> increased abdominal fat accumulation —» hyperinsulinaemia —> fail in SHBG concentration —» increased free testosterone delivery to tissues, greater visceral fat accumulation, and so on. The antilipolytic effect of insulin is less in the omental than subcutaneous adipose tissue resulting in increased portal concentrations of free fatty acids (23,24). increased delivery of free fatty acids and glycerol to the liver augments hepatic glucose production and reduces hepatic insulin clearance, thus increasing hyperinsulinaemia (24). Rates of hepatic glucose produclion correlate vvith fasting plasma glucose concentrations even wİthîn the normal range. Any rise in blood glucose augments insulin secreîion further, and the sequence of hyperinsulinaemia, low SHBG, hyperandrogenism, abdominal obesity, insulin resistance, and hyperinsulinaemia lead to type 2 diabetes in susceptİble women.

in conclusion; although the mechanisms of these associatİons remain unclear, these data do not support the hypothesis that DHEA ör DHEAS protect postmenopausal women against diabetes and obesîty, Indeed, DHEA and DHEAS may be the cause of obesity (especially abdominal obesity) and diabetes in oestrogen deficient women.

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