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 weight gain in genetically obese mice without affecting their food intake. We aimed to compare the association of DHEA and dehydroepiandrosterone sulfate (DHEAS) levels with obesity, fat distribution and insulin resistance in different groups of postmenopausal women.

Thirty postmenopausal women were divided into age-matched three groups; Group-I: 10 obese women with Type II diabetes mellitus, group-II: 10 obese women without diabetes, group III: (Controls); 10 nonobese and nondiabetic women. Body mass index (BMI), waist-hip ratio (WHR), and insulin resistance (by hyperinsulinemic euglycemic clamp studies) were calculated in all 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 significant in obese and diabetic women (group-I). Following them obese but nondiabetic women (group-II) had more insulin resistance than women without obesity and diabetes (group-III). DHEA and DHEAS levels of women with obesity and diabetes (group-I) were greater than those of group-II and group-III. Group-III had the lowest DHEA and DHEAS levels in all women. 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.

These data do not support the hypothesis that DHEA or DHEAS protect postmenopausal women against diabetes and obesity. These findings suggest that increasing levels of DHEA and DHEAS may be associated with weight gain, central obesity and reduced insulin sensitivity.

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

Introduction

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

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the mean 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 revealed 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 or obese mice (5,6).

Studies in humans, however, produced contradictory results. in a study of obese men, 1600 mg/day DHEA was administered orally for 4 weeks but this protocol could not demonstrate any effect of DHEA on body fat or fat distribution (7). in 6 obese postmenopausal women 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 in body weight or 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 sensitivity (9).

We aimed to investigate the association of DHEA and DHEAS levels with obesity, fat distribution and insulin 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 1 year, or had had an oophorectomy.

Postmenopausal women were divided into three groups:

Group-I: 10 obese women with Type II diabetes mellitus (BMI>30 kg/m²).

Group-II: 10 obese women without diabetes (BMI>30 kg/m²).

Group III: (Controls); 10 nonobese and nondiabetic women (BMI<25 kg/m²).

Body weight was measured with subjects wearing light clothes and no shoes. Body mass index (BMI) was calculated as kg/m². 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, or 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 or lung diseases, heart failure, malignancy, anemia or endocrine diseases other than diabetes.

Fasting plasma specimens were frozen at -70°C. After an average of 3 months, these specimens were first thawed for DHEA and DHEAS measurements. 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. All hormone measurements were analyzed within a single assay.

Hyperinsulinemic euglycemic clamp studies were performed according to previously described methods and tissue 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/m². Min for a total of 240 min. Serum glucose was maintained at euglycemic 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 mean of data from the last 60 min of the study.

Results
Table 1 shows comparison of age, BMI, presence of diabetes mellitus, WHR, insulin sensitivity, and DHEA, and DHEAS levels in all groups. The patients in all 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-III 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<0.041 respectively). As expected, insulin resistance was most significant in obese and diabetic women (group-I).

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>
<thead>
<tr>
<th>Parameters</th>
<th>Group-I</th>
<th>Group-II</th>
<th>Group-III</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>55.9±5.10</td>
<td>56.9±4.92</td>
<td>56.2±4.81</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.9±2.13</td>
<td>31.3±3.78</td>
<td>24.8±0.80</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>WHR</td>
<td>0.86±0.11</td>
<td>0.87±0.13</td>
<td>0.76±0.09</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>M (mg/kg/min)</td>
<td>3.62±0.46</td>
<td>4.53±0.83</td>
<td>6.7±0.75</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>DHEAS (µg/dl)</td>
<td>78.3±10.33</td>
<td>64.2±18.41</td>
<td>54.2±8.81</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>DHEA (ng/ml)</td>
<td>9.9±4.2</td>
<td>7.79±1.27</td>
<td>6.03±1.81</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

p1: Group-I vs Group-II; p2: Group-I vs Group-III; p3: 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 correlation 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/m²)                    | 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|

(p>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 findings are the reverse of what might have been predicted from animal studies. In animal studies, DHEAS was shown to have an antilipolytic and antidiabetic effect (5,6). These results are, however, concordant with a clinical trial in which DHEAS levels were found to be higher in obese postmenopausal women than in postmenopausal women with lower BMI (9).

In vitro and in vivo data suggest that DHEA and DHEAS have either oestrogen or androgen like effects, depending on sex hormone homeostasis (13). Also the DHEA metabolite 5-androstene-3(17β)-diol (ADIOL) has both androgenic and oestrogenic effects in human myometrial tissue and in mammary cancer cells (14). ADIOL is 500 times more potent as an inhibitor of oestrogen binding than DHEA (15). In women 100% and in men approximately 60% of ADIOL is derived from DHEA (16).

In literature a hypothesis of Ebeling and Koivisto tries to explain some points of DHEA(S)’s physiological importance (1). In postmenopausal women DHEA administration 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 or 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 (15). Activation of the corticolphrin-releasing factor (CRH) cortisol (DHEA) axis increases the accumulation 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 accumulation 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 —> fall 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 production correlate with fasting plasma glucose concentrations even within the normal range. Any rise in blood glucose augments insulin secretion further, and the sequence of hyperinsulinaemia, low SHBG, hyperandrogenism, abdominal obesity, insulin resistance, and hyperinsulinaemia lead to type 2 diabetes in susceptible women.
in conclusion; although the mechanisms of these associations remain unclear, these data do not support the hypothesis that DHEA or DHEAS protect postmenopausal women against diabetes and obesity. Indeed, DHEA and DHEAS may be the cause of obesity (especially abdominal obesity) and diabetes in oestrogen deficient women.

References