PITUITARY-ADRENAL-OVARIAN AXIS RESPONSE TO ORAL ADMINISTRATION OF DEHYDROEPIANDROSTERONE (DHEA) IN ADULT FEMALE RATS

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Key words: DHEA, Hormones,BMI, Female rats.

ABSTRACT

The aim of the present study is to evaluate the effect of oral administration of DHEA on Pituitary-Adrenal-Ovarian Axis in female rats. A total of forty adult female rats weighting 200-250 gm were divided into four equal subgroups and administered orally for six weeks as follows: distilled water, 0.5, 1 and 2 mg/kg B.wt DHEA for control group (C), group 1 (G1), group 2 (G2) and group 3 (G3) respectively. Blood samples were collected after 2, 4 and 6 weeks for estimation of adrenocorticotropic hormone (ACTH) and Follicle-stimulating hormone (FSH) concentrations. Body weight, length and body mass Index (BMI) were measured at these weeks. The results revealed a significant increase of serum ACTH and FSH concentrations in DHEA groups as compared with control. Besides a significant decrease in body weight and body mass index of rats received DHEA in comparison with control.

INTRODUCTION

5-Dehydroepiandrosterone (5-DHEA) is 19-carbon endogenous natural steroid hormone. Dehydroepiandrosterone (DHEA) is a hormone that is naturally made by the animal and human body. It can be made in the laboratory from chemicals found in wild yam and soy. However, the body cannot make DHEA from these chemicals, so simply eating wild yam or soy will not increase DHEA levels. DHEA and DHEAS are plentiful circulating steroids produced from adrenal gland and gonads. DHEA converted to testosterone or estrogen and show 90% decline by age(1).

Dehydroepiandrosterone (DHEA) is used for slowing or reversing aging, improving thinking skills in older people, and slowing the progress of Alzheimer’s disease.
Athletes and other people use DHEA to increase muscle mass, strength, and energy. DHEA is also used by men for erectile dysfunction (ED), and by healthy women and women who have low levels of certain hormones to improve well-being and sexuality (2&3).

It has been introduced the term of fountain of youth for DHEA. As it is an antiaging hormone. There is an epidemiological evidence that have DHEA and its metabolite DHEAS levels in serum are associated with an increase of metabolite DHEAS levels in serum are associated with an increase of metabolic syndromes related to age like cardiovascular diseases, diabetes mellitus and hypertension (4). All female animals are born with a definite number of eggs which deceases gradually with age. When the egg supply becomes very low, it is called diminished ovarian reserves (DOR) which is the most common causes of infertility in animals and women. However, one notable cause of DOR is decreased DHEA levels. Thus DHEA is used primarily to treat women with DOR which occurs either as a consequence of female aging or premature ovarian aging (POA). From the other hand, DHEA in used in menopause females which is usually associated with a sudden decline in estrogenone (5).

MATERIALS AND METHODS

A total of fortyadult female Albino Wistar rats weighting (200-250gm). Their ages ranged between (2.5 - 3.5 month). After acclimatization for 2 weeks, they were divided into four equal subgroups and administrated orally for six weeks as follows: distilled water, 0.5, 1 and 2 mg/kg B.wt DHEA for control group (C), group 1 (G1), group 2 (G2) and group 3 (G3) respectively. Blood samples were collected after 2, 4 and 6 weeks for estimation of adrenocorticotropic hormone (ACTH) and Follicle-stimulating hormone (FSH) concentrations. Body weight, length and body mass Index (BMI) were measured at these weeks. According to the results group three that received 2 mg/kg B.wt DHEA seems to give the best results(3). Thus, 5 rats from each the control (C) and the third group (G3) were continued for another two weeks for estimation of serum cortisol and estradiol concentrations. There are also showed a significant increase of estradiol with a significant decreased in cortisol for group received received 2 mg/kg B.wt DHEA as compared with control. Date were expressed as mean ± SE and P-value (< 0.05) we considered statistically significant (6).
RESULTS

The effect of different doses of DHEA at different intervals on adult female rats:

ACTH concentration:

Table (1) shows a significant increase (P > 0.05) in ACTH concentration in treated groups along the experimental periods comparing with control. At the meantime, the highest concentration of ACTH is shown in G3 (2 mg /kg B.Wt) when compared with other groups. However, this difference is significant in G2 and G3 i.e. the table showed significant increase (P > 0.05) in ACTH level after the 6th week in comparison to the 2nd and 4th week in G2 and a significant increase (P > 0.05) after the 4th week in G3 comparing with the 2nd and 6th week.

Table (1): Serum ACTH level (pg/ml) in response to oral DHEA administration at 0.5, 1, 2 mg/Kg B.wt. in adult female rats for six weeks.

<table>
<thead>
<tr>
<th>Week</th>
<th>Group</th>
<th>Control</th>
<th>G1 0.5 mg /kg B.wt</th>
<th>G2 1 mg /kg B.wt</th>
<th>G3 2 mg /kg B.wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>79.50 ± 2.75</td>
<td>102.82 ± 6.15</td>
<td>170.14 ± 3.71</td>
<td>583.58 ± 17.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D</td>
<td>C</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>73.76 ± 7.60</td>
<td>105.24 ± 7.47</td>
<td>173 ± 6.15</td>
<td>633.04 ± 13.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D</td>
<td>C</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>69.18 ± 3.34</td>
<td>± 6.48</td>
<td>104.16</td>
<td>181.44 ± 8.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D</td>
<td>C</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

Mean ± SE (n=10 rats/ group)
Capital letters indicate a significant (p> 0.05) difference between groups.
Small letters denote a significant (p> 0.05) difference within group.

FSH concentration:

The concentration of FSH shows a significant increase (p> 0.05) in G3 in comparison to control group after two weeks of DHEA administration. Whereas there is no significant increase (p≤ 0.05) in FSH level between G1 and G2 as compared to C and G3 at the 2nd week of treatment (table 2). However, this differences become significant (p > 0.05) in G3 in comparison to all groups (C, G1 and G2) after six weeks of DHEA oral administration.

Table (2): Serum FSH level (mIU/ml) in response to oral DHEA administration at 0.5, 1, 2 mg/Kg B.wt. in adult female rats for six weeks.
Estradiol and Cortisol concentration:

The values represented in table (3) reveal a significant increase \((p > 0.05)\) in estradiol concentration in rats received 2 mg/kg B.Wt DHEA as compared with control. The table also showed the effect of oral DHEA administration on serum cortisol concentration. However, the mean value of cortisol concentration reveal a significant decrease \((p > 0.05)\) in DHEA group with a mean value of \((10.56 \pm 0.18)\) as comparing with \((16.98 \pm 0.27)\) for control.

Table (3): Serum Estradiol (pg/ml) and Cortisol level (µg/dl) in response to oral DHEA administration at 2 mg/Kg B.wt, in adult female rats.

<table>
<thead>
<tr>
<th>Week</th>
<th>Group</th>
<th>C Control</th>
<th>G 1 0.5 mg/kg B.wt</th>
<th>G 2 1 mg/kg B.wt</th>
<th>G 3 2 mg/kg B.wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Control</td>
<td>9.92 ± 0.17</td>
<td>11.10 ± 0.42</td>
<td>11.32 ± 0.15</td>
<td>12.70 ± 0.42</td>
</tr>
<tr>
<td></td>
<td>A a</td>
<td>A a</td>
<td>AB a</td>
<td>AB a</td>
<td>AB a</td>
</tr>
<tr>
<td>4</td>
<td>G 1</td>
<td>9.64 ± 0.28</td>
<td>8.88 ± 0.30</td>
<td>10.76 ± 0.57</td>
<td>10.82 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>A a</td>
<td>A a</td>
<td>A a</td>
<td>A a</td>
<td>A b</td>
</tr>
<tr>
<td>6</td>
<td>G 3</td>
<td>9.04 ± 0.30</td>
<td>11.20 ± 0.35</td>
<td>10.76 ± 0.35</td>
<td>15.68 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>B a</td>
<td>B a</td>
<td>A a</td>
<td>A a</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SE (n=10 rats/ group).
Capital letters indicate a significant \((p > 0.05)\) difference between groups.
Small letters denote a significant \((p > 0.05)\) difference within group.

Measurement of body weight:

Although, the mean body weight (g) for the three treated groups were non-significantly \((p > 0.05)\) higher than that of control before DHEA administration, table (4) reveal a clear significant effect of treatment. However, there is a non-significant increase \((p \leq 0.05)\) in body weight of rats received 2 mg/kg B.Wt as compared with control after two weeks of the experiment. At the meantime, the same group showed a significant decrease \((p > 0.05)\) in comparison with rats received 1 mg/kg B.wt DHEA.

The table also shows a significant decrease \((p > 0.05)\) in the value of mean body weight in group of rats administered with 2mg/kg B.wt as compared with control and other treated groups at the fourth and sixth week of the experiment. Within the same
group, body weight of rats showed a gradual decrease according to the dose of DHEA administered. However, the total weight gain (g) was (+62), (+11), (0) and (-30) in C, G1, G2 and G3 groups respectively.

Table (4): Body weight (g) in response to oral DHEA administration at 0.5, 1, 2 mg/kg B.wt in adult female rats for six weeks.

<table>
<thead>
<tr>
<th>Group</th>
<th>Week</th>
<th>C: Control</th>
<th>G1 0.5 mg/kg B.wt</th>
<th>G2 1 mg/kg B.wt</th>
<th>G3 2 mg/kg B.wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day zero</td>
<td>168.50 ± 6.28</td>
<td>179.50 ± 10.59</td>
<td>181.21 ± 13.87</td>
<td>179.83 ± 13.66</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>171.16 ± 5.87</td>
<td>174.83 ± 9.78</td>
<td>178.16 ± 13.34</td>
<td>173 ± 13.16</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>175.33 ± 6.59</td>
<td>179.16 ± 9.75</td>
<td>177.57 ± 12.23</td>
<td>173.84 ± 13.07</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>178.83 ± 5.74</td>
<td>181.33 ± 8.72</td>
<td>180.37 ± 13.09</td>
<td>177.14 ± 12.84</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SE (n=10 rats/group).
Capital letters indicate a significant (p > 0.05) difference between groups.
Small letters denote a significant (p > 0.05) difference within group.

Figure (1). Total body gain for each group (g), C: control group received orally distilled water daily for six weeks. G1: received oral doses of 0.5 mg/Kg B.wt DHEA daily for six weeks, G2: received oral doses of 1 mg/Kg B.wt DHEA daily for six weeks and G3: received oral doses of 2 mg/Kg B.wt DHEA daily for six weeks.

Measurement of body length:

The effect of different doses of DHEA administration on body length (cm) of rats is represented in table (5). There is a non-significant increase (p ≤ 0.05) in body length of treated groups in response to DHEA as compared to control. However, according to the time of the experiment there is a gradual significant (p > 0.05) increase in the length of rats of all groups used in the study. The total length gain (cm) is (+10) for
control, (+7) for group received 0.5 mg/kg B.wt DHEA, (+10) for rats administered with 1 mg/kg B.wt. DHEA and (+12) for rats treated with DHEA at 2 mg/kg B.wt.

**Table (5):** Body Length (cm) in response to oral DHEA administration at 0.5, 1, 2 mg/kg B.wt in adult female rats for six weeks.

<table>
<thead>
<tr>
<th>Week</th>
<th>Group</th>
<th>Control</th>
<th>G1 0.5 mg/kg B.wt</th>
<th>G2 1 mg/kg B.wt</th>
<th>G3 2 mg/kg B.wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day zero</td>
<td>C Control</td>
<td>32.66 ± 0.21</td>
<td>33.40 ± 0.50</td>
<td>33.50 ± 0.56</td>
<td>33.00 ± 0.51</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>C Control</td>
<td>33.33 ± 0.33</td>
<td>33.40 ± 0.50</td>
<td>33.50 ± 0.56</td>
<td>33.66 ± 0.61</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>C Control</td>
<td>34.00 ± 0.25</td>
<td>33.80 ± 0.37</td>
<td>34.16 ± 0.60</td>
<td>33.83 ± 0.47</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>C Control</td>
<td>34.66 ± 0.42</td>
<td>34.80 ± 0.37</td>
<td>35.16 ± 0.60</td>
<td>34.66 ± 0.55</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SE (n=10 rats/group). Capital letters indicate a significant (p > 0.05) difference between groups. Small letters denote a significant (p > 0.05) difference within group.

**Figure (2).** Total body length gain for each group (cm), C: control group received orally distilled water daily for six weeks. G1: received oral doses of 0.5 mg/Kg B.wt DHEA daily for six weeks, G2: received oral doses of 1 mg/Kg B.wt DHEA daily for six weeks and G3: received oral doses of 2 mg/Kg B.wt DHEA daily for six weeks.

**Calculation of Body Mass Index (BMI) (g/cm²):**

The values of body mass index (g/cm²) for control and treated groups are represented in table (6). Day zero, BMI showed a significant (p > 0.05) increase in G3 as compared with G1, G2 and control groups. However, this value was decreased significantly (p > 0.05) in rats after receiving 2 mg/kg B.wt DHEA in comparison to
control and the other treated groups. Moreover, The table also reveal a significant decrease in BMI of all rats received different doses of DHEA compared with control which is more clear after four weeks of treatment. Within time, BMI values show a gradual significant (p > 0.05) decrease, which is more noticeable in rats administered with DHEA in a dose-response manner. i.e. the value was (1.48 ± 0.08) after six weeks of treatment while (1.65 ± 0.06) before DHEA treatment in G3. This difference was less in G2 and the table shows the value was of (1.48 ± 0.06) and (1.58 ± 0.07) in respect to after and before treatment respectively. Rats received 0.5 mg/kg B.wt have BMI value of (1.50 ± 0.03) after six weeks of administration and was (1.56 ± 0.02) before treatment.

Table (6): Body mass index (g/cm²) in response to oral DHEA administration at 0.5, 1, 2 mg/kg B.wt in adult female rats for six weeks.

<table>
<thead>
<tr>
<th>Week</th>
<th>Group</th>
<th>Control</th>
<th>G 1 0.5 mg/kg B.wt</th>
<th>G 2 1 mg/kg B.wt</th>
<th>G 3 2 mg/kg B.wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day zero</td>
<td>1.56 ± 0.02</td>
<td>1.58 ± 0.06</td>
<td>1.58 ± 0.07</td>
<td>1.65 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.55 ± 0.05</td>
<td>1.53 ± 0.04</td>
<td>1.56 ± 0.07</td>
<td>1.50 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.53 ± 0.04</td>
<td>1.46 ± 0.05</td>
<td>1.51 ± 0.08</td>
<td>1.50 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.50 ± 0.03</td>
<td>1.50 ± 0.03</td>
<td>1.48 ± 0.06</td>
<td>1.48 ± 0.08</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SE (n=10 rats/group)
Capital letters indicate a significant (p> 0.05) difference between groups.
Small letters denote a significant (p> 0.05) difference within group.

**DISCUSSION**

Hormonal profile:
The results showed that, serum levels of ACTH and FSH increased significantly after DHEA administration. However, ACTH and FSH both are among glycoprotein hormones, which are secreted from anterior pituitary gland under hypothalamic control and have a considerable influence on endocrine glands ie.adrenals, ovaries and testes respectively (7). The significant decrease in cortisol level inspite of the significant increase in ACTH level in DHEA treated rats in this first experiment, suggest that DHEA treatment may positively influence the organs response to stress and that DHEA administration to rats enhance some intra renal pathways to reduce cortisol synthesis. The histopathological study of adrenal gland in rats that received 0.5 and 1 mg DHEA appeared with normal architecture, but in rats received 2 mg
DHEA showed severe vacuolar degeneration of medullary cell with capsular thickened. DHEA oral administration to postmenopausal women at 50 mg daily for 6 month induce a significant decrease in cortisol concentration (8). Moreover, 5 g of DHEA gel (corresponding to 50 mg DHEA) when applied transdermally on the abdominal skin to men daily for 5 consecutive days cause a decrease in serum cortisol level (9). Therefore, DHEA(s) and cortisol have indicated antagonistic effects on each other. The significance of considering DHEA (s)-to-cortisol ratios considers the ratio of anabolic to catabolic hormones and may indicate susceptibility to diseases of stress and aging (10). Both DHEA (s) and cortisol are considered in the calculation of allosteric load which measure the cumulative physiological burden to the body of accommodating multiple stressors over time (11). Allosteric load scores are based on ten biological parameters including DHEA (s), cortisol, epinephrine, norepinephrine, waist-to-hip ratio, total cholesterol, high density lipoproteins (HLP), glycosylated hemoglobin (Hb AIC), systolic blood pressure, and diastolic blood pressure. However, high cortisol concentrations and low DHEA (s) concentrations contribute to increases in allosteric load score which serves as a stronger predictor of cardiovascular diseases (12). Unlike DHEA (s) concentrations that decline under conditions of medical illness and chronic stress, cortisol concentrations either rise or do not change and subsequently result in a decrease in DHEA (s)-to-cortisol ratios (13&14).

On the other hand, greater deterioration was observed in elderly women and men who showed larger decreases in plasma DHEA (s)-to-cortisol ratios over a two-year period (15). Therefore, it is concluded that the beneficial supplement of DHEA produces physiological modifications in steroid and adrenal functions may be due to changes in adrenal enzymes. Evidence shows that the physiological DHEA levels generally decrease with age as well as in condition of diminished ovarian reserves. At the meantime, DHEA contributes to the maturation and selection of follicles with FSH (16). Androgens may stimulate ovarian follicular growth and differentiation not only by acting as a metabolic precursor for steroid, but also by serving as ligands for androgen receptors (17). From the other side, the beneficial effect of DHEA may have been mediated through an increase in insulin-like growth factor-1 (IGF-1) pathway. It
reported that this factor shows a transient increase in patients undergoing exogenous gonadotrophic ovulation induction after pre-treatment with DHEA (18).

Estrogen concentration normally decline by age and the ensuring hypoestrogenic state has been linked with substantial alterations in physical and psychological functioning in females. Estrogen deficiency has been proposed to increase the susceptibility for depression (19). Therefore estrogen therapy appeared to be effective in reducing symptoms of depression during the menopausal transition, as well as an augmentation strategy to antidepressant medication (20). However, estrogen has been proposed to alleviate depression by influencing on serotonin and norepinephrine (21), as well as by changes in levels of nonreactive steroids. It had been found that nonreactive steroids also decline postmenopausal just like estrogen and DHEA (22). Our findings (first experiment) revealed a significant increase of estradiol concentration in DHEA administered rats. The DHEA antidepressant action could be attributed mainly to augmentation of serotonin and norepinephrine or to metabolism of DHEA to testosterone or estrogen (23).

5.1.2. Body weight:

Concerning the effect of DHEA on body weight, the results from this study demonstrated 6-weeks of DHEA administration to rats induced large decrease in body weight with a dose-dependent manner. However, DHEA treatment in rats and mice resulted in lower body weight, reduced visceral fat accumulation in both genetic and diet induced obesity (24&25), respectively. DHEA replacement could play a role in prevention and treatment of the metabolic syndrome associated with abdominal obesity. At the meantime, the accumulation of abdominal fat increases with advancing age which is coincided with increase the risk for hypertension, atherosclerosis, diabetes, insulin resistance (26). In addition to insufficient exercise, over eating, hormonal, metabolic changes that occur with aging may contribute to the increase in body fat. One such change is the decline in production of DHEA (s) from adrenal gland and other steroid hormones (27).

Moreover, the precise mechanisms for reduced body and abdominal fat weights in DHEA groups remain unclear. It was reported that 2 weeks of DHEA administration has been shown to activate fatty acid metabolism related enzymes, such as long-chain
fatty acyl-coenzyme A synthase, and to increase free Coenzyme A (CoA) levels in liver and thus, increasing energy expenditure (28). In other words, DHEA may function to speed up the body's metabolism, so that the body could use and burn up more energy from food than is diverted and stored as fat.

A possible explanation for our findings is that DHEA is an activator of peroxisome proliferative-activated receptor α (PPARα), a transcriptional factor that belongs to the steroid hormone nuclear receptor family. However, activation of PPARα induces transcriptional up-regulation of fatty acids transport proteins that facilitate fatty acid entry into cells and the enzymes involved in the β-oxidation of fatty acids. Activation of PPARα results in decreased expression of fatty acid synthase and acetyl Co-enzyme A carboxylase (CoA). Therefore, these changes were favor increased fat oxidation and reduced fat deposition (28). Studies continue to evaluate the role of alterations in mitochondrial metabolism in DHEA antiobesity action.

Body length:

The findings of the present study show a non-significant increase in body length of rats treated with DHEA as compared to control. The present results could be discussed according to the effect of DHEA on growth hormone (GH) and Insulin-like growth factor-1 (IGF-1). However, DHEA replacement in female patients reduce GH dose requirements in hypopituitary condition (29). On the other hand, it was reported that a daily oral 100 mg dose of DHEA for 6 months induce an elevation of circulating DHEA and DHEAS concentration which is coincided with an increase in serum IGF-1 levels in males and females with dimorphic responses were evident in fat body mass and muscle strength in favor of men. Moreover, administration of 50 mg DHEA daily for 3 months induce an elevation of levels of IGF-1 in age-advanced men and women accompanied by improvement of self-reported physical and psychological well-being (30).

Body Mass Index:

Among the studied parameters in the current experiment is the body mass index (BMI) which demonstrated a significant decrease in DHEA administered rats. This mainly attributed to the significant reduction in body weight in response to DHEA treatment to adult female rats as discussed before. Novelli et al., (2007) demonstrated
a higher abdominal circumference and BMI in rats with enhancing age up to 90 days and remained constant thereafter. Moreover, the same authors show an increase in final body weight, body mass gain, carcass fat and BMI in groups of rats received 30% suerose or high-carbohydrate diet than control. It was concluded that obesity may be easily estimated from the BMI as it shows a positive correlations with carcass fat and serum triacylglycerol (31). Therefore, alterations in BMI are associated with dyslipidemic profile and oxidative stress and considered as a marker of obesity.

Results of experiment in the present study indicate that the BMI of female adult rats showed gradual significant decrease in DHEA groups in a dose-response manner which confirm the antiobesity action of DHEA. However, the literature review lack the effect of DHEA on BMI. The results showed that, adult female rats of the control group have a mean value of 1.53 g/cm² which is differ from the results obtained from adult male rats group that showed BMI a ranged between 0.45 and 0.68 g/cm² (31). This difference in response to DHEA administration in our study may reflect gender specific response to DHEA and/or the presence of confounding factors (s) in women such as estrogen hormone (30).
REFERENCES


6-SPSS® (2002). 11.5 Syntax Reference, Guide Copyright© by SPSS Inc. All rights reserved. Printed in the United States of America (Http: www.spss.com).


