Are dehydroepiandrosterone sulphate and lipids associated with erectile dysfunction?

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Abstract

Objective: Considering the results of the Massachusetts Male Aging Study (1994) we undertook the current investigation in an attempt to clarify the role of dehydroepiandrosterone sulphate (DHEAS), testosterone and lipids on age related deterioration of erectile function.

Methods: Forty males (13 under 40 years of age and 27 over 40) with erectile dysfunction were investigated. Seventeen healthy subjects (8 under 40 and 9 over 40 years) volunteered as controls. Serum levels of DHEAS, testosterone, total cholesterol, high-density lipoprotein cholesterol (HDL-ch), low-density lipoprotein cholesterol (LDL-ch) and triglycerides were assessed in blood samples.

Results: Plasma levels of DHEAS in patients over 40 years of age (4.17 ± 2.76 μmol/l) were significantly lower in comparison with the younger group of patients (10.49 ± 3.87 μmol/l), P < 0.001. There was no statistically significant difference in the DHEAS levels between patients and controls in the same age group. DHEAS in the patients showed an inverse correlation with age (r = −0.705, P < 0.001) and a positive correlation with testosterone (r = +0.402, P < 0.01). The same was found in the controls. The HDL-ch results were in the reference range. The total cholesterol levels (5.35 ± 0.74 mmol/l) and LDL-ch levels (3.58 ± 0.76 mmol/l) of the patients with erectile dysfunction in the group under 40 years were significantly higher in comparison with the controls (4.21 ± 0.69 and 2.46 ± 0.74 mmol/l, respectively, P < 0.01).

Conclusion: The data indicates that the decline in DHEAS is an age-related process rather than a causative factor of erectile dysfunction; total cholesterol and mainly LDL-ch may contribute to erectile dysfunction, especially in younger men.

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Keywords: Erectile dysfunction; DHEAS; Testosterone; Lipids

1. Introduction

Erectile dysfunction is defined as persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity (NIH Consensus Conference, 1993) [1]. Erectile dysfunction can significantly compromise quality of life, and may result from many contributing factors [2]. Men experience a gradual decline in fertility and erectile function rather than an abrupt decrease [3]. Erectile dysfunction is commonly associated with aging. Putative causes and
clinical correlates of erectile dysfunction, many of them likewise associated with aging, include vascular insufficiency, interruption of neural pathways, psychogenic factors and side effects of therapeutic drugs. In recent years, the relationship between adrenal function and aging has been the subject of intense interest [4,5]. Clinical studies have clearly demonstrated that the administration of dehydroepiandrosterone (DHEA) in doses of 50–100 mg/day for 3–6 months increased some hormone levels and was accompanied by improvement of physical and psychological well-being [6,7–9].

In general, an annual decline of 0.4% of total testosterone and 1% of free testosterone is seen from the fifth decade, although there is great individual variability [3,10,11]. The results of the Massachusetts Male Aging Study (MMAS) on male subjects 40–70 years of age showed that only dehydroepiandrosterone sulphate (DHEAS) out of 17 studied hormones had a strong correlation to erectile dysfunction and that the probability of this disorder varied inversely with high-density lipoprotein cholesterol (HDL-ch) [12].

DHEA is a steroid retaining cholesterol’s Δ5–6 double bond and it has esterifiable 3β-hydroxyl group. More than 98% of this steroid is present in plasma as the sulfated form, dehydroepiandrosterone sulphate (DHEAS) [13]. The source of DHEAS, a substance present only in higher primates and humans, is almost exclusively the adrenals. It is a weak androgen and is thought to have a multifunctional protective role in many aspects of cellular well-being [14,15] and age-associated defects, but its precise physiological function is largely unknown.

The current study was undertaken in an attempt to acquire a better insight into the role of DHEAS, testosterone, and lipids in age-related deterioration of erectile function.

### 2. Subjects and methods

#### 2.1. Study design

A total of 40 males with erectile dysfunction (as defined in the Introduction) were investigated. We established the diagnosis according to the International Index of Erectile Function (IIEF) [16]. A thorough medical history and physical examination including measurement of arterial blood pressure and body mass index, as well as standard laboratory tests were performed on all patients. The patients were not treated at all prior to this study. Taking into consideration the MMAS [12] they were divided in two groups: 13 under 40 years of age, mean 29.0 ± 4.10 years, and 27 over 40 years, mean 52.37 ± 8.04 years. The comorbidities in the two groups are given in the Table 1. Seventeen healthy subjects with undisturbed erectile function and normal blood pressure, aged 18–77 years (8 under 40 years with mean age 29.87 ± 6.58 years and 9 over 40 years with mean age of 59.11 ± 11.01 years), served as controls. Informed consent was obtained from all participants. Serum levels of DHEAS, testosterone and some biochemical parameters such as total cholesterol, HDL-ch and triglycerides were assessed in blood samples taken in the morning between 8.00 and 9.00 a.m. after an overnight fast.

#### 2.2. Hormones

We evaluated the serum levels of DHEAS and testosterone by radioimmunoassay with commercial kits (CIS Bio International, France). For DHEAS the intra-assay coefficient of variation (CV) was 4%, the inter-assay coefficient was 4.9%, and the sensitivity of the method was 0.03 μmol/l. For testosterone they were as follows: intra-assay CV 3.8%, inter-assay CV 4.8% and the assay sensitivity −0.1 nmol/l, respectively. All samples were assayed in duplicate.

#### 2.3. Lipids

Serum total cholesterol, HDL-ch and triglycerides were determined enzymatically by an automatic ana-
lyzer (Cobas Mira Plus, Hoffmann La Rochet). Low-density lipoprotein-cholesterol (LDL-ch) concentration was calculated by the Friedewald formula [17].

2.4. Statistical methods

Statistical evaluation of the data was carried out using the nonparametric analysis of Mann–Whitney and the Student’s t-test. To analyze the relationship between erectile dysfunction and the different factors, a multiple logistic regression and Spearman’s analysis were performed. The results are expressed as the mean ± S.D. A P value of less than 0.05 was considered statistically significant.

3. Results

3.1. DHEAS and testosterone

Plasma levels of DHEAS were significantly lower in patients with erectile dysfunction over 40 years of age (4.17 ± 2.76 μmol/l) as compared to the younger group of patients (10.49 ± 3.87 μmol/l), P < 0.001. The same was true for the controls: 3.68 ± 1.55 μmol/l in the males over 40 years and 11.85 ± 4.57 μmol/l in those under 40 years, P < 0.001 (Fig. 1).

We did not find a significant difference in the testosterone levels between the patients with erectile dysfunction under 40 years (20.93 ± 7.51 nmol/l) and those over 40 years (18.48 ± 8.25 nmol/l). The same was true for the control groups (22.89 ± 7.97 nmol/l and 22.0 ± 6.34 nmol/l, respectively) (Fig. 2).

DHEAS in the patients showed an inverse correlation with age (r = −0.705, P < 0.001) and a positive correlation with testosterone (r = +0.402, P < 0.01). Likewise, similar results were established in the controls (r = −0.714, P < 0.001 for DHEAS and r = +0.135, P > 0.05 for the testosterone).

Multiple logistic regression analysis results revealed that no one of all studied factors was significant to determine patients with erectile dysfunction and controls. However, when these indices were related to age, it was determined that DHEAS was a reliable indicator for distinguishing between members of the under-40- and over-40-year-old groups (correct class 89.5%).

3.2. Lipids

There was no statistically significant difference in lipid data between the two age groups of patients, except for the ratio LDL-ch/HDL-ch (3.04 ± 0.98 under 40 years versus 2.35 ± 0.78 in those over 40 years), P < 0.05 (Tables 2 and 3).

We found a significant difference in the cholesterol levels of the patients with erectile dysfunction and the controls in the group under 40 years. The LDL-ch levels of the patients in the same age group, under 40 years, were significantly higher in comparison with the controls (Table 2). In contrast, no significant difference was established in the lipid parameters between patients and controls over 40 years (Table 3).
Table 2  
Serum lipid levels in patients with erectile dysfunction and healthy males under 40 years (mean ± S.D.)

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol (mmol/l)</th>
<th>HDL-ch (mmol/l)</th>
<th>LDL-ch (mmol/l)</th>
<th>Triglycerides (mmol/l)</th>
<th>LDL-ch/HDL-ch ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>5.35 ± 0.74</td>
<td>1.23 ± 0.23</td>
<td>3.58 ± 0.76</td>
<td>1.30 ± 0.62</td>
<td>3.04 ± 0.98</td>
</tr>
<tr>
<td>Controls</td>
<td>4.21 ± 0.69</td>
<td>1.27 ± 0.32</td>
<td>2.46 ± 0.74</td>
<td>1.47 ± 0.78</td>
<td>2.12 ± 0.89</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.01</td>
<td>&gt;0.05</td>
<td>&lt;0.01</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 3  
Serum lipid levels in patients with erectile dysfunction and healthy males over 40 years (mean ± S.D.)

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol (mmol/l)</th>
<th>HDL-ch (mmol/l)</th>
<th>LDL-ch (mmol/l)</th>
<th>Triglycerides (mmol/l)</th>
<th>LDL-ch/HDL-ch ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>5.24 ± 1.30</td>
<td>1.39 ± 0.31</td>
<td>3.19 ± 1.07</td>
<td>1.47 ± 0.85</td>
<td>2.35 ± 0.78</td>
</tr>
<tr>
<td>Controls</td>
<td>5.35 ± 1.24</td>
<td>1.43 ± 0.28</td>
<td>3.35 ± 0.89</td>
<td>1.27 ± 0.30</td>
<td>2.48 ± 0.45</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
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</table>

We found a negative significant correlation between DHEAS and the total cholesterol (r = −0.710, P < 0.01) as well as between DHEAS and LDL-ch (r = −0.614, P < 0.05) in patients under 40 years, but there was no statistically significant correlation in respect to the HDL-ch levels.

4. Discussion

DHEAS exerts an age-associated secretion pattern in humans and some higher non-human primates. The maximum blood concentration is reached during the third decade of life, when an ineluctable decline starts, cross-sectional studies indicating a decay of approximately 2%/year in the blood level, leaving a residual value of approximately 10–20% during the 8th–9th decades of life[18].

Prior studies have reported relationship between erectile dysfunction and aging. The Baltimore longitudinal study of aging found that by age 55 erectile dysfunction was a problem in 8% of all healthy men, and that for ages 65, 75 and 80 years the prevalence increased to 25%, 55% and 75%, respectively [19]. In the MMAS study, the probability of complete erectile dysfunction tripled from 5% to 15% in subjects from 40 to 70 years of age and DHEAS had a strong correlation with erectile dysfunction [12]. The age-adjusted probability of complete erectile dysfunction increased from 3.4% to 16% as DHEAS decreased from 10 to 0.5 μg/ml [12].

Our results show that DHEAS levels were in negative significant correlation with the age. The absence of any difference between the patients and the controls in the same age group (under 40 years of age as well as over 40 years) leads to the suggestion that DHEAS has no direct relationship to the erectile dysfunction.

In support of our data are the results of Arlt et al. [20] who performed therapy with DHEA in adult subjects. Dehydroepiandrosterone treatment increased serum DHEA and DHEAS to concentration usually found in young men, but the circulating androgen levels did not change. After 4 months of DHEA treatment, no effect on sexuality was observed, whereas some mood scores improved slightly. Compared to a placebo, DHEA had no effect on serum lipids, bone markers, body composition, or exercise capacity [20]. Likewise, Reiter et al. [21] established that oral DHEA treatment of erectile dysfunction was not effective in men with diabetes mellitus or with neurological disorders. Therefore, the decline of both erectile function and DHEAS are closely related with aging, but this does not mean that the low levels of DHEAS may cause or may play a main role in the development of erectile dysfunction.

The testosterone levels in patients were not significantly lower in comparison with the controls, which suggests that the serum testosterone does not contribute substantially to erectile dysfunction.

According to MMAS the probability of erectile dysfunction varied inversely with HDL-ch. For the younger men (age 40 to 55 years) the age-adjusted probability of moderate erectile dysfunction increased from 6.7% to 25% as HDL-ch decreased from 90 to 30 mg/dl. In the older men (age 56–70 years), the probability of complete erectile dysfunction increased from near zero to 16% as HDL-ch decreased from 90 to 30 mg/dl [12]. In MMAS total serum cholesterol was
not correlated with erectile dysfunction probabilities [12].

In our study a careful lipid data analyses showed that the total cholesterol and LDL-ch are significantly lower in healthy men under 40 years compared to those over 40 years, whereas in the patients with erectile dysfunction there is no such difference in these parameters. Moreover, the ratio LDL-ch/HDL-ch in patients under 40 years was enhanced compared to the controls. The levels of total cholesterol and LDL-ch in patients under 40 years were significantly higher in comparison with healthy men of the same age, which gives good grounds to assume that the increased concentration of LDL-ch is closely related with an early manifestation of erectile dysfunction and is more pronounced in younger patients. Because the erectile function is a neurovascular event modulated by psychological factors and hormone status [2], it is rather possible that the high LDL-ch levels at earlier ages may cause changes in the blood-vessel walls, disturbing normal processes that lead to erection. Consequently, it may be thought that the total cholesterol and LDL-ch influence unfavorably on the vessels as early as the age less than 40 years and may evoke vascular disturbances typical of an advanced age.

Hypercholesterolaemia is thought to foster atherosclerosis and erectile dysfunction through its effects on vascular endothelium. Low serum DHEAS levels are correlated with increased cardiovascular morbidity in men [22,23]. Feldman et al. [15] using data from MMAS at baseline examined the same people after a 9-year interval. In the analysis sample of 1167 men, those with serum DHEAS in the lowest quartile (<1.6 μg/ml) were significantly more likely to incur ischemic heart disease by follow-up, independently of a comprehensive set of known risk factors including age, obesity, diabetes, hypertension, smoking, serum lipids, alcohol intake and physical activity [15]. Some authors reported that the plasma levels of DHEAS and adrenal C19 steroid hormones correlate with the plasma lipid profiles of healthy men. Vatalas and Dionyssiou-Asteriou [24] found a positive correlation between DHEAS levels and apoA-I, a negative correlation between adrenal C19 steroid hormones and triglycerides and a positive correlation between adrenal C19 steroid hormones and LDL-ch. DHEA supplementation is reported to lower LDL-ch in humans and to reduce atherosclerotic plaque in rabbits [25].

We found a negative significant correlation between DHEAS and the total cholesterol as well as between DHEAS and LDL-ch in patients under 40 years, which shows a relationship between DHEAS, lipids and atherosclerosis. The study of Nestler et al. [26] supports our data. In healthy young men, using supra pharmacological doses of DHEA (1600 mg/day) for 4 weeks, the authors found a decrease in cholesterol and LDL-ch levels as well as a 31% decrease in body fat without changes, implying an increase in muscle mass.

Srilatha et al. [27] concluded that oxidized LDL-ch at some critical level or beyond may be capable of reverting at least some of the adverse effects of hypercholesterolaemia on erectile function.

Our data shows that the high levels of cholesterol and LDL-ch in clarifying the pathogenesis of erectile dysfunction should be taken into consideration. Wei et al. [28] found that a high level of total cholesterol and a low level of HDL-ch were important risk factors for erectile dysfunction. In contrast to our cross-sectional study the observation of Wei et al. was longitudinal, which allowed follow-up evaluation of this factors. Roumeguer et al. [29] also found that HDL-ch and total cholesterol/HDL-ch ratio were predictors of erectile dysfunction. They recruited more men than we enrolled in our study. On the other hand they did not compare young and older patients as we did. While our data does not exclude low levels of HDL-ch as a predictor of erectile dysfunction, our study stresses that the increased levels of the total cholesterol and mainly LDL-ch are closely related to erectile dysfunction, especially in younger men.

The current study is cross-sectional, as is the MMAS (1994), and it shows that the serum levels of DHEAS per se do not have a crucial direct influence on erectile function. The data indicates that the decline in DHEAS is an age-related process rather than a cause of erectile dysfunction. DHEAS shows a strong significant positive correlation with age, while the correlation of testosterone with age is weaker. On the basis of these findings, it could be accepted that DHEAS is a more precise indicator of the chronological age.

In conclusion, our study shows that from the clinical point of view DHEAS seems not to be necessary as first line diagnostic tools for erectile dysfunction. Total cholesterol and mainly low-density lipoprotein cholesterol may contribute to erectile dysfunction, especially in younger men. In older males these changes
are not well pronounced, because other additive age related processes are interpolated.

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References