**Effect of 1-Year Oral Administration of Dehydroepiandrosterone to 60- to 80-Year-Old Individuals on Muscle Function and Cross-sectional Area**

A Double-blind Placebo-Controlled Trial

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**Background:** The age-related decline of dehydroepiandrosterone and its sulfate ester levels is thought to be related to the development of age-associated usual modifications, such as neuromuscular function impairments. It is often claimed that individuals can enhance their muscular capacity by boosting dehydroepiandrosterone levels through oral supplementation. However, to our knowledge, there have been no controlled studies on a significant number of individuals demonstrating positive effects on the neuromuscular system. This study determines if 1-year administration of a replacement dose of dehydroepiandrosterone, 50 mg/d, orally administered, could have a beneficial influence on several determinants of the muscular function altered during aging.

**Methods:** This work was completed within the framework of the DHEAge Study, which was conducted in France from March 1, 1998, to October 31, 1999. It was performed on 280 healthy ambulatory and independent men and women aged 60 to 80 years. The study design was a double-blind placebo-controlled trial. Dehydroepiandrosterone sulfate serum concentration, handgrip strength, isometric and isokinetic knee muscle strength, and thigh (fat and muscle) cross-sectional area were analyzed before and just after 12 months of placebo or dehydroepiandrosterone treatment.

**Results:** The results give evidence that dehydroepiandrosterone administration restores dehydroepiandrosterone sulfate serum concentrations to the normal range for young adults (aged 20-50 years). However, no positive effect inherent to dehydroepiandrosterone treatment was observed either on muscle strength or in muscle and fat cross-sectional areas.

**Conclusions:** The compensation of the deficit of dehydroepiandrosterone during aging using a 50-mg/d dose does not induce beneficial effects on muscle state in healthy subjects. The conditions in which dehydroepiandrosterone could contribute to preserve or improve muscle strength and morphological features still need to be determined.

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ROSS-SECTIONAL and longitudinal studies have consistently documented the age-related alterations in body composition and decline in muscle functional state. Healthy older people exhibit an increased fat mass, a decreased muscle mass, and, hence, an associated decreased muscle strength. In the human muscles, the age-associated maximal strength loss seems to be correlated to a reduced cross-sectional area (CSA) of the active muscle tissues.1,2 However, besides these quantitative changes in muscle CSA, some changes in muscle quality, such as the capacity to generate force per unit muscle area, are responsible for the age-related loss of strength.3,4 These observations suggest alterations in fiber recruitment and changes in voluntary neural drive.5-9 These neuromuscular changes affect static (isometric) and dynamic performance, and the strength of proximal and distal muscles. Based on cross-sectional data, maximal muscle strength at the age of 70 years is 30% to 50% of peak muscle strength reached at the age of 30 years.2,10 As a consequence, the inherent muscle dysfunction and associated mobility impairment increase the risk of falls, fractures, and functional dependency. Among other factors, muscle weakness in elderly people could be a consequence of a decline in circulating levels of several anabolic hormones, such as growth hormone and insulinlike growth factor 1 (IGF-1), testosterone, or dehydroepiandrosterone.

Dehydroepiandrosterone and its sulfate ester are the most abundant cortico-
steroloidal products. Dehydroepiandrosterone sulfate is also the major circulating corticosteroid in humans.11 The dehydroepiandrosterone sulfate serum concentration reaches peak levels when individuals are aged between 20 and 30 years, after which it declines progressively, reaching 20% of its peak level when individuals are aged 70 years.12

Little is known about the physiological role of dehydroepiandrosterone and its sulfate ester, but human epidemiological studies13,14 have suggested that their concentrations may represent biomarkers of healthy aging. Low dehydroepiandrosterone levels have been correlated to higher cancer occurrence, obesity, risks of cardiovascular-related mortality, and diabetes mellitus.15-17 From various studies,18,19 dehydroepiandrosterone supplementation is known to improve perceived physical and psychological well-being, bone mineral density, and skin status.

Previous studies of dehydroepiandrosterone administration gave discordant results concerning muscle strength. Yen et al20 reported that older men who received a 100-mg/d dose of dehydroepiandrosterone for 6 months increased their knee muscle strength. However, the same dose of dehydroepiandrosterone had no effect on the knee muscle strength of individuals.20 In another study, Diamond et al21 showed an increase of the muscular area and a decrease of the subcutaneous femoral fat area at midthigh in elderly women. In this study, subjects received a single daily percutaneous application of a 10% dehydroepiandrosterone cream for 12 months. However, the study by Diamond et al involved placebo control only after cessation of dehydroepiandrosterone therapy on a few women. Moreover, the serum levels of dehydroepiandrosterone sulfate were not reported.

Actually, as far as physiological and pathological manifestations of aging on muscular function are concerned, the number of studies on older subjects is rather small for correlations with decrease of dehydroepiandrosterone sulfate level and responses to dehydroepiandrosterone treatment (Table 1).

In light of these considerations, assessment of the potential role of dehydroepiandrosterone in human health and disease is of biological and clinical interest. The present study defines whether dehydroepiandrosterone supplementation provides benefits on various variables of healthy muscle in aged subjects.

<table>
<thead>
<tr>
<th>Source</th>
<th>Subjects (Age Range, y)</th>
<th>Dehydroepiandrosterone Treatment</th>
<th>Duration, mo</th>
<th>Trial Design</th>
<th>Measurement of Dehydroepiandrosterone Sulfate Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yen et al,20 1995</td>
<td>8 Men and 8 women (50-65)</td>
<td>Oral, 100 mg/d</td>
<td>6</td>
<td>Crossover and placebo controlled</td>
<td>Yes</td>
</tr>
<tr>
<td>Diamond et al,21 1996</td>
<td>15 Women (60-70)</td>
<td>Percutaneous, 3-5 g/d of a 10% cream</td>
<td>12</td>
<td>Crossover and placebo controlled</td>
<td>No</td>
</tr>
<tr>
<td>Morales et al,22 1998</td>
<td>10 Women and 9 men (50-65)</td>
<td>Oral, 100 mg/d</td>
<td>6</td>
<td>Crossover, double-blind, and placebo controlled</td>
<td>Yes</td>
</tr>
<tr>
<td>Present study</td>
<td>140 Men and 140 women (60-80)</td>
<td>Oral, 50 mg/d</td>
<td>12</td>
<td>Double-blind and placebo controlled</td>
<td>Yes</td>
</tr>
</tbody>
</table>
The best score for each side was recorded. Tests were alternated for each subject and a 2-minute rest period was allowed between bilateral measurements. The effect of side (left or right) and sequence (M0, M6, and M12) was tested using analysis of variance repeated measurement with 2 between factors (treatment and the interaction between factors). t-tests were performed using nonparametric tests because these variables did not reach normality (assessed by the Shapiro-Wilks W test). For strength and morphological data, the effect of the treatment and the interaction between factors was tested using analysis of variance repeated measurement with 2 between factors (treatment placebo or dehydroepiandrosterone and sex [male or female]) and 2 within factors (side [left or right] and sequence [M0, M6, or M12]). When the effect of a factor was significant, subsequent analyses of variance were performed by splitting the factor into its levels.

Maximum voluntary contraction trials was higher than 20%, the strength value was not considered consistent and, consequently, was rejected.

KNEE MUSCLE STRENGTH MEASUREMENTS

Maximum isometric and dynamic strength were measured at peak torque for knee extension and knee flexion muscles using an isokinetic dynamometer (Biodex Medical Systems Inc, Shirley, NY). After a 5-minute warm-up on a bicycle ergometer (Cardio-Master, C.A.R.E., Bobigny, France) and a short habituation to the isokinetic ergometer, movements were performed at 180°, 150°, 120°, 90°, and 60° per second on each side. Five measurements were performed at each velocity, and the highest values were recorded. Immediately following the dynamic measurements, a 3-second maximum isometric strength measurement was taken on the quadriceps femoris muscle group at a knee angle of 90°. All movements were limited to the angles respecting subject abilities, and the first side tested was randomized.

MORPHOLOGICAL MEASUREMENTS

Weight and height were measured at M0, M6, and M12. Cross-sectional areas of the thigh were measured from bilateral computed tomographic scans performed with a specific unit (Hi-speed Advantage CT unit; General Electric Medical Systems, Milwaukee, Wis). After obtaining an x-ray “scout,” subjects’ thighs were positioned so that scans were taken perpendicular to the femur using a slice thickness of 1 mm. Cross sections were recorded every millimeter between the greater trochanter and the lateral joint line of the knee. Images were transferred automatically to a computer (Advantage Windows Workstation 3.1) through an intranet connection. Only 3 cross sections were examined from the whole measurements by the same investigator. The CSAs were analyzed at the lower quarter portion (one quarter of the femur), at midthigh (one half of the femur), and at the higher third portion (two thirds of the femur). The areas of adipose and muscular tissues were then automatically computed from the image based on pixel intensity histograms using a software application (Voxtool; General Electric Medical Systems). The quadriceps and the hamstring areas were processed by the same method after manual assignment.

STATISTICAL ANALYSES

Descriptive data were summarized and presented as mean ± SD. Some of the subjects were excluded from the trial after randomization because they did not perform all the required measurements at all examination sequences. Others were excluded for having pain during maximal strength tests or because they failed to correctly perform the tests. The number and the characteristics of subjects for each test are presented in Table 2.

All statistical tests were performed with StatView v.5.0.1 (SAS Institute Inc, Cary, NC) and Statistica v.5.5 (StatSoft Inc, Tulsa, Okla) statistical software. For hormonal data, statistical comparisons were performed using nonparametric tests because these variables did not reach normality (assessed by the Shapiro-Wilks W test). For strength and morphological data, the effect of the treatment and the interaction between factors was tested using analysis of variance repeated measurement with 2 between factors (treatment, placebo or dehydroepiandrosterone and sex [male or female]) and 2 within factors (side, left or right and sequence, M0, M6, or M12). When the effect of a factor was significant, subsequent analyses of variance were performed by splitting the factor into its levels.
DEHYDROEPIANDROSTERONE SULFATE SERUM CONCENTRATION MEASUREMENTS

Before dehydroepiandrosterone administration, no differences in dehydroepiandrosterone sulfate serum concentrations were observed between the placebo group and the treated group for men and women. Basal dehydroepiandrosterone sulfate levels were significantly higher in men than in women (96 ± 40 µg/dL [2.60 ± 1.07 µmol/L] vs 74 ± 38 µg/dL [2.00 ± 1.02 µmol/L]; P < .001).

At M6, dehydroepiandrosterone sulfate serum levels increased significantly in men and women (to 360 ± 201 µg/dL [9.73 ± 5.44 µmol/L] and 344 ± 193 µg/dL [9.29 ± 5.20 µmol/L], respectively; P < .001). These values decreased significantly between M6 and M12 for men and women (to 284 ± 166 µg/dL [7.66 ± 4.9 µmol/L] and 237 ± 122 µg/dL [6.39 ± 3.30 µmol/L], respectively; P < .01). The difference between the placebo group and the dehydroepiandrosterone-treated group for both sexes became significant at M6 and M12 (P < .001), although the response to dehydroepiandrosterone administration was variable (Figure 1). A significant decrease in the dehy-
droepiandrosterone sulfate serum concentration was observed for 12 months in the placebo group of women (P < .01), but not in the placebo group of men.

No adverse effects were reported. Physical examination and chemistry study results revealed no abnormalities or significant changes throughout the 1-year study. Other hormonal and biochemical results can be found in the study by Baulieu et al.19

HANDGRIP STRENGTH 
MEASUREMENTS

There was no significant correlation between dehydroepiandrosterone sulfate levels and handgrip strength at baseline (P > .05 for all) (Figure 1). Before treatment, handgrip strength was not significantly different between the placebo group and the dehydroepiandrosterone-treated group according to sex and side. Handgrip strength values were significantly higher in men than in women (P < .001), and strength was higher for the right hand for both sexes (P < .001), as presented in Table 3.

The handgrip strength values were unchanged in both groups of women. After 6 months, the male group presented a significant handgrip strength increase (P < .005). At M12, these values returned to baseline for this group. Finally, no significant (P = .98) effect of dehydroepiandrosterone on handgrip strength was assessed by analysis of variance during the 1 year of treatment.

KNEE MUSCLE STRENGTH MEASUREMENTS

Before treatment, no differences were observed between the placebo group and the dehydroepiandrosterone-treated group regardless of the muscle group, the side tested, or the speed of movement. Hamstring muscles were significantly weaker than quadriceps muscles (P < .001), and strength decreased with the speed of movement (P < .001) (Figure 2). At M12, knee flexion and knee extension muscle strength were unaltered in the placebo and the dehydroepiandrosterone-treated groups.

MORPHOLOGICAL MEASUREMENTS

Weight, height, and body mass index were not significantly changed in all groups of subjects (P > .05 for all).

At M0, muscle CSAs were not different between the treatment groups. However, the fat CSA was slightly higher in the dehydroepiandrosterone-treated group compared with the placebo group (P = .001). Muscle (P = .43) and fat (P = .13) CSA values were not significantly changed, regardless of the treatment and the portion of the thigh sampled (Table 4 and Figure 3). No significant (P = .53) differences were observed between the right and the left thighs. No effect of dehydroepiandrosterone on muscular morphological features was observed after 1 year of treatment.

Figure 2. Peak torque of 2 muscle groups as a function of movement speed before and after treatment in 64 elderly women (aged 60-70 years). A, Data for the quadriceps muscles after placebo treatment. B, Data for the quadriceps muscles after dehydroepiandrosterone treatment. C, Data for the hamstring muscles after placebo treatment. D, Data for the hamstring muscles after dehydroepiandrosterone treatment. M0 indicates the week before treatment commenced; M12, after 12 months of treatment.
In the present study, a 50-mg/d dose of dehydroepiandrosterone for 1 year in men and women aged 60 to 80 years had no effect on muscular structure and function. Dehydroepiandrosterone treatment was not associated with any significant improvement in muscle strength for either upper or lower limbs and with any changes in CSA for the lower limb. Despite these observations, dehydroepiandrosterone treatment restored the age-related decline of circulating dehydroepiandrosterone sulfate levels in men and women, without accumulation after prolonged administration, confirming previous reports. The possibility of an adaptive

Table 4. Values of Adipose and Muscular CSAs at M0 and M12 for 43 Women Aged 60 to 70 Years

<table>
<thead>
<tr>
<th>Area</th>
<th>Placebo Group</th>
<th>Dehydroepiandrosterone-Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M0</td>
<td>M12</td>
</tr>
<tr>
<td>Fat</td>
<td>76.1 ± 27.9</td>
<td>78.7 ± 32.0</td>
</tr>
<tr>
<td>Quadriceps muscles</td>
<td>36.0 ± 6.7</td>
<td>35.3 ± 6.2</td>
</tr>
<tr>
<td>Hamstring muscles</td>
<td>25.4 ± 3.9</td>
<td>25.1 ± 4.1</td>
</tr>
</tbody>
</table>

Dehydroepiandrosterone-Treated Group

<table>
<thead>
<tr>
<th>Area</th>
<th>M0</th>
<th>M12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>89.7 ± 30.7</td>
<td>90.3 ± 32.8</td>
</tr>
<tr>
<td>Quadriceps muscles</td>
<td>33.8 ± 5.4</td>
<td>33.8 ± 5.3</td>
</tr>
<tr>
<td>Hamstring muscles</td>
<td>22.3 ± 4.4</td>
<td>22.4 ± 5.1</td>
</tr>
</tbody>
</table>

Abbreviations: CSA, cross-sectional area; M0, the week before treatment commenced; M12, after 12 months of treatment.

*One quarter indicates the lower quarter portion of the femur; one half, one half of the femur (midthigh); and two thirds, the higher two thirds of the femur.

Figure 3. Relationship between the dehydroepiandrosterone sulfate serum concentration and cross-sectional areas (CSAs) of fat and muscle at midthigh in 43 elderly women (aged 60-70 years). A, Data for muscle the week before treatment commenced (M0). B, Data for muscle after 12 months of treatment (M12). C, Data for fat at M0. D, Data for fat at M12. To convert dehydroepiandrosterone sulfate to micromoles per liter, multiply by 0.027.
mechanism after long-term administration is suggested by the decrease of the dehydroepiandrosterone sulfate concentration between M6 and M12. Men and women who took dehydroepiandrosterone showed, after 1 year, an increase of 205% ± 192% and 275% ± 181%, respectively, of their dehydroepiandrosterone sulfate serum concentration, and their values returned to young adult (aged 20-50 years) values.

Our results on muscle strength are in contrast with those of the placebo-controlled crossover trial of Yen et al., in which beneficial effects of dehydroepiandrosterone administration on knee muscle strength were observed in men (n=8), but not in women (n=8), despite a significant modification of androgen and IGF-1 levels in both sexes. However, in the work by Yen et al, few subjects were involved, the dose was double that used in the present study, and the subjects were younger (aged 50-65 years).

After 6 months, we also observed an increase in hand-grip strength for men who had taken a 50-mg dose of dehydroepiandrosterone, which could have led us to conclude that there was a dehydroepiandrosterone effect. However, an increase in strength was also observed for the placebo group. Thus, no effect on muscle strength was proved by analysis of variance during 1 year of treatment. This slight placebo effect, noted for the muscle strength measurements, was also observed in IGF-1 expression, according to the results by Baulieu et al., conducted on the same population. This result underlines the importance of the controlled design of the study. There was in fact no proved placebo effect on muscle strength. The changes can be seen as a learning effect of the evaluation protocol. Moreover, knowing the importance of motivation on maximal voluntary contraction measurements, psychological factors could have played a role as well.

Dehydroepiandrosterone could exert an action on muscular and adipose tissues and on skeletal muscle functions following its biotransformation into active sex corticosteroids in specific target tissues and because of its ability to increase serum IGF-1 levels. After oral administration, dehydroepiandrosterone is largely absorbed and converted to its sulfate ester, which rapidly increases its serum concentration. Specific receptors for dehydroepiandrosterone sulfate have not been identified in the muscles. As a precursor of androgens and/or estrogens, the metabolism of dehydroepiandrosterone sulfate may occur in many specific peripheral cells containing sex corticosteroid receptors, and in adipose tissue and skeletal muscle cells.

Following the dehydroepiandrosterone sulfate serum concentration elevation after a dehydroepiandrosterone treatment, testosterone circulating levels increase and are restored to adult ranges in older women, but not in men. The active IGF-1 level is also increased. Sex corticosteroids and IGF-1 are known to have anabolic properties. Androgens, and particularly testosterone, are the main stimulators of muscle activity. Testosterone increases muscle mass and the rate of muscle protein synthesis, while IGF-1 is a potent stimulator of the measured anabolic process. Insulinlike growth factor 1 has induced the growth of various tissues and has stimulated muscle protein synthesis in humans.

Despite the strong elevation of the dehydroepiandrosterone sulfate level in men and women in our study, a concomitant investigation reported a sex effect on the changes in other hormones. In the male group, the increase of testosterone levels at M6 was not significant, and no changes were seen between M6 and M12. In women, at M6, testosterone levels significantly increased, then decreased between M6 and M12. Similarly, IGF-1 expression, although influenced by the dehydroepiandrosterone sulfate level, was not significantly modified. There was a tendency for the IGF-1 level to increase in placebo- and dehydroepiandrosterone-treated subjects. However, the relative increase in IGF-1 was not correlated to dehydroepiandrosterone sulfate levels at baseline. Furthermore, there seemed to be a subject- and a sex-specific response in dehydroepiandrosterone metabolism. The same daily dose of dehydroepiandrosterone did not have the same effect on all the subjects. Indeed, there was great interindividual variability with regard to hormonal and muscular status in response to dehydroepiandrosterone treatment.

The subjects treated in the present study were healthy and physically active individuals. Their dehydroepiandrosterone sulfate levels were equivalent to those observed in previous studies with respect to age and sex. Low levels would have been associated with functional limitations, according to Berr and Ravaglia and coworkers. The relative increase in IGF-1 has been greater in subjects with low dehydroepiandrosterone sulfate levels at baseline. According to this result, perhaps because of the variability observed in dehydroepiandrosterone sulfate metabolism and the weak androgenic effects reported, a 50-mg/d dose of dehydroepiandrosterone for a 1-year period had no significant beneficial effect on muscle function.

Dehydroepiandrosterone replacement therapy with a 50-mg/d dose does not improve muscle morphological features and functional abilities in elderly, healthy, functionally intact men and women. The conditions in which dehydroepiandrosterone could preserve or improve muscle strength and morphological features still need to be determined. The level of anabolic hormone responses may vary with the age and the sex of the individual, the treatment dose, the prevalent dehydroepiandrosterone sulfate and testosterone levels, and the exercise stimulus. Within the frame of the present study, the administration of dehydroepiandrosterone does affect the surrogate end point, dehydroepiandrosterone sulfate level, in a variable way, but this does not correspond to an overall clinical benefit. Thus, the dehydroepiandrosterone sulfate serum concentration may not represent a good biomarker of healthy aging in all individuals. Aged people or patients with a low dehydroepiandrosterone sulfate serum concentration and/or functional muscular deficiencies (eg, those with a myotonic dystrophy) may be more receptive to dehydroepiandrosterone therapy, which could be potentiated in association with an exercise program. This hypothesis remains to be tested.
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REFERENCES


