Physical activity and dehydroepiandrosterone sulphate, insulin-like growth factor I and testosterone in healthy active elderly people

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Abstract

Objective: to examine the association of physical activity and cardio-respiratory fitness with dehydroepiandrosterone sulphate (DHEAS), insulin-like growth factor I (IGF-I) and testosterone in healthy elderly people.

Design: cross-sectional study.

Setting: university research department and department of geriatric medicine.

Participants: 60 independent, community-dwelling elderly subjects (26 men and 34 women) aged 66–84 who volunteered to participate.

Measurements: physical activity was evaluated by the Questionnaire d’Activite Physique Saint-Etienne and expressed by three indices: mean habitual daily energy expenditure (MHDEE), daily energy expenditure (DEE) comprising activities with intensities corresponding to at least three metabolic equivalents (MET; 3.5 ml.kg⁻¹.min⁻¹ of oxygen consumption) and sport activity. Cardio-respiratory fitness was expressed by maximal oxygen consumption (VO₂max).

Results: in women, DHEAS correlated with VO₂max (partial correlation: r = 0.33; P = 0.05), MHDEE (r = 0.50; P = 0.002), DEE > 3 METs (r = 0.49; P = 0.003) and sport activity (r = 0.35; P = 0.04) whereas IGF-I correlated with MHDEE (r = 0.48; P = 0.004). DHEAS was correlated with IGF-I (r = 0.43; P < 0.02) and with testosterone (r = 0.41; P < 0.02). No such correlation was found in men.

Conclusion: lower habitual physical activity is related to lower levels of circulating DHEAS and IGF-I independently of age and anthropometric measures. Lower maximal aerobic capacity is associated with lower DHEAS concentrations, in healthy elderly women.

Keywords: ageing, dehydroepiandrosterone sulphate, exercise, fitness, insulin-like growth factor I, testosterone

Introduction

Plasma concentrations of dehydroepiandrosterone sulphate (DHEAS), insulin-like growth factor I (IGF-I) and testosterone decline with age [1−4]. These hormones share some biological activities which counteract the ageing processes: increase in fat-free mass, decrease of adipose tissue and globally increased fitness and...
well-being. There are data on attenuation of declining age-related hormone levels and trials of hormone replacement in older men and women [5–8].

Aging is usually associated with a decline in physical activity (PA) and in maximal aerobic capacity (VO_{2\text{max}}) [9, 10]. PA might counteract the age-related decline in IGF-I [11, 12]. Few studies have examined the relationship of PA and cardio-respiratory fitness with DHEAS, IGF-I and testosterone levels and none has considered all these hormones in elderly men and women. We have examined the association of PA [13, 14], cardio-respiratory fitness and body composition with DHEAS, IGF-I and testosterone concentrations in healthy elderly men and women.

Subjects and methods

Subjects

Sixty-five independent, community-dwelling elderly subjects aged between 65 and 84 years were recruited. To obtain a study population with a wide range of PA, study details were given to various associations for elderly people in Lyon. This yielded 1500 elderly subjects, of whom 65, who considered themselves healthy, agreed to participate. All volunteers had a physical examination and those with ischaemic heart disease, severe aortic stenosis, hypertrophic obstructive cardiomyopathy, osteoarthritis, hepatic or renal failure and any other chronic or progressive disorder were excluded, as were those receiving hormonal treatment or other treatment that might influence the factors to be measured. This reduced the study sample to 60 (26 men and 34 women). The study was approved by an ethics committee (Comité Consultatif de Protection des Personnes de la Recherche Biomedicale, Lyon, Centre Léon Bérard) and written informed consent was obtained from all subjects.

Protocol

The subjects reported to the laboratory at 1400 h on two consecutive days. They were asked to fast after breakfast taken at 0900 h. On the first day, the PA questionnaire was completed, anthropometric measurements taken and blood samples for hormone determinations collected. (Although blood was taken at 14.00 h, our data are representative as the circadian variation of IGF-I is minimal in young and old people and the variation of DHEAS and testosterone is blunted in the elderly population [15, 16].) On the second day, a maximal exercise test was performed.

PA

The Questionnaire d'Activité Physique Saint-Etienne (QAPSE), has been previously described [13, 14] and validated in healthy elderly subjects [17]. It retrospectively reports the activities over 1 week, including the weekend. QAPSE was completed for all participants by the same interviewer. The following QAPSE activity indices were calculated: mean habitual daily energy expenditure (MHDEE), sport activities and the sum of the activities with an intensity corresponding at least to three metabolic equivalents (where one metabolic equivalent is 3.5 ml kg^{-1} min^{-1} of oxygen consumption); this is designated DEE >3 METs.

All QAPSE activity indices are expressed in kJ day^{-1}.

Anthropometric data

Skinfold measurements were taken at four sites: triceps, biceps, subcapsular and supra-iliac. The percentage of body fat was estimated from skinfold measurements [18]. Fat-free mass was calculated by subtracting fat mass from body mass. Height and weight were also measured and the body mass index (kg m^{-2}) calculated.

VO_{2\text{max}}

Maximal treadmill exercise tests were performed [19]. After a 6-min warm-up at 0% grade and walking at 4 km h^{-1} (1.11 ms^{-1}), the grade was increased by 3% in two steps of 3 min each until 6%. Then, the speed of the treadmill was increased by 1 km h^{-1} (0.28 ms^{-1}) every 3 min until the subject became exhausted. VO_{2\text{max}} was determined by the standard open-circuit method. The expired gases were collected in a Douglas bag during the last 30 s of each 3 min-period through a low-resistance Hans Rudolf valve 2700 (Hans Rudolf, Kansas City, MO, USA). Subsequent volume determinations were carried out in a balanced Tissot spirometer. The O2 and CO2 fractions were determined using the S3A/I Ametek (Pittsburgh, PA, USA) and D-Fendt Datex (Helsinki, Finland) analysers respectively, calibrated with gas mixtures of compositions determined by Scholander's method [20].

Blood lactate concentration was determined 3 min after completion of maximal exercise on fingertip blood samples with an LA640 Kontron lactate analyser (Roche Bio-electronics, F. Hoffman-La Roche, Basel, Switzerland) [21]. Treadmill testing was supervised by a trained technician and a cardiologist. There was continuous ECG recording. All participants were strongly encouraged to give maximal effort during exercise. Oxygen uptake was accepted as maximal if the respiratory quotient was >1, blood lactate was >8 mmol l^{-1}, or oxygen uptake plateau <2 ml kg^{-1} min^{-1}, or the heart rate plateau was <5 beats min^{-1} between the two last periods of normal exercise.

Laboratory analysis

Subjects did not engage in physical exercise for at least 36 h before laboratory measurements. DHEAS, IGF-I
and testosterone assays were performed by radioimmunological methods. For DHEAS, we used the Immunotech kit with monoclonal antibody-coated tubes and $^{125}$I-labelled DHEAS. The technique is sensitive to 0.2 mmol.l$^{-1}$ and inter-assay variability is 7.8% at the mean level of 4.7 mmol.l$^{-1}$. The intra-assay accuracy test according to the instructions of manufacturer is less than 10%. IGF-I was determined by an immunoradiometric assay (Ciba-Corning Diagnostics) using $^{125}$I-labelled anti-IGF-I and anti-IGF-I monoclonal antibody-coated tubes. The samples were extracted with HCl/ethanol prior to the assay to remove IGF binding proteins [22]. Sensitivity is 0.1 nmol.l$^{-1}$ and inter-assay variability is 9-18% at the mean level of 7.6 mmol.l$^{-1}$. Testosterone was tested with an Immunotech kit. This kit used $^{125}$I-labelled testosterone and anti-testosterone antibody-coated tubes. Prior to the assay, samples were extracted by ethyl ether and chromatographed on a Celite column. Sensitivity is 0.1 nmol.l$^{-1}$ and inter-assay variability is 7.9% at the mean level of 4.57 nmol.l$^{-1}$. Serum cortisol, albumin and creatinine concentrations were determined using standard techniques in order to eliminate any confounding pathologies (data not shown).

**Statistical analysis**

Data were verified for normality of distribution and equality of variances. The one-way analysis of variance (ANOVA) and Mann-Whitney test were used to compare gender groups. DHEAS values were normalized using a log-10 transformation for the purpose of multiple regression analysis. Pearson product moment or Spearman correlations were used to determine the relationships between hormone levels and VO$_{2\text{max}}$ and QAPSE activity indices.

To control the effects of age and anthropometric characteristics, multiple regression analysis was performed and partial correlations were calculated between the residual values of hormone concentrations and residual values of PA indices and VO$_{2\text{max}}$ [23]. Stepwise regression analysis was performed to determine the relative contribution of selected independent variables to the variation of dependent variables. Analysis of covariance (ANCOVA) was used to compare the parallelism of the regression lines between men and women and to calculate interaction between MHDEE/VO$_{2\text{max}}$ and gender with hormone concentrations as dependent variables (test of homogeneity of slopes).

Results are presented as mean (standard deviation), or median (25th percentile; 75th percentile). The limit of significance was set at $P = 0.05$ for all analyses.

**Results**

All 60 subjects met the criteria for a maximal exercise test: 32 subjects had a respiratory quotient >1.0, 24 had serum lactate concentrations >8 mmol.l$^{-1}$ and 22 subjects who had not reached these levels fulfilled the criteria for oxygen uptake plateau and/or heart rate plateau.

Table 1 shows the demographic and anthropometric characteristics, VO$_{2\text{max}}$, QAPSE activity indices and hormone concentrations for the study group. There

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)/median (25th %ile; 75th %ile)$^a$</th>
<th>Statistics</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.5 (68; 72)</td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>75.4 (12.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg m$^{-2}$)</td>
<td>26.2 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>56.1 (6.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>25.1 (5.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO$_{2\text{max}}$ (ml.kg$^{-1}$.min$^{-1}$)</td>
<td>29.6 (4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHDEE (kJ.day$^{-1}$)</td>
<td>9861 (1040)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEE &gt; 3 METs (kJ.day$^{-1}$)</td>
<td>3846 (1586)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sports activities (kJ.day$^{-1}$)</td>
<td>972 (731; 1507)</td>
<td></td>
<td>0.049</td>
</tr>
<tr>
<td>IGF-I (nmol.l$^{-1}$)</td>
<td>19.2 (8.06)</td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>DHEAS (pmol.l$^{-1}$)</td>
<td>2.4 (1.62; 3.1)</td>
<td></td>
<td>0.026</td>
</tr>
<tr>
<td>Testosterone (nmol.l$^{-1}$)</td>
<td>19.3 (6.49)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

QAPSE, Questionnaire d'Activité Physique Saint-Etienne; MHDEE, mean habitual daily energy expenditure; DEE > 3 METs, sum of the activities with an intensity corresponding at least to three metabolic equivalents; IGF-I, insulin-like growth factor I; DHEAS, dehydroepiandrosterone sulphate.

$^a$For age, sports activities and DHEAS.
Table 2. Pearson product moment or Spearman correlation coefficients (upper line) and P-value for r (lower line) between the hormone concentrations and maximal aerobic capacity (VO$_{2\text{max}}$) and QAPSE activity indices in women (n = 34) and men (n = 26)

<table>
<thead>
<tr>
<th>Hormone concentration</th>
<th>IGF-I (nmol.l$^{-1}$)</th>
<th>DHEAS (nmol.l$^{-1}$)</th>
<th>Testosterone (nmol.l$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>VO$_{2\text{max}}$ (ml.kg$^{-1}$ min$^{-1}$)</td>
<td>0.32</td>
<td>0.002</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td>0.99</td>
<td>0.003</td>
</tr>
<tr>
<td>MHDEE (kJ.day$^{-1}$)</td>
<td>0.57</td>
<td>-0.16</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>0.0005</td>
<td>0.44</td>
<td>0.0002</td>
</tr>
<tr>
<td>DEE &gt;3 METs (kJ.day$^{-1}$)</td>
<td>0.41</td>
<td>-0.14</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>0.016</td>
<td>0.48</td>
<td>0.0004</td>
</tr>
<tr>
<td>Sport activity (kJ.day$^{-1}$)</td>
<td>0.37$^a$</td>
<td>0.04$^a$</td>
<td>0.46$^a$</td>
</tr>
<tr>
<td></td>
<td>0.033</td>
<td>0.84</td>
<td>0.008</td>
</tr>
</tbody>
</table>

QAPSE, Questionnaire d’Activite Physique Saint-Etienne; IGF-I, insulin-like growth factor I; DHEAS, dehydroepiandrosterone sulphate; MHDEE, mean habitual daily energy expenditure; DEE >3 METs, sum of the activities with an intensity corresponding at least to three metabolic equivalents.

$^a$Spearman correlation coefficient.

was no age difference between the men and women. Men had higher values for body mass and fat-free mass, women had higher percentages of body fat. In men there were higher values of VO$_{2\text{max}}$, MHDEE and sport activity index. Hormone concentrations in men and women were similar for IGF-I, and different for DHEAS and testosterone (as would be expected).

Table 2 shows the Pearson product moment and Spearman correlation coefficients between hormone concentrations and VO$_{2\text{max}}$ and QAPSE activity indices in men and women. In women, VO$_{2\text{max}}$ correlated positively with DHEAS. Women also showed a positive relationship between all three QAPSE activity indices and DHEAS and IGF-I levels in the female group. No such correlation could be found in men. In women, DHEAS was correlated with IGF-I ($r = 0.43; P< 0.02$) and with testosterone ($r = 0.41; P<0.02$; not shown). No anthropometric variable was correlated with hormone concentrations in either group.

The different relationship between MHDEE and DHEAS/IGF-I levels in men and women was further confirmed by significant gender. (MHDEE interactions revealed by the test of homogeneity of slopes: $P=0.014$ and $P=0.0005$ for DHEAS and IGF-I respectively.)

A multiple regression model which controlled for the effects of age, body weight, fat-free mass, body mass index and the percentage of body fat showed significant relationships between PA status and hormone concentrations in women: DHEAS correlated significantly with VO$_{2\text{max}}$ (partial correlation: $r = 0.33; P=0.05$; Figure 1), MHDEE ($r = 0.50; P=0.002$; Figure 2), DEE > 3 METs ($r = 0.49; P=0.003$) and sport activity ($r = 0.35; P=0.04$) whereas IGF-I correlated only with MHDEE ($r = 0.48; P=0.004$; Figure 3). Again, no such correlation could be found in men.

Stepwise regression analysis with all independent variables was performed to determine the factors responsible for the significant variation of hormone levels. In women, MHDEE was the only variable selected in stepwise regression analysis that predicted DHEAS and IGF-I variations. The equations for these
relationships are as follows:
\[ \log \text{DHEAS} = -1.93 + 0.0003 \times \text{MHDEE} \]
(\(SE = 0.00006; \) adjusted \(r^2 = 0.34; \) \(SEE = 0.263\))
and
\[ \text{IGF-I} = -40.5 + 0.0075 \times \text{MHDEE} \]
(\(SE = 0.0019; \) adjusted \(r^2 = 0.30; \) \(SEE = 8.16\)).

If hormonal values were introduced in the stepwise regression analysis as independent variables, testosterone concentration was also selected to predict DHEAS

\[ \text{log DHEAS} = -2.19 + 0.00027 \times \text{MHDEE} + 0.225 \times \text{testosterone} \]
(\(SE = 0.00006; \) \(SE = 0.089; \) adjusted \(r^2 = 0.43; \) \(SEE = 0.245\)).

In men, no independent variable was selected in stepwise regression analysis to predict the variation of hormone levels.

The same results were obtained by forward and backward stepwise regression analysis.

**Discussion**

We have examined simultaneously the relationship of DHEAS, IGF-I and testosterone concentrations with PA and cardio-respiratory fitness in healthy elderly men and women.

The results are from active, elderly volunteers in good health and with good functional capacity. These subjects are more likely to participate and to undergo a maximal exercise test. This methodological bias has been recently described in detail and no solution found [24].

QAPSE has been validated in an elderly population [17]. It allows a precise measurement of light PA, which is the most important component of daily energy expenditure in older subjects. MHDEE found in our study is in keeping with the values of total energy expenditure reported for elderly people [13]. Only the direct determination of \(\text{VO}_{2\text{max}}\) can be considered as a reliable measure of cardio-respiratory fitness [9, 25] and \(\text{VO}_{2\text{max}}\) levels obtained indicate that our population was at an average level of fitness when compared with standard reference values [10].

The DHEAS, IGF-I and testosterone concentrations are comparable with the values in healthy elderly subjects [1-4, 26, 27].

Assuming that hepatic function is normal, sex hormone-binding globulin and IGF-binding protein-3 (IGFBP-3) serum concentrations are probably not affected, excluding any potential interference with the levels of IGF-1 and testosterone. Although IGF-I is the major growth regulator, IGFBP-3 is the major endocrine store and modulator of IGF-I activity. However IGF-I responses to growth hormone therapy are more important than those of IGFBP-3 in healthy elderly women [28].

Short-term intensive exercise elevates circulating testosterone concentrations. Conflicting results have been reported on long-term exercise [29]. In our study, in neither men nor women were testosterone concentrations correlated with PA or fitness indices. This supports the hypothesis that testosterone is not the main factor in maintaining physical vitality in elderly people.

Low serum DHEAS concentrations are correlated with increase cardiovascular morbidity in men [30].
However, the relationship between DHEAS and PA has not been studied. Correlation between DHEAS and VO\textsubscript{2max}, MHDEE, DEE >3 METs and sport activity was found in women but not in men. The mechanisms for the modulation of DHEAS by PA (or vice versa) remain unclear. There are no differences in DHEAS concentrations between female controls and runners [31]. Perhaps regular PA influences DHEAS secretion more in elderly than younger women. However, markedly elevated DHEAS concentrations occur after marathons [32]. DHEAS is a stress-related hormone and is produced along with increasing amounts of cortisol. The increase in serum DHEAS concentration may be partially due to decreased hepatic metabolic clearance as a result of reduced hepatic blood flow during exercise [32].

The influence of training on IGF-I levels is also complex and linked to the neuroendocrine regulatory systems. As in most other surveys, we found no relationship between PA and IGF-I levels in healthy older men [33-35]. Of the two studies [12, 36] in which a positive relationship of PA and VO\textsubscript{2max} with IGF-I levels in older men was reported, the first included both younger and older men, and did not find a significant relationship in older men. In the second study only, a small sample of older men was studied. We found a relatively small but positive and significant relationship between PA and VO\textsubscript{2max} with IGF-I levels in older women [37, 11]. The precise methodology of PA assessment and VO\textsubscript{2max} measurement strengthen our findings.

The gender difference in the relationship of DHEAS and IGF-I concentrations with exercise is interesting. In women, 50% of circulating testosterone is synthesized in the adrenal cortex. Consequently, there is a stronger association between testosterone and adrenal steroids in women [29]. We confirmed a relationship between DHEAS and testosterone in women. The physiological low concentrations of testosterone in women may introduce compensative growth hormone/IGF-I axis stimulation in response to an increase in physical work in order to enhance muscle protein synthesis: after strenuous exercise, women (but not men) had increased circulating IGF-I concentrations [38].

We observed a close relationship between DHEAS and IGF-I in women. Morales et al. [6] have reported that administration of DHEAS in older men and women provokes an increase in the blood concentrations of IGF-I. Effects on liver production of IGF-I or the generation of growth hormone receptors may be underlying mechanisms. Perhaps in older women a positive influence of PA on IGF-1 production is mediated by DHEAS.

MHDEE was the only variable selected in stepwise regression analysis that predicted DHEAS and IGF-I concentrations in women. Stronger correlations of DHEAS/IGF-I with MHDEE than with DEE >3 METs or sport activity indices support previous findings and indicate that overall energy expenditure rather than exercise intensity has the most important physiological influence in older women [14]. Growth hormone and dehydroepiandrosterone replacement therapy are promising interventions for treating frail elderly subjects but there are problems with these therapies. Lower concentrations of DHEAS and IGF-I may reflect partially lower PA and maximal aerobic capacity, at least in women. The cross-sectional design of our study and relatively small correlations limit data interpretation. If longitudinal studies confirm our findings participation in exercise training might be a useful alternative to replacement therapy. DHEAS and IGF-I serum concentrations could potentially be tools in the assessment of fitness.

**Key points**

- Plasma concentration of insulin-like growth factor I (IGF-I), testosterone and dehydroepiandrosterone (DHEAS) decline with age.
- In healthy elderly male volunteers, physical activity and cardio-respiratory fitness were unrelated to the plasma concentrations of these three hormones.
- In healthy older women, reduced activity and fitness were associated with reduced plasma DHEAS concentrations.
- Women who took less exercise had lower plasma concentrations of IGF-I.
- Testosterone concentrations were unrelated to physical activity or fitness in either older men or women.

**References**


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'Morning and evening': John Robert 'Dandy' Storr and his great uncle Tom Storr. Taken on Tate Hill Pier, Whitby in 1884 by Frank Meadow Sutcliffe (1853–1941). © The Sutcliffe Gallery, Whitby.