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# Contribution of age and declining androgen levels to features of the metabolic syndrome in men

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**Abstract**

Plasma dehydroepiandrosterone sulfate (DHEA-S) and testosterone levels both decline with age in healthy men. Features of the metabolic syndrome also show age-related deteriorations. We examined the relative contribution of age and declining androgen levels to features of the metabolic syndrome in men. In a sample of 130 nonsmoking men from the Quebec Family Study, we tested the hypothesis that age-related decreases in DHEA-S and testosterone levels would explain most of the variance in alterations of the metabolic profile associated with aging. As expected, we found that plasma DHEA-S and testosterone levels were negatively associated with age. Significant negative correlations were found between androgen levels and adiposity measures, body fat distribution, and metabolic risk variables. Statistical control for age eliminated correlations with DHEA-S, whereas age-adjusted associations between testosterone and most adiposity and metabolic variables remained significant. The percentage frequency of men characterized by 3 or more features of the metabolic syndrome increased with decreasing testosterone (8.9%-44.2%, $\chi^2 = 15.89$, $P < .0005$ ) and DHEA-S levels (8.9%-41.5%, $\chi^2 = 13.02$, $P < .005$). Logistic regression analyses showed that men in the upper tertile of testosterone levels had a lower risk of being characterized by 3 or more features of the metabolic syndrome (odds ratio = 0.24, $P < .04$) independent of age, whereas tertiles of DHEA-S levels were not related to the metabolic syndrome independent of age. In conclusion, results suggest that age per se is an important correlate of the associations between DHEA-S and metabolic variables, whereas the association of plasma testosterone levels to features of the metabolic syndrome appears to be independent of age.


## 1. Introduction

The age-related decline in dehydroepiandrosterone sulfate (DHEA-S) and testosterone in men is well established. Testosterone levels are low during childhood and increase at puberty, until adult levels are reached [1]. Then, from around 25 years of age, plasma testosterone levels steadily decline by a mean of 1.0% per year (range, 0.4%-2.2% per year) [2-5]. Plasma DHEA-S levels decline to an even greater extent, by a mean of 2.3% per year (range, 2.0%-2.4% per year) [2-4]. The age-related decreases in androgen levels have been suggested to be mediated by an important decline in the activity of steroidogenic enzymes in the adrenals and a slightly lower decrease in the gonadal activity of these enzymes [3]. Some authors also suggested that age-related decreases in plasma testosterone levels may be mediated by increased aromatization in peripheral tissues as well as alterations in the hypothalamic-pituitary-adrenal/gonadal axis [6-8].

Variables of the metabolic profile, including visceral fat accumulation, blood pressure, plasma triglycerides, high-density lipoprotein cholesterol (HDL-C), and glucose

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concentrations, also deteriorate with age [9,10]. Ford et al [11] recently emphasized the strong effect of age on some simple clinical markers of the metabolic syndrome in the US population [12]. In this large epidemiologic survey, the prevalence of 3 or more clinical criteria to predict the metabolic syndrome increased from 6.7% among subjects aged 20 to 29 years to more than 40% at age 60 years and older [11]. Dehydroepiandrosterone sulfate and testosterone have been suggested to influence metabolic processes associated with the development of the metabolic syndrome [13,14]. Moreover, in some representative population–based studies, authors concluded that low testosterone levels predict future development of type 2 diabetes [15,16]. However, whether declining androgen levels per se contribute to variation in features of the metabolic syndrome independent of age remains to be studied.

The present study aimed at examining the relative contribution of age and declining androgen levels to the variation in features of the metabolic syndrome. We tested the hypothesis that decreases in DHEA-S and testosterone with aging would explain most of the age-related alterations in the metabolic profile. We examined a sample of 130 men from the Quebec Family Study (QFS) for whom detailed metabolic profiles, measures of adiposity and body fat distribution as well as DHEA-S and testosterone concentrations were available.

## 2. Subjects and methods

### 2.1. Subjects

The QFS is a cohort that includes French-Canadian families living in and around Quebec City, Canada. Families were recruited through the media for genetic studies. In the present study, all required data were available for 130 healthy men (aged 20-71 years). All subjects were nonsmokers and information about medication use was available for 82% of subjects. Subjects were excluded if they were using lipid-lowering therapy or oral hypoglycemic medication. All patients signed an informed consent document and the study was approved by the Medical Ethics Committee of Laval University.

### 2.2. Body composition and anthropometry

Body composition measurements were performed using the hydrostatic weighing technique with helium dilution, as previously described [17]. Body density was calculated as the mean of 6 measurements and the equation of Siri [18] was used to determine percentage body fat mass from body density. Standardized procedures were used to measure body weight and height [19].

### 2.3. Abdominal adipose tissue areas

Measures were performed at the abdominal level (L4-5 vertebrae) using a Siemens Somatom DRH scanner (Erlanger, Germany) as described previously [20]. Scanning position was established using a radiograph of the skeleton as reference. Measures of total, subcutaneous, and intra-abdominal adipose tissue areas were performed by delineating tissue surfaces with the software interface of the scanner using an attenuation range of −190 to −30 Hounsfield units [20].

### 2.4. Metabolic variables

A 75-g oral glucose tolerance test was performed in the morning after an overnight fast. Blood samples were collected in EDTA and Trasylol (Miles Pharmaceuticals, Etibicoke, Ontario, Canada) through a venous catheter at −15, 0, 30, 45, 60, 90, 120, 150, and 180 minutes after glucose ingestion. Fasting values were defined as the mean of measurements performed at −15 and 0 minutes. C-peptide plasma levels were determined with the A-4741 polyclonal antibody and with polyethylene glycol precipitation [21]. Plasma glucose was measured with an enzymatic method, and a radioimmunoassay with polyethylene glycol separation was used for insulin [22,23]. Cholesterol and triglyceride levels were measured in plasma and lipoprotein fractions using a Technicon RA-500 analyzer (Bayer Corp, NY). The HDL fraction was obtained after low-density lipoprotein (LDL) precipitation using heparin and manganese chloride [24]. Apolipoprotein B concentration was measured in plasma and lipoprotein fractions according to the method of Laurell [25]. Plasma sex hormone–binding globulin (SHBG) concentrations were measured by radioimmunoassay (Diagnostic Systems Laboratories, Webster, Tex).

### 2.5. Dehydroepiandrosterone sulfate and testosterone measurements

Fasting blood samples were collected in EDTA-containing tubes. Plasma was separated by centrifugation and samples were kept at −80°C with one thawing for other measurements. High-performance gas chromatography and negative chemical ionization mass spectrometry were used to measure plasma testosterone levels. The intra-assay and interassay coefficient of variation did not exceed 5.9% for this method. Dehydroepiandrosterone sulfate was determined by high-performance liquid chromatography and mass spectrometry using a PE Sciex API 300 tandem mass spectrometer (Perkin-Elmer, Foster City, Calif) including a Turbo ionspray source. The intra-assay and interassay coefficient of variation for DHEA-S measurements did not exceed 6.4%. The lower limits of quantification were 1.39 nmol/L for testosterone and 0.20 $\mu$mol/L for DHEA-S.

### 2.6. Statistical analyses

Spearman rank correlation coefficients were computed to quantify the relationships between adiposity and metabolic variables with plasma DHEA-S and testosterone. Age- and visceral fat–adjusted partial correlations were also examined. The age-related decline in androgen levels (percentage per year and per decade) was estimated by calculating the

percentage decrease in mean hormone levels between age groups 65 to 70 years and 20 to 25 years, divided by the age difference (45 years or 4.5 decades). The number of features of the metabolic syndrome was determined according to the following criteria [12,26,27]: visceral adipose tissue (VAT) area of 130 $cm^2$ or more, systolic blood pressure of 130 mm Hg or more, plasma triglyceride level greater than 1.69 mmol/L, HDL-C level less than 1 mmol/L, and fasting glycemia level of 6.1 mmol/L or more. $\chi^2$ Test was used to test metabolic syndrome prevalence differences between hormonal level tertiles. Logistic regression analysis was performed to determine the probability of being characterized by 3 or more features of the metabolic syndrome in each testosterone and DHEA-S tertile. Age was included in all models. An $\alpha$ level of $\leq .05$ was considered as statistically significant. Analyses were performed using JMP statistical analysis software (SAS Institute, Cary, NC).

## 3. Results

Physical characteristics of the sample are shown in Table 1. Subjects were overweight on average (body mass index value, 26.8 $kg/m^2$), but adiposity values covered a wide range. Based on accepted cutoffs, 16 subjects were characterized by a fasting glycemia level greater than 6.1 mmol/L (impaired fasting glucose) and 3 had a fasting glycemia level greater than 7.6 mmol/L (type 2 diabetes). Thirty-one subjects were characterized by 3 or more of the features of the metabolic syndrome considered in the present study (see "Subjects and methods" for definition).

Table 1
Characteristics of the sample (N = 130 men)

| Characteristic | Mean ± SD | Range |
|---|---|---|
| Age (y) | 43.2 ± 15.1 | 20.2-71.2 |
| Height (cm) | 173 ± 6 | 155-187 |
| Weight (kg) | 79.8 ± 15.5 | 56.4-129.0 |
| BMI ($kg/m^2$) | 26.8 ± 5.0 | 17.9-45.7 |
| Fat mass (kg) | 19.2 ± 10.1 | 3.4-50.8 |
| Fat-free mass (kg) | 60.6 ± 7.8 | 41.2-83.3 |
| Fat percentage (%) | 22.9 ± 8.2 | 5.7-43.6 |
| Waist circumference (cm) | 93 ± 14 | 68-135 |
| SAT area ($cm^2$) | 207 ± 124 | 10-669 |
| VAT area ($cm^2$) | 128 ± 79 | 23-443 |
| Systolic blood pressure (mm Hg) | 117 ± 16 | 84-174 |
| Diastolic blood pressure (mm Hg) | 73 ± 10 | 48-111 |
| Fasting glucose (mmol/L) | 5.46 ± 1.06 | 4.15-14.65 |
| Fasting insulin (pmol/L)[a] | 67 ± 42 | 7-219 |
| Fasting C-peptide (pmol/L) | 784 ± 361 | 182-1732 |
| Glucose 60 min (mmol/L) | 8.70 ± 2.82 | 3.60-23.00 |
| Insulin 60 min (pmol/L) | 638 ± 405 | 67-1975 |
| C-peptide 60 min (pmol/L) | 3674 ± 1585 | 685-8568 |
| Total cholesterol (mmol/L) | 4.94 ± 0.98 | 2.68-8.61 |
| HDL-C (mmol/L) | 1.12 ± 0.29 | 0.62-2.40 |
| LDL-C (mmol/L) | 3.15 ± 0.82 | 1.09-6.02 |
| Triglycerides (mmol/L) | 1.51 ± 0.75 | 0.43-4.17 |
| Total cholesterol/HDL-C | 4.62 ± 1.31 | 2.00-8.72 |
| Apolipoprotein B (mg/dL) | 1.01 ± 0.24 | 0.49-1.72 |
| DHEA-S ($\mu$mol/L) | 4.66 ± 2.80 | 0.48-12.32 |
| Testosterone (nmol/L) | 16.83 ± 5.45 | 3.22-33.39 |

BMI indicates body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.
[a] n = 129.

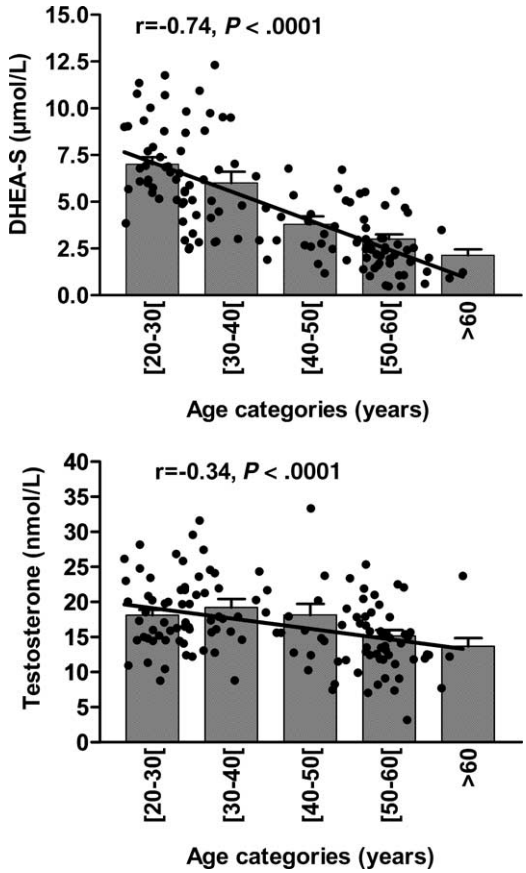


Fig. 1. Correlations between plasma androgen levels and age. Spearman rank correlation coefficients are shown.

The correlations between plasma androgen levels and age are shown in Fig. 1. We observed an age-related difference of −15.5% per decade for DHEA-S (−1.55% per year) and −5.4% per decade for testosterone (−0.54% per year) by comparing average values between age groups. Correlation coefficients between plasma androgen levels and adiposity measures are shown in Table 2. Several significant

Table 2
Spearman rank correlation coefficients between steroid hormones (DHEA-S and testosterone) and adiposity measures, unadjusted and adjusted for age

| | DHEA-S | | Testosterone | |
|---|---|---|---|---|
| | Unadjusted | Age-adjusted | Unadjusted | Age-adjusted |
| Age | −0.74* | – | −0.34* | – |
| Height | 0.26* | −0.13 | 0.17** | 0.03 |
| Weight | −0.05 | 0.08 | −0.44* | −0.40* |
| BMI | −0.15 | 0.14 | −0.53* | −0.44* |
| Fat mass | −0.28* | 0.10 | −0.56* | −0.40* |
| Fat-free mass | 0.22** | 0.03 | −0.19** | −0.28* |
| Fat percentage | −0.35* | 0.10 | −0.56* | −0.37* |
| Waist circumference | −0.28* | 0.15 | −0.63* | −0.46* |
| SAT area | −0.16 | 0.11 | −0.52* | −0.43* |
| VAT area | −0.44* | 0.10 | −0.65* | −0.44* |

* $P < .05$.
** $P < .005$.

Table 3
Spearman rank correlation coefficients between steroid hormones (DHEA-S and testosterone) and metabolic risk variables, unadjusted and adjusted for age or visceral adipose tissue area

| | DHEA-S | | | Testosterone | | |
|---|---|---|---|---|---|---|
| | Unadjusted | Age-adjusted | VAT-adjusted | Unadjusted | Age-adjusted | VAT-adjusted |
| Systolic blood pressure | −0.22* | 0.17* | −0.01 | −0.33** | −0.17 | 0.07 |
| Diastolic blood pressure | −0.24* | 0.15 | −0.04 | −0.40** | −0.25** | −0.15 |
| Fasting glucose | −0.25** | 0.14 | −0.01 | −0.33** | −0.19* | −0.04 |
| Fasting insulin[a] | −0.10 | 0.13 | 0.19* | −0.45** | −0.38** | −0.14 |
| Fasting C-peptide | −0.19* | 0.15 | 0.10 | −0.50** | −0.38** | −0.20* |
| Glucose 60 min | −0.21* | 0.12 | −0.01 | −0.30** | −0.17 | −0.08 |
| Insulin 60 min | −0.02 | 0.14 | 0.16 | −0.27** | −0.22* | −0.08 |
| C-peptide 60 min | −0.07 | 0.16 | 0.12 | −0.32** | −0.24* | −0.15 |
| Total cholesterol | −0.46** | −0.09 | −0.37** | −0.13 | 0.05 | −0.03 |
| HDL-C | 0.19* | −0.03 | 0.03 | 0.36** | 0.29** | 0.23* |
| LDL-C | −0.45** | −0.07 | −0.38** | −0.11 | 0.06 | 0.01 |
| Triglycerides | −0.31** | 0.06 | −0.06 | −0.48** | −0.33** | −0.20* |
| Total cholesterol/HDL-C | −0.44** | −0.01 | −0.23* | −0.42** | −0.24* | −0.21* |
| Apolipoprotein B | −0.45** | 0.01 | −0.29** | −0.26** | −0.07 | −0.08 |

[a] n = 129.
* $P < .05$.
** $P < .005$.

associations were noted before adjustment for age. Specifically, DHEA-S and testosterone levels both were negatively and significantly associated with total body fat mass, fat percentage, waist circumference, and VAT area. However, statistical adjustment for age eliminated all associations between DHEA-S and adiposity measures, whereas this adjustment did not affect associations between testosterone and adiposity.

Unadjusted, age-adjusted, and VAT area–adjusted correlations between plasma androgen levels and variables of the metabolic profile are shown in Table 3. Again, elevated levels of DHEA-S and testosterone were associated with a favorable metabolic profile. Specifically, significant negative associations were found between plasma DHEA-S and blood pressure, plasma glucose (fasting and 60 minutes postglucose), fasting C-peptide, total cholesterol, LDL-cholesterol (LDL-C), triglycerides, and apolipoprotein B. A significant positive correlation was observed between DHEA-S and HDL-C levels. Similarly, plasma testosterone levels were negatively correlated with blood pressure, plasma glucose, insulin, C-peptide, triglycerides, and apolipoprotein B. Testosterone was also significantly and positively associated with HDL-C levels, but negatively correlated with the total cholesterol/HDL-C ratio. Associations between DHEA-S and metabolic variables were no longer found when adjusted for age (except for the negative association with systolic blood pressure). However, most associations between plasma testosterone and metabolic variables remained significant after statistical control for age (Table 3). A previous study has shown that low plasma SHBG was also predictive of metabolic syndrome features in a sample of men from the present cohort [28]. Adjustment for plasma SHBG concentration did not change the results of the analysis (not shown).

Correlations were also computed after adjustment for visceral fat accumulation. Several associations between plasma steroids and adiposity and metabolic variables did not retain significance. However, plasma testosterone levels remained significantly associated with fasting C-peptide ($r = -0.20, P < .05$), HDL-C ($r = 0.23, P < .05$), triglyceride ($r = -0.20$, $P < .05$), and total cholesterol/HDL-C ($r = -0.21$, $P < .05$) after control for VAT area. Moreover,

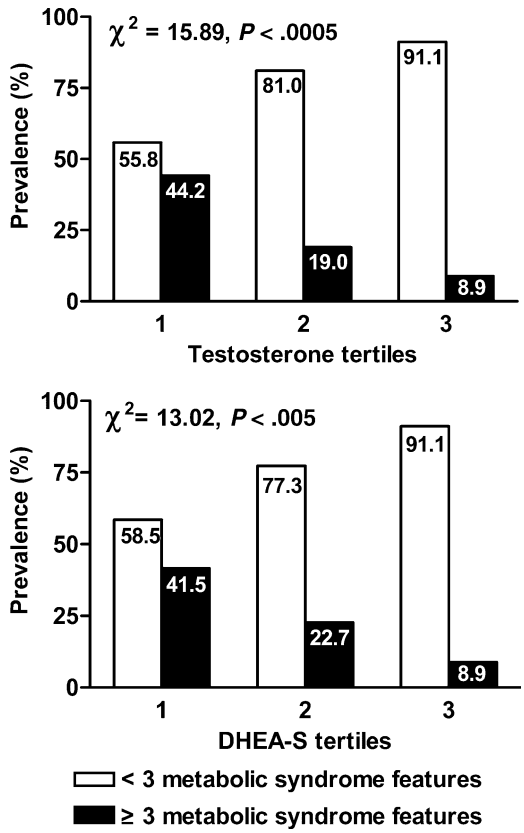


Fig. 2. Frequency distribution according to the number of components of the metabolic syndrome and plasma testosterone as well as DHEA-S tertiles in the 130 men of the study. Values presented are percentages of men in each tertile.

Table 4
Multiple logistic regression analysis of the probability of being characterized by 3 or more features of the metabolic syndrome according to testosterone and DHEA-S tertiles in men of the study (N = 130)

| | $\beta$ | OR | 95% CI | $P$ |
|---|---|---|---|---|
| Testosterone (nmol/L) | | | | |
| Tertile 1 (3.22-14.49) | 0 | 1 | – | – |
| Tertile 2 (14.49-17.99) | −0.58 | 0.56 | −1.72 to 0.54 | NS |
| Tertile 3 (18.55-33.39) | −1.44 | 0.24 | −2.84 to −0.19 | .04 |
| DHEA-S ($\mu$mol/L) | | | | |
| Tertile 1 (0.48-2.76) | 0 | 1 | – | – |
| Tertile 2 (2.76-5.52) | 0.35 | 1.42 | −1.78 to 1.50 | NS |
| Tertile 3 (5.53-12.32) | 0.41 | 0.50 | −1.52 to 2.40 | NS |

Age included in all models. OR indicates odds ratio; CI, confidence interval.

plasma DHEA-S concentration remained significantly associated with total cholesterol ($r = -0.37$, $P < .005$), LDL-C ($r = -0.38$, $P < .005$), total cholesterol/HDL-C ($r = -0.23$, $P < .05$), and apolipoprotein B ($r = -0.29$, $P < .05$) after adjustment for VAT area (Table 3).

Fig. 2 shows the percentage frequency of men characterized by either 3 or more or 2 or less features of the metabolic syndrome by androgen concentration tertiles. For both androgens, the prevalence of men with 3 or more features of the metabolic syndrome decreased with increasing testosterone and DHEA-S levels. The percentage of men with 3 features of the metabolic syndrome or more were 44.2% and 41.5% in the lower tertiles of testosterone and DHEA-S, respectively, whereas these percentages decreased to 8.9% in the upper tertiles of testosterone and DHEA-S (Fig. 2).

We then investigated whether testosterone or DHEA-S levels were significant predictors of the presence of 3 or more features of the metabolic syndrome in men of the study, independent of age. Logistic regression analyses were performed and results are shown in Table 4. Men with testosterone values in the upper tertile had a significantly lower risk of being characterized by 3 or more features of the metabolic syndrome (odds ratio = 0.24, $P < .04$) independent of age, whereas DHEA-S tertiles were not related to the metabolic syndrome after inclusion of age in the model.

## 4. Discussion

We tested the hypothesis that age-related decreases in DHEA-S and testosterone explained most of the age-related alterations in the metabolic risk profile. As expected, plasma DHEA-S and testosterone levels were lower with increasing age in the present sample. Elevated DHEA-S and testosterone levels were associated with a more favorable metabolic risk profile. However, statistical adjustment for age eliminated the correlations between DHEA-S and metabolic variables, whereas age-adjusted associations between testosterone and most adiposity and metabolic variables remained significant. We found that higher testosterone levels were associated with a lower VAT accumulation, a lower prevalence of metabolic abnormalities, reduced triglyceride levels, and higher HDL-C concentration, independent of age. On the other hand, DHEA-S level was not an independent predictor of metabolic abnormalities after considering age as a confounder. To our knowledge, this is the first study aimed at dissociating the relative statistical contributions of age and declining androgen levels to features of the metabolic syndrome. Results suggest that aging per se is a critical correlate of the associations between DHEA-S and the metabolic profile, whereas plasma testosterone levels appear to be associated with features of the metabolic syndrome, independent of age.

In a recent review of prospective studies, Wu and von Eckardstein [29] concluded that endogenous testosterone levels do not appear to be an independent risk factor for cardiovascular disease events in men. Despite the concern that only a single hormone measurement at recruitment was used in these studies and possible storage artifacts, the relatively large sample sizes and long follow-up period of these cohort studies support the notion that testosterone is not an independent risk factor for coronary artery disease in men [29]. However, plasma testosterone is strongly associated with cardiovascular disease risk factors, which may mediate the association between testosterone levels and cardiovascular disease noted in some studies [29]. Accordingly, a recent study also found that low testosterone level is an independent predictor for the development of the metabolic syndrome in men [30]. Metabolic improvements were also observed in men with abdominal obesity treated with exogenous testosterone in some studies [31,32]. The present study confirms that low plasma testosterone levels in men are related to an altered cardiovascular disease risk profile. Results suggest an independent contribution of plasma testosterone levels, although age also appears to be an independent predictor.

Whether pharmacologic DHEA should be used to replace declining DHEA and DHEA-S levels in aging individuals has attracted much attention and debate. Although a survey of the literature indicates that most DHEA replacement intervention studies observed no change on adiposity or metabolic risk variables [33], a recent randomized, double-blind, placebo-controlled trial found a significant decrease in visceral and subcutaneous fat and an improvement in insulin sensitivity after a 6-month 50 mg/d administration to 28 men aged 65 to 78 years [34]. On the other hand, studies in which the associations between DHEA-S and cardiovascular disease were examined generated unconvincing and equivocal data [29], and reports on the associations observed between DHEA(S) and obesity parameters have also been inconsistent [33]. Four studies found significant positive associations between plasma DHEA-S levels and measures of obesity or body fat distribution, whereas 9 reported significant negative associations [33]. A large number of studies also found no significant association between plasma DHEA-S levels and measures of obesity or body fat distribution [33]. Thus, whether a relationship between endogenous DHEA-S levels and adiposity variables exists

and what the direction of this association is remain unclear at the present time. In the present analysis, we found significant negative univariate associations between plasma DHEA-S and adiposity as well as abdominal adipose tissue areas. However, when adjusting for age, all significant associations between DHEA-S and adiposity and body fat distribution as well as metabolic variables were eliminated. These results suggest that age may have been an important confounder of the correlations previously observed between plasma DHEA-S levels and adiposity as well as metabolic alterations.

Statistical control for VAT area also abolished several associations between androgen levels and variables of the metabolic profile. This observation, which is consistent with previously published data [35-37], suggests that visceral fat accumulation is a critical correlate of the metabolic alterations associated with low androgen levels.

The physiological bases of the present observations are unclear at the present time. In humans, DHEA and DHEA-S are the most abundant steroid products of the adrenal gland and the most abundant steroids in peripheral blood. In men, the serum concentration of DHEA-S is approximately 300 to 500 times higher than that of DHEA, 100- to 500-fold greater than that of testosterone, and 1000- to 40 000-fold greater than that of estradiol [38,39]. Both DHEA and DHEA-S do not possess intrinsic androgenic or estrogenic activities by themselves, their biologic function being determined by steroidogenic enzymes expressed in peripheral tissues, where DHEA and DHEA-S are converted into active androgens and estrogens, providing cells with active steroids (intracrine conversion) [40]. We suggest that plasma DHEA-S is secreted largely in excess of quantities required for peripheral conversion and action, on a cellular basis, which may explain why age-adjusted correlations between DHEA-S and features of the metabolic syndrome were not significant in men of the present study. More studies are needed to confirm whether this hypothesis is true and whether DHEA supplementation should be considered as a treatment option or for the prevention of the metabolic syndrome in subjects with normal DHEA-S values. The recent study published by Villareal and Holloszy [34] that has found beneficial effects of DHEA administration in elderly subjects with low baseline plasma DHEA-S levels (mean of 2.03 $\mu$mol/L at baseline, representing 18% of values in the present sample) may highlight the possibility of a subpopulation that is especially responsive to DHEA replacement therapy.

In summary, age appears to be the major contributor to the associations found between plasma DHEA-S levels and adiposity as well as the metabolic profile. Low plasma testosterone levels, on the other hand, are significantly associated with an altered metabolic risk profile, whereas age remains a contributing factor. Whether androgen supplementation should be considered for men with low testosterone levels and features of the metabolic syndrome remains to be evaluated.

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