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Contribution of Body Fatness and Adipose Tissue Distribution to the Age Variation in Plasma Steroid Hormone Concentrations in Men: The HERITAGE Family Study*

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ABSTRACT

Obesity has been associated with alterations in plasma steroid hormone concentrations in men. Older men present an altered steroid hormone profile compared to younger individuals, and an increase in body fatness and changes in adipose tissue (AT) distribution are noted with advancing age. Thus, there is a need to examine the relative importance of increased body fatness and changes in AT distribution with advancing age to plasma steroid hormone and sex hormone-binding globulin levels in men. We, therefore, investigated the relationships among age, body fatness, AT distribution, and the plasma steroid hormone profile in a group of 217 Caucasian men (mean age ± SD, 36.2 ± 14.9 yr) who covered a wide age range (17–64 yr). Compared to young adult men, older men were characterized by increased adiposity ($P < 0.0001$) expressed either as body mass index or total body fat mass assessed by underwater weighing. Differences in AT distribution were also noted with a preferential accumulation of abdominal fat as indicated by a larger waist girth ($P < 0.0001$) and higher visceral AT accumulation ($P < 0.0001$), measured by computed tomography, in older subjects. Age was associated with decreases ($P < 0.0001$) in C_{19} adrenal steroid levels, namely reduced dehydroepiandrosterone (DHEA), DHEA fatty acid ester, DHEA sulfate, as well as androstenedione levels. Androgens, *i.e.* dihydrotestosterone and testosterone, were also affected by age, with lower levels of both steroids being found in older individuals ($P < 0.0005$). When statistical adjustment for body fatness and AT distribution was performed, differences in C_{19} adrenal steroids between the age groups remained significant, whereas differences in androgens and sex hormone-binding globulin concentrations were no longer significant. The present study suggests that age-related differences in plasma steroid hormone levels, especially androgens, are partly mediated by concomitant variation in adiposity in men. (*J Clin Endocrinol Metab* **85:** 1026–1031, 2000)

SIGNIFICANT associations among plasma sex steroid hormones, body composition, and adipose tissue (AT) distribution have been reported (1–6). Low plasma testosterone concentrations have been reported in obese subjects (1–3). Obesity is also associated with lower C_{19} adrenal steroid levels, namely dehydroepiandrosterone (DHEA), androstenedione (Δ^4-dione), and androst-5-ene-3β,17β-diol (Δ^5-diol) (1, 4). In addition, some studies have reported a relationship between AT distribution and plasma sex steroid hormone concentrations with low testosterone, Δ^4-dione, Δ^5-diol, and sex hormone-binding globulin (SHBG) levels being found in viscerally obese men (1, 3–5) along with increased plasma estrogen concentrations (1, 6).

Significant changes in body fatness and AT distribution occur with age, and older subjects are generally characterized by increased body fatness and a preferential accumulation of abdominal AT (7–9). On the other hand, aging has also been associated with a reduction in plasma sex steroid hormone concentrations, with older men having lower plasma testosterone levels (10–12). Furthermore, decreases in DHEA, DHEA fatty acid ester (DHEA-FA), and DHEA sulfate (DHEA-S) levels have been reported with advancing age (10, 11). However, to what extent these age-related alterations in the steroid hormone profile result from the concomitant increase in total and abdominal AT is not well documented. The aim of the present study was to examine age-related differences in body fatness, AT distribution, and plasma steroid hor-

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mone profile in a sample of 217 Caucasian healthy men covering a wide age range.

Subjects and Methods

Subjects

The HERITAGE Family Study cohort has been previously described (13). We report herein the results obtained from a subsample of 217 Caucasian men from the original HERITAGE cohort. Subjects were healthy and sedentary and met a number of inclusion and exclusion criteria (13). The study protocol had been previously approved by the institutional review board at each of the four clinical centers. Informed consent was obtained from each subject.

Anthropometric and body composition measurements

Body weight, height, as well as waist and hip circumferences were measured following standardized procedures (14), and the waist to hip ratio was calculated. Body density was measured using the hydrostatic weighing technique (15). The mean of the highest 3 (of 10) measurements was used in the calculation of percent body fat from body density using the equation of Siri (16). Fat mass was obtained by multiplying body weight by percent body fat. These measurements have been shown to be highly reproducible with no difference between clinical centers or drift over time in the course of data collection (17).

Computed tomography

Visceral AT accumulation was assessed by computed tomography using previously described procedures (18, 19). Briefly, the subjects were examined in the supine position with both arms stretched above the head. The scan was performed at the abdominal level (between L4 and L5 vertebrae) using an abdominal scout radiograph to standardize the position of the scan to the nearest millimeter. The total AT area was calculated by delineating the abdominal scan with a graph pen and then computing the AT surface with an attenuation range of −190 to −30 Hounsfield units (18–20). The abdominal visceral AT area was measured by drawing a line within the muscle wall surrounding the abdominal cavity. The abdominal sc AT area was calculated by subtracting the visceral AT area from the total abdominal AT area.

Plasma steroid hormone and SHBG concentrations

On two separate occasions (24-h interval), blood samples were obtained from an antecubital vein into Vacutainer tubes (Savant Instrument Co., Farmingdale, NY) with no anticoagulant in the morning between 0700–0900 h after a 12-h fast with participants in a semirecumbent position. Fasting serum was prepared according to a standard protocol. After centrifugation of blood at 2000 × *g* for 15 min at 4 C, two aliquots of 2 mL were placed in cryogenic tubes and frozen at −80 C until analysis. For nonconjugated steroids, DHEA and testosterone were differentially extracted with hexane-ethyl acetate (9:1, vol/vol), whereas petroleum ether (35–65 C) was used for the extraction of Δ^4-dione and dihydrotestosterone (DHT). In-house RIAs were performed to measure levels of these four steroids. Cortisol, estradiol, and DHEA-S were assayed directly using commercially available kits (Diagnostics Systems Laboratories, Inc., Webster, TX). For ester-conjugated steroids, *i.e.* DHEA-FA, an ethanol extraction was performed followed by C_{18} column chromatography as described by Bélanger *et al.* (21), and the resulting fatty acid derivatives were submitted to saponification. These steroids were then separated by elution on LH-20 columns. Levels of the steroids were measured by RIA as previously described (22). SHBG was determined with an IRMA-Count solid phase immunoradiometric assay using ^{125}I (Diagnostics Systems Laboratories, Inc.).

Plasma insulin concentrations

Plasma insulin levels were measured by RIA after polyethylene glycol separation, as described by Desbuquois and Aurbach (23). Polyclonal antibodies that cross-react more than 90% with proinsulin (and presumably, with its conversion intermediates) were used (24). Therefore, in this study insulin refers to immunoreactive insulin (defined as the sum of insulin, proinsulin, and split proinsulin).

Statistical analysis

The present study was performed using the pretraining data of the HERITAGE Family Study. The mean of two measurements has been used for steroid levels. Pearson product-moment correlation coefficients were used to quantify the relationships among age, body fatness, AT distribution indexes, and fasting plasma steroid hormone concentrations. The general linear model was used to analyze differences in body fatness, AT distribution, and plasma steroid concentrations between subgroups of men stratified on the basis of age, *i.e.* 1) 19 yr and younger, 2) 20–29 yr, 3) 30–39 yr, 4) 40–49 yr, and 5) 50 yr and older. A multiple regression analysis was also performed to estimate the independent contributions of age, total body fat mass, and AT distribution indexes (namely waist and hip circumferences as well as abdominal sc and visceral AT accumulations) to the variation in fasting plasma sex steroid hormone levels and SHBG concentrations. All analyses were performed using the SAS statistical package (SAS Institute, Inc., Cary, NC).

Results

Table 1 shows the physical characteristics of subjects stratified on the basis of age. We noted an age-related increase in body fatness, as body mass index and percent body fat increased throughout the age groups but reached a plateau above 30 yr of age. Concomitant changes in body fat distribution were also noted as waist circumference increased with age. Although there was a significant increase in hip girth with age, there still was a preferential accumulation of AT in

TABLE 1. Physical characteristics of men stratified on the basis of age

Variables	Age (yr)					Pearson r with age
	19 and below	20–29	30–39	40–49	50 and above	
No. of subjects	32	71	26	31	57	
Age (yr)	18 ± 1	25 ± 3[a]	34 ± 2[a,b]	47 ± 2[a,b,c]	56 ± 4[a,b,c,d]	
BMI (kg/m^2)	23.2 ± 3.3	25.3 ± 4.9[a]	27.8 ± 4.3[a,b]	29.0 ± 4.6[a,b]	28.0 ± 4.3[a,b]	0.38[e]
% Body fat	13.9 ± 8.6	18.5 ± 8.2[a]	25.5 ± 5.8[a,b]	27.0 ± 7.0[a,b]	27.7 ± 6.1[a,b]	0.57[e]
Waist girth (cm)	82.8 ± 10.0	89.3 ± 13.3[a]	98.0 ± 12.1[a,b]	101.1 ± 10.8[a,b]	101.3 ± 10.6[a,b]	0.51[e]
Hip girth (cm)	98.4 ± 7.4	101.7 ± 8.8	106.3 ± 8.8[a,b]	105.7 ± 8.0[a]	103.8 ± 8.0[a]	0.22[f]
WHR	0.84 ± 0.04	0.87 ± 0.06[a]	0.92 ± 0.05[a,b]	0.95 ± 0.05[a,b,c]	0.97 ± 0.05[a,b,c]	0.72[e]

Data are expressed as the mean ± SD.
[a] Significantly different from men of 19 yr of age and below.
[b] Significantly different from men between the ages of 20 and 29 yr.
[c] Significantly different from men between the ages of 30 and 39 yr.
[d] Significantly different from men between the ages of 40 and 49 yr.
[e] $P < 0.0001$.
[f] $P < 0.005$.

the abdominal region, as expressed by the stepwise increase with age in the waist to hip ratio.

Figure 1 illustrates body fat mass as well as sc and visceral AT areas measured by computed tomography in the various age groups. As expected, we noted an increase in total body fat mass and abdominal sc and visceral AT accumulation with age. However, as opposed to total body fat mass and the abdominal sc AT area, which reached a plateau among men 30 yr and older, there was a constant and stepwise increase in visceral AT accumulation throughout all age groups.

Plasma steroid hormone profiles of men stratified on the basis of age are presented in Table 2. Contrary to cortisol and estradiol concentrations, which were not related to age, we noted significant age-related decreases in Δ^4-dione, DHEA, DHEA-FA, and DHEA-S levels. Furthermore, older men were characterized by lower DHT and testosterone concentrations as well as higher SHBG levels; this increase was only noted among men 50 yr and older (Fig. 2).

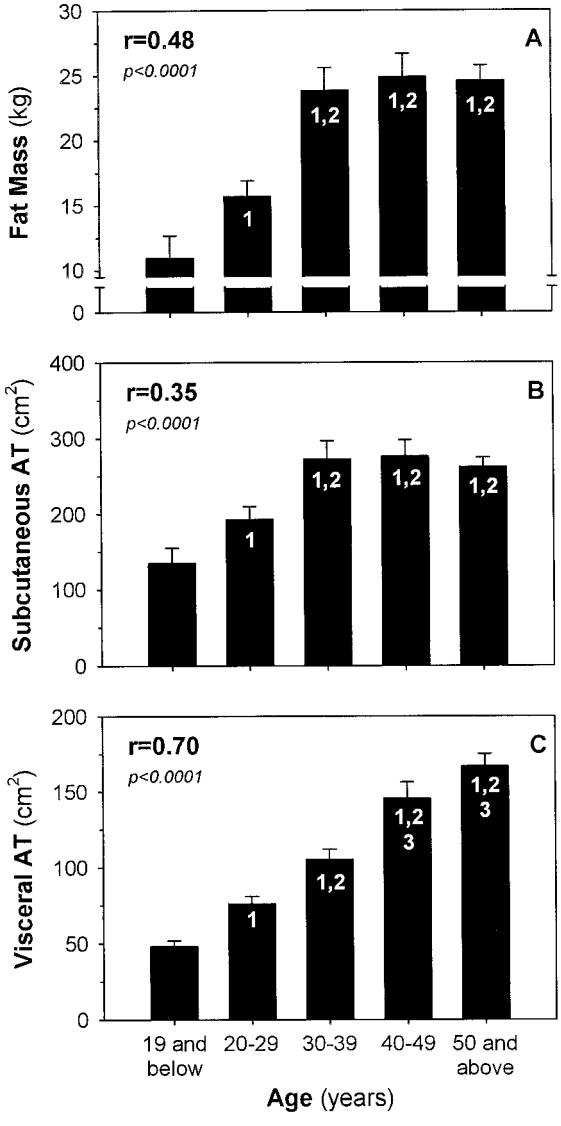

FIG. 1. Body fat mass (A), abdominal sc (B), and visceral (C) AT accumulation in men stratified on the basis of age. Data are presented as the mean ± SEM. 1, Significantly different from men 19 yr of age and below; 2, significantly different from men between the ages of 20–29 yr; 3, significantly different from men between the ages of 30–39 yr.

As differences in body fatness, AT distribution, and plasma steroid hormone levels were noted among the age groups, we examined their associations (Table 3). With the exception of cortisol, DHEA-FA, and estradiol, an increased body fatness (expressed by body mass index, percent body fat, or fat mass) and abdominal AT accumulation (Table 4) were predictive of lower plasma levels of Δ^4-dione, DHEA, DHEA-S, DHT, and testosterone as well as reduced SHBG concentrations.

The relationships between age and steroid hormone levels after adjustment for total body fatness were also examined (Table 5). Associations among Δ^4-dione, DHEA, DHEA-S, DHT, and age were maintained after statistical adjustment for total body fat mass. However, the association between testosterone concentrations and age did not resist the adjustment for body fat mass. The association between SHBG and age was unaltered by the statistical adjustment procedure.

Finally, we conducted multiple regression analyses to quantify the independent contribution of age, total body fatness, and AT distribution indexes to the variance in plasma steroid hormone and SHBG concentrations (Table 6). We found that the variance in C_{19} adrenal steroids levels was predominantly explained by age, whereas the variation in DHT, testosterone, and SHBG concentrations was best explained by abdominal AT accumulation expressed as either waist girth or computed tomography-measured sc AT area.

Discussion

With age, there is generally an increase in body fatness and a preferential accumulation of AT in the abdominal region. This latter phenomenon is mostly the result of a selective deposition of visceral AT that occurs with age (8, 9). In the present study we also found increases in total adiposity and abdominal AT accumulation from the younger to the older age groups. Although total body fat mass and abdominal sc AT accumulation seemed to reach a plateau in men above 30 yr of age, the increase in visceral AT levels was constant throughout all age subgroups, providing further support for the idea of a preferential accumulation of visceral AT with age (8, 9).

Differences in plasma steroid hormone levels were also noted among the various age groups. Indeed, as others have previously reported (10, 11), we noted significant age-related decreases in C_{19} adrenal steroids (DHEA, DHEA-FA, and DHEA-S) and androgens (testosterone and DHT). Thus, our results reinforce the well documented idea that age is related to alterations in the plasma steroid hormone profile.

Obesity is related to several metabolic alterations, including disturbances in the steroid hormone profile (25). In the present study significant associations were found among plasma steroid hormone concentrations, body fatness, and AT distribution indexes. Indeed, increased overall adiposity and abdominal fat accumulation were associated with reduced C_{19} steroid hormone and androgen levels as well as with decreased SHBG concentrations. This is in accordance

TABLE 2. Plasma hormone and SHBG concentrations of men stratified on the basis of age

Variables	Age (yr)					Pearson r with age
	19 and below	20–29	30–39	40–49	50 and above	
No. of subjects	32	71	26	31	57	
Insulin (pmol/L)	78.6 ± 54.5	62.3 ± 39.6	64.5 ± 27.9	64.0 ± 31.1	91.0 ± 79.3[a,b,c]	0.12
Cortisol (nmol/L)	374 ± 108	406 ± 122	373 ± 104	378 ± 111	371 ± 104	−0.10
Δ^4-Dione (nmol/L)	3.37 ± 1.53	3.22 ± 1.76	2.57 ± 1.09[d]	2.62 ± 1.12[d]	2.15 ± 1.26[a,d]	−0.30[e]
DHEA (nmol/L)	17.6 ± 8.5	22.0 ± 12.3[d]	15.8 ± 5.6[a]	12.3 ± 6.7[a,d]	7.9 ± 5.8[a,b,c,d]	−0.50[e]
DHEA-FA (nmol/L)	8.1 ± 4.6	11.5 ± 7.3[d]	9.1 ± 5.2	8.1 ± 3.9[a]	5.9 ± 3.2[a,b]	−0.31[e]
DHEA-S (μmol/L)	6.17 ± 3.31	7.84 ± 3.03[d]	6.12 ± 2.44[a]	4.78 ± 2.74[a,b,d]	3.20 ± 1.76[a,b,c,d]	−0.52[e]
Estradiol (pmol/L)	64.5 ± 23.0	71.7 ± 33.1	80.4 ± 85.2	66.8 ± 46.6	61.2 ± 37.7	−0.05

Data are expressed as the mean ± SD.
[a] Significantly different from men between the ages of 20 and 29 yr.
[b] Significantly different from men between the ages of 30 and 39 yr.
[c] Significantly different from men between the ages of 40 and 49 yr.
[d] Significantly different from men aged of 19 yr and below.
[e] $P < 0.0001$.

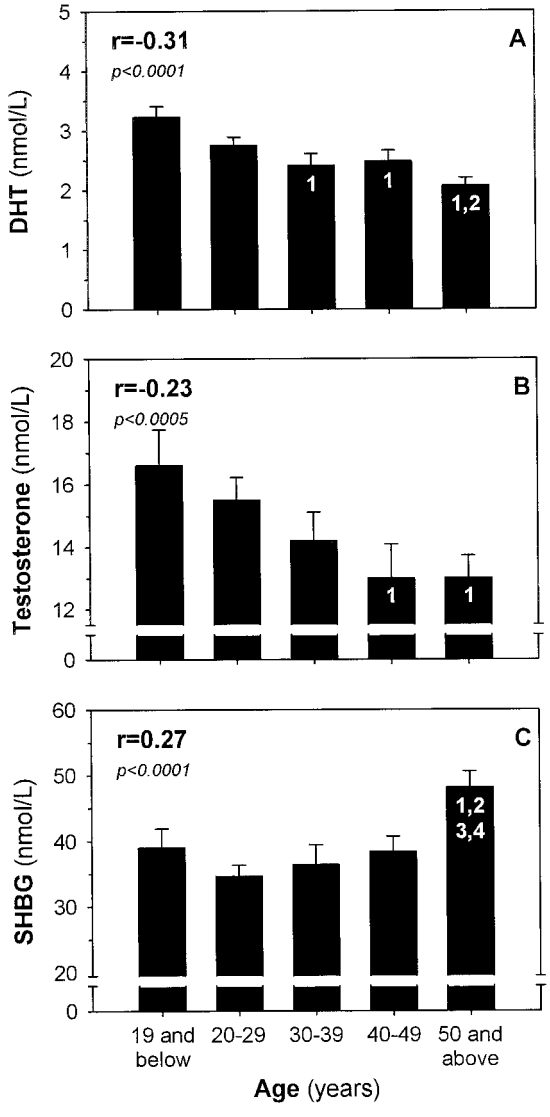

FIG. 2. Plasma DHT (A), testosterone (B), and SHBG (C) concentrations in men stratified on the basis of age. Data are presented as the mean ± SEM. 1, Significantly different from men 19 yr of age and below; 2, significantly different from men between the ages of 20–29 yr; 3, significantly different from men between the ages of 30–39 yr; 4, significantly different from men between the ages of 40–49 yr.

TABLE 3. Correlations between body fatness and plasma steroid hormone as well as SHBG levels in the 217 subjects

Variables	BMI	% Body fat	Fat mass
Cortisol	−0.09	−0.12	−0.11
Δ^4-Dione	−0.19[a]	−0.24[a]	−0.21[a]
DHEA	−0.17[b]	−0.25[c]	−0.20[a]
DHEA-FA	−0.01	−0.08	−0.06
DHEA-S	−0.17[b]	−0.28[c]	−0.23[a]
Estradiol	−0.01	−0.04	−0.01
DHT	−0.38[c]	−0.41[c]	−0.39[c]
Testosterone	−0.44[c]	−0.43[c]	−0.44[c]
SHBG	−0.26[c]	−0.13	−0.16[b]

[a] $P < 0.005$.
[b] $P < 0.05$.
[c] $P < 0.0005$.

TABLE 4. Correlations between body fat distribution and plasma steroid hormone as well as SHBG levels in the 217 subjects

Variables	Waist	Hip	WHR	sc AT	Visceral AT
Cortisol	−0.13	−0.09	−0.14[a]	−0.12	−0.07
Δ^4-Dione	−0.21[b]	−0.14[a]	−0.28[c]	−0.20[b]	−0.23[b]
DHEA	−0.26[c]	−0.11	−0.37[c]	−0.17[a]	−0.32[c]
DHEA-FA	−0.08	−0.01	−0.13	0.00	−0.13[a]
DHEA-S	−0.26[c]	−0.15[a]	−0.32[c]	−0.17[a]	−0.36[c]
Estradiol	−0.03	−0.03	−0.03	−0.02	0.00
DHT	−0.40[c]	−0.31[c]	−0.39[c]	−0.38[c]	−0.38[c]
Testosterone	−0.45[c]	−0.40[c]	−0.40[c]	−0.45[c]	−0.03
SHBG	−0.18[a]	0.18[c]	−0.03	−0.26[c]	−0.33[b]

[a] $P < 0.05$.
[b] $P < 0.05$.
[c] $P < 0.0005$.

with previous results (1–3, 5). For example, concordant with the studies of Tchernof *et al.* (1), we also found lower testosterone, DHEA, Δ^4-dione, and SHBG levels in obese individuals.

Although adiposity, body fat distribution, and plasma steroid hormone concentrations appear to be closely interrelated, to the best of our knowledge the present study is the first to examine the importance of increased adiposity and changes in AT distribution in age-related alterations in the plasma steroid hormone profile. In the present study we were able to address this issue, as we studied a sample of men covering a wide range of both adiposity values and age. We found that when adjusted for body fat mass, the associations between C_{19} adrenal steroid concentrations and age were

TABLE 5. Correlations between age and plasma steroid hormone as well as SHBG levels in the 217 subjects after adjustment for fat mass

Variables	Age adjusted for fat mass
Cortisol	−0.06
Δ^4-Dione	−0.23[a]
DHEA	−0.47[b]
DHEA-FA	−0.33[b]
DHEA-S	−0.48[b]
Estradiol	−0.04
DHT	−0.16[c]
Testosterone	−0.04
SHBG	0.42[b]

[a] $P < 0.005$.
[b] $P < 0.0005$.
[c] $P < 0.05$.

TABLE 6. Multiple regression analyses showing the independent contributions of age, body fatness, and fat distribution indexes to the variance in plasma steroid hormone and SHBG concentrations

Dependent variables	Independent variables	Partial ($r^2 \times 100$)	*P* value	Total ($r^2 \times 100$)
Cortisol	Waist girth	2.0	0.0417	2.0
Δ^4-Dione	Age	8.8	0.0001	8.8
DHEA	Age	25.3	0.0001	25.3
DHEA-FA	Age	10.2	0.0001	12.0
	Visceral AT	1.8	0.0431	
DHEA-S	Age	26.6	0.0001	26.6
Estradiol				
DHT	Waist girth	15.4	0.0001	15.4
Testosterone	Waist girth	20.1	0.0001	20.1
SHBG	sc AT	12.2	0.0001	20.3
	Age	8.1	0.0001	

The statistical model included age, total body fat mass, waist and hip girths, as well as abdominal sc and visceral AT accumulation.

maintained. On the other hand, despite the adjustment procedure for body fat mass, the relationship between testosterone and age was eliminated. Thus, testosterone levels are associated with body fatness, and this relationship appears to be largely independent of the aging process *per se*.

The mechanisms by which C_{19} adrenal steroids vary with age are not well known. Whether reduced adrenal production or changes in the activity of enzymes implicated in the metabolism of these steroids are responsible for such an observation will require further investigation. However, the reduction in testosterone in obese men could be explained by a decrease in the production of gonadal steroids. Glucocorticoids have been reported to alter testosterone secretion by the testis (25–27), and obese subjects often present an activated hypothalamic-pituitary-adrenal (HPA) axis that is associated with increased plasma glucocorticoid concentrations. In the present study the activity of the HPA axis was not investigated, but the lack of variation in cortisol levels with age and body fatness suggests that the inhibition of gonadal androgen production by glucocorticoids may not be the dominant mechanism for the age-related alterations in steroid levels. This observation is also in accordance with previous studies that have reported no change (28) or slight variation (10, 29, 30) in plasma cortisol concentrations with age. On the other hand, it is well known that plasma cortisol levels are characterized by circadian variations (31). In a study in which a 24-h cortisol profile was obtained, Van Cauter *et al.* (32) found that aging was associated with significant alterations in HPA axis activity, resulting in a decrease in the amplitude of diurnal rhythmicity of cortisol secretion. At first glance, these observations may appear to be in conflict with our results. However, we must emphasize that when Van Cauter *et al.* (32) studied morning cortisol, they did not, as in our study, find any age-related difference in cortisol levels between younger (20–29 yr) and older (50 yr and more) individuals.

Another mechanism by which adiposity may influence C_{19} adrenal steroid and androgen concentrations may be found in the AT itself. It has been proposed that AT may act as a peripheral organ for the conversion of androgens to estrogens (33, 34). Indeed, through the effect of numerous enzymes, adrenal steroids (which are precursors of androgens or estrogens) may be converted in a more potent manner to estrogens in obese patients, thus contributing to their decreases in plasma C_{19} adrenal steroid and androgen concentrations. Despite the fact that in the present study there was no increase in estradiol levels with age, the possibility of increased conversion of androgens to estrogens cannot be ruled out. Indeed, estrone concentrations, but not estradiol, have been shown to be increased in obese individuals (1). However, the absence of estrone measurement in the present study did not allow us to verify this possibility.

The association among age, body fat mass, and plasma SHBG levels may generate confusion. For instance, here we report a positive relationship between SHBG concentrations and age, whereas SHBG is negatively correlated with total body fat mass. Furthermore, we report the expected positive association between age and body fatness. Similar associations between SHBG levels and age (35–37) as well as body fatness (1, 38–41) have been reported. Thus, the increase in SHBG observed with age is unlikely to be related to differences in body fatness. Whether age *per se* or changes in lifestyle with age are responsible for the age-related increase in SHBG levels is beyond the scope of our study. However, not all studies have reported an increase in SHBG with advancing age (42, 43). On the other hand, a possible explanation for the lower SHBG levels in subjects characterized by increased adiposity may be the hyperinsulinemic state often reported in obese subjects (44). Indeed, insulin has been shown to inhibit hepatic SHBG production in HepG2 cells (45), an observation that has been supported by several cross-sectional analyses in humans (46–49). The fact that we also noted a significant positive association between fasting insulin and total body fat mass ($r = 0.43$; $P < 0.0001$) and a negative correlation between insulinemia and SHBG levels ($r = -0.20$; $P < 0.005$) would tend to support such a hypothesis.

In summary, the results of the present study indicate that the reduction in plasma testosterone concentrations often reported with age is explained at least to a certain extent by the concomitant increase in body fatness. In contrast, C_{19} adrenal steroid levels decrease with age, and this reduction does not seem to solely result from the higher adiposity of older individuals. Although the mechanisms by which adiposity contributes to the reduction in circulating testosterone concentrations are unclear, the possible conversion of androgens and their precursors to estrogens in AT should be

considered among other likely possibilities. However, further studies are needed to establish whether these relationships imply causation and to elucidate the physiological mechanisms responsible for these associations.

References

1. **Tchernof A, Després JP, Bélanger A, et al.** 1995 Reduced testosterone and adrenal C_{19} steroid levels in obese men. Metabolism. 44:513–519.
2. **Strain GW, Zumoff B, Kream J, et al.** 1982 Mild hypogonadotropic hypogonadism in obese men. Metabolism. 31:871–875.
3. **Pasquali R, Casimirri F, Cantobelli S, et al.** 1991 Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism. 40:101–104.
4. **Tchernof A, Labrie F, Bélanger A, et al.** 1997 Androstane-3α,17β-diol glucuronide as a steroid correlate of visceral obesity in men. J Clin Endocrinol Metab. 82:1528–1534.
5. **Seidell JC, Björntorp P, Sjöstrom L, Kvist H, Sannerstedt R.** 1990 Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. Metabolism. 39:897–901.
6. **Schneider G, Kirschner MA, Berkowitz R, Ertel NH.** 1979 Increased estrogen production in obese men. J Clin Endocrinol Metab. 48:633–638.
7. **Reeder BA, Angel A, Ledoux M, Rabkin SW, Young K, Sweet LE.** 1990 Obesity and its relation to cardiovascular disease risk factors in Canadian adults. Can Health Surv. 37–47.
8. **Seidell JC, Oosterlee A, Deurenberg P, Hautvast JGAJ, Ruijs JH.** 1988 Abdominal fat depots measured with computed tomography: effects of degree of obesity, sex, and age. Eur J Clin Nutr. 42:805–815.
9. **Enzi G, Gasparo M, Biondetti PR, Fiore D, Semisa M, Zurlo F.** 1986 Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. Am J Clin Nutr. 44:739–746.
10. **Bélanger A, Candas B, Dupont A, et al.** 1994 Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. J Clin Endocrinol Metab. 79:1086–1090.
11. **Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B.** 1997 Marked decline in serum concentrations of adrenal C_{19} sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab. 82:2396–2402.
12. **Vermeulen A.** 1991 Clinical review 24: androgens in the aging male. J Clin Endocrinol Metab. 73:221–224.
13. **Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J.** 1995 The HERITAGE Family Study. Aims, design, and measurement protocol. Med Sci Sports Exerc. 27:721–729.
14. **Lohman T, Roche A, Martorel R, eds.** 1988 Standardization of anthropometric measurements. The Airlie (VA) consensus conference. Champaign: Human Kinetics; 20–37.
15. **Behnke AR, Wilmore JH.** 1974 Evaluation and regulation of body build and composition. Englewood Cliffs: Prentice-Hall; 20–37.
16. **Siri W.** 1956 The gross composition of the body. Adv Biol Med Phys. 4:239–280.
17. **Wilmore JH, Stanforth PR, Domenick MA, et al.** 1997 Reproducibility of anthropometric and body composition measurements: the HERITAGE Family Study. Int J Obes. 21:297–303.
18. **Després JP, Prud'homme D, Pouliot MC, Tremblay A, Bouchard C.** 1991 Estimation of deep abdominal adipose-tissue accumulation from simple anthropometric measurements in men. Am J Clin Nutr. 54:471–477.
19. **Ferland M, Després JP, Tremblay A, et al.** 1989 Assessment of adipose tissue distribution by computed axial tomography in obese women: association with body density and anthropometric measurements. Br J Nutr. 61:139–148.
20. **Kvist H, Sjöstrom L, Tylen U.** 1986 Adipose tissue volume determinations in women by computed tomography: technical considerations. Int J Obes. 10:53–67.
21. **Bélanger A, Brochu M, Cliche J.** 1986 Plasma levels of steroid glucuronides in prepubertal, adult and elderly men. J Steroid Biochem. 24:1069–1072.
22. **Brochu M, Bélanger A, Tremblay RR.** 1987 Plasma levels of C-19 steroids and 5 alpha-reduced steroid glucuronides in hyperandrogenic and idiopathic hirsute women. Fertil Steril. 48:948–953.
23. **Desbuquois B, Aurbach GD.** 1971 Use of polyethylene glycol to separate free and antibody-bound peptide hormones in radioimmunoassays. J Clin Endocrinol Metab. 33:732–738.
24. **Roder ME, Porte D, Jr, Schwartz RS, Kahn SE.** 1998 Disproportionately elevated proinsulin levels reflect the degree of impaired B cell secretory capacity in patients with noninsulin- dependent diabetes mellitus. J Clin Endocrinol Metab. 83:604–608.
25. **Kissebah AH, Krakower GR.** 1994 Regional adiposity and morbidity. Physiol Rev. 74:761–811.
26. **Björntorp P.** 1991 Metabolic implications of body fat distribution. Diabetes Care. 14:1132–1143.
27. **Björntorp P.** 1995 Endocrine abnormalities of obesity. Metabolism. 44:21–23.
28. **Gray A, Feldman HA, McKinlay JB, Longcope C.** 1991 Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 73:1016–1025.
29. **Pavlov EP, Harman SM, Chrousos GP, Loriaux DL, Blackman MR.** 1986 Responses of plasma adrenocorticotropin, cortisol, and dehydroepiandrosterone to ovine corticotropin-releasing hormone in healthy aging men. J Clin Endocrinol Metab. 62:767–772.
30. **Touitou Y, Sulon J, Bogdan A, et al.** 1982 Adrenal circadian system in young and elderly human subjects: a comparative study. J Endocrinol. 93:201–210.
31. **Van Cauter E, Turek FW.** 1994 Endocrine and other biological rhythms. In: DeGroot LJ, ed. Endocrinology. Philadelphia: Saunders; 2487–2548.
32. **Van Cauter E, Leproult R, Kupfer DJ.** 1996 Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. J Clin Endocrinol Metab. 81:2468–2473.
33. **Deslypère JP, Verdonck L, Vermeulen A.** 1985 Fat tissue: a steroid reservoir and site of steroid metabolism. J Clin Endocrinol Metab. 61:564–570.
34. **Labrie F, Simard J, Luu-The V, et al.** 1991 Expression of 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4 isomerase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD) in adipose tissue. Int J Obes. 15(Suppl 2):91–99.
35. **Longcope C, Goldfield SR, Brambilla DJ, McKinlay J.** 1990 Androgens, estrogens, and sex hormone-binding globulin in middle-aged men. J Clin Endocrinol Metab. 71:1442–1446.
36. **Semmens JB, Rouse IL, Beilin LJ, Masarei JR.** 1983 Relationships between age, body weight, physical fitness and sex- hormone-binding globulin capacity. Clin Chim Acta. 133:295–300.
37. **Bartsch W.** 1980 Interrelationships between sex hormone-binding globulin and testosterone, 5α-dihydrotestosterone and oestradiol-17β in blood of normal men. Maturitas. 2:109–118.
38. **Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH.** 1983 Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. J Clin Endocrinol Metab. 57:304–310.
39. **Leenen R, van der Kooy K, Seidell JC, Deurenberg P, Koppeschaar HP.** 1994 Visceral fat accumulation in relation to sex hormones in obese men and women undergoing weight loss therapy. J Clin Endocrinol Metab. 78:1515–1520.
40. **Haffner SM, Katz MS, Dunn JF.** 1991 Increased upper body and overall adiposity is associated with decreased sex hormone binding globulin in postmenopausal women. Int J Obes. 15:471–478.
41. **Raison J, Bonithon-Kopp C, Egloff M, Ducimetière P, Guy-Grand B.** 1990 Hormonal influences on the relationships between body fatness, body fat distribution, lipids, lipoproteins, glucose and blood pressure in French working women. Atherosclerosis. 85:185–192.
42. **Tenover JS, Matsumoto AM, Plymate SR, Bremner WJ.** 1987 The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. J Clin Endocrinol Metab. 65:1118–1126.
43. **Kaiser FE, Viosca SP, Morley JE, Mooradian AD, Davis SS, Korenman SG.** 1988 Impotence and aging: clinical and hormonal factors. J Am Geriatr Soc. 36:511–519.
44. **Lemieux S, Després JP.** 1994 Metabolic complications of visceral obesity: contribution to the etiology of type II diabetes and implications for prevention and treatment. Diabetes Metab. 20:375–393.
45. **Plymate SR, Matej LA, Jones RE, Friedl KE.** 1988 Inhibition of sex hormone-binding globulin production in the huamn hepatoma (Hep G2) cell line by insulin and prolactin. J Clin Endocrinol Metab. 67:460–464.
46. **Haffner SM, Valdez RA, Morales PA, Hazuda HP, Stern MP.** 1993 Decreased sex hormone-binding globulin predicts noninsulin-dependent diabetes mellitus in women but not in men. J Clin Endocrinol Metab. 77:56–60.
47. **Haffner SM, Katz MS, Stern MP, Dunn JF.** 1988 The relationship of sex hormones to hyperinsulinemia and hyperglycemia. Metabolism. 37:683–688.
48. **Nestler JE, Powers LP, Matt DW, et al.** 1991 A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 72:83–89.
49. **Pasquali R, Casimirri F, Plate L, Capelli M.** 1990 Characterization of obese women with reduced sex hormone-binding globulin concentrations. Horm Metab Res. 22:303–306.