# Reduced Testosterone and Adrenal $C_{19}$ Steroid Levels in Obese Men

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**It has been reported that a high proportion of abdominal fat is associated with increased plasma androgen concentrations in women. Although less evidence is available, abdominal obesity appears to be associated with low plasma testosterone (T) levels in men. We have therefore examined in 80 men (aged 36.3 ± 3.2 years, mean ± SD) the correlations between body fatness, adipose tissue (AT) distribution measured by computed tomography (CT), and circulating levels of the following steroids measured by radioimmunoassay after extraction from serum and chromatography: dehydroepiandrosterone (DHEA), androstenedione ($\Delta^4$-DIONE), androst-5-ene-3β,17β-diol ($\Delta^5$-DIOL), T, estrone, and estradiol. Sex hormone–binding globulin (SHBG) levels were also determined. T, adrenal $C_{19}$ steroids, and SHBG levels were negatively correlated with total body fatness indices and abdominal fat deposition measured by CT ($-.23 \leq r \leq -.55$, $.0001 \leq P \leq .05$), whereas estrone showed positive correlations with these body fatness and AT distribution indices. Covariance analysis showed that after control for the concentration of the adrenal steroid precursor $\Delta^5$-DIOL, there was no residual association between T levels and adiposity variables. Furthermore, multivariate analyses showed that steroid and SHBG levels could explain from 20% (visceral AT area measured by CT) to 40% and 42% (body mass index [BMI], waist circumference, and waist to hip ratio [WHR]) of the variation in adiposity variables ($.0001 \leq P \leq .05$), with $\Delta^5$-DIOL being the best single correlate of body fatness and abdominal fat deposition in men. On the other hand, total body fat mass was the best and sole predictor of DHEA, $\Delta^5$-DIOL, estradiol, and SHBG levels, explaining up to 22% of the variance ($\Delta^5$-DIOL). These results suggest that reduced concentrations of T and of adrenal $C_{19}$ steroid precursors are associated with increased body fatness rather than with excess visceral fat accumulation. Furthermore, they emphasize the importance of adrenal steroids as correlates of body composition in men.**


THE RELATIONSHIPS between body fatness, adipose tissue (AT) distribution, and plasma sex steroid levels have been widely studied in women, and high androgen levels have been reported in abdominal obesity.[1-7] Although less evidence is available in men, it has been suggested that obesity is associated with low levels of testosterone (T), free T and sex hormone–binding globulin (SHBG).[8-12] However, the relation of steroid hormones to fat distribution in men is equivocal. Indeed, in one study, plasma T concentrations were negatively correlated with waist and hip circumferences, but not with the waist to hip ratio (WHR), suggesting no relation of androgens to body fat distribution.[8] On the other hand, Seidell et al[9] reported negative correlations between serum T levels and several indices reflecting abdominal fat accumulation that included the WHR and abdominal subcutaneous and visceral AT areas measured by computed tomography (CT). However, Khaw and Barrett-Connor[13] reported that there were no negative correlations between androstenedione ($\Delta^4$-DIONE), T, SHBG, and WHR after adjustment for age and body mass index (BMI), suggesting no independent association between androgens and fat distribution in men.

To examine further the potential associations between steroid hormones and abdominal fat deposition measured by CT, we studied a group of 80 men with a wide range of body fatness. Visceral AT areas were measured by CT, and in addition to T and estrogen levels, adrenal $C_{19}$ steroid concentrations, namely dehydroepiandrosterone (DHEA), $\Delta^4$-DIONE, and androst-5-ene-3β,17β-diol ($\Delta^5$-DIOL), were determined.

## SUBJECTS AND METHODS

Eighty men aged 29 to 42 years were recruited by solicitation through the media on the basis of their BMI values (obese men, BMI > 27 kg/m$^2$; lean men, BMI < 25 kg/m$^2$). Subjects had a complete physical examination and had to be nonsmokers and healthy (excluded were those with diabetes, endocrine disorder, genetic lipidemia, or coronary heart disease). Subjects signed an informed-consent document, and the study was approved by the medical ethics committee of Laval University.

### *Measurement of Body Fatness and AT Distribution*

Subjects' body density was measured by the hydrostatic-weighing technique,[14] with pulmonary residual volume being measured before immersion in the hydrostatic tank according to the helium dilution method.[15] The mean of six body density measurements was used, and percent body fat was derived from body density using the equation of Siri.[16] Waist and hip circumferences were determined using standardized procedures.[17]

Measurements of abdominal and femoral AT areas were performed by CT using a Siemens Somatom DHR scanner (Erlangen, Germany) according to previously described procedures.[18,19] Subjects were examined in the supine position with both arms stretched above the head. The abdominal measurement was made between L4 and L5 vertebrae, and the femoral measurement was made at the mid-distance between the knee joint and the iliac crest (mid-thigh). Total AT areas were determined using a graph pen

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**Table 1. Physical Characteristics of the 51 Obese and 29 Lean Men**

| | Mean ± SD | |
|---|---|---|
| | Lean | Obese |
| Age (yr) | 36.0 ± 3.0 | 36.5 ± 3.4 |
| Weight (kg) | 68.8 ± 6.4 | 89.8 ± 7.6* |
| Body fat (%) | 19.7 ± 4.8 | 29.7 ± 4.3* |
| BMI (kg/m$^2$) | 22.7 ± 1.4 | 29.9 ± 1.6* |
| WHR | 0.87 ± 0.05 | 0.98 ± 0.04* |
| AT areas, CT (cm$^2$) | | |
| Abdominal | | |
| Total | 220.5 ± 67.7 | 453.8 ± 91.7* |
| Subcutaneous | 141.0 ± 42.2 | 306.1 ± 43.8* |
| Visceral | 79.4 ± 30.6 | 147.8 ± 71.3* |
| Femoral | 137.8 ± 34.6 | 238.7 ± 59.3* |

*$P < .0001$.

with an attenuation range of −190 to −30 HU.[20,21] Visceral AT area was obtained by drawing a line within the muscle wall surrounding the abdominal cavity. Subcutaneous abdominal AT area was obtained by subtraction of visceral AT area from total abdominal AT area.

### *Measurement of Steroid Levels*

Five milliliters of ethanol was added to 1 mL plasma and centrifuged. The resulting pellet was further washed with 5 mL ethanol, and the two ethanol extracts were combined. After evaporation under nitrogen, the dry residue was solubilized in 1 mL isooctane/toluene/methanol (90:5:5) and deposited on Sephadex LH-20 columns (Pharmacia, Uppsala, Sweden). Elution was performed by increasing the polarity of the organic solvent mixture, and three fractions were collected. After deposition of steroids, 15 mL isooctane/toluene/methanol (90:5:5) were eluted and discarded. After addition of 20 mL isooctane/toluene/methanol (90:5:5), $\Delta^4$-DIONE and DHEA were collected. Isolation of T was achieved by elution of another 20 mL of the solvent. The mixture isooctane/toluene/methanol (70:15:15) caused the elution of $\Delta^5$-DIOL and estrone. Estradiol was obtained after elution with isooctane/toluene/ethanol (60:20:20). Steroid levels were measured by radioimmunoassay using specific antibodies as previously described.[22]

### *Statistical Analyses*

Pearson correlation coefficients were computed to quantify the relationships between body fatness accumulation and distribution indices and serum levels of steroids and SHBG. The comparison of serum steroid and SHBG levels between obese and lean men was performed by Student's $t$ test, and the paired $t$ test was used for comparisons of men individually matched for levels of body fat but having either low or high levels of visceral AT measured by CT. Linear regression analysis was performed to control for the relation of the adrenal $C_{19}$ steroid $\Delta^5$-DIOL to T concentration ($r = .45$, $P < .0001$ between these two variables). Correlational analyses were then performed between the residual scores (T levels corrected for $\Delta^5$-DIOL) and body fatness and AT distribution variables. Multiple regression analyses were performed to estimate independent contributions of serum steroid levels to the variation of different body fatness and AT distribution indices and the contribution of adiposity indices to the variation of steroid levels. All statistical analyses were performed with the SAS statistical package (SAS Institute, Cary, NC).

## RESULTS

Table 1 lists the characteristics of the sample of 80 men. Subjects were selected to include lean and obese individuals covering a wide range of body fatness values. Subjects' age ranged from 29 to 42 years, and the group included 51 obese and 29 lean men.

As shown in Fig 1, serum levels of T, SHBG, and all $C_{19}$ steroids measured, namely DHEA, $\Delta^4$-DIONE, and $\Delta^5$-DIOL, were significantly lower in obese men as compared with lean individuals. DHEA and $\Delta^5$-DIOL showed the largest differences (35% and 32% for DHEA and $\Delta^5$-DIOL, respectively) between obese and lean men ($P < .0001$). Estrone levels were significantly higher in the obese group, whereas no difference was found for estradiol levels. To assess whether observed differences in the levels of steroids and SHBG could be related to the concomitant variation in visceral AT deposition, two subgroups of 15 men each individually matched for their percentage of body fat but with either low or high levels of visceral AT were compared (Fig 2). No significant difference in steroid or SHBG levels was found among men with low versus high levels of visceral AT when they were matched for total body fat.

Although subjects recruited were included in two distinct subgroups on the basis of BMI values (obese men, BMI > 27 kg/m$^2$; lean men, BMI < 25 kg/m$^2$), measurement of body composition by hydrostatic weighing showed a continuous distribution of percent body fat values, which allowed us to conduct correlational analyses. Associations between steroid hormone levels and indices of body fatness and AT distribution are listed in Tables 2 and 3. Significant negative correlations were found between adrenal and gonadal steroids and variables reflecting total body fatness, as well as AT distribution (Table 2). Furthermore, indices of abdominal fat deposition obtained by CT were also negatively correlated with adrenal and gonadal steroid levels (Table 3). Plasma DHEA and $\Delta^5$-DIOL levels showed higher negative correlations with body fatness and fat distribution indices than did T levels. Estrogen levels showed several significant positive correlations with total adiposity indices, as well as with AT distribution variables. It should be noted that steroid hormone levels were correlated with femoral adiposity, suggesting that these steroids were more related to variations in the level of total body fat rather than to differences in the regional distribution of AT. Accordingly, none of the steroids measured were correlated with the ratio of visceral/femoral AT, and neither was SHBG related to this index of AT distribution. Since both adrenal and gonadal steroid levels were negatively correlated with body fatness and abdominal AT accumulation, their independent contribution to the variance of body fat and AT distribution variables was examined. After correction of body fatness variables for the adrenal $C_{19}$ steroid $\Delta^5$-DIOL by covariance analysis, there was no residual association between T and body fatness indices (Tables 2 and 3).

Since plasma DHEA and $\Delta^5$-DIOL levels were significantly correlated ($r = .65$, $P < .0001$), suggesting a substan-

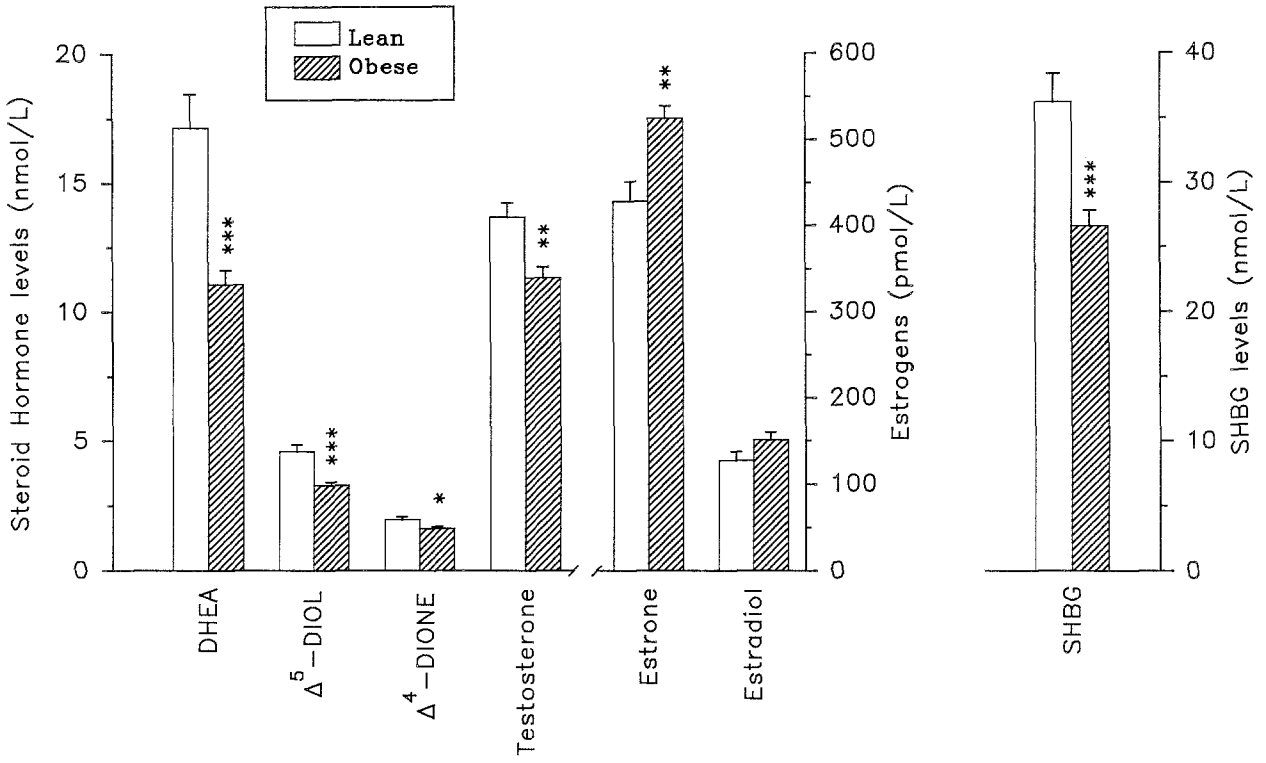


**Fig 1. Comparison of circulating steroid hormone and SHBG levels among obese (n = 51) and lean (n = 29) men. *$P < .05$, **$P < .001$, ***$P < .0001$.**

tial enzymatic interconversion of the two steroids, this common variance could partly explain the essentially similar relationships of both DHEA and $\Delta^5$-DIOL to adiposity indices. In an attempt to quantify the independent contribution of each of the steroids studied to the variance observed in body fatness and AT distribution indices, as well as the contribution of fatness variables to the variation in steroid levels, multiple regression analyses were performed using a model that first included all steroids measured and SHBG as independent variables (Table 4), and then fat mass and visceral AT areas as independent variables (Table 5). These analyses showed that $\Delta^5$-DIOL explained more variance in adiposity variables than any other steroid measured. DHEA or $\Delta^4$-DIONE did not appear to have an independent contribution to the variance in fatness and AT distribution variables after control for $\Delta^5$-DIOL levels. Circulating $\Delta^5$-DIOL levels explained up to 30% of the variance in BMI. However, it is clear that the independent contribution of T to the variance of most body fatness and AT distribution variables studied was much smaller than $\Delta^5$-DIOL.

On the other hand, when studying the contribution of adiposity indices (fat mass or visceral AT area), it appeared that fat mass was the best and only correlate of DHEA, $\Delta^5$-DIOL, estradiol, and SHBG levels (Table 5). Indeed, after inclusion of total body fat mass, indices of AT distribution could not explain further variation in these steroids. However, visceral AT area appeared to contribute more to the variation of T, $\Delta^4$-DIONE, and estrone levels, although the variance explained was low ($\leq 11\%$). After visceral AT area was entered in the multiple regression model, no other adiposity variable could account for further variance of T, $\Delta^4$-DIONE, and estrone levels.

## DISCUSSION

The present study was an attempt to better understand the relationships between various steroid hormones and AT distribution in men. It has been shown that an excess abdominal AT accumulation is associated with an increased risk of diabetes and cardiovascular disease,[23,24] with this relation being largely mediated by concomitant metabolic disturbances such as insulin resistance, hyperinsulinemia, and dyslipidemia.[25-27] Moreover, since increased androgen levels have been associated with abdominal obesity in women and since lower T and DHEA sulfate levels have been related to an increased risk of cardiovascular disease in men,[28,29] it was relevant to examine the potential associations between visceral AT deposition and steroid hormone levels in men. The present study shows that there was no differences in the levels of $C_{19}$ steroids when two subgroups of men with similar levels of total body fat but with low or high levels of visceral AT were compared. Furthermore, although related to overall body fatness indices and to absolute levels of abdominal AT, the concentrations of adrenal $C_{19}$ steroids and of T and SHBG were equally well correlated with the femoral AT area, indicating that higher levels of these steroids were related to reduced levels of total body fat rather than to a selective decrease in the accumulation of abdominal visceral AT.

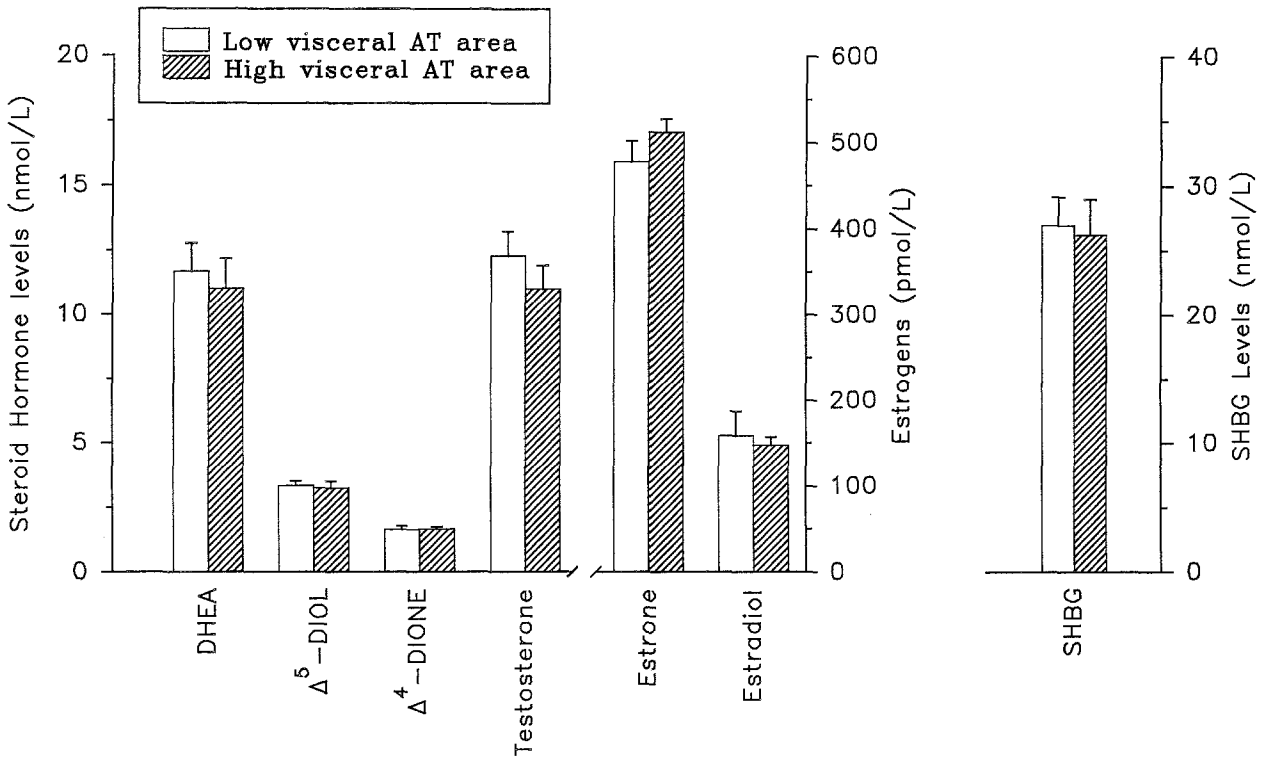


**Fig 2. Comparison of circulating steroid hormone and SHBG levels in two groups of 15 men each individually matched for percentage of body fat but with either low (109 ± 17 cm²) or high (184 ± 30) visceral AT areas. No significant differences were found for variables examined. Mean percent body fat was 30.4% ± 1.1% and 30.5% ± 1.1% in men with low and high levels of visceral fat, respectively.**

In the present study, increased adiposity was not only associated with reduced plasma T levels, but also with decreased plasma concentrations of adrenal $C_{19}$ steroid precursors and increased estrone levels (and estradiol to a lesser extent). It has been demonstrated that $C_{19}$ steroids of adrenal origin, such as DHEA, $\Delta^4$-DIONE, and $\Delta^5$-DIOL, can account for a significant part of androgenic or estrogenic activity in men. These adrenal steroids are converted into androgens and/or estrogens in peripheral tissues, with this process resulting from the action of the enzymes 17β-hydroxysteroid dehydrogenase, 3β-hydroxysteroid dehydrogenase/$\Delta^5$-$\Delta^4$isomerase, 5α-reductase, and aromatase.[30-32] The intracellular production of active steroids acting in the same cell responsible for their synthesis has been conceptually defined as intracrinology.[30,31] In addition to the enzymatic activity, mRNA encoding these enzymes

**Table 2. Pearson Correlation Coefficients for the Relationships Between Indices of Total Body Fatness, Anthropometric Indices of Abdominal Fat Accumulation, and Circulating Levels of Steroids and SHBG in a Group of 80 Men**

| Steroid Hormone | % Body Fat | BMI (kg/m²) | Fat Mass (kg) | Waist Circumference | WHR |
|---|---|---|---|---|---|
| DHEA | −.35§ | −.42§ | −.38§ | −.42§ | −.38§ |
| $\Delta^5$-DIOL | −.45§ | −.55§ | −.47§ | −.53§ | −.53§ |
| $\Delta^4$-DIONE | −.23* | −.22NS | −.22NS | −.24* | −.22NS |
| Estrone | .21NS | .37§ | .27* | .35‡ | .36‡ |
| Estradiol | .21NS | .17NS | .28* | .23* | .18NS |
| T | −.32‡ | −.35‡ | −.31† | −.40§ | −.43§ |
| T adjusted for $\Delta^5$-DIOL | −.14NS | −.13NS | −.12NS | −.18NS | −.21NS |
| SHBG | −.26* | −.42§ | −.30§ | −.33‡ | −.32‡ |

Abbreviations: T, testosterone; NS, not significant.
*$P < .05$.
†$P < .01$.
‡$P < .005$.
§$P < .001$.

**Table 3. Pearson Correlation Coefficients for the Relationships Between AT Areas Measured by CT and Circulating Levels of Steroids and SHBG in a Sample of 80 Men**

| | AT Areas | | | | |
|---|---|---|---|---|---|
| | Abdominal | | | | |
| Steroid Hormone | Total | Subcutaneous | Visceral | Femoral | Visceral/ Femoral |
| DHEA | −.41§ | −.40§ | −.33‡ | −.38§ | −.06NS |
| $\Delta^5$-DIOL | −.51§ | −.50§ | −.40§ | −.42§ | −.09NS |
| $\Delta^4$-DIONE | −.28* | −.27* | −.23* | −.35‡ | .03NS |
| Estrone | .30† | .27* | .27* | .22* | .09NS |
| Estradiol | .26† | .28* | .15NS | .15NS | .11NS |
| T | −.36‡ | −.33‡ | −.33‡ | −.29† | −.13NS |
| T adjusted for $\Delta^5$-DIOL | −.15NS | −.12NS | −.17NS | −.11NS | −.03NS |
| SHBG | −.35‡ | −.34‡ | −.28* | −.22NS | −.14NS |

*$P < .05$.
†$P < .01$.
‡$P < .005$.
§$P < .001$.

**Table 4. Multiple Regression Analyses for Independent Contributions of Circulating Steroids to the Variation in Body Fatness and AT Distribution Indices**

| Dependent Variable | Independent Variables | Partial ($R^2 \times 100$) | $P <$ | Total ($R^2 \times 100$) |
|---|---|---|---|---|
| Body fat (%) | $\Delta^5$-DIOL | 19.8 | .0001 | 23% |
| | T | 2.9 | .09 | |
| BMI (kg/m$^2$) | $\Delta^5$-DIOL | 30.5 | .0001 | 40% |
| | Estrone | 6.3 | .01 | |
| | SHBG | 3.3 | .05 | |
| Waist circumference (cm) | $\Delta^5$-DIOL | 27.9 | .0001 | 42% |
| | Estrone | 5.8 | .05 | |
| | T | 4.6 | .02 | |
| | Estradiol | 3.9 | .05 | |
| WHR | $\Delta^5$-DIOL | 28.3 | .0001 | 40% |
| | T | 7.2 | .005 | |
| | Estrone | 4.3 | .03 | |
| Visceral AT area | $\Delta^5$-DIOL | 15.6 | .0003 | 20% |
| | T | 4.4 | .05 | |

have been found to be present to a significant extent in AT,[33,34] suggesting that adrenal $C_{19}$ steroid precursors act as androgens (and/or estrogens) in AT after local transformation.

The present report is the first to examine in men the potential associations between abdominal obesity and T with control for concomitant variations in adrenal $C_{19}$ steroid precursors. Indeed, DHEA and $\Delta^5$-DIOL levels showed greater associations with body fatness and AT distribution variables than T and SHBG concentrations. Although DHEA sulfate is the major $C_{19}$ steroid secreted by the adrenals in humans, our study suggests that another adrenal steroid precursor, $\Delta^5$-DIOL, is even more closely correlated with body fatness in men than the other adrenal $C_{19}$ steroids investigated. These results suggest that the peripheral conversion of adrenal $C_{19}$ steroid precursors, especially $\Delta^5$-DIOL, may well derive its strong negative correlation with body fatness from the production of active steroids in peripheral tissues. Studies on steroid receptors have failed to demonstrate the presence of estrogen or progestin receptors in human AT.[35] However, many in vitro studies have shown significant binding to estrogen or androgen receptors in adipose cells of animal origin.[36-39] Furthermore, other studies have provided evidence that AT stores and metabolizes steroids.[40-42] Despite these results, other indirect mechanisms of steroid action may also account for the associations found in this study.

**Table 5. Multiple Regression Analyses for Independent Contributions of Body Fatness and AT Distribution Indices to the Variation in Circulating Steroid and SHBG Levels**

| Dependent Variable | Independent Variables | Partial ($R^2 \times 100$) | $P <$ | Total ($R^2 \times 100$) |
|---|---|---|---|---|
| DHEA | Fat mass | 14.4 | .0005 | 14% |
| $\Delta^4$-DIONE | Visceral AT area | 5.2 | .04 | 5% |
| $\Delta^5$-DIOL | Fat mass | 21.9 | .0001 | 22% |
| Estrone | Visceral AT area | 7.4 | .02 | 7% |
| Estradiol | Fat mass | 6.1 | .03 | 6% |
| T | Visceral AT area | 11.0 | .003 | 11% |
| SHBG | Fat mass | 9.2 | .007 | 9% |

Pasquali et al[8] reported a negative correlation between serum T and DHEA sulfate levels and WHR. In the present study, similar associations between WHR and T levels were observed. However, CT-derived indices of abdominal fat deposition showed that both subcutaneous and visceral AT areas were negatively correlated with DHEA and T levels. Our observations, which are consistent with those reported by Seidell et al,[9] do not suggest an independent association between T, adrenal $C_{19}$ steroid concentrations, and visceral fat accumulation in men. Accordingly, Khaw and Barrett-Connor[13] have shown that the association between T and WHR was not significant after adjustment for age and BMI, which provides further support to the notion that androgens are not strong independent correlates of AT distribution in men. Although the present study confirms that there are significant univariate associations between androgenic steroids and anthropometric and CT-derived measures of fat distribution, our results further suggest that the associations between adrenal and gonadal steroids and the amount of visceral AT may be due to the variance shared between AT distribution indices and total body fatness. Indeed, when men with low or high levels of visceral AT were matched for the level of total body fat, no differences in androgenic steroid and SHBG levels were noted, suggesting further that body fatness rather than AT distribution is a major correlate of $C_{19}$ steroid precursors, T, and SHBG levels in men.

It is important to emphasize that the present correlational study cannot address the issue of causality regarding the fatness-steroid associations. From the literature available, the following possibilities could be considered. First, it has been suggested that the reduced androgen levels observed in obese men may be a consequence of increased fatness. Indeed, increased T levels have been reported after weight loss,[43] although this is not a unanimous finding.[44] On the other hand, there is also evidence available suggesting that increased androgen levels may account for a reduced adiposity. Mårin et al[45,46] have shown that T treatment of obese men induced a reduction of total body and visceral fat. Furthermore, it has been reported in animal models that DHEA displays antiobesity properties,[47] although Usiskin et al[48] reported no effect of DHEA treatment in obese men. Third, Schneider et al[49] have reported apparently normal free-T and presumably T secretion rates in obese men as compared with normal-weight controls. They therefore suggested that the reduced plasma T levels noted in obese men were due to an increased clearance rate rather than to a reduced T production. They thus proposed that the expanded AT mass in obese men may represent a major site of T conversion into estrogens, since they reported significant elevation in serum estrone and estradiol levels in obese men. Results obtained in the present study are in accordance with previous observations,[49] since we found higher estrone concentrations and reduced T and adrenal $C_{19}$ levels in our obese men as compared with lean controls. However, correlations found between adiposity

indices and estradiol levels were not of very high magnitude. In this regard, it should be acknowledged that the present sample only included moderately overweight men, whereas massively obese men were examined in the study reported by Schneider et al.[49] The present study is concordant with the notion that AT plays a significant role in the conversion of circulating steroids, although further studies are warranted to clarify the mechanisms responsible for the reduced gonadal and adrenal androgens and for the negative correlations reported between body fatness and adrenal $C_{19}$ steroid precursors and T levels in men.

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