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Circulating Progesterone and Obesity in Men

Abstract

Progesterone can be detected in male plasma and has been considered to originate mainly from the adrenals. We have examined the association between circulating progesterone and obesity in a sample of thirty-eight lean to morbidly obese men aged 44.5 ± 9.9 years (BMI: 44.3 ± 12.8 kg/m^2). Plasma concentrations of progesterone, 17-OH-progesterone as well as androstendione, testosterone, DHT and DHEA-S were determined. Negative correlations were observed between plasma progesterone levels and body weight ($r = -0.47$, $p < 0.05$), BMI ($r = -0.56$, $p < 0.001$), waist circumference ($r = -0.58$, $p < 0.001$), as well as subcutaneous adipocyte diameter ($r = -0.50$, $p < 0.05$). Plasma levels of 17-OH-progesterone, DHEA-S, androstendione, testosterone and DHT were also negatively associated with body weight, BMI and waist circumference. However, the ratio of 17-OH-progesterone-to-progesterone and androstendione-to-17-OH-progesterone were not related to these variables. A positive correlation was found between circulating progesterone and DHEA-S levels ($r = 0.50$, $p < 0.002$ after adjustment for age). Accordingly, using multivariate regression analyses, the best steroid predictor of progesterone level was plasma DHEA-S. Waist circumference was the best predictor of progesterone levels in a multivariate model including steroid concentrations as well as waist circumference, BMI and subcutaneous adipocyte diameter. In conclusion, plasma progesterone was negatively associated with markers of obesity such as BMI, waist circumference and subcutaneous adipocyte diameter in this sample of men. Circulating DHEA-S level was the best steroid correlate of plasma progesterone. We suggest that the low progesterone levels observed in obese men may reflect decreased adrenal C_{19} steroid production in the adrenal cortex. Further research is needed to confirm this hypothesis.

Key words
Obesity · waist circumference · adipose tissue · progesterone · 17-hydroxyprogesterone · dehydroepiandrosterone

Introduction

Specific sites of progesterone synthesis include the adrenal cortex, the corpus luteum in the ovary, the testes and the placenta [1]. In men, adrenal and testicular progesterone is almost immediately and locally converted into other steroids, and only small amounts are released into the blood. Plasma progesterone levels in normal adult men are similar to that from children (infants and prepubertal children) and to that from women in the follicular phase [2]. Serum progesterone in men used to be considered as mainly originating from the adrenals [3].

Progesterone involvement has been suggested in the regulation of adipose tissue accumulation and distribution. It can modulate adipose tissue metabolism by stimulating fat accretion through the regulation of lipoprotein lipase activity (LPL), lipogenesis and steroid-mediated differentiation of preadipocytes [4,5]. Björntorp [6] suggested that progesterone could be involved in

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Bibliography
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the presence of a sex-specific pattern of female fat distribution via an anti-glucocorticoid action in abdominal adipose tissue. In addition, we have recently reported on the presence in adipose tissue of 20α-hydroxysteroid dehydrogenase (20α-HSD), an enzyme involved in the inactivation of progesterone [7]. Our results suggested increased progesterone metabolism in omental adipose tissue of women characterized by abdominal obesity [7,8]. This enzyme was also detected in male adipose tissue (Blanchette and Tchernof, unpublished observation).

Given 1) the fact that progesterone has been considered a marker of adrenal steroid synthesis in men; 2) the previously documented relationship between adrenal steroid levels and abdominal obesity [9,10]; and 3) the potential role of progesterone and possibly progesterone metabolism in the regulation of body fat accumulation and distribution, we examined the relationship between circulating progesterone levels and obesity in a sample of lean to morbidly obese men.

Subjects and Methods

Subjects

The men in this study were recruited for studies on adipose tissue metabolism through the surgery schedule for biliopancreatic diversion at the Laval Hospital (Laval University, Quebec City) or through the general surgery schedule at the Laval University Medical Research Center. None of the patients had identified chronic diseases such as diagnosed cardiovascular disease, cancer or cachexia. We examined thirteen lean to obese men aged from 39 to 57 years undergoing general surgeries for umbilical hernia (n = 8), endocholecystectomia (n = 2), giant parastomal hernia (n = 1) and sigmoid restriction (n = 2). The remaining twenty-five morbid obese men aged from 23 to 61 years were undergoing biliopancreatic diversion, which involves bypassing the small intestine and diverting the bile and pancreatic secretion to the distal ileum, essentially leading to malabsorption for fat and starch [11,12]. Medication used by the patients included: 1) glucose lowering/insulin sensitizing/diabetes drugs (n = 12); 2) lipid lowering medication (n = 8); 3) anti-hypertensive medication (n = 16); 4) thyroid hormone (n = 3); and 5) antidepressants (n = 6). Approbations by the medical ethics committees of Laval University, Laval Hospital and Laval University Medical Research Center were obtained. All subjects provided written informed consent before inclusion in the study. Adipose tissue samples were collected during the surgical procedure at the site of incision (subcutaneous adipose tissue, SC) and from the greater omentum (epiploon, omental adipose tissue, OM). Body weight, height and waist circumference were measured according to standardized procedures. Body mass index (BMI) was calculated in kilograms per square meter.

Plasma hormone measurements

Plasma concentrations of androstendione, testosterone and dihydrotestosterone (DHT) were determined in thirty-six subjects using high-performance gas chromatography and chemical ionization mass spectrometry. The intra- and inter-assay coefficients of variation did not exceed 5.9% for these measurements. Dehydroepiandrosterone sulfate (DHEA-S) concentrations were determined in thirty-six subjects of the study using HPLC and mass spectrometry and a PE Sciex API 3000 tandem mass spectrometer (Perkin-Elmer, Foster City, USA) equipped with a turbo ionspray source. Intra- and inter-assay coefficients of variation did not exceed 6.4% in these measurements. Progesterone and 17-hydroxyprogesterone (17-OH-progesterone) levels were determined in thirty-eight and thirty-six subjects, respectively, using radioimmunoassay from Diagnostic System Laboratories (Webster, TX, USA). Intra- and inter-assay coefficients for progesterone measurement were below 6.4% and 5.9%, respectively. Intra- and inter-assay coefficients for 17-OH-progesterone measurement were below 3.3% and 7.9%, respectively. 21-deoxycortisol levels were determined in thirty-eight men after extraction from plasma using chlorobutan/ethylacetan (75/25). Samples were analyzed and detected using an API 5000 LC/MS/MS System (MDS/Sciex, Foster City, USA). The lower limit of quantification for this assay was 0.5 ng/ml (1.4 nmol/l).

Adipocyte isolation

Tissue samples were digested with collagenase type I in Krebs-Ringer-Henseleit (KRH) buffer for 45 minutes at 37 °C according to a modified version of the Rodbell method [13]. Adipocyte suspensions were filtered through nylon mesh and washed in KRH buffer three times. For cell size measurements, mature adipocyte suspensions were visualized using a contrast microscope attached to a camera and computer interface. Pictures were taken, and Scion Image software (Scion Corporation, Maryland, USA) was used to measure the size of 250 adipocytes.

Statistical analyses

Normality of data distribution was assessed using the Shapiro-Wilk W-test. Spearman rank correlation coefficients were computed to quantify associations between circulating sex steroid levels and obesity measures or DHEA-S. Multivariate regression analyses (stepwise) were used to predict circulating levels of progesterone in models including 17-OH-progesterone, DHEA-S, androstendione, testosterone and DHT (Model 1) or waist circumference, BMI, subcutaneous adipocyte diameter, 17-OH-progesterone, DHEA-S, androstendione, testosterone and DHT (Model 2). A level of $\alpha \leq 0.05$ was considered statistically significant. Analyses were performed using the JMP statistical software (SAS Institute, Cary, NC).

Results

Characteristics of the study sample are shown in Table **1**. The men's BMI and waist circumference values indicate that the sample was obese on average, although individual values covered a wide range of body mass index (from 24.6 to 79.1 kg/m^2) with normal distributions of BMI ($p = 0.29$) and waist circumference ($p = 0.21$). Lean subjects had a mean BMI of 26.8 ± 0.9 kg/m^2 and obese subjects had a mean BMI of 47.1 ± 2.0 kg/m^2. No regional difference was observed in adipocyte size (113 ± 2 *vs.* 112 ± 2 µm omental *vs.* subcutaneous respectively, NS). Plasma progesterone was detectable in the serum of all subjects (average 5.1 nmol/l) at variable levels (1.9 – 7.6 nmol/l).

Table **2** shows Spearman rank correlation coefficients between plasma progesterone, 17-OH-progesterone, DHEA-S, androstendione, testosterone, DHT and adiposity variables (weight, BMI,

Table **1** Physical and metabolic characteristics of the thirty-eight men

Variables	*Mean ± SD*	*Range*
Age (y)	44.5 ± 9.9	22.6 – 61.2
Weight (kg)	137.0 ± 45.5	70.4 – 265.0
BMI (kg/m^2)	44.3 ± 12.8	24.6 – 79.1
Waist circumference (cm)[a]	135.3 ± 27.0	91.5 – 190.0
OM adipocyte diameter (μm)[b]	112.9 ± 12.1	85.8 – 145.5
SC adipocyte diameter (μm)[a]	112.2 ± 11.7	88.7 – 134.1
Progesterone (nmol/l)	5.1 ± 1.6	1.9 – 7.6
17-OH-progesterone (nmol/l)[b]	6.1 ± 0.4	2.3 – 11.6
DHEA-S (μmol/l)[b]	4.1 ± 2.4	0.5 – 10.3
Androstendione (μmol/l)[b]	2.4 ± 0.7	1.4 – 4.5
Testosterone (nmol/l)[b]	10.1 ± 4.5	2.8 – 22.5
Dihydrotestosterone (nmol/l)[b]	0.7 ± 0.1	0.2 – 2.1

[a] n = 37, [b] n = 36
OM, Omental; SC, subcutaneous; 17-OH-progesterone, 17-hydroxyprogesterone; DHEA-S, dehydroepiandrosterone sulfate

Table **2** Spearman rank correlation coefficients between circulating steroid levels and adiposity measures

Variables	*progesterone*	*17-OH-progesterone*	*DHEA-S*	*A-dione*	*testosterone*	*DHT*
Weight (kg)	– 0.47*	– 0.41*	– 0.30	– 0.37*	– 0.53**	– 0.64**
BMI (kg/m^2)	– 0.56**#	– 0.43*	– 0.35*	– 0.33*	– 0.60**	– 0.70**
Waist circumference (cm)	– 0.58**#	– 0.46*	– 0.41*	– 0.39*	– 0.65**	– 0.70**
OM adipocyte diameter (μm)	– 0.24	– 0.27	– 0.21	– 0.48*	– 0.28	– 0.36*
SC adipocyte diameter (μm)	– 0.50*#	– 0.42*	– 0.33*	– 0.46*	– 0.41*	– 0.40*

* $p \leq 0.05$; ** $p \leq 0.001$
# Shown in figure form; OM, Omental; SC, subcutaneous; 17-OH-progesterone, 17-hydroxyprogesterone; DHEA-S, dehydroepiandrosterone sulfate; A-dione, androstendione; DHT, dihydrotestosterone

waist circumference, omental and subcutaneous adipocyte diameter). We found significant negative correlations between circulating progesterone and body weight ($r = -0.47$, $p < 0.05$), BMI ($r = -0.58$, $p < 0.001$), waist circumference ($r = -0.58$, $p < 0.001$) and subcutaneous adipocyte diameter ($r = -0.50$, $p < 0.001$) (Fig. **1**). We also found negative correlations between testicular and adrenal androgen levels and these measurements. The correlation pattern between plasma androgens was similar to that found for plasma progesterone. Statistical control for age did not affect these results (not shown) with the exception of the correlation between age-adjusted DHEA-S and body weight, which became significant ($r = -0.34$, $p < 0.05$). 17-OH-progesterone levels were also negatively correlated with weight ($r = -0.41$, $p < 0.05$), waist circumference ($r = -0.46$, $p < 0.05$), BMI ($r = -0.44$, $p < 0.05$) and subcutaneous adipocyte diameter ($r = -0.42$, $p < 0.05$) (Table **2**). Ratios of 17-OH-progesterone to progesterone or androstendione to 17-OH-progesterone [14] were not significantly associated with any measure of obesity.

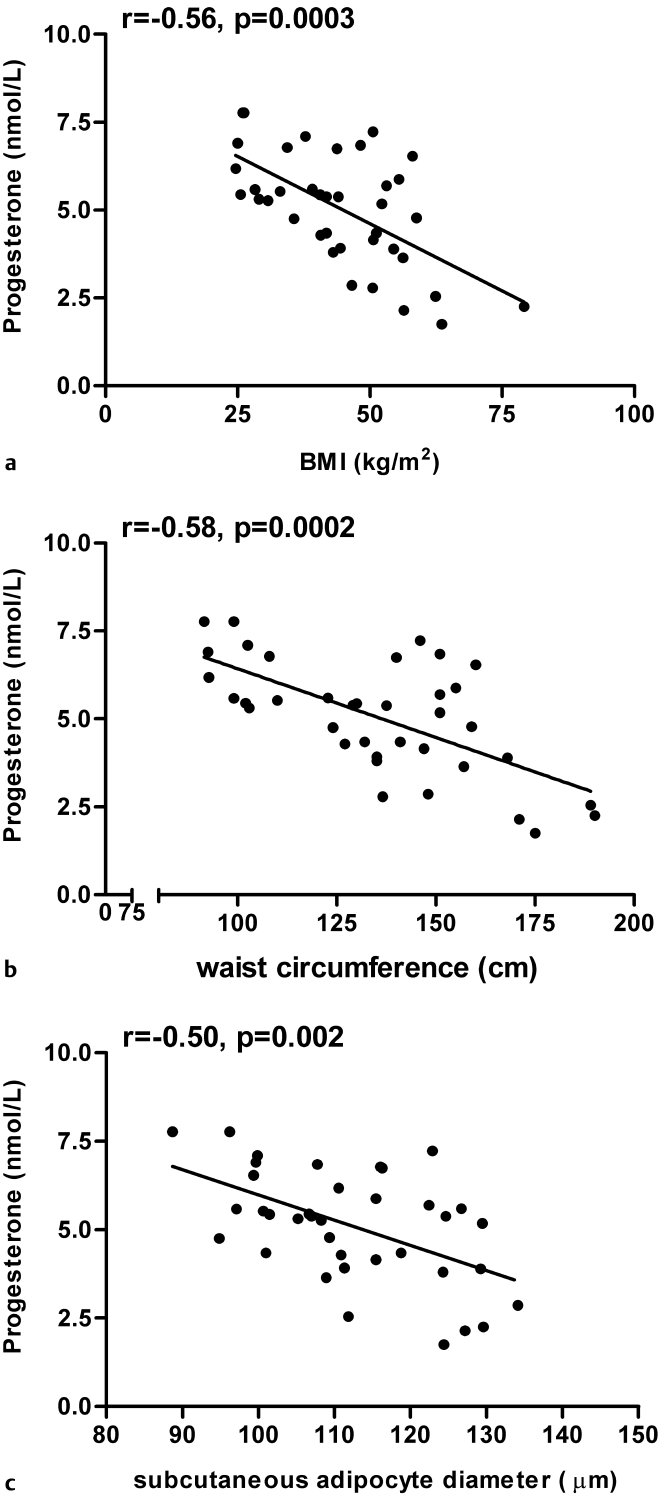

Fig. **1** Correlations between plasma progesterone and **a)** body mass index (BMI) (n = 38), **b)** waist circumference (n = 37) and **c)** subcutaneous adipocyte diameter (n = 37).

Adjustment for the time of blood drawing or successively excluding patients using medication such as glucose lowering/insulin sensitizing/diabetes drugs, lipid lowering medication, anti-hypertensive medication, thyroid hormone or antidepressant medicine, had a minor effect on the associations shown in Table **2**. Plasma 21-deoxycortisol concentrations were all below the limit of quantification (0.5 ng/ml), indirectly suggesting that patients of our study were not characterized by classical forms of congen-

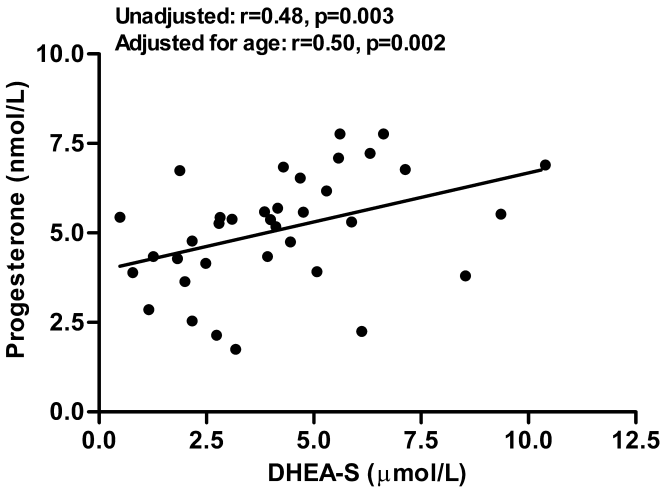

Fig. **2** Correlation between plasma progesterone and dehydroepiandrosterone sulfate (DHEA-S) before and after statistical adjustment for age (n = 36).

ital adrenal hyperplasia and were unlikely to be characterized by heterozygous 21-hydroxylase deficiency [15,16].

To examine the variable that could best predict plasma progesterone levels in men, we performed multivariate regression analyses (Table **3**) using models including steroid levels (17-OH-progesterone, DHEA-S, androstendione, testosterone and DHT, Model 1), or both adiposity measures and steroid levels (waist circumference, BMI, subcutaneous adipocyte diameter, 17-OH-progesterone, DHEA-S, androstendione, testosterone and DHT, Model 2). Using the first model, we identified DHEA-S as the only significant predictor of plasma progesterone levels. Circulating DHEA-S levels explained 22.8% of the total variance in plasma progesterone. Fig. **2** shows the positive correlation between plasma progesterone and DHEA-S, which was independent of age. When including adiposity variables in the second model, DHEA-S was no longer a significant predictor of plasma progesterone level. In this model, waist circumference was the only significant correlate of circulating progesterone. Waist circumference explained 49.2% of the total variance in plasma progesterone in men. Accordingly, statistical adjustment for waist circumference abolished all correlations between plasma progesterone and other adiposity variables (not shown). Adjustment for blood drawing time or addition of this variable in the models did not affect the results.

Discussion

The present study was prompted by the poor knowledge we have on progesterone in men, despite the fact that this hormone has been postulated to exert significant effects in adipose tissue [6] and adipocytes from both males and females [4,5,17,18]. We observed negative correlations between plasma progesterone and body weight, BMI, waist circumference and subcutaneous adipocyte diameter, with waist circumference as the strongest correlate of serum progesterone levels in men. Other negative correlations were found between androgen levels and adiposity, specifically between DHEA-S, androstendione, testosterone and DHT and these adiposity variables. The best steroid predictor of plasma progesterone was the level of the adrenal steroid DHEA-S. This is the first study to report on the association between circulating progesterone and obesity in men.

Table **3** Multivariate regression analyses to identify independent predictors of plasma progesterone levels

Models	*Dependant variable*	*Independent variables*	*r^2 partial*	*r^2 total*	*p value*
Model 1	Progesterone level	17-OH-progesterone	–	–	NS
		DHEA-S	22.8	22.8	0.004
		Androstendione	–	–	NS
		Testosterone	–	–	NS
		DHT	–	–	NS
Model 2	Progesterone level	Waist circumference	49.2	49.2	< 0.001
		BMI	–	–	NS
		SC adipocyte diameter	–	–	NS
		17-OH-progesterone	–	–	NS
		DHEA-S	–	–	NS
		Androstendione	–	–	NS
		Testosterone	–	–	NS
		DHT	–	–	NS

17-OH-progesterone, 17-hydroxyprogesterone; DHEA-S, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; SC, subcutaneous

The cross-sectional nature of the present study prevents us from reaching any conclusions on whether the low progesterone levels found in abdominal obese men are a cause or a consequence of the obese state. However, previous literature on sex hormones and adipose tissue distribution may help in suggesting hypotheses to explain this association. Potential sources of circulating progesterone in men include the testes and the adrenals, which synthesize progesterone as an intermediate in C_{19} and/or C_{21} steroid production. Previous experiments by Vermeulen and Verdonck [3] indicated that ACTH injection leads to parallel increases in DHEA, androstendione and progesterone, while testosterone slightly decreases, suggesting that circulating progesterone primarily reflects adrenal C_{19} steroid production. Several studies have examined alterations in the hypothalamus-pituitary-adrenal (HPA) axis and adrenal C_{19} steroid levels in abdominal obesity. A recent survey of the literature [19] indicates that while several studies reported negative correlations between DHEA or DHEA-S and obesity or abdominal fat accumulation, other studies reported positive associations or non-significant trends. Age differences in the populations examined have been postulated to be an important confounder in these reports [19]. On the other hand, obese children appear to be characterized by higher plasma DHEA-S [20]. The present results are concordant with previous reports showing negative associations between circulating DHEA-S and measures of overall or abdominal obesity. Studies have shown an increased metabolic clearance rate of DHEA or DHEA-S in obese subjects [21–23], which has been proposed to explain the lower levels of these steroids observed at least in some obese populations [24–26]. Other investigators suggested that very obese individuals may be unable to increase adrenal

DHEA production to parallel the increase in the hormone metabolic clearance rate [27].

In addition to the possibility of an obesity-related increase in the metabolic clearance of DHEA [21 – 23], high insulin levels, which are frequently observed in the obese state [6,28], have been suggested to mediate the decrease in DHEA-S concentrations often related to this condition [29]. Specifically, insulin inhibition of the 17,20-lyase activity in the adrenals was demonstrated by higher circulating 17α-hydroxyprogesterone and decreased androstendione under insulin and ACTH infusion in men [14,29]. These results are supported by the finding that improvements in insulin sensitivity induced by diet, sulfonylurea or glitazone treatment led to increased 17,20-lyase activities in men or women with PCOS in their follicular phases [30,31]. However, the effect of insulin on ACTH-stimulated progesterone production by the adrenals was non-significant in at least two studies [14,29], suggesting that insulin regulation of the P450C17 enzyme is limited to the 17,20-lyase activity, with little effect on its 17α-hydroxylase activity. In the present study, the ratios of 17-OH-progesterone to progesterone or androstendione to 17-OH-progesterone, which have been used as indicators of adrenal 17α-hydroxylase or 17,20-lyase activities were not related to obesity, thus we propose that servo regulation of the P405C17 enzyme by insulin may not necessarily account for the lower progesterone concentrations we report in male obesity.

Alternate factors related to obesity and/or abdominal fat accumulation may, therefore, be proposed as potential modulators of progesterone release by the adrenals. Leptin is an adipose tissue-derived peptide hormone that is elevated in the plasma of obese individuals [32]. Studies on bovine and human adrenocortical cells have shown clear inhibitions of ACTH-induced expression of several enzymes involved in the adrenal steroid synthesis pathway, including P450 side chain cleavage enzyme, the 17α-hydroxylase activity of the P450c17 enzyme and the P450c21 enzyme [33,34]. Accordingly, leptin treatment induces a reduction in cortisol release both *in vitro* [35] and *in vivo* under stress conditions [36]. The steroidogenic acute regulatory protein (StAR) has also been shown to be inhibited by leptin in adrenal glands from neonatal rodents [37]. Leptin inhibition of the adrenal steroid synthesis enzyme system may potentially explain the finding of lower progesterone in obese men.

Tumor necrosis factor α was shown to substantially decrease the ACTH-induced expression of several enzymes involved in adrenal steroidogenesis including P450scc, P450c17 and P450c21 [38]. Interestingly, TNF-α has been shown to play a role in insulin resistance [39], and to be increased in abdominal obesity [40], possibly as the result of an increased secretion from macrophages located within an enlarged intra-abdominal adipose tissue mass [41,42]. The modulation of adrenal steroidogenesis by TNF-α could potentially contribute to the strong negative correlation we observed between waist circumference and progesterone levels in the present study. However, studies on the possible negative impact of leptin and TNF-α on adrenal steroidogenesis must be balanced with a recent study by Ehrhart-Bornstein et al. [43], in which incubation of human adrenocortical cells with culture medium conditioned with isolated adipocytes showed that adipocyte-secreted products stimulate DHEA production. These effects were apparently not attributable to either leptin or TNF-α, which suggests that other adipocyte secretory products may be involved in the link between adipose tissue and adrenal DHEA secretion.

Additional mechanisms proposed for the lower DHEA-S observed in some obese populations included increased uptake and conversion of DHEA in adipose tissue [44] and increased DHEA metabolite formation [14]. Adipose tissue uptake of both DHEA and progesterone has been demonstrated long ago, and several adipose tissue-expressed steroid-synthesizing and steroid-inactivating enzymes have been identified to date (reviewed in [45]). Increased progesterone metabolism in adipose tissue could also be raised as a possibility for the reduced progesterone levels observed in the present sample of obese men. Accordingly, we recently reported on the high expression levels of progesterone-inactivating 20α-hydroxysteroid dehydrogenase enzyme in abdominal adipose tissue depots and positive correlation of this activity with adiposity measures [7,8]. This enzyme was also recently detected in subcutaneous and omental adipose tissue in men (Blanchette and Tchernof, unpublished). Future studies are required to elucidate whether the presence of this enzyme in adipose tissue is responsible for low progesterone levels in obese men and whether it is involved in the pathophysiology of abdominal obesity, or only represents a means by which progesterone action in adipose tissue is prevented.

In summary, this study has found a strong negative relationship between obesity, especially abdominal obesity, and circulating progesterone levels in men. The best steroid predictor of plasma progesterone was the adrenal C_{19} steroid DHEA-S. We suggest that the low progesterone levels observed in obese men may reflect decreased adrenal C_{19} steroid production in the adrenal cortex. Further research is needed to confirm this hypothesis.

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References

[1] Vermeulen A. Plasma levels and secretion rate of steroids with anabolic activity in man. Environ Qual Saf 1976; 5: 171 – 180
[2] Tea NT, Castanier M, Roger M. Simultaneous radioimmunoassay of plasma progesterone and 17-hydroxyprogesterone normal values in children, in men and in women throughout the menstrual cycle and in early pregnancy. J Steroid Biochem 1975; 6: 1509 – 1516
[3] Vermeulen A, Verdonck L. Radioimmunoassay of 17beta-hydroxy-5alpha-androstan-3-one, 4-androstene-3,17-dione, dehydroepiandrosterone, 17-hydroxyprogesterone and progesterone and its application to the human male plasma. J Steroid Biochem 1976; 7: 1 – 10

[4] Lacasa D, Le Liepvre X, Ferre P, Dugail I. Progesterone stimulates adipocyte determination and differentiation 1/sterol regulatory element-binding protein 1c gene expression. potential mechanism for the lipogenic effect of progesterone in adipose tissue. J Biol Chem 2001; 276: 11512 – 11516
[5] Wiper-Bergeron N, Wu D, Pope L, Schild-Poulter C, Hache RJ. Stimulation of preadipocyte differentiation by steroid through targeting of an HDAC1 complex. EMBO J 2003; 22: 2135 – 2145
[6] Björntorp P. Endocrine abnormalities in obesity. Diabetes Rev 1997; 5: 52 – 68
[7] Blanchette S, Blouin K, Richard C, Dupont P, Luu-The V, Tchernof A. Expression and activity of 20-hydroxysteroid dehydrogenase (AKR 1C1) in abdominal subcutaneous and omental adipose tissue in women. J Clin Endocrinol Metab 2005; 90: 264 – 270
[8] Blouin K, Blanchette S, Richard C, Dupont P, Luu-The V, Tchernof A. Expression and activity of steroid aldoketoreductases 1C in omental adipose tissue are positive correlates of adiposity in women. Am J Physiol Endocrinol Metab 2005; 288 : E398 – E404
[9] Tchernof A, Labrie F, Bélanger A, Després JP. Obesity and metabolic complications: contribution of dehydroepiandrosterone and other steroid hormones. J Endocrinol 1996; 150: S155 – S164
[10] Salehi M, Ferenczi A, Zumoff B. Obesity and cortisol status. Horm Metab Res 2005; 37: 193 – 197
[11] Marceau P, Biron S, Hould FS, Marceau S, Simard S, Thung SN, Kral JG. Liver pathology and the metabolic syndrome X in severe obesity. J Clin Endocrinol Metab 1999; 84: 1513 – 1517
[12] Marceau P, Hould FS, Lebel S, Marceau S, Biron S. Malabsorptive obesity surgery. Surg Clin North Am 2001; 81: 1113 – 1127
[13] Rodbell M. Metabolism of isolated fat cells. J Biol Chem 1964; 239: 375 – 380
[14] Nestler JE, McClanahan MA, Clore JN, Blackard WG. Insulin inhibits adrenal 17,20-lyase activity in man. J Clin Endocrinol Metab 1992; 74: 362 – 367
[15] Fiet J, Villette JM, Galons H, Boudou P, Burthier JM, Hardy N, Soliman H, Julien R, Vexiau P, Gourmelen M. The application of a new highly-sensitive radioimmunoassay for plasma 21-deoxycortisol to the detection of steroid-21-hydroxylase deficiency. Ann Clin Biochem 1994; 31: 56 – 64
[16] Cristoni S, Cuccato D, Sciannamblo M, Bernardi LR, Biunno I, Gerthoux P, Russo G, Weber G, Mora S. Analysis of 21-deoxycortisol, a marker of congenital adrenal hyperplasia, in blood by atmospheric pressure chemical ionization and electrospray ionization using multiple reaction monitoring. Rapid Commun Mass Spectrom 2004; 18: 77 – 82
[17] Mendes AM, Madon RJ, Flint DJ. Effects of cortisol and progesterone on insulin binding and lipogenesis in adipocytes from normal and diabetic rats. J Endocrinol 1985; 106: 225 – 231
[18] Shirling D, Ashby JP, Baird JD. Effect of progesterone on lipid metabolism in the intact rat. J Endocrinol 1981; 90: 285 – 294
[19] Tchernof A, Labrie F. Dehydroepiandrosterone, obesity and cardiovascular disease risk: a review of human studies. Eur J Endocrinol 2004; 151: 1 – 14
[20] l'Allemand D, Schmidt S, Rousson V, Brabant G, Gasser T, Gruters A. Associations between body mass, leptin, IGF-I and circulating adrenal androgens in children with obesity and premature adrenarche. Eur J Endocrinol 2002; 146: 537 – 543
[21] Kurtz BR, Givens JR, Komindr S, Stevens MD, Karas JG, Bittle JB, Judge D, Kitabchi AE. Maintenance of normal circulating levels of delta-4-androstendione and dehydroepiandrosterone in simple obesity despite increased metabolic clearance rates: evidence for a servo-control mechanism. J Clin Endocrinol Metab 1987; 64: 1261 – 1267
[22] Fehér T, Halmy L. Dehydroepiandrosterone and dehydroepiandrosterone sulfate dynamics in obesity. Can J Biochem 1975; 53: 215 – 222
[23] Kirschner MA, Samojlik E, Silber D. A comparison of androgen production and clearance in hirsute and obese women. J Steroid Biochem 1983; 19: 607 – 614
[24] Tchernof A, Després JP, Bélanger A, Dupont A, Prud'homme D, Moorjani S, Lupien PJ, Labrie F. Reduced testosterone and adrenal C19 steroid levels in obese men. Metabolism 1995; 44: 513 – 519
[25] Abbasi A, Duthie EH Jr, Sheldahl L, Wilson C, Sasse E, Rudman I, Mattson DE. Association of dehydroepiandrosterone sulfate, body composition, and physical fitness in independent community-dwelling older men and women. J Am Geriatr Soc 1998; 46: 263 – 273
[26] Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Després JP, Bouchard C. Contribution of body fatness and adipose tissue distribution to the age variation in plasma steroid hormone concentrations in men: the HERITAGE family study. J Clin Endocrinol Metab 2000; 85: 1026 – 1031
[27] de Pergola G, Giagulli VA, Garruti G, Cospite MR, Giorgino F, Cignarelli M, Giorgino R. Low dehydroepiandrosterone circulating levels in premenopausal obese women with very high body mass index. Metabolism 1991; 40: 187 – 190
[28] Després JP, Moorjani S, Ferland M, Tremblay Y, Lupien PJ, Nadeau A, Pinault S, Thériault G, Bouchard C. Adipose tissue distribution and plasma lipoprotein levels in obese women: importance of intra-abdominal fat. Arteriosclerosis 1989; 9: 203 – 210
[29] Moghetti P, Castello R, Negri C, Tosi F, Spiazzi GG, Brun E, Balducci R, Toscano V, Muggeo M. Insulin infusion amplifies 17a-hydroxycorticosteroid intermediates responses to adrenocorticotropin in hyperandrogenic women: apparent relative impairment of 17,20-lyase activity. J Clin Endocrinol Metab 1996; 81: 881 – 886
[30] Ueshiba H, Shimizu Y, Hiroi N, Yakushiji F, Shimojo M, Tsuboi K, Miyachi Y. Decreased steroidogenic enzyme 17,20-lyase and increased 17-hydroxylase activities in type 2 diabetes mellitus. Eur J Endocrinol 2002; 146: 375 – 380
[31] Guido M, Romualdi D, Suriano R, Giuliani M, Costantini B, Apa R, Lanzone A. Effect of pioglitazone treatment on the adrenal androgen response to corticotrophin in obese patients with polycystic ovary syndrome. Hum Reprod 2004; 19: 534 – 539
[32] Considine RV, Caro JF. Leptin: genes, concepts and clinical perspective. Horm Res 1996; 46: 249 – 256
[33] Kruse M, Bornstein SR, Uhlmann K, Paeth G, Scherbaum WA. Leptin down-regulates the steroid producing system in the adrenal. Endocr Res 1998; 24: 587 – 590
[34] Harle P, Pongratz G, Weidler C, Buttner R, Scholmerich J, Straub RH. Possible role of leptin in hypoandrogenicity in patients with systemic lupus erythematosus and rheumatoid arthritis. Ann Rheum Dis 2004; 63: 809 – 816
[35] Bornstein SR, Uhlmann K, Haidan A, Ehrhart-Bornstein M, Scherbaum WA. Evidence for a novel peripheral action of leptin as a metabolic signal to the adrenal gland: leptin inhibits cortisol release directly. Diabetes 1997; 46: 1235 – 1238
[36] Wilson ME, Fisher J, Brown J. Chronic subcutaneous leptin infusion diminishes the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis in female rhesus monkeys. Physiol Behav 2005; 84: 449 – 458
[37] Salzmann C, Otis M, Long H, Roberge C, Gallo-Payet N, Walker CD. Inhibition of steroidogenic response to adrenocorticotropin by leptin: implications for the adrenal response to maternal separation in neonatal rats. Endocrinology 2004; 145: 1810 – 1822
[38] Jaattela M, Ilvesmaki V, Voutilainen R, Stenman UH, Saksela E. Tumor necrosis factor as a potent inhibitor of adrenocorticotropin-induced cortisol production and steroidogenic P450 enzyme gene expression in cultured human fetal adrenal cells. Endocrinology 1991; 128: 623 – 629
[39] Borst SE. The role of TNF-alpha in insulin resistance. Endocrine 2004; 23: 177 – 182
[40] Katsuki A, Sumida Y, Murashima S, Murata K, Takarada Y, Ito K, Fujii M, Tsuchihashi K, Goto H, Nakatani K, Yano Y. Serum levels of tumor necrosis factor-alpha are increased in obese patients with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1998; 83: 859 – 862
[41] Fain JN, Bahouth SW, Madan AK. TNFalpha release by the nonfat cells of human adipose tissue. Int J Obes Relat Metab Disord 2004; 28: 616 – 622
[42] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AWJr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; 112: 1796 – 1808
[43] Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A, Langenbach J, Willenberg HS, Barthel A, Hauner H, McCann SM, Scherbaum WA, Bornstein SR. Human adipocytes secrete mineralocorticoid-releasing factors. Proc Natl Acad Sci U S A 2003; 100: 14211 – 14216
[44] Lavallée B, Provost PR, Nestler JE, Kahwash Z, Bélanger A. Effect of insulin on serum levels of dehydroepiandrosterone metabolites in men. Clin Endocrinol 1997; 46: 93 – 100
[45] Bélanger C, Luu-The V, Dupont P, Tchernof A. Adipose tissue intracrinology: potential importance of local androgen/estrogen metabolism in the regulation of adiposity. Horm Metab Res 2002; 34: 737 – 745