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Relationship of androgens to body composition, energy and substrate metabolism and aerobic capacity in healthy, young women

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ABSTRACT

Objective: To evaluate the role of physiologic levels of androgens and their precursors in the regulation of body composition, energy and substrate metabolism and aerobic capacity in healthy, cycling, premenopausal women.
Experimental: We evaluated 30 young (27 ± 1 year) premenopausal, non-obese (23 ± 0.5 kg/m^2), normally-cycling women, without clinical or chemical evidence of hyperandrogenism or hyperinsulinemia, for parameters of total and regional body composition, glucose tolerance, aerobic capacity and resting energy expenditure and substrate oxidation. Serum was assayed for androgens and androgen precursors by techniques optimized to assess the low androgen levels in this population.
Results: Higher serum testosterone levels correlated with greater fat mass ($r = 0.377$; $p = 0.04$), but not abdominal adiposity or other metabolic/physiologic variables. Additionally, dehydroepiandrosterone (DHEA) was negatively related to visceral fat content ($r = -0.569$; $p = 0.02$). Other serum androgens did not correlate with total or regional adiposity, skeletal muscle mass, aerobic capacity, glucose tolerance, or resting energy and substrate metabolism.
Conclusion: In this group of non-obese, premenopausal women with no clinical or chemical evidence of hyperandrogenemia, serum testosterone levels were positively related with fat mass, but not with abdominal adiposity; whereas, DHEA was negatively related to visceral adiposity. Our data suggest that within the normal physiologic range, testosterone is a predictor of overall adiposity, but that this effect does not appear to be associated with concomitant alterations in resting energy or substrate metabolism that could predispose to weight gain.

1. Introduction

The role of testosterone in the regulation of body composition, physical capacity, and energy and substrate metabolism in women remains undefined. Current knowledge regarding the effects of testosterone stems primarily from clinical disease processes that result in testosterone excess or deficiency, most notably polycystic ovarian syndrome (PCOS).[1] Characterized by androgen and estrogen excess, PCOS is associated with obesity, insulin resistance and increased cardiovascular morbidity. While studies in patients with PCOS provide insight into derangements of physiologic and/or metabolic function related to hyperandrogenemia, these data may not adequately reflect the effects of androgens within the normal physiological range. Perhaps more importantly, additional confounding factors (e.g., obesity and hyperinsulinemia in PCOS) complicate the ability to relate physiologic and metabolic sequelae to the unique effects of testosterone. Contrary to the detrimental effects suggested from studies in PCOS, recent studies from our laboratory in post-menopausal women have shown that higher levels of androgens, within the physiological range, may have beneficial effects on body composition, metabolic function and aerobic fitness [1]. Understanding the role of testosterone in the regulation of adiposity and metabolic function in premenopausal women may provide valuable insight into the nature of changes in metabolic and cardiovascular risk in pathological conditions (e.g., PCOS), as well as clinical interventions that modify androgen levels (e.g., oral contraceptives, or testosterone replacement for sexual dysfunction).

The primary goal of this study, therefore, was to evaluate the relationship of circulating androgens and androgen precursors as potential determinants of total and regional body composition,

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[1] *Abbreviations*: PCOS, polycystic ovary syndrome; OGTT, oral glucose tolerance test; T, testosterone; Δ^4A, androstenedione; DHEA, dehydroepiandrosterone, DHEA-S, dehydroepiandrosterone-sulfate; SHBG, sex hormone binding globulin; AUC, area under curve.

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energy and substrate metabolism and aerobic fitness in premenopausal women. We recruited healthy, non-obese, glucose tolerant, cycling females with no history or clinical evidence of endocrine pathology for studies evaluating the effect of ovarian steroid hormones on metabolic function [2–5]. These criteria were chosen to avoid the confounding affects of obesity, insulin resistance, and hyperandrogenemia. Equally as important, we utilized validated techniques that were optimized to measure the low circulating androgen levels in this population.

2. Experimental

2.1. Subjects

Thirty healthy, young cycling women were recruited in conjunction with studies designed to evaluate the effects of ovarian suppression with gonadotropin hormone releasing agonist (GnRHa) on metabolic and physiologic function [2–5]. Women were selected who were non-obese (BMI < 30 kg/m^2; mean ± SE, 23.3 ± 0.5 kg/m^2), had a stable body weight (±2 kg) for 6 months prior to study, were healthy based on medical history, physical exam and routine blood tests, were glucose tolerant (glucose <7.77 mmol/L 2 h following 75 g oral glucose load), had no history of tobacco use, and were not on any medication that could affect glucose metabolism or ovarian/reproductive function. None of the volunteers had clinical or biochemical evidence of hyperandrogenemia, a history of polycystic ovary disease, or had been exposed to any form of hormone-based contraceptive therapy for at least 6 months prior to study. Women reported having at least 2 spontaneous cycles in the 3 months prior to recruitment and a cycle length of between 25 and 32 days. The nature, purpose and possible risks of the study were explained to each subject before she gave written consent to participate. The experimental protocol was approved by the Committee on Human Research at the University of Vermont. The current report represents an analysis of baseline GnRHa data to evaluate the potential relationship of circulating testosterone levels to body composition, energy and substrate metabolism and aerobic capacity. All data were collected in the mid-luteal phase of the subject's menstrual cycle.

2.2. Body composition

Body mass was measured on a metabolic scale (Scale-Tronix, Inc., Wheaton, IL). Fat mass, lean body mass, abdominal adiposity and bone mineral mass were each measured by dual energy X-ray absorptiometry using a GE Lunar Prodigy densitometer (GE Lunar Co., Madison, WI). Abdominal adiposity was measured between the L1 and L4 vertebral bodies using the Region of Interest option of the software following the general approach of Glickman et al. [6] with minor modifications, as described previously [2]. This measurement will heretofore be designated as "abdominal fat" measured in kg. Visceral and subcutaneous adiposity were assessed by computed tomography (CT) with a Phillips Billiance 40 or 64 CT scanner (Phillips Medical Systems, Cleveland, OH) as described previously [7], Visceral and subcutaneous adiposity were available on 16 out of the 30 subjects because this measurement was not performed in one of the aforementioned trials.

2.3. Peak aerobic capacity (peak VO_2)

Peak VO_2 was measured during a graded, treadmill test to volitional fatigue. Briefly, a comfortable initial walking speed was found for each volunteer and was maintained throughout the test. The grade was increased 2.5% every two minutes until volitional fatigue. Peak VO_2 was defined as the highest 30-s average VO_2 value measured during the last 2 min of the test.

2.4. Oral glucose tolerance test

A 75-g OGTT was performed after an overnight fast (at 08:00 h). Blood samples were collected at 0, 60, 90 and 120 min for analysis of glucose levels via the glucose oxidase technique (YSI Life Sciences, Yellow Springs, OH). Glucose AUC was determined using the trapezoid method.

2.5. Indirect calorimetry

Resting energy expenditure and substrate oxidation were performed using the ventilated hood technique (DeltaTrac, Yorba Linda, CA), as described [5]. The subject was gently awakened (at 06:30 h), allowed to void if necessary, returned to bed and placed under the hood for 30 min. Carbon dioxide production and oxygen consumption were utilized to calculate the respiratory quotient.

2.6. Hormone measurements

Serum levels of testosterone, androstenedione (Δ^4A), dehydroepiandrosterone (DHEA), and DHEA-sulfate (DHEA-S) were measured by radioimmunoassay. Prior to measurement, steroids were extracted from serum with hexane: ethyl acetate (3:2). Androstenedione, DHEA and testosterone were then separated by Celite column partition chromatography using increasing concentrations of toluene in trimethylpentane. Dehydroepiandrosterone sulfate (DHEA-S) and sex-hormone binding globulin (SHBG) were measured by direct chemiluminescent immunoassays using the

Table 1
Physical, metabolic, and functional characteristics of the study population.

	Mean ± SE	Range
Age (year)	27.3 ± 0.8	21–36
Weight (kg)	64.3 ± 1.7	49.0–82.7
Height (cm)	166.1 ± 1.5	151.0–180.8
Fat mass (kg)	20.1 ± 1.2	7.0–37.1
Body fat (%)	31.6 ± 1.4	15.2–46.9
Lean body mass (kg)	42.1 ± 0.9	31.2–52.7
Appendicular skeletal muscle mass (kg)	18.5 ± 0.5	13.8–24.0
Abdominal fat (kg)[a]	1.7 ± 0.2	0.4–4.2
Visceral fat (cm^2)[b]	52.6 ± 3.7	32.0–91.0
Subcutaneous fat (cm^2)[b]	256.7 ± 23.1	79.0–413.0
Glucose AUC ($\times 10^{-3}$ mmol/L min^{-1})	0.59 ± 0.14	0.44–0.77
VO_2 max (ml/kg lean body mass min^{-1})	39.5 ± 1.3	23.8–50.1
Resting energy expenditure (kcal/day)	1358 ± 28	1100–1690
Respiratory quotient	0.84 ± 0.01	0.73–0.92

AUC, Area under the curve; VO_2 max, peak aerobic capacity; $n = 30$ for all data with the exception of visceral and subcutaneous fat measurements, where $n = 16$.
[a] DEXA measurement.
[b] CT measurement.

Table 2
Hormonal characteristics of the study population.

	Mean ± SE	Range
Total testosterone (ng/dl)	32.8 ± 1.6	8.5–53.5
Free testosterone (pg/ml)	5.9 ± 0.3	1.8–8.9
DHEA (ng/ml)	6.4 ± 0.5	1.2–13.4
DHEA-S (μg/ml)	133.1 ± 11.0	22.6–314.0
Androstenedione (pg/ml)	1.4 ± 0.1	0.4–2.2
SHBG (nmol/l)	52.7 ± 3.1	15.0–111.0

DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone-sulfate; SHBG, sex hormone binding globulin.

Table 3
Correlations between circulating androgen levels and morphological, physiological, and metabolic variables.

	Pearson correlation coefficients					
	T	Free T	DHEA	DHEA-S	Δ^4A	SHBG
Body fat percentage	0.354	0.162	0.195	−0.033	0.097	0.325
Fat mass	0.377*	0.226	0.153	−0.058	0.036	0.252
Appendicular skeletal muscle mass	−0.026	0.128	−0.111	−0.039	−0.188	−0.278
Abdominal fat[a]	0.192	0.167	−0.087	−0.090	−0.113	0.006
Visceral fat[b]	−0.375	−0.120	−0.569*	−0.377	−0.410	−0.380
Subcutaneous Fat[b]	0.171	0.003	−0.251	−0.097	−0.251	0.149
Glucose AUC	0.066	0.035	0.131	0.055	0.267	0.041
Resting energy expenditure	0.226	0.034	0.106	−0.203	−0.049	0.342
Respiratory quotient	0.030	−0.137	−0.016	−0.216	−0.202	0.186
VO_2 max	−0.020	−0.268	−0.099	0.213	−0.039	0.301

T, testosterone; DHEA, dehydroepiandrosterone; DHEA-S dehydroepiandrosterone-sulfate; Δ4A, androstenedione; AUC, area under the curve; VO_2 max, peak aerobic capacity.
Note that all variables were normally distributed with the exception of DHEA, which was $\log_{10}$ transformed prior to correlation analysis.
* $P < 0.05$.
[a] DEXA measurement.
[b] CT measurement.

Immulite analyzer (Diagnostic Products Co., Inglewood, CA). Free testosterone was calculated using its respective total serum concentration, sex-hormone binding globulin levels and an assumed constant for albumin in a validated algorithm [8]. Intra- and inter-assay CV for steroid hormones and their binding proteins varied from 4% to 8% and 8% to 13%, respectively.

2.7. Statistical analysis

Prior to statistical analysis, the normality of the distribution of variables was assessed using the Shapiro Wilks test. Any variable that was not normally distributed (e.g., DHEA) was $\log_{10}$ transformed and normality was reassessed. All variables with skewed distributions were normally distributed following $\log_{10}$ transformation. For correlation analyses, all relationships were statistically adjusted for age, and insulin sensitivity data were adjusted for lean body mass using analysis of covariance. Relationships between variables were assessed by Pearson correlation coefficients. All data are presented as means ± SE.

3. Results

Baseline physical characteristics and steroid hormone levels of the 30 participants are outlined in Tables 1 and 2. Based on these data, it is apparent that subjects were non-obese, glucose tolerant, and of average fitness level. Subjects had no evidence of biochemical hyperandrogenemia, according to testosterone and free testosterone levels. The androgen precursors DHEA, DHEA-S, and Δ^4A were also within normal ranges.

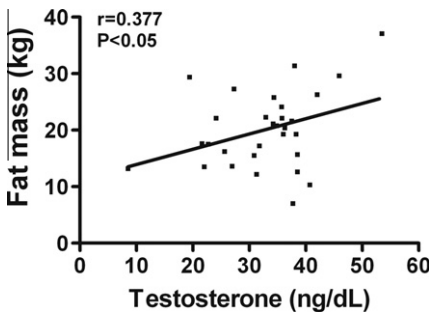

Fig. 1. Relationship between serum testosterone levels and fat mass in 30 healthy, cycling, premenopausal.

Correlations between steroid hormones levels and body composition, aerobic capacity, and metabolic parameters are shown in Table 3. Higher serum testosterone levels correlated with greater fat mass ($r = 0.377$, $p = 0.04$; Fig. 1). Log-transformed DHEA correlated negatively with visceral adiposity as measured by CT ($r = -0.569$, $p = 0.02$). None of the serum androgens, nor SHBG, correlated with appendicular skeletal muscle mass, abdominal adiposity, VO_2 max, or insulin sensitivity. Because of the well-known relationship of testosterone to adiposity, we also evaluated the relationship of testosterone and other steroids to physiological factors that presage weight gain: resting energy expenditure, substrate oxidation and insulin sensitivity (as reflected by glucose AUC during the oral glucose tolerance test) [9]. No relationship of any androgen or SHBG was found to resting energy expenditure or substrate oxidation.

4. Discussion

This study evaluated healthy, non-obese, pre-menopausal women with no history of hyperandrogenemia, hyperinsulinemia, or hirsutism to evaluate the association of endogenous androgen levels to body composition, energy and substrate metabolism and aerobic fitness. We found that higher serum testosterone levels, within the normal physiologic range, correlated with greater fat mass, but were not related to abdominal adiposity or other metabolic and functional indices. Although cause–effect cannot be discerned from these associations, further analysis revealed no association between greater testosterone levels and metabolic predictors of weight gain, such as reduced resting energy expenditure or fat oxidation, or increased insulin sensitivity [9], arguing against androgens as effectors of fat accumulation. Additionally, we found that serum levels of the sex-steroid precursor DHEA negatively correlated with visceral adiposity. No other androgen or precursor was related to adiposity or other metabolic and function indices. A particular strength of our study is the careful selection of volunteers to permit the evaluation of these associations without the confounding effects of hyperinsulinemia, hyperandrogenemia, PCOS, or obesity. Equally important is our use of validated hormonal assays that permit the precise assessment of low circulating androgen levels evident in this population.

This study was spurred by our recent work in healthy, non-obese, post-menopausal women, which showed that increasing endogenous androgen levels, within the normal physiologic range, correlated with body composition, metabolic function, and physical function. Specifically, in non-obese post-menopausal women,

higher serum testosterone levels were related to greater maximal aerobic capacity and reduced fat mass, while androgen precursors and metabolites were positively associated with insulin sensitivity [1]. These prior results align with a number of studies in post-menopausal women demonstrating a favorable relationship between physiologic androgen levels and body morphometry, insulin sensitivity, and functional capacity [10–14]. Why these relationships differ between pre- and post-menopausal women, however, is not clear. We hypothesize that differences relate to the complexities of the pre- and post-menopausal hormonal environments; more specifically, to higher levels of ovarian estrogens in pre-menopausal women. That is, the effects of androgens on these variables may be overshadowed by stronger regulatory effects of estrogens.

To date, our understanding of the relationship between sex steroids, body composition, and metabolic function in pre-menopausal females stems largely from patients with hormone excess, as observed in PCOS. The positive correlation found in the present study between testosterone and total body fat mass in non-obese subjects parallels the well-recognized relationship between excess androgens and adiposity in the PCOS-phenotype [15–17]. In PCOS, whether the rise in androgens precedes increased adiposity and insulin resistance or whether hyperinsulinemia triggers the increase in androgen production remains controversial. Because of the cross-sectional nature of the current study, we are likewise unable to determine whether greater testosterone levels promote increased adiposity or are simply a consequence of greater levels of body fat. However, we attempted to address this issue by assessing the relationship of androgen levels to metabolic predictors of weight gain; namely, reduced resting energy expenditure, decreased fat oxidation or greater insulin sensitivity (as evidenced by glucose tolerance measures). The fact that circulating testosterone levels were not related to any of these variables argues against a causative role for testosterone in promoting greater adiposity. Instead, our data favor the interpretation that increasing amounts of body fat may promote increased circulating testosterone, possibly through an effect on tissue insulin sensitivity [18,19]. Importantly, we cannot discount the possibility that testosterone promotes fat gain via modulation of energy intake, which some animal models have suggested [20,21]. In the present study, we did not assess food intake because of the well-known inaccuracies of this measurement [22]. Acknowledging that we cannot ascribe cause–effect directionality, our data nonetheless argue against a role for testosterone contributing to fat accumulation via effects on a variety of metabolic predictors of weight gain.

Despite the relationship to overall adiposity, circulating testosterone levels did not correlate to abdominal adiposity. Conventional wisdom regarding the effects of testosterone on body fat patterns derives primarily from PCOS, where a hyperandrogenic state is believed to promote greater abdominal adiposity [23]. In agreement with these findings in PCOS, data in male- to- female transsexuals receiving supra-physiologic testosterone therapy over the course of 1–3 years demonstrates an increase in visceral fat deposition [24,25]. However, these data are contradicted by studies showing that suppression of androgenemia with gonadotropin-releasing hormone agonist actually increases visceral adiposity in women with PCOS [26]. Such an effect of testosterone to prevent fat accumulation is consistent with *in vitro* studies showing an inhibitory effect on pathways of lipid accumulation in adipocytes [27]. Thus, there appears to be a complex relationship between circulating androgen levels and abdominal adiposity that is dependent on the integrity of ovarian function and testosterone levels. Our work adds to this literature by suggesting a minimal role for physiologic testosterone concentrations in regulating abdominal adiposity in non-obese, cycling premenopausal women.

Further contributing to the complexity of the relationship between sex steroids and regional adiposity is the intracrine conversion of steroid precursors to active hormones. Specifically, it is unclear whether circulating concentrations of hormones are comparable to tissue levels, and therefore whether they reflect end-organ exposure to androgens. In this study, we identified a negative relationship between the steroid precursor DHEA and visceral adiposity. DHEA and DHEA-S are inactive steroids which circulate in the highest concentrations of any steroid hormone [28] and are converted to active androgens and estrogens in peripheral target tissues, including adipose depots, depending on the local expression of steroidogenic enzymes [29,30]. In this context, whether the relationships we noted reflect the effects of estrogens or androgens is uncertain. Studies consistently demonstrate an inverse relationship between DHEA and total adiposity [31–33], but the relationship between body fat distribution and DHEA is less clear and may be confounded by the effects of aging on both DHEA levels and adiposity [30]. Our data agree with clinical trials showing that DHEA administration promotes the loss of visceral fat [12], although this result is controversial [34]. Considering the balance of evidence, our data suggest a favorable effect of circulating DHEA levels on visceral adiposity, possibly through the aforementioned androgenic effect on adipocyte physiology [27].

In summary, the association between circulating androgens and adiposity in women is complex. While the relationship of hyperandrogenemia to overall and regional adiposity in women is presumed based on data from PCOS, this interpretation should be made with caution [26]. Our current data suggest that, within the physiologic range, elevated testosterone levels in pre-menopausal women are associated with increased adiposity, but not with regional fat distribution. In fact, the androgen precursor DHEA was negatively related to visceral adiposity. The failure of testosterone and other androgens and their precursors to correlate to metabolic predictors of weight gain suggests that the relationship of testosterone to adiposity is unlikely explained by its effect to alter energy expenditure, fat oxidation or insulin sensitivity. Moreover, unlike post-menopausal women [1], androgens and their precursors did not correlate with other metabolic or physiologic outcomes. Further studies that manipulate circulating androgen levels and/or block their effects are needed to clarify the relationships observed in our study. Additionally, similar studies in post-menopausal women will be needed to discern why circulating androgens show unique, beneficial relationships to adiposity and metabolic parameters following ovarian senescence.

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