Adrenal Androgen Excess and Body Mass Index in Polycystic Ovary Syndrome

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Context: Adrenal hyperandrogenism affects approximately 25% of polycystic ovary syndrome (PCOS) patients but its relation to obesity is not totally understood.

Objective: This study aimed to assess dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) levels in relation to body mass index (BMI) in PCOS.

Design and Setting: This was a prospective observational study at an institutional practice at an obstetrics/gynecology hospital.

Participants: The study included 136 PCOS patients, 20–35 years old, and 42 age-matched control women. The participants were classified with the BMI cutoff value of 27 kg/m^2 as follows: 1) high-BMI PCOS patients; 2) low-BMI PCOS patients; 3) high-BMI control women; and 4) low-BMI control women. The data were reanalyzed with the BMI cutoff value of 30 kg/m^2 to corroborate the findings in obese and nonobese patients.

Main Outcome Measure(s): Blood samples were taken and LH, FSH, insulin, T, androstenedione (A4), DHEA, DHEAS, and glucose levels were determined. Homeostatic model assessment was calculated. Pelvic and abdominal ultrasound for ovarian morphology and adipose tissue, respectively, were performed.

Results: Obese PCOS patients presented significantly more insulin resistance than nonobese PCOS patients. The LH levels and LH/FSH ratio were significantly higher in low-BMI than in high-BMI PCOS patients. The A4 and DHEAS levels were significantly higher in nonobese than in obese PCOS patients. A significant correlation between LH and A4 in nonobese PCOS patients was observed. The frequency of hyperandrogenism by increased A4, and DHEA along with DHEAS was significantly higher in low-BMI PCOS patients compared with high-BMI PCOS patients. Some findings observed with the BMI cutoff value of 27 kg/m^2 changed with the cutoff value of 30 kg/m^2.

Conclusions: Low BMI more so than high BMI is associated with increased LH, high A4, DHEA, and DHEAS levels in PCOS patients. The BMI cutoff value of 27 kg/m^2 classified better than 30 kg/m^2 for hormonal and metabolic characteristics. **(*J Clin Endocrinol Metab* 100: 942–950, 2015)**

Polycystic ovary syndrome (PCOS) affects 4–8% of women of reproductive age (1–4), and is one of the most common endocrine disorders (4). In addition, PCOS is found in more than 80% of patients with hyperandrogenism, and obesity affects approximately 50–60% of PCOS patients (5).

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Abbreviations: A4, androstenedione; AE-PCOS, Androgen Excess and Polycystic Ovary Syndrome Society; BMI, body mass index; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; HOMA, homeostasis model assessment; PCOS, polycystic ovary syndrome.

In normal adult women, androstenedione (A4) is derived in roughly equal amounts from the ovaries and the adrenals; T is derived 25% from the ovaries, 25% from the adrenals, and 50% from peripheral conversion of A4, whereas dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are derived almost exclusively from the adrenals (6). The adrenals produce approximately 70% of DHEA and 98% of DHEAS (7).

It has been reported that the predominant source of androgen overproduction in hirsute women with PCOS is more from ovaries than adrenals (8, 9). High DHEAS levels are found in 22–25% of patients with PCOS (10). However, some studies have reported frequencies of DHEAS levels as high as 48–52% in PCOS (11). Another finding is that patients with high DHEAS levels are younger, thinner, and more hirsute than PCOS patients with normal DHEAS levels (10).

Hyperandrogenism is a criterion for the diagnosis of PCOS associated with ovarian dysfunction (12–14). The major pathophysiological components of PCOS are dissociation of gonadotropins and insulin resistance (15–17). It has been observed that nonobese PCOS patients have more dissociation of gonadotropins than obese PCOS patients (15), although other studies have not found these results (16–19). In contrast, obese PCOS patients present more insulin resistance than nonobese PCOS patients (15–17). With respect to hyperandrogenism, in some studies T levels have been found higher in obese PCOS patients than in nonobese PCOS patients (20–22); in contrast, A4 levels have been found to be higher in nonobese PCOS patients than in obese PCOS patients (22, 23).

The hypersecretion of DHEA and DHEAS is another pathophysiological component of PCOS not totally understood. The relationship of adrenal androgen excess and body mass index (BMI) is also poorly comprehended. The objective of the present study was to explore adrenal androgen excess in PCOS patients in relation to BMI, taking into account the hypothesis that PCOS is a complex disorder with genetic and environmental factors involved in its pathogenesis, in which obesity plays a fundamental role in metabolic and hormonal features.

Patients and Methods

Subjects

One-hundred thirty-six PCOS patients, 20–35 years old, were included in this study. In addition, 42 control women of similar age without PCOS or endocrine diseases such as diabetes, hypothyroidism, adrenal hyperplasia, and hyperprolactinemia were included. Women who did not agree to participate in the full protocol and pregnant women were excluded. This prospective observational study was approved by the Institutional Review Board of the hospital. Informed written consent was obtained from PCOS patients and control women.

Definition of variables

PCOS was defined according to the criteria of Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS): 1) hyperandrogenism: hirsutism and/or hyperandrogenemia; 2) ovarian dysfunction: oligo-anovulation and/or polycystic ovaries; and 3) exclusion of other androgen excess or related disorders (14). Patients with the following diseases were not included: hyperprolactinemia, diagnosed by the presence of prolactin values greater than 25 ng/mL; hypothyroidism, considered by finding the TSH greater than 5 μU/mL, and nonclassic adrenal hyperplasia, which was diagnosed in case of basal or ACTH-stimulated 17-hydroxyprogesterone greater than 10 ng/mL (4). All PCOS patients and control women underwent height and weight measurements. The BMI was calculated by dividing weight (kg) by squared height (m). Patients with PCOS or control women with a BMI lower than 30 kg/m^2 were considered as nonobese, and those with a BMI equal or higher than 30 kg/m^2 as obese (24). However, there is information considering that a BMI of 27 kg/m^2 detects the obesity better than a BMI of 30 kg/m^2 when compared with the World Health Organization reference standard of obesity as percent of body fat higher than 35% in women (25), we evaluated all the results in relation to both a BMI of 27 kg/m^2 and a BMI of 30 kg/m^2, to corroborate the results, and to be in accordance with the more universal reference values of obesity (24). A BMI less than 27 kg/m^2 was considered low BMI, and a BMI 27 kg/m^2 or greater was considered high BMI (25). All the results in which we used the term obesity in this study were found for both cutoff points of 27 kg/m^2 and 30 kg/m^2. When we found a result only with the cutoff value of 30 kg/m^2, we used the term obesity but we noted the issue. When we found a result only with the cutoff point of 27 kg/m^2, we used the terms high BMI or low BMI.

In the first analysis, in accordance with the BMI cutoff value of 27 kg/m^2, the participants were classified in four groups: 1) high-BMI PCOS patients (n = 100; BMI $\geq$27 kg/m^2); 2) low-BMI PCOS patients (n = 36; BMI $<$27 kg/m^2); 3) high-BMI control women (n = 16; BMI $\geq$27 kg/m^2); and 4) low-BMI control women (n = 26; BMI $<$27 kg/m^2). In the second analysis, taking into account the BMI cutoff value of 30 kg/m^2, the participants were classified in four groups: 1) obese PCOS patients (n = 69; BMI $\geq$30 kg/m^2); 2) nonobese PCOS patients (n = 67; BMI $<$30 kg/m^2); 3) obese control women (n = 9; BMI $\geq$30 kg/m^2); and 4) nonobese control women (n = 33; BMI $<$30 kg/m^2).

The date of onset and frequency of menses were determined via medical histories. Anovulation or oligo-anovulation was considered present when menstrual cycles were found to be less than 26 days or greater than 34 days (4, 5, 22). Clinical hyperandrogenism was determined by the presence of hirsutism, evaluated using a modification of the Ferriman-Gallwey method (26, 27). For the determination of biochemical hyperandrogenism, the mean + 3 SDs of each androgen of all the control group of this same study was taken as the cutoff value. These values were: 49.0 ng/dL for T, 5.6 ng/mL for A4, 18.4 ng/mL for DHEA, and 3.0 μg/mL for DHEAS.

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Table 1. Clinical and Anthropometrical Variables in PCOS Patients and Control Women According to BMI Cutoff Value of 27 kg/m^2

Characteristics	High BMI PCOS (n = 100)	Low BMI PCOS (n = 36)	High BMI Control (n = 16)	Low BMI Control (n = 26)
Age, y	27.7 ± 3.4	27.4 ± 4.1	29.3 ± 4.4	28.4 ± 3.9
Weight, kg	80.9 ± 11.3[a,b]	62.4 ± 6.2[a,c]	79.1 ± 15.6[c,d]	59.1 ± 5.6[b,d]
BMI, kg/m^2	32.8 ± 3.9[a,b]	25.2 ± 1.7[a,c]	32.1 ± 5.2[c,d]	24.0 ± 1.6[b,d]
Waist, cm	97.9 ± 8.8[a,b]	82.8 ± 7.5[a,c]	96.3 ± 13.6[c,d]	78.4 ± 5.8[b,d]
Hip, cm	111.5 ± 9.0[a,b]	97.1 ± 4.9[a,c]	111.5 ± 13.2[c,d]	95.7 ± 4.7[b,d]
WHR	0.88 ± 0.06[a]	0.85 ± 0.09	0.86 ± 0.06	0.82 ± 0.05[a]
Subcutaneous adipose tissue, mm	47.5 ± 12.5[a,b]	36.3 ± 7.8[a]	46.8 ± 17.5[c]	28.6 ± 8.4[b,c]
Visceral adipose tissue, mm	48.3 ± 15.4[a,b]	34.9 ± 13.1[a]	40.9 ± 10.6	34.1 ± 10.7[b]

Abbreviation: WHR, waist-to-hip ratio.

Data express mean ± SD.

[a,b,c,d] Similar superscripts indicate a statistically significant difference ($P < .05$).

Hormonal and metabolic determinations

Samples were taken in the early follicular phase (days 3–5) in women with regular menstrual cycles or oligomenorrhea and on any other day in patients with amenorrhea.

Hormonal determinations were performed in duplicate according to previously published methodology (4). The levels of prolactin, insulin, FSH, LH, TSH, 17-hydroxyprogesterone, T, and A4 were determined by RIA with commercial kits (Diagnostic Products Corporation). Also, DHEA and DHEAS were determined by RIA with commercial kits (Diagnostic Systems Laboratories). Inter- and intra-assay coefficients of variation for each analysis were less than 9%. Glucose concentration was determined by the glucose oxidase method (Stanbio Laboratory), using a Gilford Express 550 machine (Ciba Corning Diagnostics). The patients underwent hormonal and metabolic measures and the homeostasis model assessment (HOMA) was calculated (28).

Ultrasound

Pelvic ultrasounds were performed on each patient to observe ovarian morphology and abdominal ultrasound to determine thickness of sc and visceral adipose tissue. The pelvic ultrasounds were performed by a 5-MHz transducer through the vagina in the early follicular phase (days 3–8) in women with regular menstrual cycles or in patients with oligomenorrhea, and on any given day in patients with amenorrhea (22). Both ovaries were evaluated morphologically for polycystic ovaries by the presence of 12 or more follicles of 2–9 mm in diameter in each ovary (29). The abdominal ultrasounds were carried out by a 3.5-MHz linear transducer. The sc adipose thickness was measured on the midline and 5 cm above the navel between the skin and the anterior aponeurosis of rectus abdominis muscle, and visceral thickness was determined by the distance from the posterior aponeurosis of rectus abdominis to the anterior wall of the abdominal aorta (29, 30).

Statistical analysis

The PCOS patients and control women were classified in four groups in two different statistical analyses, with the BMI cutoff value of 27 kg/m^2 and also considering the BMI cutoff value of 30 kg/m^2. Clinical and anthropometric variables were analyzed using one-way ANOVA. Nonnormally distributed data were transformed prior to ANOVA analysis by reciprocal transformation. Nontransformed data were reported to facilitate interpretation and comparisons with previously published data; therefore, these variables were expressed as means ± SD. Hormonal measurements were expressed as medians and ranges (minimum and maximum). All these hormonal data were nonparametric; thus, ANOVA on ranks (Kruskal-Wallis method) was performed using Dunn's method for post-hoc correction. Frequencies are reported as percentages. Comparison of the proportions of patients with hyperandrogenism among the study groups was performed by Fisher's exact test. Pair-wise correlation of the hormonal and anthropometric variables was performed by the Pearson correlation coefficient. $P < .05$ was considered statistically significant.

Results

Clinical and anthropometric variables

The data for clinical and anthropometric variables are shown in Table 1 for the cutoff value of 27 kg/m^2 and in Table 2 for the cutoff value of 30 kg/m^2. Age was similar in the four groups of PCOS patients and control women.

As expected, because of the design of the groups classification, weight and BMI were significantly higher ($P < .05$) in obese groups compared with nonobese groups. The waist and hip circumferences separately were significantly higher ($P < .05$) in obese groups than in nonobese groups. However, the waist-to-hip ratio was significantly higher ($P < .05$) only in the group of obese PCOS patients compared with the group of nonobese control women. The sc and visceral adipose tissue was significantly higher ($P < .05$) in the group of obese PCOS patients than in nonobese groups. Other anthropometrical differences corresponding to only one of the BMI cutoff values are shown in Tables 1 and 2.

Typical morphology of polycystic ovaries was found in 71% of high-BMI PCOS patients and 58.3% of low-BMI PCOS patients; alternatively, it was observed in 75.4% of obese PCOS patients and 59.7% of nonobese PCOS pa-

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Table 2. Clinical and Anthropometrical Variables in PCOS Patients and Control Women According to BMI Cutoff Value of 30 kg/m^2

Characteristics	Obese PCOS (n = 69)	Nonobese PCOS (n = 67)	Obese Control (n = 9)	Nonobese Control (n = 33)
Age, y	27.6 ± 3.4	27.6 ± 3.7	29.4 ± 4.4	28.5 ± 4.0
Weight, kg	85.0 ± 10.6[a,b]	66.8 ± 7.9[a,c,d]	88.2 ± 14.8[c,e]	60.8 ± 6.5[b,d,e]
BMI, kg/m^2	34.6 ± 3.4[a,b]	27.0 ± 2.3[a,c,d]	35.3 ± 4.8[c,e]	24.9 ± 2.2[b,d,e]
Waist, cm	100.7 ± 8.0[a,b]	86.8 ± 8.4[a,c,d]	104.6 ± 12.3[c,e]	80.0 ± 6.3[b,d,e]
Hip, cm	114.7 ± 8.6[a,b]	100.5 ± 6.2[a,c]	117.7 ± 14.5[c,d]	97.4 ± 5.7[b,d]
WHR	0.88 ± 0.06[a]	0.86 ± 0.08[b]	0.89 ± 0.06[c]	0.82 ± 0.05[a,b,c]
Subcutaneous adipose tissue, mm	50.1 ± 12.8[a,b]	38.7 ± 8.9[a,c]	51.7 ± 16.4	31.0 ± 11.8[b,c]
Visceral adipose tissue, mm	50.3 ± 16.4[a,b]	39.0 ± 13.2[a]	47.7 ± 9.4	33.8 ± 9.6[b]

Abbreviation: WHR, waist-to-hip ratio.

Data express mean ± SD.

[a,b,c,d] Similar superscripts indicate a statistically significant difference ($P < .05$).

tients (not significantly different for any comparison). None of the control women had characteristic morphology of polycystic ovaries.

Glucose, insulin, and HOMA

Data for the hormonal and metabolic variables are shown in Table 3 for the cutoff value of 27 kg/m^2 and in Table 4 for the cutoff value of 30 kg/m^2. The serum glucose values of the group of obese PCOS patients were significantly higher ($P < .05$) compared with that of nonobese PCOS patients and nonobese control women. Glucose values of nonobese PCOS patients were significantly higher ($P < .05$) than those of nonobese control women. In addition, serum glucose values of the high-BMI control women were significantly higher ($P < .05$) than those of low-BMI control women.

The values of insulin and HOMA of the group of obese PCOS patients were significantly higher ($P < .05$) than those of the other groups. In contrast, insulin and HOMA values of nonobese PCOS patients were significantly higher ($P < .05$) than those of nonobese control women. Also, values of HOMA and insulin levels of high-BMI control women were significantly higher ($P < .05$) than those of low-BMI control women.

Gonadotropins

LH levels and LH/FSH ratio were significantly higher ($P < .05$) in PCOS groups than in control women groups. However, the group of low-BMI PCOS patients compared with that of high-BMI PCOS patients presented LH levels and LH/FSH ratio significantly higher ($P < .05$). FSH values did not show significant differences between the groups.

Androgens

The T levels were significantly higher ($P < .05$) in groups of PCOS patients than in control groups. However, there was no difference in the values of T between obese and nonobese PCOS patients.

Table 3. Metabolic and Hormonal Variables in PCOS Patients and Control Women According to BMI Cutoff Value of 27 kg/m^2

Analyte/Hormone/ Hormonal Ratio	High BMI PCOS (n = 100)	Low BMI PCOS (n = 36)	High BMI Control (n = 16)	Low BMI Control (n = 26)
Glucose, mg/dL	91 (57–115)[a,b]	87 (61–100)[a,c]	89.5 (71–119)[d]	81 (62–99)[b,c,d]
Insulin, μU/mL	18.6 (4.5–131.3)[a,b,c]	13.1 (3.0–34.9)[a,d]	9.7 (3.3–25.2)[b,e]	5.1 (0.5–30.0)[c,d,e]
HOMA	4.0 (0.9–28.6)[a,b,c]	2.8 (0.5–7.3)[a,d]	2.1 (0.7–6.4)[b,e]	1.1 (0.1–6.0)[c,d,e]
LH, U/L	4.4 (0.1–14.4)[a,b,c]	6.5 (0.4–26.5)[a,d,e]	1.5 (0.3–5.9)[b,d]	2.1 (0.1–5.4)[c,e]
FSH, U/L	5.0 (1.3–12.5)	5.4 (1.0–11.0)	5.5 (4.2–8.0)	5.4 (2.6–17.0)
LH/FSH	0.84 (0.02–3.02)[a,b,c]	1.01 (0.18–4.80)[a,d,e]	0.27 (0.06–0.91)[b,d]	0.29 (0.02–1.17)[c,e]
T, ng/dL	45.2 (4.2–195.4)[a,b]	46.7 (11.8–139.4)[c,d]	11.3 (5.3–36.5)[a,c]	14.8 (1.0–39.6)[b,d]
A4, ng/mL	3.5 (1.0–7.4)[a,b]	4.7 (1.5–9.9)[a,c,d]	3.4 (2.0–4.9)[c]	3.1 (1.3–4.9)[b,d]
T/A4	0.12 (0.02–0.45)[a,b,c]	0.11 (0.03–0.24)[a,d,e]	0.04 (0.02–0.14)[b,d]	0.05 (0.01–0.20)[c,e]
DHEA, ng/mL	11.6 (2.2–33.6)[a,b]	11.7 (4.1–45.7)[c,d]	8.4 (4.3–17.9)[a,c]	8.4 (2.4–16.8)[b,d]
DHEAS, μg/mL	1.6 (0.1–4.0)[a,b]	1.7 (0.5–6.8)[c,d]	1.1 (0.4–2.3)[a,c]	1.3 (0.3–2.6)[b,d]
A4/DHEA	0.30 (0.06–1.72)	0.38 (0.06–0.88)	0.40 (0.11–0.85)	0.34 (0.17–0.53)

Data express median and range (in parenthesis).

[a,b,c,d,e] Similar superscripts indicate a statistically significant difference ($P < .05$).

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Table 4. Metabolic and Hormonal Variables in PCOS Patients and Control Women According to BMI Cutoff Value of 30 kg/m^2

Analyte/Hormone Hormonal Ratio	Obese PCOS (n = 69)	Nonobese PCOS (n = 67)	Obese Control (n = 9)	Nonobese Control (n = 33)
Glucose, mg/dL	92 (57–115)[a,b]	88 (61–110)[a,c]	89 (71–97)	85 (62–119)[b,c]
Insulin, μU/mL	19.6 (4.5–131.3)[a,b,c]	13.8 (3.0–36.3)[a,d]	10.5 (3.3–23.7)[b]	6.1 (0.5–30.0)[c,d]
HOMA	4.3 (1.1–28.5)[a,b,c]	3.0 (0.5–8.8)[a,d]	2.2 (0.7–5.0)[b]	1.2 (0.1–6.3)[c,d]
LH, U/L	4.7 (0.1–14.4)[a,b]	5.2 (0.4–26.5)[c,d]	1.5 (0.3–5.9)[a,c]	1.6 (0.1–5.4)[b,d]
FSH, U/L	5.0 (1.3–9.6)	5.3 (1.0–12.5)	5.8 (4.2–7.3)	5.3 (2.6–17.0)
LH/FSH	0.85 (0.02–3.02)[a,b]	0.90 (0.20–4.80)[c,d]	0.30 (0.1–0.90)[a,c]	0.27 (0.02–1.20)[b,d]
T, ng/dL	47.2 (8.2–195.4)[a,b]	44.1 (4.2–139.4)[c,d]	13.6 (7.1–36.5)[a,c]	12.6 (1.0–39.6)[b,d]
A4, ng/mL	3.3 (1.0–7.4)[a]	4.1 (1.5–9.9)[a,b]	3.3 (2.0–4.9)	3.2 (1.3–4.9)[b]
T/A4	0.12 (0.02–0.45)[a,b,c]	0.11 (0.01–0.29)[a,d,e]	0.04 (0.02–0.09)[b,d]	0.04 (0.01–0.20)[c,e]
DHEA, ng/mL	11.3 (2.2–33.6)[a]	11.7 (4.1–45.7)[b,c]	8.1 (4.3–17.9)[b]	8.4 (2.4–16.8)[a,c]
DHEAS, μg/mL	1.5 (0.1–4.0)[a]	1.7 (0.5–6.8)[a,b]	1.3 (0.3–2.3)	1.2 (0.3–2.6)[b]
A4/DHEA	0.30 (0.06–1.72)	0.38 (0.06–0.88)	0.40 (0.11–0.85)	0.34 (0.17–0.53)

Data express median and range (in parenthesis).

[a,b,c,d,e] Similar superscripts indicate a statistically significant difference ($P < .05$).

The A4 levels were significantly higher ($P < .05$) in the group of nonobese PCOS patients than in the group of obese PCOS patients. The A4 levels of nonobese PCOS patients were significantly higher ($P < .05$) than those of nonobese control group. In addition, A4 levels in high-BMI PCOS patients were significant higher ($P < .05$) compared with low-BMI control women; also A4 levels in low-BMI PCOS patients were significant higher ($P < .05$) than in high-BMI control women.

The T/A4 ratio was significantly higher ($P < .05$) in the group of obese PCOS patients than in that of nonobese PCOS patients and obese and nonobese control women. In addition, the T/A4 ratio was significantly higher ($P < .05$) in the group of nonobese PCOS patients than in groups of obese and nonobese control women.

The DHEA levels were significantly higher ($P < .05$) in the group of nonobese PCOS patients than in control groups. The DHEA levels of obese PCOS patients were significantly higher ($P < .05$) than those of nonobese control women. Also, the DHEA levels of high-BMI PCOS patients were significantly higher than those of high-BMI controls. There were no significant differences in the A4/DHEA ratio among all groups.

DHEAS levels were significantly higher ($P < .05$) in nonobese PCOS patients than in obese PCOS patients (with the BMI of 30 kg/m^2). The DHEAS levels of the group of nonobese PCOS patients were significantly higher ($P < .05$) than those of nonobese control women. In addition, DHEAS levels of high-BMI PCOS patients were significantly higher than those of high-BMI control group; and DHEAS levels of low-BMI PCOS patients were significantly higher compared with high-BMI controls.

Distribution of hyperandrogenism according to obesity

The analysis of the proportion of hyperandrogenism in PCOS patients revealed that hyperandrogenism by T was not significantly different in nonobese and obese PCOS patients. However, there was a significantly higher ($P < .01$) percentage of hyperandrogenism by A4 in low-BMI PCOS patients compared with high-BMI PCOS patients (25.0% vs 8.0%). There was not a significant difference between the percentages of patients with hyperandrogenism by DHEA and DHEAS separately between nonobese and obese PCOS patients. However, the hyperandrogenism by higher concentrations of DHEA along with DHEAS was observed to be significantly higher ($P = .04$) in the group of low-BMI PCOS patients than in high-BMI PCOS patients (13.9% vs 3.0%, respectively), with the BMI cutoff value of 27 kg/m^2. This significant difference was not found with the BMI cutoff value of 30 kg/m^2 (Figure 1).

Hormonal and metabolic correlations

For both BMI cutoff values, 27 and 30 kg/m^2, there was a significant positive correlation ($r = 0.33$, $P < .002$ and $r = 0.35$, $P < .002$, respectively) between LH and A4 levels in nonobese PCOS patients; however, no significant correlations were found between LH and A4 levels in obese PCOS patients, or in obese and nonobese control groups.

No significant correlations were found between DHEA and DHEAS levels with metabolic variables such as glucose levels, HOMA, anthropometric variables such as BMI, waist-to-hip ratio, or thickness of adipose tissue. The coefficients of correlations of DHEA and DHEAS with hormonal variables are listed in Table 5.

A significant positive correlation was found between DHEA and A4 levels in obese and nonobese PCOS patients, as well as in nonobese control women. Similarly, the levels of DHEA and DHEAS correlated positively in obese and nonobese PCOS patients, as well as in nonobese control women.

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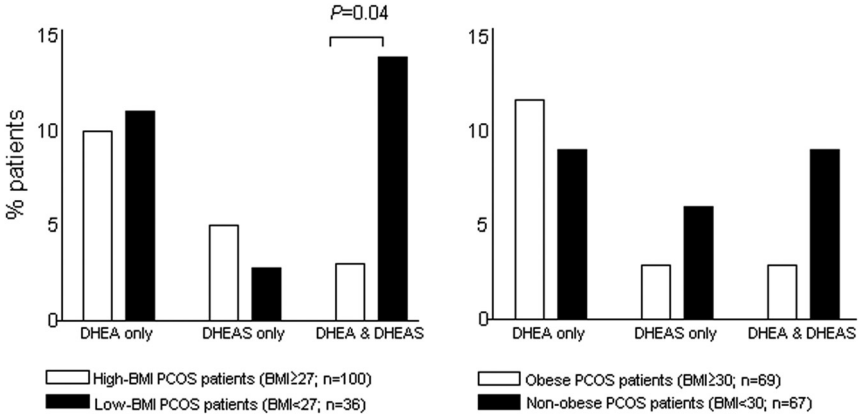

Figure 1. Comparison of the percentages of patients with hyperandrogenism by DHEA only, DHEAS only, as well as DHEA along with DHEAS in the groups of high-BMI and low-BMI PCOS patients (left panel), classified by the BMI cutoff value of 27 kg/m^2, and in the groups of obese and nonobese PCOS patients (right panel), classified by the BMI cutoff value of 30 kg/m^2. It is observed a significantly higher percentage ($P = .04$) of hyperandrogenism by DHEA and DHEAS together in the group of low-BMI PCOS patients compared with that of high-BMI PCOS patients. This significant difference is not observed between the groups when classified as nonobese and obese PCOS patients.

In addition, a significant positive correlation was found between DHEAS and T levels in obese PCOS patients. Also, a positive correlation was found between DHEAS and A4 levels in obese and nonobese PCOS patients, as well as in nonobese control women. Finally, the levels of DHEAS showed a significant negative correlation with the A4/DHEA ratio in obese and nonobese PCOS patients, as well as nonobese control women.

Discussion

This study found that patients with PCOS have metabolic and hormonal differences in relation to body mass; these findings suggest an important role for obesity in pathogenesis and clinical presentation of PCOS. It was observed that obese PCOS patients have more insulin resistance evidenced by the HOMA index than nonobese PCOS patients, as previously reported (15–17). In contrast, PCOS patients with low BMI (<27 kg/m^2) presented increased gonadotropic dysfunction, evidenced by more circulating LH levels and increased dissociation of LH/FSH than PCOS patients with high BMI (≥27 kg/m^2), a finding that has been found in some (15) but not other previous studies (16–19). This finding may be complemented by the correlation between LH and A4 in nonobese PCOS patients. This study also found that some circulating androgens may be influenced by body mass.

In the present study we found no significant differences in the concentration of T among obese and nonobese PCOS patients. There are studies where basal T levels are found higher in obese than in nonobese PCOS patients (20–22) and other reports where the production of T is similar between obese and nonobese PCOS patients (15, 18, 19). However, the basal A4 levels were found to be higher in nonobese than in obese PCOS patients, as reported in some studies (22, 23). In fact, the A4 levels were higher in nonobese PCOS patients than in any other group. Moreover, the frequency of hyperandrogenism by

Table 5. Correlation of DHEA and DHEAS with Hormonal Variables in PCOS Patients and Controls According to BMI Cutoff Value of 27 and 30 kg/m^2

	PCOS BMI				Control BMI			
Hormone, Variable	≥27 kg/m^2 (n = 100)	≥30 kg/m^2 (n = 69)	<27 kg/m^2 (n = 36)	<30 kg/m^2 (n = 67)	≥27 kg/m^2 (n = 16)	≥30 kg/m^2 (n = 9)	<27 kg/m^2 (n = 26)	<30 kg/m^2 (n = 33)
DHEA, Insulin	−0.14	−0.18	0.16	0.13	−0.47	−0.63[a]	0.09	0.03
DHEA, LH	0.18	0.18	0.23	0.25[a]	0.31	0.36	0.01	0.04
DHEA, FSH	0.15	0.23[a]	−0.11	−0.08	0.04	0.24	−0.23	−0.23
DHEA, T	0.19	0.18	0.28	0.25[a]	0.26	0.09	0.40[a]	0.44[b]
DHEA, A4	0.39[b]	0.40[b]	0.35[a]	0.37[b]	−0.32	−0.50	0.56[b]	0.52[b]
DHEA, DHEAS	0.68[b]	0.72[b]	0.84[b]	0.80[b]	0.47[a]	0.54	0.67[b]	0.61[b]
DHEA, LH/FSH	0.08	0.06	0.26	0.28[a]	0.32	0.32	0.16	0.18
DHEA, T/A4	0.01	0.01	0.10	0.10	0.39	0.40	−0.02	0.05
DHEAS, Insulin	−0.18	−0.19	0.18	0.11	−0.27	−0.56	−0.04	0.07
DHEAS, LH	0.04	−0.02	0.06	0.11	0.07	−0.13	−0.27	−0.13
DHEAS, FSH	0.04	0.04	0.07	0.04	0.03	0.04	−0.16	−0.14
DHEAS, T	0.23[a]	0.22[a]	0.38[a]	0.34	0.20	0.35	0.19	0.16
DHEAS, A4	0.50[b]	0.46[b]	0.47[b]	0.50[b]	0.36	0.33	0.40[a]	0.38[a]
DHEAS, LH/FSH	−0.02	−0.07	0.01	0.07	0.07	−0.14	−0.11	−0.01
DHEAS, T/A4	−0.08	−0.06	0.05	0.01	−0.03	0.09	−0.11	−0.11
DHEAS, A4/DHEA	−0.32[b]	−0.37[b]	−0.40[b]	−0.31[b]	−0.35	−0.48	−0.35[a]	−0.30[a]

Data express the value of Pearson coefficient of correlation.

[a] Similar superscripts indicate a statistically significant difference, $P < .05$.

[b] Similar superscripts indicate a statistically significant difference, $P < .01$.

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A4 was greater in low-BMI than in high-BMI PCOS patients. In contrast, other studies have found similar A4 levels in obese and nonobese PCOS patients (15, 18, 20). The differences in comparisons of androgen levels between obese and nonobese PCOS patients can be explained by varying inclusion criteria for PCOS, different BMI cutoff points for obesity, variable sensitivity of the methodology for androgen measurement, as well as by heterogeneous ethnic/race characteristics.

It is interesting that DHEAS levels were significantly higher in nonobese PCOS patients than in obese PCOS patients with the BMI cutoff value of of 30 kg/m^2. Although frequency of increased DHEA and DHEAS separately were not significantly different between obese and nonobese PCOS patients, the frequency of hyperandrogenism by DHEA along with DHEAS was found to be higher in low-BMI PCOS patients than in high-BMI PCOS patients. In this regard, this article is conceptually consistent with a previous study (10), which found that patients with hyperandrogenism and higher DHEAS levels showed less BMI than those with normal DHEAS levels.

To date it is unknown why some data reveal higher adrenal androgen excess in nonobese PCOS. Some previous studies have found that production of these androgens was inversely related to the degree of insulin resistance (31, 32). However, this study did not find any correlation between the DHEA or DHEAS levels and insulin levels or HOMA. Although some findings were found with different BMI cutoff values in this study, it is likely that low adiposity in PCOS patients is associated with increased LH levels, high A4 and DHEAS levels.

The relationship between ovarian and adrenal production of DHEA and DHEAS in PCOS is controversial and not well understood (33). The administration of GnRH agonist to PCOS patients with adrenal androgen excess suppressed A4 and T and produced a partial decrease of DHEAS levels, showing that ovarian steroids promoted adrenal androgen excess; however, there was a maximal ACTH-stimulated incremental increase of DHEA and DHEAS during GnRH agonist administration, indicating an unaltered adrenal androgen capacity (34). In PCOS patients with adrenal androgen excess treated with long-term GnRH analogs, A4 and DHEA responsiveness to CRH was suppressed; however, it was restored by estradiol (35). PCOS patients with adrenal androgen excess presented greater A4 levels than PCOS patients without it under ACTH stimulation (36). Finally, PCOS patients with characteristic morphology of polycystic ovaries tended to have higher concentrations of DHEAS than PCOS patients with normal ovarian morphology (29).

The production of DHEA and DHEAS and the relationship between the ovarian and adrenal secretion has been evaluated in other clinical situations (eg, women with oophorectomy or premature ovarian failure). Exogenous T administration produced a decrease in DHEA and an increase of DHEAS in women with oophorectomy (37). In women with premature ovarian failure and hypoestrogenemia, the DHEAS concentrations have been found to be decreased (38). However, in another study, the consecutive dexamethasone inhibition and ACTH stimulation produced lower A4 and T levels but similar DHEA levels in women with premature ovarian failure in comparison with controls with normal ovarian function (39).

One limitation of this study is the use of AE-PCOS criteria instead of Rotterdam criteria for PCOS diagnosis. The Rotterdam criteria generate different phenotypes in PCOS with the inclusion of the "two out of three criteria for PCOS diagnosis: oligo-anovulation, hiperandrogenism, and polycystic ovaries." The difficulty of using those criteria (13) is they include the phenotype of oligo-anovulation and polycystic ovarian morphology without hyperandrogenism, which some studies considered to be a different disorder with another pathogenesis pathway (40). In the present study, which focuses in women with hyperandrogenism, we considered it pertinent to work with the AE-PCOS criteria, which establish that PCOS should be considered as a predominantly hyperandrogenic disorder (14). In addition, all the phenotypes of AE-PCOS are included in those of Rotterdam consensus. In contrast, not all the phenotypes of Rotterdam consensus are included in those of AE-PCOS criteria. So, we consider that the scientific findings of clinical studies performed with AE-PCOS criteria can be extrapolated with pertinent explanations to studies with Rotterdam consensus criteria, but the opposite is not reasonably possible.

An additional limitation of this study, but under controversy, is the point concerning the selection of the best BMI cutoff value to define obesity. We solved this problem doing the data analysis with both BMI cutoff values. The fact that some findings observed with the BMI cutoff value of 27 kg/m^2 changed with the BMI cutoff value of 30 kg/m^2, in PCOS patients and control women, can be another clue to support 27 kg/m^2 as a better tool to detect obesity, at least in some populations (25).

Another limitation of this study is it did not use methodology aimed at clarifying the differentiation of ovarian or adrenal source of DHEA and DHEAS hyperandrogenism. However, the main objective of this study was not to determine the origin of ovarian or adrenal hyperandrogenism, but rather the relationship of hyperandrogenism by DHEA and DHEAS levels with body mass in PCOS.

In conclusion, higher A4 levels were found in nonobese PCOS patients than in obese PCOS patients, as well as a significant correlation between LH and A4 in nonobese

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PCOS patients, but not in obese PCOS patients. In addition, it was observed significantly higher DHEAS levels in nonobese PCOS patients than in obese PCOS patients and a greater proportion of hyperandrogenism by A4, DHEA along with DHEAS in low-BMI PCOS patients compared with high-BMI PCOS patients. These finding may point in the direction that there might be different pathways involved in the pathogenesis of PCOS. It is likely that the production of DHEA and DHEAS in PCOS patients is related to that of A4 of adrenal or ovarian origin in nonobese patients. More studies are needed to determine the etiology of adrenal androgen excess.

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