Basal metabolic rate is decreased in women with polycystic ovary syndrome and biochemical hyperandrogenemia and is associated with insulin resistance

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Objective: To evaluate basal metabolic rate (BMR) in women with PCOS and to determine its association with insulin resistance (IR).
Design: Prospective assessment of BMR in women with PCOS.
Setting: Outpatient clinic of the Division of Reproductive Endocrinology.
Patient(s): The study included 91 Greek women with PCOS and biochemical hyperandrogenemia, with mean age 24.03 ± 0.55 years and mean body mass index (BMI) 26.67 ± 0.69 kg/m^2, and 48 matched regularly menstruating women, with mean age 26.33 ± 0.93 years and mean BMI 23.35 ± 0.85 kg/m^2, as control subjects.
Intervention(s): Assessment of BMR by indirect calorimetry, IR by HOMA and QUICKI indices, fasting insulin, and fasting glucose/insulin ratio.
Main Outcome Measure(s): Reduced BMR in PCOS with or without IR.
Result(s): Adjusted BMR was 1,868 ± 41 kcal/day in the control group, 1,445.57 ± 76 in all PCOS women, 1,590 ± 130 in PCOS women without IR and 1,116 ± 106 in PCOS women with IR. Adjusted BMR showed a statistically significant difference between women with PCOS and control subjects, with lowest values in the group of PCOS women with IR, even after adjusting all groups for age and BMI.
Conclusion(s): Women with PCOS, particularly those with IR, present a significantly decreased BMR. (Fertil Steril® 2009;92:250–5. ©2009 by American Society for Reproductive Medicine.)

Key Words: PCOS, insulin resistance, basal metabolic rate, BMR

Polycystic ovary syndrome (PCOS) is the leading cause of anovulatory infertility in women (1). It is characterized by hirsutism, anovulation, and hyperandrogenemia and is highly associated with obesity and insulin resistance (IR) (2). Insulin resistance plays a significant role as both a cause and as a result of the syndrome (3); altering lifestyle or pharmacologic intervention has been shown to improve hyperandrogenism and infertility and reduce cardiovascular risk (4). A reduction of insulin sensitivity has been shown in lean PCOS patients compared with lean control subjects (5). Insulin, androgens, and body mass index (BMI) are in correlation in women both with and without PCOS (3). Phenotypic expression varies from hyperinsulinemic and nonhyperandrogenic obesity to nonhyperinsulinemic obese PCOS. Women with PCOS have a 35%–40% decrease in insulin sensitivity, similar to that seen in type 2 diabetes mellitus (6). Approximately, 50%–70% of obese women present various degrees of IR (7). Insulin resistance affects over 25% of the general population and depends upon the degree of obesity (7).

Basic metabolic rate (BMR) is the energy expenditure of a healthy subject at rest and at least 12 h after eating in a thermally neutral environment. It represents 50%–70% of total daily energy expenditure (8) Basic metabolic rate is associated with lean body mass, gender, age, and climate.

Many studies have been conducted on BMR in obesity, presuming that low energy expenditure could play a role in the energy imbalance that characterizes obesity. The reported values of BMR in obesity, when expressed in relationship to lean body mass or to the body surface area, are usually within normal range (9, 10). In other studies, BMR has been associated with obesity (11), but BMR appears to be linked to morbid rather than to moderate obesity (12). A low BMR is considered to be a factor predisposing to obesity, as was shown in a Finnish study (13), and PCOS is characterized by an increased BMI, although not all PCOS women are obese.

Low BMR might be a predisposing factor for obesity and increased IR in women with PCOS. Therefore, the aim of

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the present study was to evaluate BMR in women with PCOS and biochemical hyperandrogenemia and to determine its association with IR.

SUBJECTS AND METHODS

Subjects

The study included 91 Greek women with PCOS, with a mean age of 24.03 ± 0.55 years and a mean BMI of 26.67 ± 0.69 kg/m^2, and 48 age- and BMI-matched regularly menstruating women, with a mean age of 26.33 ± 0.93 years and a mean BMI 23.35 ± 0.85 kg/m^2, as control subjects. Institutional Review Board approval was obtained by the University Hospital Ethical Committee.

The diagnosis of PCOS was based on the presence of biochemical hyperandrogenism and chronic anovulation (14) and polycystic ovarian morphology on ultrasound (14), thus meeting the criteria of the experts meeting in Rotterdam in 2003, sponsored by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (14). Biochemical hyperandrogenism was defined as an increased serum T and/or an increased free androgen index (FAI). We considered a woman to have hyperandrogenemia when she had serum T levels and/or serum FAI higher than 2 standard deviations above the mean levels of a normal control population.

Exclusion criteria were congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing syndrome. All subjects had normal thyroid, kidney, and liver function, and none had excessive alcohol intake (<28 g/day). None were taking drugs known to affect BMR, blood pressure, or glucose metabolism. All physical and biochemical data were obtained in the morning after a 12-h fast using standardized methods. Physical measurements included weight, height, fat-free mass, fat mass, systolic and diastolic blood pressure, and resting heart rate.

Biochemical parameters included serum T, free T, androstenedione, total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and glucose levels.

A standard oral glucose tolerance test (OGTT) with 75 g glucose was carried out. Insulin resistance was assessed by determining fasting insulin levels, fasting glucose levels, the fasting glucose/insulin ratio, the homeostasis model assessment (HOMA), the quantitative insulin sensitivity check index (QUICKI), and the area under the curve (AUC) for the OGTT-derived insulin and glucose values.

METHODS

Body composition was determined by bioelectric impedance (BC-418 Body Composition Analyzer; Tanita, Middlesex, U.K.). The BMR was measured by indirect calorimetry (Pulmolab EX505; Morgan Medical, Kent, U.K.) as previously described by Ferrannini (15) and expressed as kcal/day. Each subject's BMR was adjusted for fat-free mass, fat mass (calculated by Hume's formula) (16), gender, and age as previously described (15), using the equation:

$$\text{adjusted BMR} = (\text{group mean BMR}) + (\text{measured BMR} - \text{predicted BMR})$$

For each subject the predicted BMR was obtained by substituting the individual lean body mass, fat mass, gender, and age in the linear regression equation generated by the data of all patients. The study complied with the principles of the Helsinki Declaration; all subjects gave their informed consent.

Insulin Resistance was assessed by HOMA and QUICKI, the fasting serum insulin, and the fasting serum glucose/insulin ratio.

Calculation of HOMA and QUICKI was made according to the following formulas:

$$\text{HOMA} = 22.5 \times 18/\text{fasting insulin} \times \text{fasting glucose}\ (17, 18)$$

$$\text{QUICKI} = 1/\log(\text{fasting insulin}) + \log(\text{fasting glucose})(18)$$

The AUC for insulin and glucose values derived from the OGTT were calculated based on Tai's mathematical model (19):

Impaired glucose tolerance (IGT) was indicated by glucose levels between 140 and 200 mg/dL 2 h after an oral 75 g glucose load (OGTT).

All assays for hormonal determinations were performed by electrochemiluminescence quantitation (Elecsys 2010; Roche Diagnostics, Laval, Quebec) with the exception of serum androstenedione and 17OH-progesterone, which were determined by radioimmunoassay using commercially available kits (B-1400; BioSource, Nivelles, Belgium). Serum lipids were determined by an automatic biochemical analyzer (Medicon, Olympus, Greece).

Ovarian morphology was assessed using a 5-MHz linear-array transvaginal transducer in days 2–4 of the menstrual cycle.

Statistics

The Pearson product-moment correlation coefficient, with two-tailed test of significance, was used to assess all studied relationships. The independent-sample *t* test, with two-tailed test of statistical significance, and the Levene test for equality of variances were used to assess the power of all relationships within the groups of women with PCOS with or without IR and the control group. Correlations with a critical value of $P<.05$ were considered to be significant. All statistical procedures were performed using SPSS 15.0 for Windows (SPSS, Chicago, IL).

RESULTS

The general characteristics of PCOS patients are shown in Table 1.

In the control group (n = 48), the adjusted BMR was 1,841.05 ± 44 kcal/day and BMI was 23.35 ± 0.85 kg/m^2, whereas in PCOS women (n = 91) the adjusted BMR was 1,445.57 ± 76 kcal/day and BMI was 26.67 ± 0.69 kg/m^2. The adjusted BMR was significantly lower in PCOS women compared with the control group ($P<.001$).

The BMI was correlated to all parameters of IR. More specifically, it was positively correlated to fasting insulin ($P<.001$), AUC-glucose ($P<.001$) and AUC-insulin ($P<.001$); it was negatively correlated to fasting glucose/insulin ratio ($P=.004$), HOMA ($P<.001$), and QUICKI ($P<.001$). In addition, BMI presented a positive correlation with triglycerides ($P=.014$) and a negative correlation with HDL ($P<.001$). The AUC-insulin and AUC-glucose showed correlation with all indices of IR. Additionally, the AUC-glucose was correlated with LDL and cholesterol ($P<.01$), and the AUC-insulin with triglycerides ($P<.01$).

Serum T was positively correlated to fasting glucose/insulin ratio ($P<.001$), HOMA ($P<.001$), and QUICKI ($P=.007$).

Impaired glucose tolerance was noted in 7 out of 110 women with PCOS (6.36%).

Subsequently, we divided all PCOS women according to IR indices into two subgroups: those with IR (PCOS-IR; n = 25; fasting insulin >12 mU/mL, Glu/Ins <6.4, HOMA <47, QUICKI <0.333), and those without IR (PCOS-NIR;

TABLE 1

General characteristics of all of the women with PCOS (PCOS-Total), PCOS women without IR (PCOS-NIR), and PCOS women with IR (PCOS-IR) (mean ± SEM).

	PCOS-Total	PCOS-NIR	PCOS-IR	*P* value[a]
Age (yrs)	23.85 ± 0.46 n = 123	23.56 ± 0.68 n = 59	23.97 ± 1.03 n = 31	.733
BMI (kg/m^2)	26.74 ± 0.67 n = 92	24.79 ± 0.76 n = 46	30.45 ± 1.51 n = 25	.002
BMR (kcal/day)	1461.28 ± 75.72 n = 90	1553.87 ± 805.90 n = 46	1174.56 ± 454.38 n = 25	.013
Fasting insulin (μIU/mL)	11.37 ± 0.70 n = 110	6.32 ± 0.30 n = 59	20.86 ± 1.13 n = 31	<.001
Fasting glucose/insulin	10.46 ± 0.80 n = 108	14.84 ± 1.19 n = 59	4.24 ± 0.18 n = 31	<.001
HOMA	70.40 ± 6.43 n = 108	103.38 ± 9.85 n = 59	25.27 ± 1.41 n = 31	<.001
QUICKI	0.351 ± 0.00 n = 108	0.38 ± 0.00 n = 59	0.310 ± 0.00 n = 31	<.001
Cholesterol (mg/dL)	201.32 ± 4.90 n = 91	200.52 ± 7.97 n = 46	195.83 ± 7.33 n = 24	.703
Triglycerides (mg/dL)	99.37 ± 4.84 n = 90	92.49 ± 6.00 n = 45	98.42 ± 9.27 n = 24	.579
HDL (mg/dL)	57.50 ± 1.63 n = 90	60.07 ± 2.54 n = 46	55.00 ± 3.25 n = 24	.235
LDL (mg/dL)	124.81 ± 4.15 n = 89	123.93 ± 6.59 n = 45	121.22 ± 5.78 n = 24	.758
Testosterone (ng/mL)	2.46 ± 0.18 n = 115	2.66 ± 0.32 n = 59	2.11 ± 0.20 n = 30	.239
Androstenedione (ng/mL)	3.14 ± 0.13 n = 112	3.18 ± 0.17 n = 58	3.04 ± 0.26 n = 28	.639
Free androgen index	0.64 ± 0.15 n = 107	0.73 ± 0.28 n = 54	0.60 ± 0.17 n = 28	.748

Note: BMI = body mass index; BMR = basal metabolic rate; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; IR = insulin resistance; LDL = low-density lipoprotein; PCOS = polycystic ovary syndrome; QUICKI = quantitative insulin sensitivity check index.

[a] *P* values refer to correlations between PCOS-NIR and PCOS-IR.

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n = 43; fasting insulin <12 mU/mL, Glu/Ins >6.4, HOMA >47, QUICKI >0.333). Twenty-three out of 91 PCOS women did not fit all the applied criteria for IR and therefore were not included in these two subgroups.

The results of these two subgroups (PCOS-IR and PCOS-NIR) concerning all parameters, including age, BMI, and adjusted BMR, are shown in Table 1. The adjusted BMR was significantly lower in both PCOS-IR and PCOS-NIR compared with the control group ($P<.001$). Furthermore, we adjusted the two subgroups (PCOS-IR and PCOS-NIR) and the control group for both age and BMI, and these results are shown in Table 2. To match all three subgroups for both age and BMI, the included patients had to be further decreased to 40 PCOS-NIR patients, 20 PCOS-IR patients, and 35 control subjects. Adjusted BMR still showed a statistically significant difference among all three age- and BMI-adjusted groups, with higher values in the control group and lowest in the PCOS-IR group ($P=.007$ between PCOS-NIR and PCOS-IR; $P<.001$ between PCOS-IR and control; $P=.048$ between PCOS-NIR and control; Table 2).

DISCUSSION

Polycystic ovary syndrome is a multifactorial syndrome characterized by hirsutism, chronic anovulation, and hyperandrogenemia and highly associated with obesity and insulin resistance (3). The selection criteria for the women with PCOS included in the present study were based on the presence of biochemical hyperandrogenism, chronic anovulation, and polycystic ovarian morphology on ultrasound. The aim for these strict selection criteria was to eliminate "gray zones" from the study group to achieve the maximum presence of the basic characteristics of the syndrome, namely the hyperandrogenism and the chronic anovulation. Accordingly, for the selection of the two subgroups of PCOS women with and without IR, we also applied strict criteria by excluding all women that only partly fulfilled the criteria of IR and by including only those PCOS women which were insulin resistant based on four different criteria for the evaluation of IR. The aim of the study was to create a clearly defined group of women with PCOS and IR. Finally, the obtained BMR of all patients included in the study was modified for fat-free body mass, percentage body fat, age, and gender, to be evaluated independently of these parameters, which are known to affect its estimation (20).

To our knowledge, BMR in women with PCOS has not been extensively studied. In a small group of PCOS patients, no differences were detected (21), although, after meal, thermogenesis in women with PCOS is diminished (22), as in women with obesity (23). The studies of BMR in obesity are contradictory. The BMR values in obesity are reported to be within normal range (9, 10) or increased (11), but BMR appears to be linked to morbid rather than to moderate obesity (12). Furthermore, although in a previous study from Finland, obesity has been reported to result from low basal metabolism (13), other studies have shown that obese individuals, compared with lean, present increased energy consumption (24).

In women with PCOS in the present study, adjusted BMR was decreased compared with control subjects, independently of obesity and IR. Adjusted BMR was significantly decreased both in women with PCOS with or without IR and particularly in women with PCOS and IR.

Chronic anovulation can partly explain the presence of decreased BMR in women with PCOS. The BMR has been reported to be decreased in athletes with menstrual disturbances and chronic anovulation (25, 26). Nevertheless, low energy consumption has been reported in menopausal women owing to their deficit in serum estrogens and P (27), whereas women with PCOS, though hyperestrogenic rather than hypoestrogenic, have constantly low serum P levels. The fact that PCOS women present a low metabolic rate could be the result of an adaptation to an environment of caloric deprivation which might begin even from the intrauterine life.

TABLE 2

Adjusted age, BMI, and BMR in PCOS women with (PCOS-IR) and without (PCOS-NIR) IR and the control group.

	PCOS-IR (n = 19) vs. PCOS-NIR (n = 43)	PCOS-IR (n = 19) vs. control (n = 23)	PCOS-NIR (n = 43) vs. control (n = 23)
Age (yrs)	23.12 ± 1.07 vs. 23.38 ± 0.67 *P*=ns	23.12 ± 1.07 vs. 25.17 ± 0.78 *P*=ns	23.38 ± 0.67 vs. 25.17 ± 0.78 *P*=ns
BMI (kg/m^2)	27.10 ± 1.38 vs. 24.54 ± 0.78 *P*=ns	27.10 ± 1.38 vs. 23.70 ± 1.02 *P*=ns	24.54 ± 0.78 vs. 23.70 ± 1.02 *P*=ns
BMR (kcal/day)	1,087 ± 106 vs. 1,562 ± 124 *P*=.012	1,087 ± 106 vs. 1,795 ± 0.820 *P*=.012	1,562 ± 124 vs. 1,795 ± 0.820 *P*=.004

Note: Correlation coefficients. Abbreviations as in Table 1.

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It is reported that girls with precocious puberty presented lower birth weights (28), while among postmenarcheal girls with a history of premature pubarche birth weights were lower in those with a functional ovarian hyperandrogenism and insulin hyperresponsiveness (28). Therefore, low basal metabolism in women with PCOS, particularly in those with IR, could be regarded to be the result of a deviation from normal, starting very early in life. This deviation might be an adaptation started during intrauterine life, in an environment of low energy input, which has led to a compensatory increase in body fat and a decrease in energy expenditure.

Women with PCOS and IR presented a significantly lower adjusted BMR compared with both women with PCOS without IR and normal women and a significantly greater BMI compared with women with PCOS without IR. It is known that obesity and IR are related to an imbalance in energy input and energy consumption. Fat tissue, not only as a deposit tissue, but also through its function as a hormone-producing tissue plays a critical role in the homeostasis of body fuels (29). Studies in the general population concerning the influence of IR on BMR results are conflicting. In obese individuals it was reported that basal energy expenditure was related neither to IR nor to dietary intake (20). In obese women with noninsulin-dependent diabetes mellitus (NIDDM) a negative energy consumption rate was reported (30), whereas in lean NIDDM a low thermogenesis was found (31).

In the present study, adjusted BMR was decreased in PCOS women without IR and even more decreased in PCOS women with IR. Based on the calculation of the adjusted BMR, which is corrected for body fat and body weight, obesity per se can not explain the above findings. Furthermore, women with PCOS with and without IR were matched for age and BMI with the control group of normally menstruating women. It appears, therefore, that IR constitutes an independent aggravating parameter which contributes in the greater reduction of the decreased BMR in PCOS women. The BMR remains constant throughout the day, representing 60%–70% of the total energy consumption. Therefore, based on the results of the present study, women with PCOS are consuming a decreased amount of energy and should decrease their caloric energy intake to maintain their body weight within normal limits. Increase in body weight further augments IR and menstrual disturbances, creating a vicious circle. It is well known that weight reduction is a major priority in the management of PCOS. In obese PCOS, weight reduction restores normal ovulatory cycling, decreases IR, increases basal metabolic rate, and ameliorates the clinical consequences metabolic syndrome. The decrease in energy intake should be coupled with a significant increase in energy expenditure by aerobic exercise. It was shown that BMR in women with PCOS was increased after a 12-week period of endurance and resistance exercise followed by a trend toward an improved hormonal profile (32). In addition, insulin sensitizers can be very helpful, particularly in obese PCOS women with IR (33). Administration of insulin sensitizers should always be coupled with low-caloric diet and lifestyle change.

In conclusion, women with PCOS, particularly those with IR, present a significantly decreased basal metabolic rate and should restrict their energy intake by diet and enhance their energy expenditure by exercise to maintain their body weight. Weight reduction is a gold standard in the management of obese PCOS. Every attempt to decrease body weight, either by diet alone or by diet and medication, must include a serious reduction in daily caloric intake, especially as derived from carbohydrates, and a significant increase in daily aerobic exercise.

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