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## RESTING METABOLIC RATE AND POSTPRANDIAL THERMOGENESIS IN POLYCYSTIC OVARIAN SYNDROME

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To determine whether the high frequency of obesity in women with polycystic ovary syndrome (PCO) is related to a defect in energy expenditure, resting metabolic rate (RMR) and the thermic response to a standard meal were compared in 10 obese PCO women, nine obese but otherwise normal women, and 11 lean women. All groups were matched with respect to age and fat-free mass and the two obese groups were matched for degree of obesity. RMR was measured by indirect calorimetry for 3 h on two days: (1) in the postabsorptive state; and (2) after a 720 kcal (3014 kJ) liquid mixed meal. The thermic effect of food, calculated as 3 h postprandial minus fasting RMR, was significantly greater for the lean [ $52.9 \pm 5.5$  kcal/3 h ( $221 \pm 23$  kJ/3 h)] than the obese [ $17.2 \pm 5.1$  kcal/3 h ( $72 \pm 21$  kJ/3 h)] and the PCO women [ $22.8 \pm 5.2$  kcal/3 h ( $95 \pm 22$  kJ/3 h)],  $P < 0.001$ . The thermic effect of food was negatively related to percent body fat ( $r = -0.694$ ,  $P < 0.001$ ). Resting metabolic rate did not differ significantly among the three groups, and was strongly related to fat-free mass ( $r = 0.687$ ,  $P < 0.001$ ). These results confirm previous reports of blunted thermogenesis in obese individuals, but provide no evidence of altered resting metabolic rate or postprandial thermogenesis in women with PCO compared with normal women of similar degree of obesity.

**Keywords:** energy expenditure, thermogenesis, fat-free mass, polycystic ovarian syndrome.

### *Introduction*

There is a high prevalence of obesity among women with polycystic ovary syndrome (PCO)<sup>1,2</sup>. It is not known whether obesity associated with PCO is related to the energy intake and/or energy expenditure components of the energy balance equation. Women with PCO are hyperandrogenemic<sup>1,2</sup>, which may stimulate food intake<sup>3,4</sup> and thereby possibly contribute to their obesity. There is a large body of evidence that impaired energy expenditure may be associated with some human obesity, such that a subtle metabolic defect favors the conservation and subsequent storage, rather than the dissipation of energy<sup>5</sup>. The specific component of total energy expenditure which has been shown to be reduced in obese subjects is postprandial thermogenesis, which is the increment in metabolic rate after ingestion of a meal<sup>6–10</sup>. Recent studies have demonstrated that impaired glucose tolerance and insulin resistance are associated with, and indeed may be

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the mechanism for defective thermogenesis<sup>11-13</sup>. Since women with PCO have been shown to be more hyperinsulinemic, and more insulin resistant compared with obese but otherwise normal women<sup>14,15</sup>, it is possible that thermogenesis may be impaired in these women.

Resting metabolism and thermogenesis have not previously been studied in women with PCO. The purpose of this study was to examine energy expenditure in PCO by comparing resting metabolic rate and postprandial thermogenesis in obese women with PCO, obese normal women, and lean women.

#### Methods

##### Subjects

Ten obese women with clinical and biochemical features of polycystic ovarian syndrome (PCO) were recruited for this study. PCO was diagnosed by elevation of one or more plasma androgen levels in the presence of chronic oligomenorrhea or amenorrhea<sup>1,14,16</sup>. The diagnosis of PCO was not based on ovarian morphology, because normal-appearing ovaries can be associated with the syndrome<sup>16</sup>. All of the PCO women had documented biochemical evidence of hyperandrogenemia, and 8/10 PCO women were hirsute. The androgen data on all of the women have been presented in detail elsewhere<sup>14</sup>. Eleven lean women with normal reproductive function and nine obese women with normal reproductive function also participated in this study. Consistent with the biochemical profile of PCO, testosterone, androstenedione, and estrone levels were significantly higher for the PCO women than the lean or obese normal women<sup>14</sup>.

The lean and obese women were matched to the PCO women with respect to age and fat-free mass (FFM), determined by hydrostatic weighing (see below). The lean women were less than 26 percent body fat, with no personal or family history of obesity, and two groups of obese women were greater than 33 percent body fat. All subjects were healthy with no personal or family history of diabetes mellitus or other metabolic disease, or cardiovascular disease. An oral glucose tolerance test was administered (see below) to ensure that all subjects were non-diabetic and had normal glucose tolerance, according to the criteria of the National Diabetes Data Group<sup>17</sup>. Two women in the PCO group were found to have impaired glucose tolerance and were excluded from the study. Women who engaged in regular aerobic exercise and women with high aerobic fitness, as determined from a graded exercise test (see below), were not accepted into the study, in order to eliminate possible confounding due to differences among the groups in level of cardiorespiratory fitness. All subjects were weight-stable at the time of the study with no more than a 2 kg weight loss or gain over the 6 months prior to the study. The subjects consumed a weight-maintenance diet containing at least 250 g carbohydrate per day several days prior to and throughout the duration of their participation in the study. The women were nonsmokers and were not taking any medications. The written informed consent of all subjects was obtained and the protocol was approved by the Institutional Review Board of the Mount Sinai School of Medicine.

##### Densitometry

Body fat content and fat-free mass were determined by densitometry. The subjects were tested in the morning after a 12 h fast. Body density was determined by hydrostatic weighing according to the method described by Akers and Buskirk<sup>18</sup>, with the modification that the force transducers are mounted inside the underwater weighing tank. The subjects submerged beneath the surface of the water while expiring maximally and remained as motionless as possible at the point of maximal expiration for roughly 5 seconds while underwater weight was recorded. After several practice trials to familiarize the subjects with the test procedure, 10 trials were performed. The estimated underwater weight was the highest value which was reproduced three times. Residual lung volume was estimated by means of the closed-circuit oxygen dilution method of Wilmore<sup>19</sup>, with use of a Collins 9-liter spirometer (Warren E. Collins, Braintree, MA) and a Med-Science nitrogen analyzer (Fiske Med-Science, St Louis, MO). Two trials were performed while the subjects assumed a sitting position that duplicated body position in the tank during underwater weighing. Body density was

calculated from the formula of Goldman and Buskirk<sup>20</sup> and percent body fat was derived from body density by use of the Siri equation<sup>21</sup>: percent body fat =  $4.95/\text{density} - 4.5$ . Fat-free mass (FFM) is the difference between total body weight and fat weight, where fat weight = total body weight  $\times$  percent body fat.

##### Oral glucose tolerance test (OGTT)

An oral glucose tolerance test (OGTT) was performed after an overnight (12 h) fast. After a fasting blood sample was drawn, a 75 g glucose load (Koladex, Custom Laboratories Inc., Baltimore, MD) was given and venous blood samples were drawn at 30 min intervals for 2 h. The plasma was separated and analyzed for glucose and insulin. A Beckman glucose analyzer II (Beckman Instruments, Fullerton, CA) was used for measuring plasma glucose<sup>22</sup>. Plasma insulin was measured by radioimmunoassay with charcoal absorption with use of a human insulin standard<sup>23</sup>. The integrated areas under the glucose and insulin curves were calculated according to the trapezoidal rule.

##### Aerobic fitness test

Maximal aerobic fitness ( $VO_2 \text{ max}$ ) was determined by a continuous multistage exercise test on a Bosch electromagnetically braked cycle ergometer (Robert Bosch GmbH, Berlin, FRG). Prior to the test, time was allotted for the subjects to become familiar with cycling on an ergometer at a constant pedalling rate and to breathing through the apparatus used for metabolic measurements. The subjects began cycling at a rate of 60 revolutions per minute (r.p.m.) with zero external resistance (unloaded cycling). The work rate was increased in 25 W increments every 2 minutes until volitional exhaustion was reached and the subject refused to continue despite vocal encouragement, or until she was unable to maintain the pedalling rate. Ventilatory measurements were made continuously by open-circuit respirometry with use of a Sensormedics Horizon Metabolic Measurement Cart (Sensormedics Corporation, Anaheim, CA), which includes a turbine volume transducer, a Beckman OM-11 polarographic oxygen ( $O_2$ ) analyzer, and a Beckman LB-2 non-dispersive infrared carbon dioxide ( $CO_2$ ) analyzer. The subjects breathed through a Hans-Rudolf non-rebreathing valve (Hans Rudolph Inc., Kansas City, MO) and used a mouthpiece and noseclips. The gas analyzers were calibrated before and after each aerobic fitness test with 100 percent nitrogen, room air, and a gas mixture containing 4 percent  $CO_2$  and 16 percent  $O_2$ . For each measurement, the fractional concentrations of  $O_2$  and  $CO_2$  ( $FEO_2$  and  $FECO_2$ ), oxygen consumption ( $VO_2$ ), carbon dioxide production ( $VCO_2$ ), and minute ventilation were obtained.

##### Thermogenesis tests

Prior to the thermogenesis tests the subjects visited the laboratory to become familiarized with all procedures and to become accustomed to the measurement of metabolic rate. The subjects refrained from vigorous physical activity for 3 days before each trial and consumed a weight-maintenance diet containing at least 250 g carbohydrate per day. All studies were performed in the follicular phase of the menstrual cycle on days 2-11 in the normal women and during a period of amenorrhea in the PCO women. The follicular phase was documented by plasma progesterone levels in the follicular range. These data have been presented elsewhere<sup>14</sup>. The women reported to the laboratory at 9:00 a.m. on two nonconsecutive days in the postabsorptive state after a 12 h fast. The laboratory was maintained at 24 °C throughout the study.

The order of the two thermogenesis trials was randomized independently for each woman. Baseline postabsorptive metabolic rate was measured on each day, after a 30 min rest period. Three 5-min measurements were made within a 30 min period (at 5-10, 15-20 and 25-30 min) in order to avoid discomfort from continuous use of the mouthpiece. The three measures were averaged and the coefficient of variation across the three measurements was less than 3 percent. We have shown that in healthy subjects similar results are obtained when metabolic rate is measured continuously with use of a ventilated hood, or intermittently with use of a mouthpiece and noseclips, or a breathing mask<sup>24</sup>. Furthermore, some subjects experience claustrophobia within a ventilated hood, leading to agitation, hyperventilation, and an increased metabolic rate<sup>24</sup>. The small degree of variation among intermittent measurements within 30 minute periods, and between days (see Results) indicate the reliability and accuracy of this method. The gas analyzers were re-calibrated (see above) every half hour to correct for drift in the analyzers. The two treatments were: (1) postabsorptive resting

metabolic rate (RMR) was measured for the last 6 minutes of every half-hour for 3 h while the subjects sat quietly; (2) postprandial RMR was measured for the last 6 min of every half-hour for 3 h after the subjects consumed a 720 kcal (3014 kJ) liquid mixed meal (Sustacal, Mead Johnson Nutrition Division, Evansville, IN) which was 24 percent protein, 21 percent fat and 55 percent carbohydrate. The meal was consumed within 5 min.

For each metabolic measurement the respiratory exchange ratio ( $VCO_2/VO_2$ ) was calculated and results were converted to kilocalories by use of the Weir equation<sup>25</sup>:

$$\text{kcal} = [(1.1 \times \text{RQ}) + 3.9] \times VO_2$$

#### *Analysis of data*

The thermic effect of the meal was compared in the three groups by applying a  $3 \times 2 \times 6$  three-way analysis of variance with repeated measures<sup>26</sup> to the RMR from 0 to 180 minutes from the two trials, using group (lean, obese, or PCO), food (meal or no meal) and time as the factors. Metabolic rate was expressed both as oxygen consumption and as caloric expenditure. A direct comparison of the thermic effects of food was carried out by applying a one-way analysis of variance to the calculated thermic effect of the meal, using group as the factor. The thermic effect of food was calculated by subtracting the 3 h energy expenditure during the postabsorptive trial from the postprandial trial. The thermic effect of food was expressed as kcal/3 h. For each of the above analyses, significant F-ratios from the analyses of variance were followed by *post hoc* comparisons<sup>26</sup>.

An analysis of variance with repeated measures was applied to the baseline RMR values obtained on the two test days and the pre-test RMR measurement in order to determine whether there was significant day-to-day variation in fasting RMR. The reliability of repeated fasting RMR measurements was tested by the intraclass correlation method<sup>26</sup>.

Comparisons of maximal aerobic fitness, RMR and the results of the OGTT in the three groups were made by application of one-way analyses of variance to each of these variables. Correlations between the thermic effect of food, and variables such as FFM, percent body fat, aerobic fitness, and plasma glucose and insulin levels were calculated in order to examine the relationships among thermogenesis, body composition, aerobic fitness, and insulin and glucose.

For all statistical analyses the 0.05 level of significance was used.

#### *Results*

The subjects' characteristics are shown in Table 1. The three groups did not differ significantly with respect to age and FFM, but body fat content and total body weight were significantly greater for the obese and PCO women than the lean women.  $VO_2$  max was not significantly different between the two groups when expressed in absolute form (ml/min), which is appropriate for weight-supported exercise such as cycling. The  $VO_2$  max values in both groups were within the range observed in healthy but not aerobically trained women. Fasting plasma glucose was not significantly different among the three groups (see Table 1), but fasting plasma insulin levels were significantly greater for the obese than the lean women, and significantly greater for the PCO than the obese women (see Table 1). The area under the glucose curve during the OGTT (see Table 1) was significantly greater for the PCO than the lean and obese women, but not significantly different between the lean and obese normal groups. The insulin response area was significantly different among all three groups: greater for the PCO than the obese women and greater for the obese normal than the lean women (see Table 1).

Table 1. *Subject characteristics.*

	<i>Lean (n = 11)</i>	<i>Obese (n = 9)</i>	<i>PCO (n = 10)</i>	<i>P value</i>
Age	28 ± 1	29 ± 2	25 ± 2	n.s.
Height (cm)	171 ± 1	164 ± 3	163 ± 2	< 0.05; L > O,P
Weight (kg)	62.5 ± 1.5	86.9 ± 5.8	84.1 ± 2.7	< 0.001; L < O,P
Percent body fat	21.8 ± 1.4	41.3 ± 1.4	41.4 ± 1.3	< 0.001; L < O,P
FFM (kg)	48.8 ± 1.0	50.4 ± 2.5	48.7 ± 1.2	n.s.
Maximum aerobic fitness				
$VO_2$ max (ml/min)	1914 ± 73	1885 ± 115	1781 ± 60	n.s.
Maximum workload (W)	185 ± 10	171 ± 8	167 ± 7	n.s.
RMR (kcal/min)	1.029 ± 0.023	1.082 ± 0.043	1.047 ± 0.037	n.s.
Oral glucose tolerance (OGTT) <sup>a</sup>				
Fasting glucose (mm)	4.5 ± 0.2	4.8 ± 0.1	4.9 ± 0.1	n.s.
Fasting insulin (pm)	72 ± 7	122 ± 14	223 ± 43	< 0.005; P > O > L
Glucose area (mm) <sup>b</sup>	9.9 ± 0.2	9.9 ± 0.2	12.4 ± 0.9	< 0.05; P > O,L
Insulin area (pm) <sup>b</sup>	653 ± 7	1300 ± 294	2872 ± 381	< 0.001; P > O > L

Values are mean ± s.e.m. <sup>a</sup> Oral glucose tolerance test data are missing for one lean and one obese woman. <sup>b</sup> Integrated over 2 h following a 75 g oral glucose load.

the two treatment days: coefficient of variation in baseline RMR across the two trials was less than 3 percent. The intraclass correlation coefficient was  $r = 0.982$ , indicating that the measurement of RMR was extremely reliable. RMR (see Table 1) was not significantly different among the three groups, and was strongly related to fat-free mass ( $r = 0.687$ ,  $P < 0.001$ ).

The analyses of variance on the thermogenesis data yielded identical results when caloric expenditure and oxygen consumption were used as the dependent variables. The analysis of variance which used group, meal (meal or no meal), and time (the half-hourly measurements) as the factors yielded a significant group-by-meal effect, indicating that the thermic effect of food was significantly greater for the lean than the obese or PCO women. None of the interactions with time were significant, indicating that the time course of the thermic effect of the meal was not significantly different among the groups. Since none of the interactions with time and group was significant, the data are presented as the calculated thermic effect of food (postprandial minus postabsorptive energy expenditure over 3 h) in Fig. 1. The thermic effect of food was significantly greater for the lean group than the other two groups, but not significantly different between the obese and PCO women.

Percent fat was the best predictor (among body composition parameters, which included percent fat, FFM and body weight; the OGTT results; and aerobic fitness parameters) of the thermic effect of food [ $r = -0.694$ ,  $P < 0.0001$ ;  $Y = 33.824 - 150.421 \times X$ , where  $Y$  = thermic effect of food (kcal/3 h), and  $X$  = percent body fat (expressed as a decimal); s.e.e. = 16.8 kcal]. No other variable added significantly to the explained variance in the thermal effect of food, after body fat.

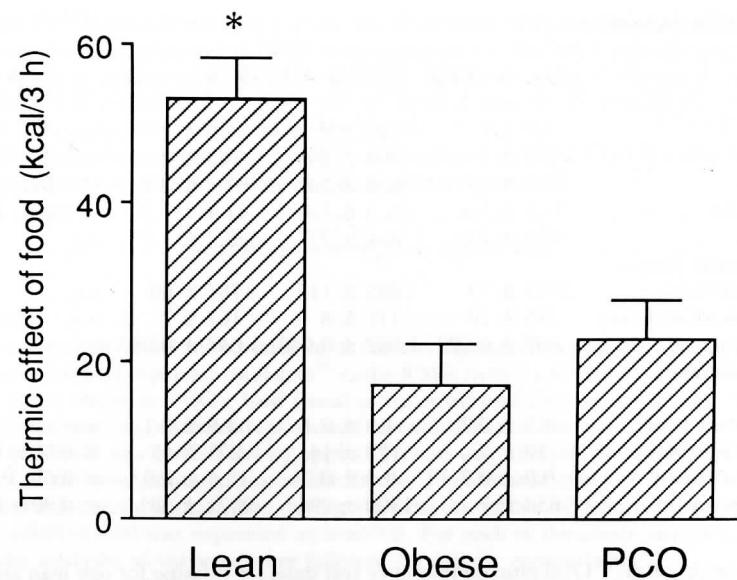


Fig. 1. Thermic effect of a 720 kcal (3014 kJ) meal in lean, obese and PCO women. The thermic effect of food is calculated as postprandial minus fasting RMR (kcal/3 h).

\*  $P < 0.01$  lean v. obese and PCO. Values are means  $\pm$  s.e.m.

### Discussion

This study found no significant difference in the thermic response to a meal in women with polycystic ovarian syndrome, compared with similarly obese but otherwise normal women, and confirmed previous reports of a blunted rise in postprandial energy expenditure in obese (in both the PCO and obese groups) compared with lean women.

The role of blunted thermogenesis in obesity is controversial because despite smaller increases in metabolic rate in response to thermic stimuli, total, absolute energy expenditure is generally greater in obese than lean people, owing in part to the elevated FFM in the obese<sup>27-29</sup>. In the present study, we held FFM constant by matching the three groups with respect to FFM. Under these conditions, fasting energy expenditure was not significantly different among the groups, but the increase in metabolic rate after meals was significantly reduced in the obese and PCO women compared with the lean subjects.

Several studies have shown that the blunted thermogenesis in obesity is related to insulin resistance and impaired glucose tolerance<sup>11-13</sup>. In fact, when the insulin resistance in the obese was overcome during the euglycemic clamp by infusing sufficient insulin for the obese to achieve the same rate of glucose disposal as lean subjects, the thermic effect of glucose was no longer blunted in the obese<sup>12</sup>. The blunted thermogenesis associated with insulin resistance is related to a reduced rate of nonoxidative glucose disposal (glucose storage) which has a greater energy cost than glucose oxidation<sup>30,31</sup>. In the present study, all subjects had normal glucose tolerance. However, the obese and PCO women were hyperinsulinemic compared with the lean women, in the fasting state and after the 75-g glucose load

(OGTT). The larger insulin response to oral glucose for the PCO and obese subjects in the present study is suggestive of degree of insulin resistance<sup>32</sup>.

It is interesting to note that the thermic effect of food was not different between the obese and PCO women despite significant differences in their fasting insulin and glucose and insulin response areas, all suggestive of greater insulin resistance in the PCO group. *In vivo* insulin action has been determined in PCO, including most of the subjects in the present study. These data have been reported elsewhere<sup>14</sup>. We found that both PCO and obesity are significantly and independently related to insulin resistance; obese women with PCO are more insulin resistant than normal women of the same degree of obesity<sup>14</sup>. The comparison of the PCO and obese women in the present study provides a new model for assessing the independent impact of obesity and insulin resistance on postprandial thermogenesis. The fact that the thermic effect of food was not significantly different between two groups of women who were matched on degree of obesity but differed with regard to insulin sensitivity suggests that obesity *per se* may have an overriding impact on the blunting of thermogenesis, which may be independent of insulin resistance.

Obesity and insulin resistance are usually colinear, and therefore, are confounding factors. Statistical control can be applied by such techniques as partial correlation in order to distinguish between effects of obesity and of insulin resistance; however, in cases where variables are colinear, it is virtually impossible to tease out the isolated effects of each variable<sup>33</sup>. The present study makes use of a controlled experimental model in which obesity and insulin resistance are partially orthogonal to one another, by comparing the thermic effect of food for two groups of women matched on body fatness but different with respect to their level of insulin sensitivity. The finding of no difference in the thermic responses of obese and PCO women with similar obesity but different degrees of insulin resistance suggests that when the colinearity of obesity and insulin resistance is uncoupled, impaired thermogenesis may reflect a defect intrinsic to the obese state.

However, it is possible that the insulin resistance in the PCO women blunts the thermogenesis even further than in the obese women but this effect is counterbalanced by some other hormonal effects related to PCO (such as androgen excess) which may have a positive effect on thermogenesis. In other words, the profound insulin resistance in PCO women could lead to a blunted capacity for thermogenesis, compared with obese but otherwise normal women, but this effect might be opposed by an effect of hyperandrogenism. Further study of the independent effects of hormonal differences related to PCO on energy metabolism are needed to further clarify this issue.

It has been reported that above ~28 percent body fat, obesity is uncorrelated with *in vivo* insulin action, determined by the glucose clamp<sup>34</sup>. However, there is a strong negative correlation between percent body fat and postprandial thermogenesis throughout the entire range of obesity<sup>8,9</sup>. This supports the idea that there may be an independent relationship between fatness and impaired thermogenesis which is unassociated with the insulin resistance in obesity.

Currently, the specific relationships among obesity, blunted thermogenesis and insulin resistance are uncertain. For example, it is unclear whether insulin

resistance is accompanied by a defect in postprandial energy expenditure, thus predisposing an individual to obesity by means of a defect in one component of total energy expenditure, or whether both insulin resistance and defective thermogenesis are consequences of obesity which in a subtle way perpetuate the obese state. Further longitudinal investigations are needed to resolve the nature of the interrelationships among obesity, insulin resistance, and thermogenesis.

In summary, the results of this study indicate that postprandial thermogenesis is blunted in obese but otherwise normal women and obese women with PCO compared with lean subjects but that when matched for fat-free mass, RMR is similar among the three groups.

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