What Are the Physical Characteristics Associated with a Normal Metabolic Profile Despite a High Level of Obesity in Postmenopausal Women?*

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ABSTRACT

Although obesity is often associated with insulin resistance and a cluster of metabolic disturbances, the existence of a subgroup of healthy but obese individuals has been postulated. It is unclear why some obese individuals fail to show traditional risk factors associated with the insulin resistance syndrome despite having a very high accumulation of body fat. To address this issue, we identified and studied a subgroup of metabolically normal but obese (MNO) postmenopausal women to gain insight into potential physiological factors that may protect them against the development of obesity-related comorbidities.

We carefully examined the metabolic characteristics of 43 obese, sedentary postmenopausal women (mean ± SD, 58.0 ± 6.0 yr). Subjects were classified as MNO or as metabolically abnormal obese (MAO) based on an accepted cut-point for insulin sensitivity (measured by the hyperinsulinemic/euglycemic clamp technique). Thereafter, we determined 1) body composition (fat mass and lean body mass), 2) body fat distribution (abdominal visceral and sc adipose tissue areas, mid thigh sc adipose tissue and muscle attenuation), 3) plasma lipid-lipoprotein levels, 4) plasma glucose and insulin concentrations, 5) resting blood pressure, 6) peak oxygen consumption, 7) physical activity energy expenditure, and 8) age-related onset of obesity with a questionnaire as potential modulators of differences in the risk profile.

We identified 17 MNO subjects who displayed high insulin sensitivity (11.2 ± 2.6 mg/min/kg lean body mass) and 26 MAO subjects with lower insulin sensitivity (5.7 ± 1.1 mg/min/kg lean body mass).

Despite comparable total body fatness between groups (45.2 ± 5.3% vs. 44.8 ± 6.6%; P = NS), MNO individuals had 49% less visceral adipose tissue than MAO subjects (141 ± 53 vs. 211 ± 85 cm²; P < 0.01). No difference was noted between groups for abdominal sc adipose tissue (453 ± 126 vs. 442 ± 144 cm²; P = NS), total fat mass (38.1 ± 10.6 vs. 40.0 ± 11.8 kg), muscle attenuation (42.2 ± 2.6 vs. 43.6 ± 4.8 Hounsfield units), and physical activity energy expenditure (1060 ± 323 vs. 1045 ± 331 Cal/day). MNO subjects had lower fasting plasma glucose and insulin concentrations and lower insulin levels during the oral glucose tolerance test (P values ranging between 0.01–0.001). No difference was observed between groups for 2-h glucose levels and glucose area during the oral glucose tolerance test. MNO subjects showed lower plasma triglycerides and higher high density lipoprotein cholesterol concentrations than MAO individuals (P < 0.01 in both cases). Results from the questionnaire indicated that 48% of the MNO women presented an early onset of obesity (<20 yr old) compared with 29% of the MAO subjects (P = 0.09). Stepwise regression analysis showed that visceral adipose tissue and the age-related onset of obesity explained 22% and 13%, respectively, of the variance observed in insulin sensitivity (total r² = 0.35, P < 0.05 in both cases).

Our results support the existence of a subgroup of obese but metabolically normal postmenopausal women who display high levels of insulin sensitivity despite having a high accumulation of body fat. This metabolically normal profile is associated with a lower accumulation of visceral adipose tissue and an earlier age-related onset of obesity. (J Clin Endocrinol Metab 86: 1020–1025, 2001)
of insulin sensitivity and a favorable metabolic profile (10, 11).

Although the existence of a subgroup of MNO individuals has been proposed, it is presently unclear why this subset of individuals is protected against the metabolic consequence of excessive body fatness. To address this issue, we identified obese postmenopausal women with high and low levels of insulin sensitivity based on the euglycemic/hyperinsulinemic clamp technique. Individuals with high levels of insulin sensitivity were classified as MNO, whereas obese subjects with lower insulin sensitivity were classified as metabolically abnormal obese (MAO). Thereafter, we examined the metabolic characteristics that may potentially explain the favorable metabolic status in MNO postmenopausal women.

Subjects and Methods

Subjects

The study population consisted of 43 obese (percent body fat, 45.2 ± 6.1%; mean ± sd) postmenopausal women, aged 50–71 yr (58.0 ± 6.0 yr; mean ± sd). Because the menopause transition and the aging process are associated with a decrease in lean body mass and an increase in fat mass (12), BMI is an inadequate index to accurately identify the level of obesity in older subjects (13). Thus, for the purpose of the present study, subjects were first selected on the basis of their percent body fat (≥35%), following previously proposed standard values (14, 15). To identify those with impaired insulin sensitivity, we used a glucose disposal rate (M values) cut-point of 8.0 mg·min⁻¹·kg⁻¹lean body mass, as previously suggested (16). Women with M values greater than the cut-point were classified as having high insulin sensitivity and placed in the MNO group, whereas women with values below the cut-point M value were classified as low insulin sensitivity and categorized as MAO subjects (17).

Women were included in the study if they had stopped menstruating for more than 1 yr and had a FSH level greater than 30 U/L. Participants were sedentary (less than two times a week of structured exercise), nonsmokers, low to moderate alcohol consumers (<2 drinks/day), and not taking hormone replacement therapy. All participants were apparently healthy and had no history or evidence on physical examination of 1) cardiovascular disease, peripheral vascular disease, or stroke; 2) diabetes; 3) moderate to severe hypertension (resting blood pressure >170/100 mm Hg); 4) orthopedic limitations; 5) body weight fluctuation more than 5 kg in the previous 6 months; 6) thyroid or pituitary disease; or 7) medication that could affect cardiovascular function or metabolism. Subjects were excluded if they had 1) cardiovascular disease, peripheral vascular disease, or stroke; 2) any disease that could affect insulin sensitivity; 3) moderate to severe hypertension (resting blood pressure >120/80 mm Hg); 4) orthopedic limitations; 5) body weight fluctuation more than 5 kg in the previous 6 months; 6) thyroid or pituitary disease; or 7) medication that could affect cardiovascular function or metabolism.

Subjects performed a graded exercise test on treadmill to voluntary exhaustion to measure peak VO₂ as previously described (24). Standard 12-lead electrocardiograms were performed at the end of each 2-min stage. Peak VO₂ (liters per min) was considered to be the highest value obtained during the test. Expired gas was analyzed during the exercise protocol using a Sensormedics Horizon metabolic cart (Yorba Linda, CA). Data collection included VO₂ and respiratory equivalent ratio (CO₂ production/O₂ consumption).

Diet stabilization period

Before the study, participating volunteers were submitted to a weight stabilization period (within 2 kg BW) that lasted, on the average, 38 ± 18 days. Macronutrient intake was also stabilized 3 days before testing with a standard diet provided by the metabolic kitchen of the General Clinical Research Center containing 55% carbohydrate, 30% fat, and 15% protein.

Body composition

Body weight was measured to the nearest 0.1 kg on a calibrated balance. Determination of fat mass, lean body mass (LBM), and percentage of body fat were assessed using dual energy x-ray absorptiometry (model DPX-L, Lunar Corp., Madison, WI) as previously described (18, 19). During the scan procedure, subjects were asked to wear only a standard hospital gown and to maintain a supine position.

Computed tomography (CT)

Visceral adipose tissue and sc adipose tissue were measured by CT as previously described (20) using a GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI). The subjects were examined in the supine position with both arms stretched above the head. The position of the scan was established at the L4–L5 level using a scout image of the body. Visceral adipose tissue area was quantified by delineating the intraabdominal cavity at the internal-most aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. Adipose tissue was highlighted and computed using an attenuation range of −190 to −30 Hounsfield units (HU). The sc adipose tissue area was quantified by highlighting adipose tissue located between the skin and the external-most aspect of the abdominal muscle wall. Deep and superficial sc adipose tissue areas were measured by delineating the sc fascia at the L4–L5 level and by computing areas of the layers of fat on each side of the fascia (21).

CT was also used to measure midtibial cross-sectional skeletal muscle and adipose tissue areas and muscle attenuation, the latter representing an estimate of muscle fat content (22, 23). Areas of skeletal muscle, adipose tissue, and muscle attenuation were calculated by delineating the regions of interest and then computing the surface areas using an attenuation range of −190 to −30 HU for adipose tissue and 0–100 HU for skeletal muscle. Test-retest measurements of the different body fat distribution indexes on 10 CT scans yielded a mean absolute difference of <1%.

Peak oxygen consumption (VO₂)

Subjects performed a graded exercise test on treadmill to voluntary exhaustion to measure peak VO₂ as previously described (24). Standard 12-lead electrocardiograms were performed at the end of each 2-min stage. Peak VO₂ (liters per min) was considered to be the highest value obtained during the test. Expired gas was analyzed during the exercise protocol using a Sensormedics Horizon metabolic cart (Yorba Linda, CA). Data collection included VO₂ and respiratory equivalent ratio (CO₂ production/O₂ consumption).

Measurements of energy expenditure

Total daily energy expenditure (TEE). TEE was determined from the doubly labeled water technique over a 10-day period. During that period, subjects were asked to maintain their normal daily physical activity routines. These individuals, however, were not participating in any structured exercise training program. Specific details about the doubly labeled water technique have been reported extensively by our laboratory (18, 25).

Resting metabolic rate (RMR). RMR was measured by indirect calorimetry using the ventilated hood technique (24) after an overnight 12-h fast at the General Clinical Research Center. Respiratory gas analysis was performed using a Deltatrac metabolic cart (Sensormedics, Yorba Linda, CA). The RMR (kilocalories per day) was calculated from the equation of Weir (26). The test-retest correlation coefficient within 1 week has been shown to be 0.90 for RMR in our laboratory (27).

Daily physical activity energy expenditure (PAEE). Doubly labeled water in conjunction with indirect calorimetry was used to measure PAEE. PAEE was calculated as the difference between TEE and RMR, and the thermic effect of a meal using the equation: PAEE (Cal/day) = [TEE (Cal/day) × (0.9 – RMR (Cal/day))] as previously described (18, 25). This approach assumes that the thermic effect of feeding is 10% of TEE in the elderly (27).

Glucose and insulin metabolism

During an out-patient visit to the GCRC, a 2-h 75-g oral glucose tolerance test (OGTT) was performed after 3 days of standardized diet (>250 g carbohydrate consumption) according to the guidelines of the American Diabetes Association (28). Insulin and glucose concentrations were measured at 0, 60, 90, and 120 min during the OGTT. The total area under the curve was determined with the trapezoid method.

Insulin sensitivity measurement during the clamp

Basal and insulin-stimulated glucose kinetics were measured by the hyperinsulenic-euglycemic clamp technique as described by De-
TABLE 1. Characteristics of metabolically normal obese (MNO) and metabolically abnormal obese (MAO) subjects

<table>
<thead>
<tr>
<th></th>
<th>MNO (n = 17)</th>
<th>MAO (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.0 ± 6.3</td>
<td>58.6 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>84.9 ± 18.2</td>
<td>91.9 ± 17.6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.5 ± 5.6</td>
<td>34.7 ± 6.5</td>
<td>NS</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>37.3 ± 10.8</td>
<td>39.0 ± 12.3</td>
<td>NS</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>43.8 ± 5.5</td>
<td>48.1 ± 7.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Bone mineral content</td>
<td>2.7 ± 0.3</td>
<td>3.0 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>% Body fat</td>
<td>45.2 ± 5.3</td>
<td>44.8 ± 6.6</td>
<td>NS</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg · min)</td>
<td>19.3 ± 3.8</td>
<td>18.1 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Measures of energy expenditure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEE (Cal/day)</td>
<td>2955 ± 430</td>
<td>3051 ± 520</td>
<td>NS</td>
</tr>
<tr>
<td>RMR (Cal/day)</td>
<td>1512 ± 188</td>
<td>1651 ± 271</td>
<td>NS</td>
</tr>
<tr>
<td>PAEE (Cal/day)</td>
<td>1060 ± 323</td>
<td>1045 ± 331</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>M (mg/min)</td>
<td>483 ± 112</td>
<td>275 ± 68</td>
</tr>
<tr>
<td></td>
<td>M/LBM (mg/min · kg LBM)</td>
<td>11.2 ± 2.6</td>
<td>5.7 ± 1.1</td>
</tr>
</tbody>
</table>

Values are the mean ± sd. RMR, Resting metabolic rate; TEE, total energy expenditure; PAEE, physical activity energy expenditure.

*MNO, n = 9; MAO, n = 19 (for assessment from doubly labeled water).
As expected from the use of insulin sensitivity levels to categorize our sample of subjects, MNO women had lower values of fasting plasma insulin and glucose concentrations, 2-h plasma insulin concentrations, and insulin areas during the OGTT. No difference was observed between groups for 2-h glucose concentrations, but there was a trend for a lower glucose area during the OGTT in MNO women (P = 0.07).

Results from the questionnaire indicated that 48% of the MNO women presented an early onset of obesity (obese between 13–19 yr of age) compared with 29% of MAO subjects (P = 0.09). Based on these observations, the age-related onset of obesity was included as an independent variable in stepwise regression analyses to predict insulin sensitivity (see Table 4). First, our results indicated that visceral adipose tissue accumulations and an earlier age-related onset of obesity were the only independent predictors of insulin sensitivity, explaining 22% (P = 0.005) and 13% (P = 0.02) of the variances observed, respectively. Second, visceral adipose tissue accumulation was the only independent predictor of fasting plasma triglyceride concentrations (r² = 0.22, P = 0.008). Finally, peak VO₂, age, visceral adipose tissue, and an earlier age-related onset of obesity were the best predictors of plasma HDL-Chol concentrations, explaining 65% of the variance observed in our cohort of obese postmenopausal women (P values ranging between 0.0001–0.05).

**Discussion**

The present study supports the existence of a subgroup of metabolically normal but obese postmenopausal women. These individuals display remarkably high levels of insulin sensitivity despite having high levels of body fat. The additive effect of lower visceral adipose tissue levels and a longer duration of obesity may explain in part metabolic factors that may be protective against obesity-related comorbidities in this unique population.

Our subgroup of MNO postmenopausal women displayed remarkably high levels of insulin sensitivity despite having half of their weight as body fat. In fact, glucose disposal levels in this group are comparable to values observed in healthy young nonobese women (11.0 ± 2.2 mg/min/kg LBM) (17). This is a striking finding given that women in the present study were older (57 ± 6 vs. 28 ± 4 yr), were more obese (38.1 ± 10.6 vs. 15.3 ± 4.4 kg fat mass), and had lower fitness levels (19.3 ± 3.8 vs. 39.3 ± 7.3 mL/kg/min) than younger women in our previous study (17). Collectively, in combination with previous studies (11, 37), the identification of a subpopulation of obese individuals who are quite insulin sensitive is a reproducible finding.

The results reported herein are based on the classification of individuals as having high (≥8 mg/min/kg LBM) or low (<8 mg/min/kg LBM) levels of insulin sensitivity, as previously suggested to initially identify MNO and MAO subjects (16). We have previously validated this cut-point as predictive of a cluster of deleterious phenotypes, including abdominal obesity, lipid- lipoprotein abnormalities, and low energy expenditure (17).

This study provides new information by identifying phenotypic characteristics that are protective against metabolic factors associated with the insulin resistance syndrome. Furthermore, the direct assessment of our outcome variables using radiological imaging techniques and stable isotope methodologies lends credibility to our findings. We observed a 50% lower accumulation of visceral adipose tissue in MNO women compared with the MAO group. Thus, our results suggest that lower amounts of visceral adipose tissue, despite high levels of body fat, probably contribute to their favorable metabolic profile. Additional support for this idea is found in our multiple regression approach, which showed that visceral adipose tissue accounted for the greatest source of unique variance in our population, explaining 22% of the variation observed. This finding is in accordance with numerous studies in the literature suggesting that the amount of visceral fat is an important factor associated with variations in insulin sensitivity (38, 39). However, these findings extend previous investigations by suggesting that even in the presence of large quantities of total body fat, lower accumulations of visceral adipose tissue may be partially protective against metabolic abnormalities. Although it has been suggested that a visceral fat accumulation greater than 130 cm² is associated with deleterious changes in glucose and insulin metabolism (40), this is not the case in our study, where the

**TABLE 2. Body fat distribution measured by computed tomography in metabolically normal obese (MNO) and metabolically abnormal obese (MAO) subjects**

<table>
<thead>
<tr>
<th></th>
<th>MNO (n = 17)</th>
<th>MAO (n = 27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAT area (L4–L5, cm²)</td>
<td>447 ± 144</td>
<td>434 ± 130</td>
<td>NS</td>
</tr>
<tr>
<td>Superficial SAT area (cm²)</td>
<td>247 ± 89</td>
<td>240 ± 99</td>
<td>NS</td>
</tr>
<tr>
<td>Deep SAT area (cm²)</td>
<td>206 ± 56</td>
<td>202 ± 55</td>
<td>NS</td>
</tr>
<tr>
<td>VAT area (L4–L5, cm²)</td>
<td>141 ± 53</td>
<td>211 ± 85</td>
<td>0.01</td>
</tr>
<tr>
<td>Leg SAT (cm²)</td>
<td>208 ± 64</td>
<td>187 ± 62</td>
<td>NS</td>
</tr>
<tr>
<td>Leg muscle area (cm²)</td>
<td>103 ± 13</td>
<td>113 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>Leg muscle attenuation (Hounsfield)</td>
<td>42.2 ± 2.6</td>
<td>43.6 ± 4.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are the mean ± SE. SAT, Subcutaneous adipose tissue; VAT, visceral adipose tissue.

a MNO, n = 12; MAO, n = 22.

**TABLE 3. Metabolic characteristics of metabolically normal obese (MNO) and metabolically abnormal obese (MAO) subjects**

<table>
<thead>
<tr>
<th></th>
<th>MNO (n = 17)</th>
<th>MAO (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids and lipoproteins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.14 ± 0.80</td>
<td>4.84 ± 0.91</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.50 ± 0.85</td>
<td>2.02 ± 0.87</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.28 ± 0.72</td>
<td>3.00 ± 0.85</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.16 ± 0.47</td>
<td>0.91 ± 0.31</td>
<td>0.01</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>5.0 ± 1.8</td>
<td>5.7 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Oral glucose tolerance test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>4.78 ± 0.30</td>
<td>5.21 ± 0.61</td>
<td>0.01</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>55.2 ± 14.3</td>
<td>136.3 ± 82.2</td>
<td>0.001</td>
</tr>
<tr>
<td>2-h glucose (mmol/L)</td>
<td>6.02 ± 2.31</td>
<td>7.28 ± 1.67</td>
<td>NS</td>
</tr>
<tr>
<td>2-h insulin (pmol/L)</td>
<td>250.4 ± 96.3</td>
<td>955.7 ± 754.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Glucose area (mmol/L × 10⁻³)</td>
<td>0.79 ± 0.14</td>
<td>0.91 ± 0.17</td>
<td>0.07</td>
</tr>
<tr>
<td>Insulin area (pmol/L × 10⁻³)</td>
<td>31.6 ± 16.5</td>
<td>108.3 ± 64.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Resting blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>137.2 ± 14.5</td>
<td>139.7 ± 14.8</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>72.5 ± 11.1</td>
<td>75.6 ± 8.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are the mean ± SD. SAT, Subcutaneous adipose tissue; VAT, visceral adipose tissue.
a MNO, n = 12; MAO, n = 23.
mean value for visceral adipose tissue is 141 ± 53 cm² in the MNO group.

Consistent with the lower amount of visceral adipose tissue in MNO women, we found lower levels of plasma triglycerides and higher plasma HDL-Chol concentrations. The lower accumulation of visceral adipose tissue and the high insulin sensitivity reported in this subgroup are, therefore, in accordance with the idea that insulin resistance is associated with an unfavorable body fat distribution and disturbances in lipid-lipoprotein profile independent of the level of obesity (41, 42).

The second variable associated with a more favorable metabolic profile in MNO women was an earlier onset of obesity. That is, an earlier onset of obesity was associated with higher insulin sensitivity and a more favorable plasma lipid profile, although this variable appeared to be less robust than visceral adipose tissue. Support for this finding is derived from two lines of evidence. First, we noted a greater percentage of our previous work (17), a unifying hypothesis relates to the importance of visceral adipose tissue (and not general indexes of adiposity) as a strong predictor of metabolic risk in young and older women independent of their body fatness.

In summary, our results support the existence of a subgroup of obese postmenopausal women who display high levels of insulin sensitivity despite having a large quantity of body fat. This is associated in part with lower levels of visceral adipose tissue and an earlier onset of obesity.

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