Limb Fat to Trunk Fat Ratio in Elderly Persons Is a Strong Determinant of Insulin Resistance and Adiponectin Levels

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Background. Similar to lipodystrophy syndromes, aging results in increased visceral adiposity with loss of subcutaneous adipose tissue in the extremities. The hypothesis of this study is that the distribution of limb fat to trunk fat (LF/TF) ratio in elderly persons has a stronger correlation than trunk fat alone to insulin resistance and adiponectin levels.

Methods. Thirty-eight elderly participants were divided into an insulin-resistant (IR) group and an insulin-sensitive (IS) group. Limb fat and trunk fat were measured by dual-energy x-ray absorptiometry. Insulin resistance was measured by a hyperinsulinemic–euglycemic clamp.

Results. There was no significant difference between the IS and IR groups with respect to body mass index, body fat index, absolute amount of trunk fat, or percent body fat. However, the difference in LF/TF ratio between the IS (1.02 ± 0.05) and the IR groups (0.77 ± 0.05) was highly significantly different (p < .001). Insulin resistance had a stronger correlation to the LF/TF ratio (r = 0.61, p < .001) than to absolute trunk fat (r = −0.32, p = .051). Adiponectin levels had a strong association with the LF/TF ratio (r = 0.63, p < .001), but did not correlate to absolute trunk fat (r = −0.24, p = .18).

Conclusions. The distribution of body fat (LF/TF ratio) in elderly persons is a stronger determinant of insulin resistance and adiponectin levels than is trunk fat alone. The LF/TF ratio can be a useful tool to assess insulin sensitivity in the elderly population.
basal sampling, the participants were infused with 1.2 mU of insulin (Human; Eli Lilly, Indianapolis, IN)/(kg body weight/min) to elevate plasma insulin levels to ~40 μU/mL, sufficient to suppress hepatic glucose production in insulin-resistant states (14). Dextrose (10%) was administered intravenously at variable rates to maintain the plasma level of 90 mg/dL. Plasma glucose levels were assessed in arterialized blood samples obtained by the heated hand technique (15). Insulin sensitivity was determined between the second and third hour of insulin infusion. To normalize for differences in body composition, insulin sensitivity was expressed as milligrams of glucose per kilogram of lean body mass (LBM) as determined by dual-energy x-ray absorptiometry (DEXA).

Body Composition

Body composition, including LBM and total body fat, was determined by DEXA performed with a whole-body scanner (Hologic Inc., Bedford, MA). Limb fat was calculated as the total fat in arms and legs (g). In the upper arms, the limb fat included subcutaneous adipose tissue from the shoulder to the wrist. In the lower extremities, limb fat included subcutaneous adipose tissue from the hip to the ankle. Trunk fat was the amount of fat measured by the DEXA from below the neck to the pelvis. Trunk fat was measured as a surrogate for abdominal adiposity, as the DEXA scan software does not permit measurement of abdominal fat. More so, measuring the trunk fat from below the neck to the pelvis establishes easily identified and reproducible boundaries (neck and pelvis) between participants, whereas measuring abdominal fat may lead to variability between participants due to individual variation in abdominal shape. To correct for differences in height, body fat and trunk fat were also expressed as body fat mass and trunk fat mass indices, which were calculated by dividing these parameters by the square of the height (m²).

Biochemical Analysis

Plasma glucose levels were determined by the glucose oxidase method, using a Beckman Glucose Analyzer II (Brea, CA). High-density lipoprotein (HDL) was measured by enzymatic calorimetric assays performed on a Hitachi Modular Machine. Insulin levels were analyzed by radio-immunoassay (RIA; Diagnostic Products Corporation, Los Angeles, CA). C-reactive protein levels were analyzed by RIA. Serum adiponectin levels were measured by using a human enzyme-linked immunosorbent assay (ELISA) kit (LINCO Research, St. Charles, MO). Serum nonesterified fatty acids were measured by using the Wako NEFA C test kit (Wako Chemicals USA, Inc., Richmond, VA). The coefficient of variation within each assay was <5%.

Table 1. Comparison of Body Fat Distribution in Insulin-Sensitive Versus Insulin-Resistant Elderly Persons

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>Insulin-Sensitive Group</th>
<th>Insulin-Resistant Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Insulin sensitivity (Rd.)</td>
<td>10.4 ± 0.85</td>
<td>5.68 ± 0.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Men/Women</td>
<td>12/10</td>
<td>13/3</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>65.3 ± 5.02</td>
<td>70.0 ± 6.52</td>
<td>.01</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.8 ± 2.19</td>
<td>77.0 ± 2.49</td>
<td>.21</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>97.87 ± 2.27</td>
<td>105.03 ± 2.90</td>
<td>.06</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>0.89 ± 0.34</td>
<td>2.31 ± 0.70</td>
<td>.07</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.0 ± 0.19</td>
<td>0.9 ± 0.21</td>
<td>.97</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.28 ± 0.61</td>
<td>25.25 ± 0.59</td>
<td>.53</td>
</tr>
<tr>
<td>Body fat index, kg/m²</td>
<td>7.72 ± 0.49</td>
<td>7.59 ± 0.54</td>
<td>.87</td>
</tr>
<tr>
<td>Trunk fat index, kg/m²</td>
<td>3.61 ± 0.26</td>
<td>4.16 ± 0.26</td>
<td>.15</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>30.08 ± 1.94</td>
<td>29.56 ± 1.67</td>
<td>.84</td>
</tr>
<tr>
<td>Trunk fat, g</td>
<td>10,526.5 ± 735.3</td>
<td>12,307.9 ± 610.6</td>
<td>.09</td>
</tr>
<tr>
<td>Limb fat, g</td>
<td>10,322.4 ± 787.8</td>
<td>9105.9 ± 566.3</td>
<td>.22</td>
</tr>
<tr>
<td>Limb fat/trunk fat ratio</td>
<td>1.02 ± 0.05</td>
<td>0.77 ± 0.05</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: Data are means ± standard error. Rd, glucose disposal rate (mg glucose/kg lean body mass/min).

Statistical Analysis

All data are presented as means ± standard error of the mean. Differences between the insulin-sensitive and insulin-resistant participants were analyzed with the Student’s t test. Pearson correlations were used to assess bivariate associations, and multiple regression modeling was used to assess multivariate associations and to identify factors predictive of insulin resistance. Differences were considered statistically significant if p < .05.

RESULTS

Whereas as a group elderly persons are known to be more insulin resistant than young persons, about half of elderly individuals may be insulin sensitive (16). Comparing participants with insulin resistance to those who were insulin sensitive controlled for any effects on metabolism that arose solely due to aging. Baseline characteristics of the participants are shown in Table 1. The participants were divided into an insulin sensitive (IS) and insulin resistant (IR) group. A glucose infusion rate of 8 mg glucose/kg LBM/min was used as a cutoff to divide the sample into an IS and IR group (8 mg glucose/kg LBM/min is the mean and median insulin sensitivity in the group). As illustrated in Table 1, the insulin sensitivity of the IS group is 10.40 ± 0.85, whereas that of the IR group is 5.68 ± 0.48 (p < .001). The IR group was ~5 years older (p = .01), confirming that even within a group of elderly persons, insulin resistance increases with increasing age. The body weight of the IR group was ~5 kg higher than that of the IS group; however, this difference did not reach statistical significance. As expected, fasting glucose levels were higher in the IR group; this finding indicates impaired fasting glucose by current American Diabetes Association criteria. Insulin levels were also higher in the IR group than in the IS group. In these participants, with a BMI of 20–30 kg/m², the BMI was not significantly different between the IR and IS groups (Table 1). The amount of trunk fat was somewhat higher in the IR group than in the IS group (Table 1); however, when normalized for height (divided by height squared) there was no statistically significant difference. Body fat index (kg/height m²), trunk fat index (kg/m²), and percent body fat were not significantly different between the two groups (Table 1). Limb fat (arms and legs) was somewhat higher in the IS group compared to the IR group (Table 1), although this difference did not reach statistical significance. The distribution of fat, represented by LF/TF ratio, demonstrated the strongest difference between the two groups.
IS (1.02 ± 0.05) and the IR group (0.77 ± 0.05, p < .001) (Table 1).

Further analysis of the participants (IS and IR) as a group was performed with respect to insulin resistance. As previously described by others, the absolute amount of trunk fat was inversely correlated with insulin sensitivity (r = −0.32, p = .051) (17). However, the amount of limb fat was not significantly related to insulin sensitivity (r = 0.21, p = .20) (Figure 1A). In contrast, the LF/TF ratio was highly correlated with insulin sensitivity (r = 0.61, p < .001) (Figure 1B), to a larger extent than was absolute amount of trunk fat. To control for potential gender effects, a subgroup analysis of only elderly men also demonstrated the stronger correlation of insulin sensitivity with LF/TF ratio (r = 0.62, p = .001) than to trunk fat (r = −0.50, p = .01). Multivariate analysis revealed LF/TF ratio as the strongest determinant of insulin sensitivity in our participants (r = 0.56, p < .001), with age as the second strongest determinant (r = −0.34, p = .009).

The body fat distribution in all the participants (IS and IR combined) was also related to circulating levels of adiponectin. In the participants, the relationship of adiponectin levels to trunk fat (r = −0.24, p = .18) (Figure 2A) or to limb fat (r = 0.33, p = .07) were not statistically significant; however, adiponectin levels were highly correlated with the LF/TF ratio (r = 0.63, p < .001) (Figure 2B). The high correlation between adiponectin levels and LF/TF ratio was higher than the correlation between adiponectin levels and insulin sensitivity (r = 0.47, p = .003). Again, a subgroup analysis to control for gender indicated a strong correlation between adiponectin levels and the LF/TF ratio
in elderly men \((r = 0.77, p < .001)\), with no significant relationship of adiponectin levels to trunk fat in the elderly men \((r = -0.31, p = .15)\). As dyslipidemia is associated with insulin resistance \((18–20)\), the relationship between the LF/TF ratio and lipoprotein values was investigated. The LF/TF ratio was associated with HDL \((r = 0.50, p < .01)\) and triglycerides \((r = -0.30, p = .04)\), but not fatty acid levels \((r = -0.03, p = .88)\).

**Discussion**

In the present study, we show to our knowledge for the first time that the LF/TF ratio is a stronger determinant of insulin resistance than either limb fat or trunk fat independently. This information can be obtained by a simple calculation from a DEXA scan. We also show an association of LF/TF ratio to HDL levels. It is well known that women store fat more peripherally, and men store body fat more centrally, but the relationship of LF/TF to insulin sensitivity does not depend on gender. Men-only analysis still indicated the strong correlation between insulin sensitivity and LF/TF ratio.

Aging is well known to result in loss of subcutaneous fat \((4–8,21)\). Prospective anthropometric measurements of elderly persons over a 6- to 10-year period have detected about a 17% decrease of skin-fold thickness in the extremities \((4,7)\). In a comparison of healthy young and older men, computed tomography measurements revealed that elderly persons had a thigh subcutaneous fat area that was about half that of young men \((156.3 \pm 69.3 \text{ vs } 82.4 \pm 29.7 \text{ cm}^2)\) \((5)\). Recent studies of elderly persons have also suggested a protective effect of subcutaneous adipose tissue of the limbs on the development of insulin resistance and cardiovascular diseases \((18–20,22–24)\). In the Health, Aging and Body Composition study of elderly individuals, a larger amount of subcutaneous adipose tissue in the thigh (from computed tomography scan) was independently associated with lower glucose and lipid levels in men only \((19)\). Similarly, in the Hoorn Study, a larger leg fat mass (from DEXA) in 275 men and 284 women was associated with lower glucose levels in women only \((18)\). In contrast, multiple studies have demonstrated an independent effect of truncal fat and percent body fat on the development of insulin resistance in elderly persons \((17,25–29)\).

In a study of 166 healthy postmenopausal women, trunc fat was the strongest independent predictor of insulin resistance \((20)\). In yet another study of older men and women, insulin resistance is more closely associated with abdominal adiposity than with age \((17)\). Whereas previous studies have demonstrated independent effects of both trunk fat and limb fat on insulin sensitivity, this study demonstrates that combining peripheral (LF) and central (TF) substantially improves the ability of body composition to predict insulin sensitivity. The strong correlation of LF/TF ratio, rather than absolute limb fat or trunk fat, with insulin resistance suggests a new paradigm—that aging is a form of acquired lipodystrophy.

In addition to a relationship with insulin sensitivity, the LF/TF ratio is also strongly associated with the lipid-derived hormone, adiponectin. This hormone is inversely associated with insulin sensitivity, and is reduced in obese persons, type 2 diabetics, and individuals with congenital or acquired lipodystrophy syndrome \((11,12,30,31)\). Similarly, in elderly persons, a decrease in adiponectin levels was associated with insulin resistance \((11,28)\). Interestingly, the present study revealed that adiponectin levels did not correlate with trunk fat or limb fat independently, but were strongly correlated with the LF/TF ratio, suggesting a close link between peripheral and central fat distribution and adiponectin levels. The role of adiponectin and body fat distribution associated with aging needs to be further investigated.

Although the DEXA scan does not permit separate measurements of visceral and abdominal subcutaneous fat, or separate measurements of intermuscular, intramyocellular, and subcutaneous fat in the legs, it does provide potential clinically important information from a relatively simple procedure.

**Conclusion**

This work confirms by a more sensitive technique (hyperinsulinemic–euglycemic clamp) that, in elderly individuals, maintenance of body fat stores in the periphery is associated with maintaining insulin sensitivity. It also advances our understanding that the relationship of limb fat to trunk fat in the elderly population, expressed as LF/TF ratio, indicates a stronger relationship to both insulin resistance and to adiponectin levels, more so than does each adipose tissue depot independently. The correlation of the LF/TF ratio to insulin sensitivity persists even after adjusting for gender (men only). It provides a new paradigm that insulin resistance of aging is a form of an acquired lipodystrophy.

**Acknowledgments**

This work was supported by National Institutes of Health (NIH) Grant R01 AG17446-01A2 (to MAM), by NIH General Clinical Research Center Grant M01 RR0710-02 (Clinical Research Scholar Program, Center for Translational Research, School of Medicine, Health Sciences Center, State University of New York at Stony Brook, to SG), and by the Empire Clinical Research Investigators Program (to JFF and MMM).

We thank the participants in the study, Joyce Quick for her clinical assistance on the General Clinical Research Center, Jeannie Kidd for her help in coordinating this research, and the nursing and core laboratory staff of the General Clinical Research Center for their assistance.

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**References**


