Relation Between Leptin and the Metabolic Syndrome in Elderly Women

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Background. Leptin has been shown to be linked to adiposity and insulin resistance in middle-aged participants. However, the association between leptin and metabolic syndrome independently of body fat and body fat distribution has not been evaluated in healthy elderly people.

Methods. We studied the independent relation between leptin and the components of the metabolic syndrome in 107 women aged 67–78 years with body mass index (BMI) ranging from 18.19 to 36.16 kg/m². In all participants, we evaluated BMI, waist and hip circumferences, body composition by dual energy X-ray absorptiometry, fasting, and 2-hour glucose, lipids, insulin, homeostasis model assessment of insulin resistance (HOMA), systolic (SBP), diastolic blood pressure (DBP), and leptin.

Results. Significant correlation was found between leptin, BMI, waist circumference, fat mass, DBP, SBP, cholesterol, triglycerides, insulin, and HOMA. After adjusting for age and waist circumference, as well for age and fat mass, leptin was significantly related to insulin levels, HOMA, and cholesterol. In a stepwise multiple regression analysis using insulin levels or HOMA as dependent variables and age, waist circumference, fat mass, leptin, SBP, DBP, cholesterol, and triglycerides as independent variables, leptin entered the regression first, waist circumference second, and age third.

Conclusion. Our study shows that leptin is significantly related to indices of adiposity in elderly women, and leptin is significantly associated with insulin levels, HOMA, and cholesterol independent of age, body fat, and fat distribution. Leptin, waist circumference, and age together explained 31% and 33% of insulin levels and HOMA variance, respectively, in healthy elderly women.

Obesity and, in particular, body fat distribution are associated with diabetes, insulin resistance, and other components of the metabolic syndrome (1,2). In humans, adipocyte-derived peptide leptin has been linked to adiposity and insulin resistance (3,4). In middle-aged men and women, the rate of insulin mediated glucose uptake has been found to be significantly associated with leptin levels even after adjustment for percentage of body fat (5). Thus, leptin may play a central role in the development of the metabolic syndrome by postulating that leptin resistance contributes to obesity or independently affects insulin resistance. It has been recently proposed that, at least in rats, leptin resistance may play a causative role in the metabolic decline seen with aging (6). With aging, the prevalence of the metabolic syndrome increases (7), as well as the amount of body fat (8,9) and, in particular, visceral fat. It is known that body fat distribution is associated with several components of the metabolic syndrome in elderly people (10). However, no data are currently available on the association between leptin, insulin levels, insulin resistance, and the metabolic syndrome independent of body fat and body fat distribution in healthy elderly individuals. To study this relationship seems particularly important because previous studies have reported conflicting results regarding the association between body fat and leptin in elderly persons. In fact, some reports showed no age effect on leptin levels (11,12), while others reported age-dependent disruption of the relation between leptin and body fat (13,14) with higher age-dependent leptin decline in women than in men (15).

The aim of our study was to examine the independent relation between leptin and indices of adiposity as well as between leptin, insulin levels, insulin resistance, and the components of the metabolic syndrome in a sample of elderly women without diabetes after taking into account age, body fat, and body fat distribution.

Methods

Participants

A total of 107 women, with ages ranging from 67 to 78 years and body mass index (BMI) ranging from 18.19 to 36.16 kg/m², living independently in Verona, Italy, participated in the study. All participants were weight stable in the previous 6 months. At the beginning, all volunteers underwent a careful clinical assessment. None of the participants engaged in regular physical exercise. The presence of acute and chronic conditions as well as the use of medications was determined with standardized questionnaires. The participants were eligible if free from drugs and diseases known to affect lipids and/or glucose metabolism. All women were postmenopausal and were not on hormonal replacement therapy. Participants with diabetes according to American Diabetes Association diagnostic
terol; HDL-Ch

were taken at 0 and 120 minutes. Plasma glucose was measured by using a compact chemistry analyzer method (Ektachem DT-60; Eastman Kodak, Inc., Rochester, NY). This method had an interassay coefficient of variation of 2% (18).

Plasma immunoreactive insulin underwent duplicate measurements by double antibody radioimmunoassay using a commercial kit (Diagnostic Products Corp., Los Angeles, CA). The determination limit of the insulin assay was 6 pmol/L and the intra-assay CV was 4.9%. The homeostasis model assessment of insulin resistance (HOMA) index was computed in all participants (19).

Cholesterol and triglycerides were determined using a compact chemistry analyzer (Eastman Kodak) method; this method had an interassay CV of 2.2% for triglycerides and 2% for cholesterol (20). Dextran-magnesium precipitation was used for high-density lipoprotein (HDL) separation (21).

Plasma leptin was measured by using a specific radioimmunoassay kit (Linco Research, Inc., St. Charles, MO). Sensitivity was 0.1 ng/l and the intra-assay and interassay CVs were 0.7% and 7.8%, respectively.

Blood Pressure

Blood pressure was measured three times over a period of 30 minutes in the left arm with the participant seated. The average of the three blood pressure readings was used for all analyses.

Statistical Analysis

Results are shown as mean ± standard deviation (SD). Triglycerides, fasting, and 2 hours glucose during oral glucose tolerance test, insulin, HOMA, and leptin concentrations were log-transformed in order to normalize the data before analyses. Pearson’s, partial, and Spearman’s rank correlations were used to test associations between variables. Stepwise multiple regression analysis was used to test the joint effects of independent variables age, waist circumference, body fat, leptin, systolic blood pressure (SBP), diastolic blood pressure (DBP), cholesterol, HDL cholesterol, and triglycerides on insulin levels as well as on HOMA. All statistical analyses were done using the SPSS statistical package (22).

RESULTS

A correlation matrix between age, body weight, anthropometric variables, leptin, components of the metabolic syndrome, insulin, and HOMA is shown in Table 2. A significant correlation was found between leptin, waist circumference, fat mass, and several components of the metabolic syndrome (DBP, SBP, cholesterol, triglycerides, insulin, and HOMA).

After adjustments respectively for age and waist circumference and for age and body fat, leptin was still significantly related to insulin (respectively, r = .27, p < .01; r = .33, p < .001), HOMA (r = .25, p < .01; r = .32, p < .001), and cholesterol (r = .23, p < .05; r = .31, p < .001) (data not shown in Table).

Table 3 shows stepwise multiple regression analysis in which insulin levels and HOMA are used as dependent variables and age, waist circumference, body fat, leptin,

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Table 1. Characteristics of the Study Population (n = 107)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>71.93 ± 2.29</td>
<td>67–78</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.60 ± 5.92</td>
<td>140–170</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.52 ± 10.38</td>
<td>45.40–104.50</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.36 ± 3.99</td>
<td>18.19–36.16</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.43 ± 9.55</td>
<td>68–112</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>99.01 ± 7.33</td>
<td>84–125.5</td>
</tr>
<tr>
<td>Fat mass (kg)*</td>
<td>26.18 ± 7.22</td>
<td>9.63–49.54</td>
</tr>
<tr>
<td>Fat mass (%)*</td>
<td>40.96 ± 6.05</td>
<td>17.90–54.00</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>137.21 ± 17.01</td>
<td>105–175</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.26 ± 7.27</td>
<td>60–98</td>
</tr>
<tr>
<td>Ch (mmol/L)</td>
<td>6.35 ± 0.91</td>
<td>4.24–8.33</td>
</tr>
<tr>
<td>HDL-Ch (mmol/L)</td>
<td>1.70 ± 0.37</td>
<td>0.93–2.87</td>
</tr>
<tr>
<td>Tg (mmol/L)</td>
<td>1.55 ± 0.79</td>
<td>0.55–5.35</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>16.42 ± 10.24</td>
<td>1.70–49.50</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.08 ± 0.53</td>
<td>3.89–6.66</td>
</tr>
<tr>
<td>2-hour glucose (mmol/L)</td>
<td>6.49 ± 1.44</td>
<td>3.33–9.83</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>62.14 ± 33.36</td>
<td>7.18–166.39</td>
</tr>
<tr>
<td>HOMA</td>
<td>2.16 ± 1.24</td>
<td>0.22–6.25</td>
</tr>
</tbody>
</table>

Notes:
*Evaluated by dual energy X-ray absorptiometry.

Mean ± SD = mean ± standard deviation; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; Ch = total cholesterol; HDL-Ch = high-density lipoprotein cholesterol; Tg = triglycerides; HOMA = homeostasis model assessment of insulin resistance.

Anthropometric Measurements

With the participants wearing light indoor clothes and no shoes, body weight was measured to the nearest 0.1 kg (Salus, Milan, Italy), and height to the nearest 0.5 cm using a stadiometer (Salus). BMI was calculated as body weight adjusted by stature (kg/m²). Waist circumference was obtained with a measuring tape as the minimum circumference between the xyphoid process and the umbilicus. Hip bitrochanteric circumference was measured at the outermost points on the great trochanters.

Body Composition Assessment

Body composition was measured using dual energy X-ray absorptiometry (DXA) (Hologic QDR 2000, Waltham, MA) (software version 7.2). Total body fat (FM) expressed in kg as well as a percentage of body weight (FM%) were also determined. Characteristics and physics concepts of DXA measurement have been described elsewhere (17). Daily quality assurance tests were performed according to the manufacturer’s directions. All the scans were subsequently analyzed by a single trained investigator. Coefficient of variation (CV) for double determination in 11 women aged 68 to 75 years was 1% for FM and 2.3% for FM%.

Metabolic Variables

Venus blood samples for all metabolic assessments were obtained after the participants had fasted overnight. For the oral glucose tolerance test, patients were given a 75 g glucose load. Blood samples for determining glucose levels were taken at 0 and 120 minutes. Plasma glucose was
SBP, DBP, cholesterol, HDL cholesterol, and triglycerides as independent variables. Leptin entered the regression first \((r = .49\) and \(r = .48\) for insulin levels and HOMA, respectively). Waist circumference entered the regression second \((r = .53\) and \(r = .53\) for insulin levels and HOMA, respectively), and age as a third and last variable \((r = .56\) and \(r = .57\) for insulin levels and HOMA, respectively). Leptin, waist circumference, and age together explained 31% and 33% of insulin levels and HOMA variance, respectively.

**DISCUSSION**

Our study shows that leptin is significantly related to BMI, body fat, and waist circumference in elderly women and that leptin is significantly associated with insulin levels, insulin resistance, and cholesterol independent of age, body fat, and fat distribution. Furthermore, in our participants, leptin, waist circumference, and age explained up to 31% and 33% of insulin levels and HOMA total variance, respectively.

A number of studies have been published in recent years on leptin and its relation to body fat and insulin resistance (3,4). However, only a few studies were performed in order to investigate the relationship between leptin and body fat in old age, yielding contradictory results (11–15). To the best of our knowledge, no data are currently available on the relationship between leptin, insulin levels, insulin resistance, and the components of the metabolic syndrome in elderly people. Insulin resistance increases with age \((23)\), as well as the prevalence of the metabolic syndrome \((7)\). With age, body fat and visceral fat also increase \((8,9)\); their increase, mostly in visceral fat, has been shown to be significantly associated with metabolic alterations even in old age \((9,10)\). In fact, both age-dependent increase of insulin resistance and visceral fat may explain the increased risk of the metabolic syndrome in old age.

Our findings of a significant association between leptin and several components of the metabolic syndrome seem to suggest that leptin contributes to the pathogenesis of the metabolic syndrome in elderly people. These findings seem to be at least partially in contrast with those of Kennedy and colleagues \((24)\), who observed a significant association between leptin and fasting insulin and cholesterol but not between leptin and triglycerides, HDL cholesterol, SBP, DBP, and insulin sensitivity in a sample of 35 young nondiabetic women. However, in young nondiabetic men, a significant relation between plasma leptin concentrations and the components of the metabolic syndrome has been previously observed \((24,25)\).

Previous studies carried out in premenopausal women show that, in a multiple linear regression analysis, leptin was significantly correlated only with BMI and the degree of insulin resistance \((26)\). In our elderly participants, the association between leptin, insulin levels, and HOMA is still significant, even after adjustments for age and waist circumference, as well as for age and body fat. Leptin is known to be strongly related to the amount of body fat \((3,4)\), and its relation to insulin resistance is well known \((1)\). Thus, our findings of its independent relation to insulin levels and HOMA after adjustments for body fat and fat distribution support a role for leptin in the development of the metabolic syndrome in elderly people, not only as a surrogate of adiposity, but also because of its effect on insulin resistance. In fact, in our participants, about 22% of insulin levels and HOMA may be explained by leptin alone. Leptin, waist circumference, and age together explain 31% and 33% of insulin and HOMA variance, respectively. Independent association between leptin and insulin concentration after adjustment for BMI has been previously observed by Zimmet and colleagues in Polynesian men and women with a wide age range with and without diabetes \((27)\). Donahue and colleagues \((5)\) reported an association between leptin and insulin resistance as evaluated by
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Table 3. Variables Identified as Independent Predictors of Insulin Circulating Levels and Homeostasis Model Assessment of Insulin Resistance in Stepwise Multiple Regression Analyses Models

<table>
<thead>
<tr>
<th>Dependent and Independent Variables</th>
<th>R</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 1: leptin</td>
<td>.49</td>
<td>.00</td>
<td>.24</td>
</tr>
<tr>
<td>Step 2: waist circumference</td>
<td>.53</td>
<td>.01</td>
<td>.28</td>
</tr>
<tr>
<td>Step 3: age</td>
<td>.56</td>
<td>.02</td>
<td>.31</td>
</tr>
<tr>
<td>HOMA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step1: leptin</td>
<td>.48</td>
<td>.00</td>
<td>.23</td>
</tr>
<tr>
<td>Step 2: waist circumference</td>
<td>.53</td>
<td>.01</td>
<td>.28</td>
</tr>
<tr>
<td>Step 3: age</td>
<td>.57</td>
<td>.01</td>
<td>.33</td>
</tr>
</tbody>
</table>

Note: HOMA = homeostasis model assessment of insulin resistance.

Some limitations of our study should be recognized. First, we evaluated only fasting insulin and HOMA as surrogates for insulin resistance. However, fasting insulin and the HOMA index have been validated as indices of insulin resistance in several clinical and epidemiological studies (32). Second, waist circumference was used as a surrogate for visceral fat. Adjustment for visceral fat as evaluated by computed tomography, instead of adjustment for waist circumference, could lead to different results; however, in clinical settings, waist circumference has been suggested to be a useful index of body fat distribution in elderly participants (33). Third, only a few of the women could be classified as insulin resistant on the basis of HOMA values (34); thus, our findings should be verified in a study sample of the same age with more insulin-resistant participants. Finally we evaluated healthy elderly women after a careful clinical screening with a wide range of BMI. As a consequence, our findings cannot be generalized for all elderly women.

Conclusion

Our study shows that leptin is significantly related to body fat in elderly women. We also found that leptin is significantly associated with insulin levels, insulin resistance, and cholesterol independent of age, body fat, and fat distribution. Finally, we observed that leptin, waist circumference, and age together explained 31% and 33% insulin levels and HOMA variance, respectively, in elderly women; in these participants, approximately 23% of insulin levels and HOMA may be explained by leptin alone.

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REFERENCES


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