Association of Obesity and Central Fat Distribution With Carotid Artery Wall Thickening in Middle-Aged Women

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Background and Purpose—The association between obesity and atherosclerotic disease is controversial. In the present analysis, we evaluated whether common carotid intima-media thickness (IMT) and area, 2 markers of preclinical atherosclerosis, were increased in obese subjects.

Methods—More than 5000 middle-aged women (n=5062; age, 30 to 69 years) living in the area of Naples, Southern Italy, were recruited for a prospective, currently ongoing study on the etiology of cardiovascular disease and cancer in the female population (the Progetto ATENA study). A subsample of 310 participants underwent high-resolution B-mode ultrasound examination, and the IMTs, intima-media areas, and lumen diameters of common carotid arteries were measured with a semiautomated computerized program. Subjects were divided into 3 groups on the basis of the recently published obesity guidelines for body mass index (BMI), a marker of general obesity, and tertiles of waist-to-hip ratio (WHR), a marker of regional obesity.

Results—Women with a BMI ≥30 kg/m² showed higher systolic and diastolic blood pressures, triglycerides, and fasting glucose and insulin, as well as lower high-density lipoprotein concentrations, than subjects with lower BMI. A gradual increase in common carotid IMT and intima-media area was observed when lean women (0.94±0.01 mm and 19.8±0.5 mm², respectively) were compared with overweight (0.98±0.01 mm and 21.0±0.4 mm²) and obese (1.02±0.02 mm and 22.6±0.8 mm², P<0.005 for linear trend) individuals. Similarly, women in the highest tertile of WHR (>0.85) had adverse risk factor profiles and thicker carotid intima-media complex than those in the first 2 tertiles (P<0.01 and P<0.05 for IMT and intima-media area, respectively). In multivariate analyses, BMI and WHR were significant predictors of carotid wall thickness, independently of other traditional and nontraditional cardiovascular risk factors (age, blood pressure, lipid abnormalities, fasting insulin).

Conclusions—The present results indicate a graded and independent association between general and abdominal obesity—reflected by high BMI and WHR—and carotid artery wall thickening in a population of middle-aged women.

Key Words: atherosclerosis ■ carotid arteries ■ obesity ■ women

Obesity is a major public health issue in the United States and Europe, with a rapidly increasing prevalence among both men and women.1,2 Several large-scale prospective studies have shown that obese people, defined on the basis of high body mass index (BMI), have a much greater risk of developing myocardial infarction and stroke than subjects with normal levels of total body fatness.3–5 Furthermore, it has become progressively clear that the relationship between obesity and cardiovascular disease depends not only on the amount of body fat but also on its distribution. Individuals with increased fat accumulation in the abdominal region, indicated by high waist-to-hip ratio (WHR), often have atherogenic lipid profiles and are at increased cardiovascular risk.6–8 Despite such evidence, angiographic and postmortem studies evaluating the association between obesity and atherosclerotic disease have provided conflicting results.9–12

Over the last decade, high-resolution B-mode ultrasound has been used for the noninvasive assessment of carotid intima-media thickness (IMT), a marker of early atherosclerosis.13–16 Recently, cross-sectional carotid intima-media (IM) area, a parameter that incorporates changes in both vessel wall and lumen diameter, has been demonstrated to be another accurate predictor of coronary atherosclerosis.17

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In the present analysis, we sought to determine whether general and abdominal obesities were associated with common carotid wall thickening in a sample of middle-aged women from Southern Italy participating in a large, ongoing, prospective study (Progetto ATENA study) designed to investigate the causes of those chronic diseases (cardiovascular disease and cancer) that have a major impact on the female population. Our study was done in a geographical area where changes in dietary pattern (increasing caloric intake and increasing intake of animal fat), together with sedentary habits, have led to a high prevalence of overweight and obesity.

Methods

Study Population

We studied a cohort of 310 middle-aged women living in the area of Naples (Southern Italy) and participating in the Progetto ATENA study. The total study cohort, enrolled within a 4-year period, consisted of 5062 women from 30 to 69 years of age. Less than 5% of the total cohort had ever used hormone replacement therapy. Potential participants with a previous diagnosis of myocardial infarction, stroke, and major cancers were excluded. Subjects with a previous diagnosis of myocardial infarction, stroke, and major cancers were excluded. Subjects with diabetes, viral or bacterial acute diseases affecting blood and urine biochemistry were asked to delay their participation. During a 6-month period, the older 3 of 10 daily participants—those at potentially higher risk of atherosclerotic cardiovascular disease—were invited to undergo an ultrasound examination of the carotid arteries and additional biochemical tests. Of the 400 women invited, 310 (response rate, 77%) accepted the additional investigations and constituted the present study sample. All women gave written, informed consent, and the study was approved by the ethics committees of the institutions involved.

Clinical and Biochemical Assessment

Anthropometric measurements were made with the subjects in indoor clothing and without shoes. BMI, used as a measure of general obesity, was calculated as weight (in kilograms) divided by height squared (m²). Waist circumference was measured midway between the bottom of the rib cage and the top of the iliac crest. Hip circumference was measured at the level of the trochanter major. WHR, an index of abdominal obesity, was calculated as the ratio of waist to hip circumferences.

Sitting brachial blood pressure was measured by trained research assistants using a standard mercury sphygmomanometer twice at 2-minute intervals, a procedure similar to other epidemiological studies. A standard questionnaire was used to collect information about smoking habits.

Blood specimens were collected after a 12- to 14-hour fast, between 8 and 9:30 AM, to reduce the influence of circadian variation. Total cholesterol and triglyceride concentrations were measured with standard enzymatic methods. High-density lipoprotein (HDL) cholesterol was measured after precipitation of very-low-density lipoprotein and low-density lipoprotein (LDL) cholesterol with phosphotungstic acid, and LDL cholesterol was calculated according to the Friedewald formula. Fasting glucose levels were enzymatically determined by the hexokinase method. Fasting insulin levels, used as a surrogate measure of insulin resistance, were determined by enzyme immunoassay (Boehringer Mannheim Immuno- diagnostics on an ES 300 instrument).

High-Resolution Carotid Ultrasound

Carotid B-mode ultrasound examinations were performed by a certified sonographer using a Biostec 2000 II SA (Biosound Inc). The study protocol involved scanning the distal 1.0 cm of the near and far walls of the common carotid arteries. The crest at the origin of the bifurcation was used as an anatomical landmark to identify this segment. In each examination, the sonographer used different scanning angles (anterior, lateral, and posterior) to identify the greatest IMT in each wall.

### Table 1. Clinical and Biochemical Characteristics of the Study Sample Stratified According to Guideline Criteria for Body Mass Index

<table>
<thead>
<tr>
<th>Group</th>
<th>BMI &lt;25</th>
<th>BMI 25–29.9</th>
<th>BMI=30</th>
<th>P by ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±0.9</td>
<td>55±0.6</td>
<td>55±0.8</td>
<td>0.36</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.0±0.1</td>
<td>27.2±0.1*</td>
<td>33.8±0.3†</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.50±0.15</td>
<td>6.37±0.11</td>
<td>6.34±0.14</td>
<td>0.63</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.19±0.14</td>
<td>4.09±0.10</td>
<td>4.01±0.12</td>
<td>0.61</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.76±0.05</td>
<td>1.63±0.03</td>
<td>1.58±0.03*</td>
<td>0.007</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.19±0.07</td>
<td>1.34±0.05</td>
<td>1.52±0.08*</td>
<td>0.004</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>133.9±2.2</td>
<td>141.5±1.9*</td>
<td>144.7±2.4*</td>
<td>0.004</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>79.9±1.1</td>
<td>83.7±0.8*</td>
<td>86.8±1.1*</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>54.7±1.7</td>
<td>57.7±1.6</td>
<td>57.8±1.8</td>
<td>0.37</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>49</td>
<td>38</td>
<td>24</td>
<td>0.007</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>20±2</td>
<td>19±2</td>
<td>18±2</td>
<td>0.68</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.29±0.08</td>
<td>5.55±0.11</td>
<td>5.72±0.09*</td>
<td>0.04</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>26.2±2.7</td>
<td>28.5±2.4</td>
<td>55.5±4.1†</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lipid-lowering drugs, %</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypotensive drugs, %</td>
<td>8</td>
<td>11</td>
<td>5</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Values are means ± SE.
BMI indicates body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure.
*Significantly different from group 1.
†Significantly different from group 2.
Scans were recorded on super 0.5-in VHS videotape for offline analysis. At the Division of Vascular Ultrasound Research (Winston Salem, NC), certified ultrasound readers unaware of subjects’ clinical characteristics reviewed the examinations and made quantitative IMT and lumen diameter measurements using a computerized system. Readers selected the frame that contained the thickest IMT for each of the 4 carotid walls. The mean of these 4 maximum thicknesses was used as the ultrasound end point of the study. It was possible to obtain common carotid IMT measurements in all 310 subjects.

The common carotid lumen diameter was measured as the distance between the leading edge of the echo produced by the intima-lumen interface of the near wall and the leading edge of the echo produced by the lumen-intima interface of the far wall. The cross-sectional IM area, calculated according to the formula $\pi(\text{IMT}^2 - \frac{1}{2}(\text{lumen diameter})^2)$, was used as further morphological end point of the present study.

Continuously monitored quality control data, derived from a large international multicenter trial being conducted during this time at the Division of Vascular Ultrasound Research, showed a coefficient of reliability for the common carotid IMT of 0.85. This figure includes instrument, subject, sonographer, and reader variabilities. For lumen diameter, the coefficient of variation in replicate blind determination was 4.5%.

### Statistical Analyses

All statistical analyses were performed with SPSS for Windows, version 9.0. Continuous variables were described as mean and SE, and categorical variables were reported as percentages. Logarithmic transformation of triglycerides and insulin was performed to normalize the distribution before analyses. Comparisons among subgroups of women classified on the basis of BMI and WHR values were performed with 1-way analysis of variation (ANOVA) and Pearson’s $\chi^2$. The association of common carotid IMT and IM area measurements with measures of obesity, independent of other risk factors, was examined by stepwise multiple regression analyses in which obesity measures and other risk factors were introduced as independent variables. BMI and WHR were not included in the same model because of collinearity.

### Results

After age adjustment, there were no statistically significant differences between the sample of women who underwent carotid ultrasound evaluation and the remaining cohort of Progetto ATENA with regard to BMI, systolic and diastolic blood pressures, cholesterol and triglyceride concentrations, and the prevalence of current smokers.

The clinical and biochemical characteristics of the study population classified on the basis of recent obesity guidelines for BMI are reported in Table 1. Women with a BMI $\geq 30$ kg/m² showed higher values of systolic and diastolic blood pressures, triglycerides, fasting glucose, and insulin and lower HDL concentrations compared with subjects in the other 2 groups. A gradual increase in common carotid IMT was observed from lean (0.94±0.01 mm) to overweight (0.98±0.01 mm) to obese (1.02±0.01 mm) individuals (the Figure). Although lumen diameter was larger in the obese subjects (5.99±0.08 versus 5.71±0.06 and 5.76±0.04 mm in the lean and overweight groups, respectively; $P<0.008$), the increase in internal dimension was disproportionate to that in wall thickness, so the cross-sectional IM area remained statistically greater in obese individuals (22.6±0.8 versus 19.8±0.5 and 21.0±0.4 mm² in the lean and overweight groups, respectively; $P<0.005$) (the Figure).

Characteristics of the study subjects according to tertiles of WHR are presented in Table 2. Increasing WHR was closely associated with increased concentrations of triglycerides, fasting glucose, and insulin, as well as with decreased concentrations of HDL cholesterol. Women in the top WHR tertile had greater IMT (1.02±0.01 versus 0.94±0.01 and 0.98±0.01 mm, $P<0.01$) and IM area (22.1±0.6 versus 20.2±0.4 and 21.1±0.6 mm², $P<0.05$) but similar lumen diameter as women in the other 2 tertiles. When we used waist circumference as an index of regional obesity in the analyses, women with a waist circumference of $>91$ cm (the highest third) had significantly higher levels of triglycerides and fasting blood glucose than women with a waist circumference of $<80$ cm (the lowest third). A borderline significant linear trend was found across the thirds of waist circumference for common carotid IMT and IM area.
In multivariable regression analyses (Table 3) with arterial parameters used as dependent variables, BMI and WHR were determinants of carotid wall thickness independently of other traditional and nontraditional cardiovascular risk factors (age, blood pressure, lipid abnormalities, fasting insulin).

**Discussion**

The main finding of the present study is that subjects with high BMI or WHR showed increased carotid artery IMT and cross-sectional IM area, 2 indicators of preclinical atherosclerosis. Such an increase in arterial wall thickness was graded and persisted after adjustment for other traditional and nontraditional cardiovascular risk factors.

In our analysis, WHR was used as a marker of central fat distribution. Among the female population of Naples, there is a high prevalence of overweight and obesity, which is strongly represented in the cohort of Progetto ATENA, from which our study group derives. The 90th percentile of waist circumference for ATENA participants is 99 cm; its distribution (median, 84 cm) expresses >70% of individuals with a

| Table 2. Clinical and Biochemical Characteristics of the Study Sample Stratified According to Waist/Hip Ratio Tertiles |
|-----------------|----------------|----------------|----------------|----------------|
|                  | Group 1   | Group 2   | Group 3   | P by ANOVA |
|                  | WHR<0.81 | WHR 0.81–0.85 | WHR>0.85 |          |
| Age, y           | 54±0.7   | 55±0.7    | 56±0.8    | 0.09       |
| BMI, kg/m²       | 26.4±0.4 | 27.0±0.4  | 30.2±0.4* | 0.0001     |
| Total cholesterol, mmol/L | 6.28±0.11 | 6.32±0.13 | 6.61±0.13 | 0.18       |
| LDL cholesterol, mmol/L | 3.95±0.12 | 4.03±0.12 | 4.31±0.12 | 0.10       |
| HDL cholesterol, mmol/L | 1.77±0.03 | 1.65±0.04 | 1.54±0.03* | 0.0001 |
| Triglycerides, mmol/L | 1.15±0.05 | 1.36±0.06 | 1.55±0.07* | 0.0001 |
| Systolic BP, mm Hg | 136.8±1.9 | 139.9±2.3 | 144.2±2.2 | 0.06       |
| Diastolic BP, mm Hg | 81.9±0.9  | 82.7±1.0  | 85.4±1.1  | 0.06       |
| Pulse pressure, mm Hg | 54.8±1.6  | 56.2±1.7  | 58.9±1.9  | 0.26       |
| Current smokers, % | 43       | 37        | 32        | 0.25       |
| Pack-years       | 21±2     | 19±2      | 18±2      | 0.47       |
| Fasting glucose, mmol/L | 5.33±0.06 | 5.53±0.13* | 5.70±0.12* | 0.004     |
| Fasting insulin, pmol/L | 31.9±2.8  | 34.2±3.1  | 45.1±3.4* | 0.01       |

Values are means±SE. WHR indicates waist/hip ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure.

*Significantly different from group 1.
†Significantly different from group 2.

**Table 3. Independent Relations Between Cardiovascular Risk Factors and Common Carotid IMT and IM Area as Determined by Multiple Regression Analyses**

<table>
<thead>
<tr>
<th></th>
<th>IMT β (SE)</th>
<th>IMT P</th>
<th>IM Area β (SE)</th>
<th>IM Area P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>0.008 (0.001)</td>
<td>0.0001</td>
<td>0.19 (0.04)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic</td>
<td>0.001 (0.001)</td>
<td>0.022</td>
<td>0.09 (0.02)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td>0.007 (0.002)</td>
<td>0.003</td>
<td>0.28 (0.06)</td>
<td>0.0001</td>
</tr>
<tr>
<td>R²</td>
<td>30%</td>
<td></td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>0.007 (0.001)</td>
<td>0.0001</td>
<td>0.19 (0.04)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic</td>
<td>0.001 (0.001)</td>
<td>0.02</td>
<td>0.08 (0.01)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td>0.41 (0.15)</td>
<td>0.006</td>
<td>12.3 (4.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>R²</td>
<td>28%</td>
<td></td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

The following variables did not enter the regression models: LDL cholesterol, triglycerides, diastolic blood pressure, cigarette smoking, and insulin.

β (SE) indicates regression coefficient (standard error). R², the coefficient of determination, represents the percentage of the variation in the dependent variable explained by the independent variables in the model.
waist circumference above the limit indicated by the World Health Organization. On this basis, the variance of risk resulting from fatness and its biological complexity in our population may be better represented by WHR than by waist circumference. The increase in regional gluteal fat, which is mostly determined by long-term exposure to endogenous estrogens, may be an indicator of a favorable risk condition for atherosclerosis and interact with the unfavorable risk condition resulting from the increase in waist circumference. Moreover, the epidemiological evidence in women of the role of fat distribution in determining cardiovascular events is derived from the evaluation of WHR.

A number of previous studies have evaluated the relationship between obesity and atherosclerosis, but only a few, focusing on either general or abdominal obesity, used high-resolution B-mode ultrasound end points. In a small case-referent study, Karason et al found that 39 obese patients (79% men) with a BMI of 30 to 40 kg/m² had thicker IM complexes in the carotid bifurcation but not in the common carotid at baseline and had higher IMT progression rates during a 4-year follow-up compared with 35 lean subjects. In the Kuopio Ischemic Heart Disease follow-up study carried out in middle-aged men from eastern Finland, abdominal obesity was associated with an accelerated 4-year increase in the maximum and mean common carotid IMTs, independently of general obesity and other risk factors. In a recently published article, severely obese children showed early abnormalities of the arterial wall, such as lower common carotid compliance and distensibility, and lower brachial arterial reactivity, a marker of endothelial dysfunction, than did control children.

Subjects with a BMI ≥30 kg/m² exhibited structural modifications of the common carotid artery characterized not only by wall thickening but also by lumen enlargement. However, the carotid cross-sectional IM area, a parameter that takes into account changes in both wall thickness and internal diameter that therefore is a more appropriate measure of arterial wall size than IMT alone, was significantly increased in subjects with higher BMI, suggesting a greater impact of body mass excess on carotid wall thickness than on lumen diameter. The calculation of the cross-sectional IM area used in the present study assumes a cylindrical arterial geometry and a quite-constant IMT along the vessel circumference, conditions found in the common carotid artery but not in the bifurcation or internal carotid artery.

The thickening process of the arterial wall observed in obese subjects could be related to an increase in both intimal proliferation and extracellular matrix increase. Obesity has been also demonstrated to affect left ventricular geometry, increasing wall thickness and diastolic diameter. It is thus conceivable that similar hemodynamic and neurohormonal factors cause both arterial and cardiac preclinical structural changes. Obesity is associated with an elevation in total blood volume, basic cardiac output, and heart rate, which can induce neointima proliferation through changes in arterial wall stress. There also is evidence that insulin resistance and the hyperactivity of the renin-angiotensin-aldosterone system described in obese subjects can play an important role in modulating cardiovascular changes.

In the present study, however, the association of BMI and WHR with carotid wall thickening was independent of fasting insulin concentration, an indirect measure of insulin resistance.

Because carotid wall thickening reflects the presence of preclinical atherosclerotic disease at other sites, eg, the coronary arteries, and most importantly is an independent predictor of future cardiovascular events, it could be useful to include carotid ultrasound assessment in screening evaluations of obese subjects to identify those at especially high cardiovascular risk who may require more aggressive therapy. High-resolution B-mode ultrasound also provides an objective tool to determine the possible benefits of dietetic or pharmacological antiobesity treatment because studies using ultrasonographic end points have shown that weight loss slows the yearly rate of increase in carotid-wall thickness.

Although we were able to control for a number of risk factors for atherosclerosis, we cannot, however, exclude the possibility of residual confounding resulting from some unmeasured factors. Prospective, large, population-based studies are needed to confirm our findings.

In conclusion, the present study indicates a graded and independent association between general and abdominal obesity and preclinical carotid artery structural changes in a population of middle-aged women.

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