Relation of Carotid Artery Wall Thickness to Diabetes Mellitus, Fasting Glucose and Insulin, Body Size, and Physical Activity

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Background and Purpose We tested the hypothesis that body mass, waist-to-hip circumference ratio, physical inactivity, diabetes, hyperglycemia, and fasting insulin are each positively associated with asymptomatic carotid artery wall thickness.

Methods Average intimal-medial carotid wall thickness (an indicator of atherosclerosis) was measured noninvasively by B-mode ultrasonography in cross-sectional samples of 45- to 64-year-old adults, both blacks and whites, free of symptomatic cardiovascular disease, in four US communities.

Results Sample mean carotid wall thickness was approximately 0.7 mm in women (n=7956) and 0.8 mm in men (n=6474). Body mass, waist-to-hip ratio, work physical activity, diabetes, and fasting insulin were associated (P<.05) with carotid wall thickness in the hypothesized direction. Adjusted for age, race, smoking, body mass index, artery depth, and carotid intimal-medial wall thickness, suggesting these factors contribute to atherogenesis. (Stroke. 1994;25:66-73.)

Key Words • atherosclerosis • insulin • carotid arteries • diabetes mellitus • obesity

two-fold increase in CVD incidence. Body mass has been associated positively with CVD in many studies, although other studies reported a U-shaped or no association. More recently, studies of fat distribution have shown that abdominal adiposity is an important determinant of CVD risk.

A shortcoming of epidemiologic studies employing clinical CVD end points is an inability to disentangle the two processes related to most atherosclerotic events, namely atherosclerosis and thrombosis. Noninvasive techniques such as B-mode ultrasound can more directly assess atherosclerosis. We report here the relation of carotid artery wall thickness to diabetes, fasting hyperglycemia, fasting insulin, body shape and size, and physical activity in a large sample of middle-aged adults.

Subjects and Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective investigation of atherosclerosis and clinical atherosclerotic diseases in four US communities: Forsyth County, NC; Jackson, Miss; the northwest suburbs of Minneapolis, Minn; and Washington County, Md. A population sample totaling 15 800 persons aged 45 to 64 years was selected; only blacks were sampled in Jackson. The complete study design, sampling strategy, and examination techniques have been published. The response rate was 46% of all eligible subjects in Jackson and 65% to 67% in the other three communities.

Received July 19, 1993; final revision received September 16, 1993.
Measurements

After informed consent, a home interview and clinic examination were conducted. The home interview included assessment of socioeconomic factors, education level, smoking status, medication use, and history of cardiovascular disease and diabetes mellitus. The clinic examination included measurements of cardiovascular risk factors and a B-mode ultrasound examination of selected arterial sites.

Subjects were asked to fast for 12 hours before the clinic examination. Blood specimens were collected into vacuum tubes containing serum separator gel (insulin and glucose) and EDTA (lipids). The tubes were centrifuged at 3000g for 10 minutes at 4°C. After separation, aliquots were quickly frozen at -70°C until analysis within a few weeks. Serum glucose was assessed by the hexokinase method. Serum insulin was assessed using a radioimmunoassay (Institut Kiit; Cambridge Medical Diagnostics, Inc, Billerica, Mass). Total cholesterol and triglycerides were measured by enzymatic methods, and low-density lipoprotein (LDL) cholesterol was calculated. High-density lipoprotein (HDL) cholesterol was measured after dextran-magnesium precipitation. The lipid laboratory participated in the Centers for Disease Control Standardization Program throughout the study.

Body mass index (kg/m²) was computed from height and weight. Circumferences of the waist (umbilical level) and hip (maximum buttocks) were measured to the centimeter. The ratio of waist-to-hip circumferences was calculated as a measure of fat distribution.

Physical activity was assessed by interview using a questionnaire developed by Baecke. The questionnaire included 16 items about usual exertion, and three indexes ranging from 1 (low) to 5 (high) were derived for physical activity at work, during leisure time, and in sports. Leisure time physical activity showed no relation with carotid atherosclerosis, so associations are shown for the work and sport indexes only. Systolic and diastolic fifth phase blood pressures were measured three times in the right arm of seated participants. The mean of the last two measurements was used in analysis.

Prevalent hypertension was defined as systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg or use of antihypertensives. Because an oral glucose tolerance test was not performed, glyceremia status was defined by fasting values and self-reported medical history. Prevalent diabetes mellitus was defined as a fasting glucose ≥7.8 mmol/L (≥140 mg/dL), a nonfasting glucose ≥11.1 mmol/L (≥200 mg/dL), and/or a history of or treatment for diabetes. Hyperglycemia was defined as a fasting glucose of 6.4 to 7.7 mmol/L (115 to 139 mg/dL) and/or a history of treatment for diabetes. Prevalent CVD was defined as a positive history of angina or intermittent claudication by the Rose questionnaire; a self-reported physician-diagnosed history of a heart attack or stroke; evidence of old myocardial infarction by electrocardiogram; or a self-reported history of cardiovascular surgery or angioplasty.

Carotid artery atherosclerosis was determined by high-resolution B-mode ultrasound. Trained technicians in each field center scanned the extracranial carotid arteries bilaterally (and one popliteal artery, not reported here). The carotid arteries were divided into three segments: the distal 1.0-cm straight portion of the common carotid artery, the carotid bifurcation, and the proximal 1.0 cm of the internal carotid artery. Thus, including both sides, six artery segments were scanned. B-mode ultrasound data were recorded onto high-resolution 3/4-in. cassettes and interpreted by trained readers according to a standardized protocol. Using magnified images, readers recorded for each segment up to 11 coordinate points from each echogenic interface that identified an arterial boundary. Between-reader and within-reader coefficients of reliability for average artery wall thickness in the three points from each echogenic interface that identified an arterial boundary. The remaining analyses were performed after excluding those with prevalent CVD to focus on early carotid atherosclerosis in asymptomatic subjects. The distribution of carotid artery intimal-medial wall thickness was slightly right-skewed. The sample mean (SD) wall thickness in those without CVD was 0.69 (0.16) mm in white women (n=11682), 0.73 (0.21) mm in black women (n=3645), and 0.77 (0.17) mm in black men (n=1047). The respective medians were 0.66, 0.69, 0.75, and 0.75 mm.

Figs 1 and 2 illustrate for the four race-sex groups the distribution of carotid artery intimal-medial wall thickness with body mass index, waist-to-hip ratio, the sport index, and self-reported medical history. Prevalent diabetes mellitus was defined as a positive history of angina or intermittent claudication by the Rose questionnaire; a self-reported physician-diagnosed history of a heart attack or stroke; evidence of old myocardial infarction by electrocardiogram; or a self-reported history of cardiovascular surgery or angioplasty.

Carotid artery atherosclerosis was determined by high-resolution B-mode ultrasound. Trained technicians in each field center scanned the extracranial carotid arteries bilaterally (and one popliteal artery, not reported here). The carotid arteries were divided into three segments: the distal 1.0-cm straight portion of the common carotid artery, the carotid bifurcation, and the proximal 1.0 cm of the internal carotid artery. Thus, including both sides, six artery segments were scanned. B-mode ultrasound data were recorded onto high-resolution 3/4-in. cassettes and interpreted by trained readers according to a standardized protocol. Using magnified images, readers recorded for each segment up to 11 coordinate points from each echogenic interface that identified an arterial boundary. Between-reader and within-reader coefficients of reliability for average artery wall thickness in the three points from each echogenic interface that identified an arterial boundary. The remaining analyses were performed after excluding those with prevalent CVD to focus on early carotid atherosclerosis in asymptomatic subjects. The distribution of carotid artery intimal-medial wall thickness was slightly right-skewed. The sample mean (SD) wall thickness in those without CVD was 0.69 (0.16) mm in white women (n=34340), 0.72 (0.15) mm in black women (n=1682), 0.79 (0.20) mm in white men (n=3645), and 0.77 (0.17) mm in black men (n=1047). The respective medians were 0.66, 0.69, 0.75, and 0.75 mm.

Figs 1 and 2 illustrate for the four race-sex groups the association of age-adjusted average carotid wall thickness with body mass index, waist-to-hip ratio, the sport index,
TABLE 1. Selected Baseline Characteristics of Participants by Race and Sex in the ARIC Study, 1987 to 1989

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White (n=5520)</td>
<td>Black (n=2436)</td>
</tr>
<tr>
<td>Age, y</td>
<td>54.0±5.7</td>
<td>53.4±5.7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6±5.5</td>
<td>30.8±6.5</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.89±0.08</td>
<td>0.90±0.08</td>
</tr>
<tr>
<td>Sport index*</td>
<td>2.4±0.8</td>
<td>2.1±0.7</td>
</tr>
<tr>
<td>Work index*</td>
<td>2.0±0.9</td>
<td>2.3±1.0</td>
</tr>
<tr>
<td>Fasting serum glucose, mmol/L</td>
<td>5.7±1.6</td>
<td>6.3±2.7</td>
</tr>
<tr>
<td>Fasting serum insulin, mmol/L†</td>
<td>68±54</td>
<td>105±75</td>
</tr>
<tr>
<td>Diabetes mellitus, %‡</td>
<td>6.3</td>
<td>14.7</td>
</tr>
<tr>
<td>Plasma LDL cholesterol, mmol/L</td>
<td>3.5±1.0</td>
<td>3.6±1.1</td>
</tr>
<tr>
<td>Plasma HDL cholesterol, mmol/L</td>
<td>1.5±0.5</td>
<td>1.5±0.5</td>
</tr>
<tr>
<td>Cigarette smoking, pack-years</td>
<td>12±18</td>
<td>8±15</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>26.1</td>
<td>55.7</td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. Values are mean±SD or percent.

*Range 1 to 5 (low to high).
†Excludes pharmacologically treated diabetics.
‡Reported and/or treated diabetes, fasting glucose ≥7.8 mmol/L, or nonfasting glucose ≥11.1 mmol/L.

fasting insulin, fasting glucose, and diabetes. Tables 3 and 4 show the associations by sex from regression modeling. Twelve separate models were run, two (models 1 and 2) for each characteristic considered separately. Simultaneous adjustment was viewed as inappropriate because body size, physical activity, and glucose and insulin metabolism are causally intertwined; yet adjustment for body mass index was required to account for possible nonrandom missing wall thickness data (see "Methods"). Therefore, the most appropriate assessment of the overall associations is model 1, which adjusted for age, race, pack-years of smoking, artery depth, ARIC field center, and body mass index. Model 2 assessed whether the associations in model 1 might be explained by several mediating factors, ie, HDL cholesterol, LDL cholesterol, and hypertension. The regression coefficients, for the most part, were larger for men than for women. Most of the associations were statisti-

TABLE 2. Characteristics of Participants With or Without Cardiovascular Disease* at Baseline, by Race and Sex in the ARIC Study, 1987 to 1989

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White (n=728)</td>
<td>Black (n=4677)</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.0</td>
<td>53.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.9</td>
<td>26.4</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.916</td>
<td>0.887</td>
</tr>
<tr>
<td>Sport index</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Work index</td>
<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Fasting serum glucose, mmol/L</td>
<td>6.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Fasting serum insulin, mmol/L†</td>
<td>81</td>
<td>66</td>
</tr>
<tr>
<td>Diabetes mellitus, %§</td>
<td>13.5</td>
<td>5.4</td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities; CVD, cardiovascular disease. Values are mean or percent.

*Self-reported heart attack, stroke, angioplasty, cardiovascular surgery; positive Rose questionnaire for angina or claudication; or electrocardiographic evidence of myocardial infarction.
†P<.05 for sex- and race-specific comparison between CVD and no CVD.
‡Excludes pharmacologically treated diabetic subjects.
§Reported and/or treated diabetes, fasting glucose ≥7.8 mmol/L, or nonfasting glucose ≥11.1 mmol/L.
Fig 1. Sex- and race-specific associations of average carotid artery intimal-medial wall thickness with body mass index, waist-to-hip ratio, sport index, and fasting insulin (excluding pharmacologically treated diabetics), in participants free of cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) Study, 1987 to 1989.

Age-adjusted average carotid intimal-medial wall thickness increased steadily with increasing body mass and waist-to-hip ratio in each sex-race group. From model 1, the predicted increase in wall thickness for a 5-kg/m² (1 SD) increase in body mass was about 0.017 mm for women and about 0.026 mm for men. The predicted increase in wall thickness for an increase of 0.07 unit (1 SD) in waist-to-hip ratio was 0.020 mm in women and 0.029 mm in men. (To place these in perspective, a 0.02-mm increase would represent about a 3% increase in average carotid wall thickness.) Both the body mass and waist-to-hip ratio associations with wall thickness were reduced but remained statistically significant (P<.01) after adjustment for other major risk factors.

Wall thickness decreased with increasing physical exertion at work for both men and women; by model 1

TABLE 3. Adjusted Regression Coefficients ($\beta$) for Multiple Linear Regressions of Average Carotid Artery Intimal-Medial Wall Thickness (mm) on Selected Characteristics in Women Free of Cardiovascular Disease in the ARIC Study, 1987 to 1989

<table>
<thead>
<tr>
<th>Characteristic* (separately considered)</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Body mass index, kg/m$^2$</td>
<td>0.0033</td>
<td>0.0021</td>
</tr>
<tr>
<td>(2) Waist-to-hip ratio, 1 unit</td>
<td>0.2885</td>
<td>0.2135</td>
</tr>
<tr>
<td>(3) Work index, 1 unit</td>
<td>-0.0063</td>
<td>-0.0060</td>
</tr>
<tr>
<td>(4) Sport index, 1 unit</td>
<td>-0.0009</td>
<td>0.0011</td>
</tr>
<tr>
<td>(5) Diabetes (yes vs no)</td>
<td>0.0716</td>
<td>0.0605</td>
</tr>
<tr>
<td>Hyperglycemia (yes vs no)$^t$</td>
<td>0.0203</td>
<td>0.0113</td>
</tr>
<tr>
<td>(6) Fasting insulin, mmol/L$^t$</td>
<td>0.00017</td>
<td>0.00009</td>
</tr>
</tbody>
</table>

*Average wall thickness was the dependent variable, and 12 separate regression models were run with the six listed characteristics as separately considered independent variables adjusted successively for two sets of covariates.

Model 1 coefficients were adjusted for age, race, pack-years of smoking, artery depth, Atherosclerosis Risk in Communities (ARIC) field center, and body mass index [except (1)]; Model 2 coefficients were adjusted also for hypertension (yes, no), plasma low-density lipoprotein cholesterol, and plasma high-density lipoprotein cholesterol.

$^t$Hyperglycemia indicates fasting glucose of 6.4 to 7.7 mmol/L.

By model 1 estimation, the decrease was 0.006 to 0.010 mm per unit increase in the work index. Inclusion of the other major risk factors (model 2) did not appreciably alter this estimate. The association for sports participation, however, was not statistically significant in either sex.

By model 1 estimation, in both sexes, diabetic subjects had carotid artery walls about 0.07 mm thicker and subjects with fasting glucose equal to 6.4 to 7.7 mmol/L had artery walls about 0.02 mm thicker than subjects with fasting glucose <6.4 mmol/L (Fig 2 and Tables 3 and 4). Adjustment for hypertension and plasma lipids reduced these estimates somewhat. Among those not pharmacologically treated for diabetes, a 100-mmol/L greater fasting insulin was associated in model 1 with thicker carotid artery walls by about 0.017 mm in women and 0.016 mm in men.

It has been suggested that the sex difference in cardiovascular disease may be due to a lower waist-to-hip ratio in women$^{19}$ and is greatly diminished in diabetic subjects.$^{20}$ However, the waist-to-hip ratio and diabetes graphs in Figs 1 and 2 suggest that carotid atherosclerosis is higher in men than women both for each level of waist-to-hip ratio and for participants with diabetes. In a linear regression model that included age, race, pack-years of smoking, body mass index, artery depth, and ARIC field center, women were predicted to have a 0.08-mm lower average wall thickness than men. When a term for waist-to-hip ratio was added to the model, this male/female difference was mildly reduced to 0.06 mm. Alternatively, when terms for hyperglycemia and diabetes were added, the male/female difference of 0.08 mm was unchanged.

We also ran model 1 regressions separately for the average wall thickness of the common carotid, the bifurcation, and the internal carotid artery segments. Associations tended to be in the same direction for all

TABLE 4. Adjusted Regression Coefficients ($\beta$) for Multiple Linear Regressions of Average Carotid Artery Intimal-Medial Wall Thickness (mm) on Selected Characteristics in Men Free of Cardiovascular Disease in the ARIC Study, 1987 to 1989

<table>
<thead>
<tr>
<th>Characteristic* (separately considered)</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Body mass index, kg/m$^2$</td>
<td>0.0052</td>
<td>0.0037</td>
</tr>
<tr>
<td>(2) Waist-to-hip ratio, 1 unit</td>
<td>0.4155</td>
<td>0.3632</td>
</tr>
<tr>
<td>(3) Work index, 1 unit</td>
<td>-0.0102</td>
<td>-0.0093</td>
</tr>
<tr>
<td>(4) Sport index, 1 unit</td>
<td>-0.0043</td>
<td>-0.0034</td>
</tr>
<tr>
<td>(5) Diabetes (yes vs no)</td>
<td>0.0731</td>
<td>0.0698</td>
</tr>
<tr>
<td>Hyperglycemia (yes vs no)$^t$</td>
<td>0.0184</td>
<td>0.0147</td>
</tr>
<tr>
<td>(6) Fasting insulin, mmol/L$^t$</td>
<td>0.00016</td>
<td>0.00013</td>
</tr>
</tbody>
</table>

*Average wall thickness was the dependent variable and 12 separate regression models were run with the six listed characteristics as separately considered independent variables adjusted successively for two sets of covariates.

Model 1 coefficients were adjusted for age, race, pack-years of smoking, artery depth, Atherosclerosis Risk in Communities (ARIC) field center, and body mass index [except (1)]; Model 2 coefficients were adjusted also for hypertension (yes, no), plasma low-density lipoprotein cholesterol, and plasma high-density lipoprotein cholesterol.

$^t$Hyperglycemia indicates fasting glucose of 6.4 to 7.7 mmol/L.

$^t$Excludes pharmacologically treated diabetes.
three arterial segments, but there was some variation in the strength. For example, associations of wall thickness with obesity status, the waist-hip ratio, and waist-hip ratio were generally stronger for the bifurcation and internal carotid segments than for the common carotid.

Discussion

Epidemiologic studies of atherosclerotic diseases typically study clinical end points, such as myocardial infarction or coronary heart disease death. However, among those with underlying atherosclerosis, clinical atherosclerotic events occur only infrequently, usually because of rupture of a plaque and subsequent thrombosis. A theoretical advantage of B-mode ultrasound is that risk factors for atherosclerosis might be directly quantifiable. Indeed, the clinical use of B-mode in measuring symptomatic carotid artery stenoses is well established. However, because most ARIC participants do not have stenotic carotid lesions, we measured average carotid intimal-medial wall thickness. It is possible that greater than average wall thickness may represent not only early atherosclerosis, but also medial hypertrophy or hyperplasia from other causes such as hypertension. The validity of intimal-medial wall thickness as a measure of atherosclerosis and its reliability in the ARIC Study have been described.16,17 Wall thickness in ARIC, is strongly associated with atherogenic lipids and smoking, as well as hypertension, suggesting that the atherosclerotic process is reflected in intimal-medial wall thickness (see "Methods").

The strengths of ARIC are its size and its biracial population-based samples. We found that greater body mass index was not an independent risk factor. We nevertheless tested in regression models accounting for hyperglycemia and diabetes, may explain the sex difference in wall thickness. Accounting for waist-to-hip ratio reduced the strength. For example, associations of wall thickness with obesity status, the waist-hip ratio, and waist-hip ratio were generally stronger for the bifurcation and internal carotid segments than for the common carotid.
factor being partly responsible for sex differences in CVD.

There are several mechanisms by which the examined risk factors may be associated with atherosclerosis. Theories of atherosclerosis suggest that two crucial steps are 

- endothelial injury and LDL uptake by subendothelial macrophages to form foam cells and eventually atherosclerotic plaques. Greater body mass, waist-to-hip ratio, physical inactivity, fasting insulin, and diabetes all tend to be associated with higher blood pressure, which may injure endothelium. They are also associated with higher plasma triglycerides and LDL, and with lower HDL.43,44 Observed associations with wall thickness were weakened when hypertension and plasma lipids were included in the regressions (model 2), suggesting that hypertension and atherogenic lipids may indeed partly mediate the associations. It is also possible that the examined risk factors directly promote endothelial injury, LDL uptake, or smooth muscle proliferation. For example, insulin has been shown to enhance cholesterol transport into arteriolar smooth muscle cells, and to increase the proliferation and cholesterol synthesis of these cells.45 Regardless of the cellular mechanisms, this study provides additional support for the assertion that abdominal obesity, physical inactivity, and abnormal glucose metabolism are atherogenic and that efforts for reducing them must be considered.

Acknowledgments

This study was supported by grant contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022 from the National Heart, Lung, and Blood Institute. The authors thank the ARIC coinvestigators and staff for their important contributions and Laura Kemmis, Larry Crum, and Gretchen Marcucci for their help in manuscript preparation.

References


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Stroke. 1994;25:66-73
doi: 10.1161/01.STR.25.1.66

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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