Association of Multiple Risk Factors and Insulin Resistance With Increased Prevalence of Asymptomatic Coronary Artery Disease by an Electron-Beam Computed Tomographic Study

Yadon Arad, David Newstein, Fredrick Cadet, Marguerite Roth, Alan D. Guerci

Abstract—The insulin resistance syndrome, consisting of resistance to insulin and several metabolic abnormalities, is associated with an increased risk of symptomatic coronary artery disease. Asymptomatic persons with increased coronary calcification have increased coronary plaque and an increased likelihood of future cardiovascular events. Electron-beam computed tomography–derived coronary artery calcium scores, metabolic and anthropometric parameters, and fasting and stimulated concentrations of glucose and insulin were measured in 1160 asymptomatic men and women. Coronary artery calcium scores were positively correlated with glucose, insulin, and homeostasis model assessment (HOMA) insulin resistance. Calcium scores were positively correlated with intra-abdominal adiposity, age, total cholesterol/high density lipoprotein (HDL) ratio, low density lipoprotein, triglycerides, blood pressure, and HOMA beta cell function and inversely correlated with HDL and peripheral fat. These correlations, except for 2-hour glucose, remained significant for all subjects with fasting serum glucose <126 mg/dL or all subjects with fasting serum glucose 110 mg/dL. In a multivariate analysis, age, sex, family history of premature coronary artery disease, intra-abdominal adiposity, low density lipoprotein, and smoking independently predicted calcium scores. Blood pressure, HDL, triglycerides, glucose, insulin, and HOMA insulin resistance or beta cell function were not independently correlated with coronary artery calcium scores. Asymptomatic individuals with insulin resistance have elevated coronary calcium scores. The association between insulin resistance and coronary calcification persists with impaired glucose tolerance and normal fasting serum glucose. Central/visceral adiposity may be a determinant of insulin resistance and atherosclerosis even in asymptomatic nondiabetic persons. (Arterioscler Thromb Vasc Biol. 2001;21:2051-2058.)

Key Words: calcium ■ electron-beam computed tomography ■ risk factors ■ insulin ■ glucose

Type II diabetes mellitus and impaired glucose tolerance are associated with an increased risk of coronary and peripheral vascular atherosclerosis,1-7 and this association persists even in persons with glucose and hemoglobin A1c concentrations at the upper limit of the normal range.8 Insulin resistance, defined as peripheral resistance to the actions of insulin and characterized by a combination of elevated insulin and glucose concentrations, is associated with a constellation of abnormalities, including hypertension,9,10 intra-abdominal (“central” or “visceral”) adiposity,11,12 and lipid abnormalities, in particular, elevated triglycerides, reduced HDL cholesterol, and small dense LDL.13,14 The increased propensity of persons with insulin resistance for cardiovascular events may be due to smaller arterial diameter (which is possibly due to increased diffuse atherosclerosis),15 impaired endothelial function,16,17 the propensity of insulin-resistant persons to develop hypertension,10 or an exaggerated inflammatory and proliferative response to injury.18-22 Nonetheless, the predisposing risk factors for, and the pathological characteristics of, coronary artery disease (CAD) in diabetic subjects are similar to those of the general population.23,24

Previous attempts to correlate glucose homeostasis with asymptomatic CAD have been limited by the inability to quantify preclinical coronary disease in asymptomatic persons. For practical purposes, stress tests are unable to detect nonobstructive coronary disease and although carotid artery intima-media thickness is associated with coronary disease,25-28 this association is relatively weak.29-32

Electron-beam computed tomography (CT)–derived coronary artery calcium (CAC) scores are closely correlated with total plaque burden,33-35 angiographic obstruction,36-39 and future cardiovascular events in symptomatic and asymptomatic persons.40-44 Furthermore, the relationships of CAC scores with the severity of coronary atherosclerosis and with the likelihood of future CAD events are independent of traditional CAD risk factors.38,42,43,45

Given the graded prognostic importance of coronary atherosclerosis,46 we performed metabolic testing and electron-beam CT on 1160 asymptomatic persons selected randomly from a population-based study. Our goals were to determine the relationship between insulin resistance, its associated metabolic abnormalities, and coronary calcification and, to
the extent possible, to shed light on the cause(s) of insulin resistance.

**Methods**

The St. Francis Heart Study is a population-based natural history and randomized clinical trial of 50- to 70-year-old men and women with no clinical or historical evidence of CAD. The study is designed to explore new correlates of subclinical CAD by use of electron-beam CT and to test whether treatment with atorvastatin and antioxidants affects the likelihood of future cardiovascular events in men and women with elevated age- and sex-adjusted CAC scores. The present report describes the correlations of baseline CAC scores with CAD risk factors and insulin resistance parameters in a randomly selected subgroup of the St. Francis Heart Study.

The recruitment scheme for the St. Francis Heart Study is shown in Figure 1. Approximately 300,000 recruitment letters and questionnaires were sent to residents of Nassau and Queens counties in New York. Approximately one third of these were sent to every age-eligible subscriber of the Health Insurance Program of New York. The rest were sent to members of a variety of local organizations, such as the police department, YMCA, and chamber of commerce and to ~5000 local physicians. In addition, persons responded to advertising in a variety of local newspapers and local radio stations, including those targeted to an African American and Spanish audience, including the Anton Community Newspaper chain (24 newspapers with a readership of 60,000). Approximately 20,000 questionnaires were returned and screened for the exclusion criteria. Five thousand five hundred eighty-two subjects met the enrollment criteria (see below) and were invited for a screening coronary electron-beam CT.

One third of the subjects with CAC scores above the 80th percentile for age and sex and one fifth of the subjects with scores below the 80th percentile were randomly selected to participate in the risk factor analysis sub-study. The choice of this particular cutoff point is based on the study of Raggi et al., in which subjects in the top 20th percentile of calcium scores had a risk ratio of 20 for future cardiovascular events, and the report by Rubmerger et al. on the sensitivity and specificity of various calcium score thresholds for obstructive disease in men and women of various ages. We believed that enrolling a higher percentage from the high-score group should result in a more useful range of observations by reducing the number of subjects with a zero score. The determination of age- and sex-adjusted percentile CAC scores was based on previous analysis of 5000 asymptomatic individuals who had previously undergone coronary screening at our institution, which is similar to the distribution of CAC scores in a cohort of 35,000 individuals scanned at the University of Illinois and in nearly 19,000 at the Cooper Clinic in Dallas.

Patients were excluded from the study for any of the following conditions: (1) clinical evidence of atherosclerosis, including symptomatic coronary artery, cerebrovascular, or peripheral vascular disease, or other symptomatic heart disease; (2) diabetes mellitus requiring treatment with insulin; (3) any disease anticipated to cause death within 5 years; (4) bleeding diatheses; (5) cancer within the previous 5 years (except for skin cancer); (6) anemia requiring medical workup; (7) current systemic hormone therapy, including prescription estrogens or glucocorticoids; (8) current therapy with anticoagulants, cyclosporin, or lipid-lowering drugs or the intake of more than twice the required daily allowance of vitamin E (total >60 IU/d) or vitamin C (total >120 mg/d); (9) a coronary angiogram within the past 5 years; and (10) weight greater than the upper limit for the electron-beam CT scanner (300 lb).

Screening coronary electron-beam CT was performed by using an Imatron C-150XP scanner. Forty contiguous 3-mm-thick slices were obtained during a single breath-holding, beginning at the lower edge of the carina. The field of view was 35 cm, and the scan time was 100 ms per slice, with synchronized ECG triggering at 80% of the RR interval. CAC scores were calculated according to the method of Agatston et al. At least 2 adjacent pixels with a density >130 Hounsfield units were required to define a lesion.

In addition to coronary artery scanning, a single CT slice was obtained at the level of the umbilicus to assess intra-abdominal and subcutaneous fat distribution. The abdominal cavity was outlined on the computer screen, and the numbers of pixels appearing as fat (densities between −130 and 0 Hounsfield units) inside the abdominal cavity, as well as in the whole slice, were calculated. The amount of extra-abdominal (subcutaneous) fat was calculated by subtracting intra-abdominal fat from total abdominal fat. This method limits the radiation exposure, and the results are highly correlated with total abdominal fat. Abdominal height was determined as the distance between 2 parallel horizontal lines touching the most posterior and most anterior edges of the abdomen.

During the screening visit, we obtained a complete medical history and performed a comprehensive physical examination, including supine vital signs, standing height, weight, waist, and hip circumference, and triceps and subscapular skinfold thickness. A resting ECG was obtained. Patients with Q waves ≥40 ms in 2 contiguous leads were excluded from the study. Those with Q waves ≥30 ms in 2 contiguous leads or poor R-wave progression underwent transthoracic echocardiography. Those with hypokinesia in areas corresponding to the ECG abnormalities were also excluded from the study.

During the same visit, we obtained fasting blood samples for the determination of lipid profile, including total cholesterol, triglycerides, HDL cholesterol, and calculated LDL cholesterol, a comprehensive chemistry profile, and a complete blood count. On a subsequent visit, the subjects underwent an oral glucose tolerance test.
test. Serum concentrations of glucose and insulin were measured in the fasting state and again 2 hours after the oral administration of 75 g glucose.

Laboratory tests were performed on standard commercial instruments (LabCorp, Inc.). Coefficients of variations for the lipids and chemistry assays were all <2%. Insulin was measured by a radioimmunoassay (Coat-A-Count) with interassay and intra-assay coefficient of variation of <10%.

**Statistical Analyses**

For analyses using discrete variables, insulin resistance markers were defined as follows: (1) HDL cholesterol concentration <35 mg/dL; (2) a history of hypertension, systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mg Hg; (3) intra-abdominal fat, abdominal height, or waist/hip ratio greater than the median for the 1160 subjects (120.9 cm2, 25.2 cm, and 0.9237, respectively); (4) a history of diabetes, fasting insulin, or 2-hour insulin greater than the median; and (5) fasting serum triglyceride concentration >116 mg/dL.

Insulin resistance without diabetes (or impaired glucose tolerance) is defined as serum glucose concentrations between 111 and 126 mg/dL.

Homeostasis model assessment (HOMA) insulin resistance is defined as follows: (FI/FG)22.5. The HOMA beta cell function is defined as follows: (20×FI)/(FG−3.5), where FI is fasting insulin, and FG is fasting glucose. These values correlate with measurements of insulin resistance and beta cell function by use of the euglycemic-hyperinsulinemic clamp and the hyperglycemic clamp, respectively.

The associations between continuous baseline risk factors and CAC scores and among the CAD risk factors were assessed by use of Spearman correlations. Analyses were performed for the whole group, for men and women separately, for subjects with fasting serum glucose <112 mg/dL, and for subjects with fasting serum glucose <110 mg/dL.

Stepwise multivariate analyses of the correlation of various risk factors with the CAC scores were performed after logarithmic transformation of the calcium score and without forcing any variables into the models.

**Results**

Enrollment began in August 1996 and was completed in March 1999. One thousand one hundred sixty subjects were enrolled in the risk factor analysis substudy. More men than women volunteered and qualified for electron-beam CT screening (3479 men versus 2103 women) and for the risk factor analysis study (73.6% men versus 26.4% women). Percentages were as follows: 92.9% were white, 3.3% were African American, 1.8% were Hispanic, 1.3% were Asian, and 0.7% listed their race as “other.” Mean age was 59±5.9 years. Mean CAC score was 169±348, with a range from 0 to 4057. Other baseline characteristics are shown in Table 1.

Table 2 shows the relationship between CAC scores and glucose, insulin, HOMA-derived insulin resistance, and HOMA-derived beta cell function. In the group as a whole, all parameters were positively and significantly associated with increased CAC, even in subjects with impaired glucose tolerance (fasting serum glucose 111 to 126 mg/dL) or normal fasting glucose. There were some differences between men and women. For example, fasting and 2-hour glucose levels were significantly correlated with calcium scores in women but not in men.

CAC scores increased progressively with an increasing number of insulin resistance markers (Figure 2, P for trend <0.0001).

CAC scores were positively correlated with fasting and postchallenge glucose and insulin concentrations, HOMA insulin resistance, and HOMA beta cell function (Table 2). Most of these correlations remained significant for men and women analyzed separately and for subjects with fasting serum glucose <110 mg/dL and those with fasting serum glucose <110 mg/dL. The correlations across these subgroups were most consistent for HOMA insulin resistance.

CAC scores were also correlated positively (in decreasing order) with waist/hip ratio, age, abdominal height, intra-abdominal fat, systolic blood pressure, triglycerides, diastolic blood pressure, LDL cholesterol concentration, and subcapular skinfold thickness. CAC scores were inversely correlated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Subjects</th>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Median</td>
<td>Mean±SD</td>
<td>Median</td>
<td>Mean±SD</td>
<td>Median</td>
</tr>
<tr>
<td>Age</td>
<td>58.7±6.9</td>
<td>59.0</td>
<td>58.4±5.9</td>
<td>58</td>
<td>59.1±6.0</td>
<td>59</td>
</tr>
<tr>
<td>CAC scores</td>
<td>169±348</td>
<td>17.2</td>
<td>281.0±501.6</td>
<td>67</td>
<td>98.2±285.0</td>
<td>1.5</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>147.7±34.0</td>
<td>143.5</td>
<td>141±33.0</td>
<td>142</td>
<td>152.0±35.3</td>
<td>147</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>51.4±14.4</td>
<td>49.0</td>
<td>47.0±12.1</td>
<td>45</td>
<td>61.2±15.8</td>
<td>60</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>129.7±105.0</td>
<td>105.0</td>
<td>153.0±121.0</td>
<td>121</td>
<td>115.6±69.9</td>
<td>93</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>95.7±20.0</td>
<td>91.5</td>
<td>98.4±19.0</td>
<td>95</td>
<td>93.0±13.0</td>
<td>91</td>
</tr>
<tr>
<td>2-Hour glucose, mg/dL</td>
<td>106.4±92.5</td>
<td>92.5</td>
<td>116.0±53.5</td>
<td>105</td>
<td>111.6±44.3</td>
<td>99</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL</td>
<td>15.0±10.1</td>
<td>11.6</td>
<td>14.2±10.0</td>
<td>13.3</td>
<td>12.3±9.0</td>
<td>10</td>
</tr>
<tr>
<td>2-Hour insulin, μU/mL</td>
<td>81.1±78.3</td>
<td>54.1</td>
<td>78.1±71.2</td>
<td>57.8</td>
<td>77.4±69.3</td>
<td>54.9</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.917±0.095</td>
<td>0.92</td>
<td>0.96±1.27</td>
<td>0.95</td>
<td>0.84±0.09</td>
<td>0.83</td>
</tr>
<tr>
<td>IAF, mm2</td>
<td>136.5±80.0</td>
<td>120.9</td>
<td>144.7±76.1</td>
<td>133.6</td>
<td>93.8±58.7</td>
<td>81.0</td>
</tr>
<tr>
<td>SST, mm</td>
<td>27.2±11.0</td>
<td>27.0</td>
<td>30.7±12.5</td>
<td>30</td>
<td>30.6±12.5</td>
<td>29</td>
</tr>
<tr>
<td>TST, mm</td>
<td>18.9±8.6</td>
<td>18.0</td>
<td>15.8±8.2</td>
<td>14</td>
<td>26.9±8.7</td>
<td>27</td>
</tr>
</tbody>
</table>

LDL-C indicates LDL cholesterol; HDL-C, HDL cholesterol; IAF, intra-abdominal fat; SST, subcapular skinfold thickness; and TST, triceps skinfold thickness.
TABLE 2. Correlations of Glucose Homeostasis Parameters With CAC Scores

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (n=1160)</th>
<th>Men (n=854)</th>
<th>Women (n=306)</th>
<th>Fasting Blood Glucose, mg/dL (n=801)</th>
<th>Fasting Blood Glucose, mg/dL &lt;110 (n=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>0.14</td>
<td>&lt;0.0001</td>
<td>0.06</td>
<td>0.08</td>
<td>0.15</td>
</tr>
<tr>
<td>2-Hour glucose, mg/dL</td>
<td>0.10</td>
<td>0.0014</td>
<td>0.06</td>
<td>0.08</td>
<td>0.19</td>
</tr>
<tr>
<td>Fasting insulin, (\mu U/mL)</td>
<td>0.13</td>
<td>0.001</td>
<td>0.10</td>
<td>0.007</td>
<td>0.12</td>
</tr>
<tr>
<td>2-Hour insulin, (\mu U/mL)</td>
<td>0.10</td>
<td>0.0018</td>
<td>0.06</td>
<td>0.09</td>
<td>0.22</td>
</tr>
<tr>
<td>HOMA insulin resistance</td>
<td>0.15</td>
<td>&lt;0.0001</td>
<td>0.11</td>
<td>0.0023</td>
<td>0.14</td>
</tr>
<tr>
<td>HOMA beta cell function</td>
<td>0.09</td>
<td>0.0032</td>
<td>0.08</td>
<td>0.0251</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Values are univariate correlations of fasting and stimulated glucose and insulin, HOMA insulin resistance, and HOMA beta cell function with CAC scores. Shown are the data for the whole population, for men and women separately, for individuals with fasting blood glucose 126 mg/dL, and for individuals with fasting blood glucose 110 mg/dL.

P<0.05 is considered significant.

with HDL concentration and with triceps skinfold thickness and were not correlated with subcutaneous (extra-abdominal) fat (Table 3). There were some differences between men and women. For example, triglycerides, LDL, fasting and stimulated glucose and insulin, and subscapular skinfold thickness were significantly correlated with CAC scores in women, but only fasting insulin was correlated with CAC scores in men. Most of these correlations again remained significant for subjects with fasting serum glucose <126 mg/dL or <110 mg/dL.

As expected, many features of the insulin resistance syndrome were correlated with each other. The 3 measures of central/visceral adiposity were positively correlated with one another (\(r=0.42\) to 0.82, \(P<0.0001\)). Visceral obesity was positively correlated with fasting and 2-hour glucose and insulin, systolic and diastolic blood pressures, and triglycerides and was inversely correlated with HDL (\(r=0.22\) to 0.50, \(P<0.0001\) for all parameters). There was no correlation between central obesity and LDL cholesterol. Subcutaneous fat was correlated with triceps skinfold thickness (both measures of peripheral fat accumulation). Fasting and stimulated insulin and glucose were correlated positively with triglycerides and systolic and diastolic blood pressures and negatively with HDL cholesterol (\(r=0.15\) to 0.37, \(P<0.0001\) for all parameters).

Multivariate Analyses

The final multivariate model included (in decreasing order) age, sex, a family history of premature atherosclerosis, LDL cholesterol, central obesity, and smoking (Table 4). The inclusion of any measure of central obesity, while excluding the other 2, resulted in a similar final model. All together, these 6 factors accounted for 82% of the overall variability in CAC scores (Figure 3). These correlations remained significant for subjects with fasting serum glucose <126 mg/dL and for subjects with fasting serum glucose <110 mg/dL. After adjustment for these 6 variables, HDL, triglycerides, glucose and insulin levels, HOMA insulin resistance and beta cell function, triceps skinfold thickness, and subcutaneous fat were no longer correlated with CAC scores in the multivariate model.

Discussion

The present study extends previous observations regarding the relationship of impaired glucose tolerance and insulin resistance with atherosclerosis. Using coronary electron-beam CT, we demonstrate for the first time that insulin resistance and its associated metabolic abnormalities are correlated with increased coronary atherosclerosis even in asymptomatic persons and even in the absence of elevated fasting serum glucose concentrations. Furthermore, HOMA beta cell function was positively correlated with CAC scores, indicating that asymptomatic CAD may be correlated with increased, rather than decreased, beta cell function.

Additionally, we found that intra-abdominal obesity was correlated with insulin resistance and with its associated metabolic characteristics. Furthermore, intra-abdominal obesity was the only parameter of the insulin resistance syndrome (including glucose, insulin, and HOMA insulin resistance) that remained independently correlated with CAC scores after the multivariate analysis.

These observations suggest that intra-abdominal adiposity but not peripheral adiposity is a significant contributor to insulin resistance and asymptomatic atherosclerosis. This interpretation of our data is consistent with epidemiological data correlating the increased incidence of insulin resistance and diabetes in western societies with increased obesity and with the effects of insulin sensitizers such as troglitazone to decrease intra-abdominal fat.\(^{53,54}\) It is also consistent with the observation by Barzi and colleagues\(^{55,56}\) that surgical removal of intra-abdominal fat in Sprague-Dawley rats reverses hepatic insulin resistance.
Previous studies have reported that persons with diabetes but without evidence of CAD have a risk of future CAD events similar to persons with previous CAD but no diabetes; these reports led to the suggestion that diabetics without symptoms of CAD should be treated according to secondary prevention guidelines. Increased coronary calcification increases the risk of future cardiovascular events with odds ratios ranging from 8 to 25. The presence of increased coronary artery calcification in nondiabetic subjects with insulin resistance or high normal glucose suggest that such subjects might also benefit from reduction of LDL cholesterol to secondary prevention goals.

Other studies have documented a relationship between the presence of diabetes and coronary or peripheral calcification. Siitonen et al found increased aortic calcification in diabetic men by use of conventional chest radiography. Other investigators have reported a relationship between electron-beam CT–derived CAC scores and type II and type I diabetes. Yoshida et al found that increased coronary calcification was associated with increased likelihood of diabetic microvascular complications. In an autopsy study of sudden death cases, Burke et al found that coronary calcification was also associated with diabetes, as well as with an increased the likelihood of acute and healed plaque rupture. Finally, Mahoney et al found that markers of insulin resistance, such as increased body mass index, decreased HDL, and increased blood pressure in childhood, predict increased coronary calcification in young adults.

However, the present study is unique because of its large size, the unbiased selection of the study population, the careful exclusion of subjects with CAD, the direct assessment of insulin resistance and intra-abdominal adiposity, and the multivariate analyses. In addition, the exclusion of insulin-treated subjects and the separate analyses for nondiabetic subjects with milder degrees of insulin resistance should prevent the inclusion of complications that would otherwise be expected among such patients.

### Table 3. Univariate Analysis of the Correlation of CAD Risk Factors and Insulin Resistance Markers With CAC Scores for the Same Groups as in Table 1

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (n=1160)</th>
<th>Men (n=854)</th>
<th>Women (n=306)</th>
<th>Fasting Blood Glucose, mg/dL (n=801)</th>
<th>Fasting Blood Glucose, mg/dL &lt;110 (n=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.23 &lt;0.0001</td>
<td>0.25 &lt;0.0001</td>
<td>0.23 &lt;0.0001</td>
<td>0.22 &lt;0.0001</td>
<td>0.21 &lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.17 &lt;0.0001</td>
<td>0.10</td>
<td>0.17 &lt;0.0001</td>
<td>0.17 &lt;0.0001</td>
<td>0.16 &lt;0.0001</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.20 &lt;0.0001</td>
<td>-0.09</td>
<td>-0.09</td>
<td>-0.19 &lt;0.0001</td>
<td>-0.19 &lt;0.0001</td>
</tr>
<tr>
<td>LDL</td>
<td>0.07 0.017</td>
<td>0.09</td>
<td>0.20 &lt;0.0001</td>
<td>0.10 &lt;0.001</td>
<td>0.10 0.002</td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>0.21 &lt;0.0001</td>
<td>0.13</td>
<td>0.20 &lt;0.001</td>
<td>0.21 &lt;0.0001</td>
<td>0.20 &lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.18 &lt;0.0001</td>
<td>0.13</td>
<td>0.18 &lt;0.0002</td>
<td>0.17 &lt;0.0001</td>
<td>0.17 0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.14 &lt;0.0001</td>
<td>0.13</td>
<td>0.18 &lt;0.0002</td>
<td>0.13 &lt;0.0001</td>
<td>0.13 &lt;0.0001</td>
</tr>
<tr>
<td>Triceps skinfold thickness</td>
<td>-0.15 &lt;0.0001</td>
<td>0.003</td>
<td>0.053</td>
<td>-0.15 &lt;0.001</td>
<td>-0.16 &lt;0.0001</td>
</tr>
<tr>
<td>Subscapular skinfold thickness</td>
<td>0.08 0.0065</td>
<td>0.06</td>
<td>0.15</td>
<td>0.06 0.04</td>
<td>0.05 NS</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.32 &lt;0.0001</td>
<td>0.19</td>
<td>0.17 &lt;0.0001</td>
<td>0.32 0.0001</td>
<td>0.30 &lt;0.0001</td>
</tr>
<tr>
<td>Abdominal height</td>
<td>0.25 &lt;0.0001</td>
<td>0.15</td>
<td>0.22 &lt;0.0001</td>
<td>0.23 0.0001</td>
<td>0.21 &lt;0.0001</td>
</tr>
<tr>
<td>Intra-abdominal fat</td>
<td>0.20 &lt;0.0001</td>
<td>0.10</td>
<td>0.16</td>
<td>0.18 0.001</td>
<td>0.18 &lt;0.0001</td>
</tr>
<tr>
<td>Subcutaneous abdominal fat</td>
<td>0.002</td>
<td>0.01</td>
<td>0.05</td>
<td>0.03 NS</td>
<td>0.003 NS</td>
</tr>
</tbody>
</table>

Shown are the data for the whole population, for men and women separately, for individuals with fasting blood glucose <126 mg/dL, and for individuals with fasting blood glucose <110 mg/dL.

### Table 4. Stepwise Multivariate Analysis of the Correlations of CAD Risk Factors With Coronary Artery Calcification

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>SE (β)</th>
<th>F</th>
<th>P&lt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0741</td>
<td>0.1301</td>
<td>68.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history</td>
<td>0.8072</td>
<td>0.1783</td>
<td>20.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.0625</td>
<td>0.2468</td>
<td>18.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abdominal height</td>
<td>0.1509</td>
<td>0.0382</td>
<td>15.80</td>
<td>0.0003</td>
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<tr>
<td>LDL cholesterol</td>
<td>0.0824</td>
<td>0.0227</td>
<td>13.22</td>
<td>0.0003</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.6321</td>
<td>0.2559</td>
<td>6.10</td>
<td>0.0137</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>2.1141</td>
<td>1.1925</td>
<td>3.14</td>
<td>0.0766</td>
</tr>
<tr>
<td>Triceps skinfold thickness</td>
<td>-0.0183</td>
<td>0.0106</td>
<td>2.97</td>
<td>0.0851</td>
</tr>
<tr>
<td>Total fat</td>
<td>-0.0015</td>
<td>0.0008</td>
<td>2.90</td>
<td>0.0889</td>
</tr>
</tbody>
</table>

Figure 3. Percentage of the total regression explained the variability in CAC scores that was incrementally explained by risk factors and insulin resistance indicators. The listed risk factors accounted for 82% of the variability, and no other parameter had a significant additional contribution (defined as P<0.15; see Table 4).
contribute to a more reliable determination of the relationship of endogenous hyperinsulinemia and CAD.

### Study Limitations

It is possible that the recruitment scheme resulted in selection bias. However, we believe that our recruitment efforts were wide enough and reached a large enough population to make this unlikely. In particular, when every potential subject was approached, as in the case of Health Insurance Plan of NY patients, which constituted almost a third of the final population, no selection bias is possible. Naturally, our conclusions can be applied only to populations with similar demographics.

It is possible that insulin resistance is implicated in the calcification process rather than in atherogenesis, per se. Although this possibility is difficult to exclude, plaque composition is similar in diabetic and nondiabetic persons, and CAC scores are well correlated with the severity of coronary atherosclerosis in pathological and angiographic studies, independent of traditional risk factors. Moreover, the increased incidence of CAD in diabetic patients is paralleled by the increase in coronary calcification. Therefore, we believe that the use of CAC scores as a measure of coronary atherosclerosis is justified.

Our conclusions are also limited by the inaccuracies inherent in the oral glucose challenge test compared with glucose clamp studies. However, it is not feasible to perform clamp studies on large populations, and HOMA model insulin resistance has been accepted as a surrogate measure for epidemiological studies.

Finally, the correlation coefficients of the univariate analyses were relatively weak, although highly significant. We believe that this is the case because so many independent factors play a role in coronary calcification (and atherosclerosis itself) and that each must be relatively weak. In a multicausal disease such as atherosclerosis, one would expect each of many factors to have a relatively small contribution. Although age and sex explain a large part of the results, age and sex are also correlated with other risk factors, such as hypertension, increased cholesterol, and central obesity. In a multivariate analysis, these cross correlations will diminish the apparent contribution of associated risk factors. Similarly, male sex and aging are associated with increased insulin resistance, thus diluting the apparent contribution of insulin resistance in a multivariate analysis. Nonetheless, the data suggest that the presence of multiple risk factors, in particular, those associated with insulin resistance, is associated with increased risk of subclinical atherosclerosis.

We conclude that coronary atherosclerosis in asymptomatic individuals is correlated with insulin resistance and its associated metabolic abnormalities even in the absence of diabetes or impaired glucose intolerance. Additionally, intra-abdominal adiposity appears to be a major contributor to insulin resistance and increased atherosclerosis in such persons.

### Acknowledgment

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