The Metabolic Syndrome, Diabetes, and Subclinical Atherosclerosis Assessed by Coronary Calcium

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OBJECTIVES We compared the prevalence and extent of coronary artery calcium (CAC) among persons with the metabolic syndrome (MetS), diabetes, and neither condition.

BACKGROUND The prevalence and extent of CAC has not been compared among those with MetS, diabetes, or neither condition.

METHODS Of 1,823 persons (36% female) age 20 to 79 years who had screening for CAC by computed tomography, 279 had MetS, 150 had diabetes, and the remainder (n = 1,394) had neither condition. Metabolic syndrome was defined with ≥3 of the following: body mass index ≥30 kg/m²; high-density lipoprotein cholesterol <40 mg/dl if male or <50 mg/dl if female; triglycerides ≥150 mg/dl; blood pressure ≥130/85 mm Hg or on treatment; or fasting glucose 110 to 125 mg/dl. The prevalence and odds of any and significant (≥75th percentile) CAC among these groups and by number of MetS risk factors were determined.

RESULTS Those with neither MetS nor diabetes, MetS, or diabetes had a prevalence of CAC of 53.5%, 58.8%, and 75.3% (p < 0.001), respectively, among men and 37.6%, 50.8%, and 52.6% (p < 0.001), respectively, among women. Coronary artery calcium increased by the number (0 to 5) of MetS risk factors (from 34.0% to 58.3%) (p < 0.001). Forty-one percent of subjects with MetS had either a >20% 10-year risk of CHD or CAC ≥75th percentile for age and gender. Risk factor-adjusted odds for the presence of CAC were 1.40 (95% confidence interval [CI] 1.05 to 1.87) among those with MetS and 1.67 (95% CI 1.12 to 2.50) among those with diabetes, versus those with neither condition.

CONCLUSIONS Those with MetS or diabetes have an increased likelihood of CAC compared with those having neither condition.

METHODS We examined clinical characteristics of 1,823 persons age 20 to 79 years, free of known clinical CHD, who underwent CAC scanning by an Imatron C-150 (Imatron Inc., South San Francisco, California) electron beam tomographic scan-
ner during 1999 to 2001 at Cedars-Sinai Medical Center. Subjects were self-referred, referred by their physician, or recruited as part of ongoing research protocols. The current study was approved by the Cedars-Sinai Medical Center Institutional Review Board (IRB #3354). The imaging protocol involved an experienced licensed radiologic technician acquiring a single scan on each patient, consisting of 30 to 40 3-mm slices sufficient to scan the entire heart, done at 50% electrocardiogram triggering in an attempt to minimize motion artifact. Breath-holding instructions were also given to minimize misregistration. Foci of coronary artery calcification were identified and scored by an experienced technician, using semiautomated commercial software (ScImage, Inc., Los Altos, California), and the scoring was verified by an imaging cardiologist. The software initially calculated lesion-specific scores as the product of the area of each calcified focus and peak computerized tomography number (scored as 1 if 131 to 199 Hounsfield units [HU], 2 if 200 to 299 HU, 3 if 300 to 399 HU, and 4 if 400 HU or greater). These were summed across all lesions identified within left main, left anterior descending, left circumflex, and right coronary arteries to provide arterial-specific calcium scores, and across arteries to provide a total Agatston calcium score used for analysis in this report (10).

A fasting lipid profile (total cholesterol, HDL cholesterol, and triglycerides, with calculated LDL cholesterol) plus glucose was performed on each study participant by a Cholestech (Hayward, California) desktop chemical analyzer. Two readings of blood pressure (with mean systolic and diastolic readings used for analysis) and weight and height for calculation of body mass index (BMI) (weight in kg/height squared in meters) were also obtained at the same visit. A brief medical history to assess prior history of cardiac disease, diabetes, and medication usage was also taken. Diabetes was defined as a self-reported history of being told by a physician that diabetes was present or having a fasting glucose of 126 mg/dl or greater.

The presence of MetS was determined by criteria as defined by the Third Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) (1), modified to use BMI instead of waist circumference cutpoints. Therefore, this required subjects to have three of the following criteria: 1) BMI of 30 kg/m² or greater (in lieu of using ATP waist circumference cutpoints, as waist circumference measures were not available in our study sample); 2) serum triglycerides of at least 150 mg/dl; 3) HDL cholesterol levels of <40 mg/dl in men and <50 mg/dl in women; 4) impaired fasting glucose of 110 to 125 mg/dl; or 5) blood pressure of at least 130/85 mm Hg or treated hypertension. A recently published analysis of the Third National Health and Nutrition Examination Survey showed a high concordance of obesity at or above our BMI cutpoint and a high waist circumference as defined by NCEP III criteria (12), lending support to the validity of our measure.

Initially, age, gender, and risk factor distributions were compared among those without disease, those defined with the MetS, and those with diabetes, using the chi-square test of proportions for categorical risk factors and analysis of covariance (adjusted for age and gender) for comparing levels of continuous risk factors. The prevalence of coronary calcium (percent with positive scores >0), as well as the prevalence of coronary calcium at or above the 75th percentile for age and gender (as determined by data on a large sample of men and women programmed into the ScImage database) (13), were compared between disease groups, as well as by number of metabolic risk factors as described above (0 to 5). The 75th percentile has been suggested as a criterion for significant coronary calcium warranting more aggressive risk factor intervention (14). We also examined the proportion of individuals with MetS who achieved a >20% estimated 10-year risk of CHD based on Framingham risk score algorithms (1) or CAC ≥75th percentile as another means to estimate the proportion of such subjects that may warrant aggressive risk factor modification. Logistic regression presented the odds of CAC (any CAC and CAC at or above the 75th percentile to indicate significant CAC) in those with MetS or diabetes in comparison to those with neither condition (with 95% confidence interval [CI] also presented), initially age- and gender-adjusted, and then adjusted additionally for total cholesterol, reported cholesterol-lowering medication (because of its relation to both disease status and CAC), and cigarette smoking (because other risk factors such as HDL cholesterol and systolic blood pressure were included in the definition of MetS, they were not adjusted for in these models). Separate models were also run where subjects classified as having neither MetS nor diabetes, but who had two MetS risk factors and indicated they were on lipid-lowering therapy, were censored (n = 96, of which 68 were positive for CAC); these individuals were among those most likely to have been classified as having MetS had they not been on lipid-lowering therapy.

**RESULTS**

In our study, 279 persons (15%) were defined as having MetS and 150 persons (8%) met the definition for diabetes out of the total sample of 1,823 persons. Table 1 shows a
significantly different in all coronary risk factors between those without disease, those with MetS, and those with diabetes. Those with MetS were less likely to be women (24%); were younger (mean age 52.7 years) compared with the other groups; had the highest levels of BMI (mean 30.2 kg/m²), triglycerides (mean 238.5 mg/dl), total cholesterol (mean 215.8 mg/dl), and diastolic blood pressure (mean 82.2 mm Hg); and had the lowest levels of HDL cholesterol (39.5 mg/dl). In those with MetS, systolic blood pressure (mean 142.9 mm Hg) was similar to those with diabetes, but significantly higher (p < 0.0001) than in those with neither condition.

Overall, 57% of persons with the MetS had coronary calcium, compared with 67% of those with diabetes and 47% of those with neither condition (p < 0.0001). The prevalence of CAC in women with MetS was 51%, similar to those with diabetes (53%), but higher than those with neither condition (38%) (p = 0.02). In men, the prevalence of CAC in those with MetS was 58%, compared with 75% in those with diabetes and 54% in those with neither condition (p = 0.0007) (Fig. 1). Among men, 25% of those with MetS had CAC at or above the 75th percentile, compared with 41% of those with diabetes and 21% of those with neither condition (p < 0.0001). For women, these figures were 25%, 30%, and 20%, respectively (p = 0.21) (Fig. 1). There was also a graded association between the prevalence of CAC and the number of metabolic risk factors (excluding persons with diabetes) (Fig. 2). Coronary artery calcium prevalence ranged from 34% in those without any metabolic risk factors to 50%, 56%, 54%, 63%, and 58% in those with one, two, three, four, and five metabolic risk factors, respectively (trend p < 0.001). For the prevalence of

Table 1. Prevalence and Mean (SD) Levels of Baseline Characteristics by Presence of Metabolic Syndrome, Diabetes, or Neither Condition (n = 1,823)

<table>
<thead>
<tr>
<th></th>
<th>Neither Condition (n = 1,394)</th>
<th>Metabolic Syndrome (n = 279)</th>
<th>Diabetes (n = 150)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>38.7</td>
<td>24.0</td>
<td>38.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>53.4 ± 9.8</td>
<td>52.7 ± 9.9</td>
<td>57.2 ± 9.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Glucose (mg/dl)*</td>
<td>94.6 ± 17.7</td>
<td>98.5 ± 17.7</td>
<td>140.1 ± 17.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>25.1 ± 4.1</td>
<td>30.2 ± 4.1</td>
<td>29.0 ± 4.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)*</td>
<td>106.1 ± 109.6</td>
<td>238.5 ± 109.7</td>
<td>209.6 ± 110.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)*</td>
<td>206.1 ± 41.4</td>
<td>215.8 ± 41.5</td>
<td>202.7 ± 41.8</td>
<td>= 0.0007</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)*</td>
<td>58.5 ± 16.6</td>
<td>39.5 ± 16.6</td>
<td>49.4 ± 16.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)*</td>
<td>132.3 ± 17.5</td>
<td>142.9 ± 17.5</td>
<td>141.6 ± 17.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)*</td>
<td>76.1 ± 10.6</td>
<td>82.2 ± 10.6</td>
<td>79.2 ± 10.7</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for age and gender.

BMI = body mass index; BP = blood pressure; HDL = high density lipoprotein.

Figure 1. Prevalence of coronary artery calcium (CAC) by disease category and gender. Gray bars = neither condition; striped bars = metabolic syndrome (MetS); black bars = diabetes. p = 0.0002 for men and p = 0.02 for women for any CAC and p = 0.01 for men and p = 0.19 for women for CAC ≥75th percentile across groups (MetS, diabetes, and neither condition).
CAC ≥75th percentile, the respective figures were 15%, 22%, 24%, 23%, 33%, and 25% (trend p < 0.001) (Fig. 2). Of those with MetS, 21% of such individuals had ≥20% Framingham calculated risk of CHD over 10 years (defined by ATP as a CHD "risk equivalent"; 23% had CAC scores at or above the 75th percentile (based on age and gender), and 41% had one or both characteristics (Fig. 3).

From logistic regression analyses, the odds ratio (OR) of CAC (compared with those with neither condition) was significantly higher among those with MetS (OR 1.45, 95% CI 1.09 to 1.94) or diabetes (OR 1.67, 95% CI 1.12 to 2.48). Additional adjustment for total cholesterol, lipid-lowering medication use, and cigarette smoking (risk factors not among those defining MetS) showed these relations to persist (OR 1.40, 95% CI 1.05 to 1.87 for MetS and OR 1.67, 95% CI 1.12 to 2.50 for diabetes) (Table 2). In predicting the presence of significant CAC (≥75th percentile), diabetes bore a stronger relation (OR 2.01, 95% CI 1.40 to 2.89), but findings regarding the likelihood of significant CAC in persons with MetS were attenuated (OR 1.29, 95% CI 0.95 to 1.75), with similar findings after additional adjustment for total cholesterol, lipid-lowering medication, and smoking (Table 2). In separate models where those on lipid-lowering medication who had neither MetS nor diabetes (but had two MetS risk factors) were censored, increased age-, gender-, and risk factor-adjusted odds for CAC in those with MetS (OR 1.7, 95% CI 1.3 to 2.3) and diabetes (OR 2.3, 95% CI 1.5 to 3.3) (as compared with those having neither condition) were observed. Analysis for predicting the presence of CAC at or above the 75th percentile similarly resulted in increased adjusted odds for CAC in those with MetS (OR 1.5, 95% CI 1.1 to 2.0) and diabetes (OR 2.5, 95% CI 1.7 to 3.6) (as compared to those with neither condition).

**DISCUSSION**

Our results suggest a high prevalence of subclinical coronary atherosclerosis, as evidenced by CAC, an aspect of atherosclerosis, among both men and women defined to have...
MetS. Several studies have documented an increased risk of CHD associated with CAC in subjects with multiple risk factors (8–11), although the magnitude of risk associated with a given level of calcium varies from study to study, and whether CAC predicts CHD events independent of carefully measured risk factors remains controversial. Moreover, the relation of CAC to clinical events in persons with MetS is unknown.

In our study, women with MetS have a prevalence of CAC as high as women with diabetes, despite age being similar (whereas the higher prevalence of coronary calcium among men with diabetes compared with those with MetS may be partially due to the greater age among those with diabetes). In addition, there was a graded association between the number of metabolic risk factors and coronary calcium. The increased likelihood and extent of CAC in persons with MetS, as compared with normal persons, is largely explained by cardiovascular risk factors that comprise the definition of MetS, namely HDL cholesterol, which is significantly lower among those with MetS. Although the odds of any calcium were significantly higher both in persons with MetS and those with diabetes, findings regarding the relation to significant calcium (75th percentile or greater) showed only diabetes to remain predictive in our primary, uncensored analyses (but MetS did remain modestly associated with significant CAC in censored analyses). This suggests that although earlier atherosclerosis is more common among both those with MetS and diabetes, more advanced atherosclerosis as evidenced by greater levels of coronary calcium is most apparent in those with diabetes.

Current estimates are that approximately 47 million adults in the United States would be defined to have the MetS on the basis of the most recent definition as recommended by NCEP-ATP III (1). Although such persons do have lower levels of HDL cholesterol and higher levels of total cholesterol and systolic blood pressure, traditional components of the Framingham risk equations, nontraditional Framingham risk factors such as BMI (or central obesity) and triglyceride levels are markedly higher in these individuals, and are similar to those who have clinical diabetes. In fact, in our study sample, we show levels of triglycerides and total cholesterol to be significantly higher, and HDL cholesterol significantly lower in those defined to have the MetS compared to diabetes.

Both the NCEP (1) and the American Diabetes Association (15) recommend aggressive risk factor management of persons with clinically defined diabetes on par with secondary prevention guidelines for cardiovascular disease management. This includes treatment of elevated LDL cholesterol, if present, to a goal of <100 mg/dl, and even more aggressive blood pressure goals to <130 mm Hg systolic and <80 mm Hg diastolic blood pressure. Moreover, those with a >20% 10-year Framingham estimated risk of CHD are considered CHD risk-equivalents warranting lipid treatment according to secondary prevention guidelines (1), and those with CAC scores ≥75th percentile have also been recommended for more aggressive treatment (14). Although these reports do not give specific goal levels for risk factors in persons with the MetS that are distinct from others with multiple risk factors, our report estimates approximately 20% of those with MetS have an estimated Framingham 10-year risk of CHD of >20%, 25% have coronary calcium levels in the highest quartile, and 41% have one or both characteristics. These findings suggest that screening results for subclinical disease (such as by coronary calcium detection) in patients with MetS may identify a substantial number of additional individuals for whom more aggressive risk factor intervention might be warranted.

Recently, the American Heart Association Prevention V conference (16) has suggested that persons at intermediate CHD risk based on known risk factors may be candidates for screening of CAC by computed tomography. An upcoming Bethesda Report from the American College of Cardiology due to be released in 2003 will provide further guidance into the appropriate use of noninvasive testing for atherosclerosis in asymptomatic persons, including specifically what constitutes sufficient CHD risk potentially warranting such testing. Considering that the NCEP (1) considers those at 10% to 20% estimated risk of CHD to be at intermediate risk, many persons with MetS would be

Table 2. Multivariable Analysis of CAC and Disease Status

<table>
<thead>
<tr>
<th>Age- and gender-adjusted (n = 1,833)</th>
<th>Neither Condition</th>
<th>Metabolic Syndrome</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age- and gender-adjusted (n = 1,833)</td>
<td>1.0 (referent)</td>
<td>1.44 (1.08–1.93) p = 0.01</td>
<td>1.71 (1.14–2.54) p = 0.009</td>
</tr>
<tr>
<td>Odds of CAC present</td>
<td>1.0 (referent)</td>
<td>1.28 (0.94–1.72) p = 0.12</td>
<td>2.10 (1.47–3.01) p &lt; 0.0001</td>
</tr>
<tr>
<td>Odds of CAC ≥75th percentile</td>
<td>1.0 (referent)</td>
<td>1.87 (1.09–3.21) p = 0.02</td>
<td>1.67 (1.12–2.50) p = 0.01</td>
</tr>
</tbody>
</table>

CAC = coronary artery calcium.
suitable candidates for such noninvasive testing if this definition were to be adopted.

**Study limitations.** Given that our cohort is composed primarily of self-referred volunteers, it is possible our sample identified with MetS is not entirely representative of those in the general population. We report, however, a similar combined prevalence of MetS (15%) and diabetes (8%) (total 23%) to that been reported previously in U.S. adults (24%) (3).

As we utilized measures of BMI instead of waist circumference, which were not available, it is possible we may have misclassified some individuals that would have been classified differently based on waist circumference measures that constitute the accepted criterion for MetS (1). However, in a recently published report (11) among adults in the Third National Health and Nutrition Examination Survey showed the vast majority of individuals with a BMI ≥30 kg/m² also had a high waist circumference as defined by NCEP criteria, lending support to our revised definition; moreover, 97% of those we identify with MetS (incorporating BMI instead of waist circumference) would have also been identified by the definition using waist circumference, and of those we do not identify with MetS, 96.5% would not have been identified by the NCEP definition (unpublished data). This high correspondence in definitions may be due to many individuals with either increased BMI or waist circumference having the same accompanying MetS risk factors such as elevated triglycerides, low HDL cholesterol, and increased blood pressures. This provides reasonable certainty as to the robustness of our definition. Also, other published definitions (2,4,5,17) vary more markedly from the NCEP definition, making comparability to the NCEP definition more difficult to establish.

Finally, because some individuals with neither MetS nor diabetes (especially those borderline for being defined as MetS—for example, with two but not three MetS risk factors) who were on lipid-lowering therapy might have been classified as having MetS if they were not on therapy, our uncensored analysis may have underestimated the relation of MetS or diabetes with CAC. Censoring these individuals does result in higher ORs (significant for both any CAC and for CAC ≥75th percentile) associated with MetS or diabetes. This suggests that if such misclassification were present among these individuals, accounting for this would have increased the strength of our associations. However, as these results are somewhat speculative, our uncensored analysis remains most conservative.

**Conclusions.** Our study demonstrates that individuals with MetS have a higher likelihood and prevalence of CAC than patients without MetS. Moreover, those with diabetes have an increased likelihood of having significant CAC. The presence of MetS indicates a moderately increased likelihood for subclinical disease. Although the extent of subclinical atherosclerosis (for example, with CAC as an aspect of atherosclerosis) may not be as significantly advanced as in persons with diabetes, the mere presence of such disease may be a potent motivator of lifestyle changes and improved compliance to risk-reducing medical therapy, as we have previously suggested (18). Further study in larger, prospective cohorts (including the Early Identification of Subclinical Atherosclerosis Using Noninvasive Research [EISNER] study currently being performed at Cedars-Sinai Medical Center) will provide further information on this issue. In addition, it will be important to determine whether individuals with MetS or diabetes, but who additionally have subclinical disease, may identify a subset at greater risk of future cardiovascular events. The ongoing National Institutes of Health Multiethnic Study of Atherosclerosis (MESA) (19) will provide further insight into these and other questions among high-risk individuals with multiple risk factors, including those with MetS and diabetes.

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**REFERENCES**