

Metabolic Syndrome and Diabetes Are Associated With an Increased Likelihood of Inducible Myocardial Ischemia Among Patients With Subclinical Atherosclerosis

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OBJECTIVE — Coronary artery calcification (CAC) is associated with cardiac events and the likelihood of inducible myocardial ischemia. Because metabolic syndrome contributes to atherosclerosis, we assessed whether it also influences the relationship between CAC levels and myocardial ischemia.

RESEARCH DESIGN AND METHODS — We evaluated 1,043 patients without known coronary artery disease (CAD) who underwent stress myocardial perfusion scintigraphy (MPS) and computed tomography. Metabolic syndrome was defined by modified National Cholesterol Education Program criteria. Metabolic abnormalities were present in 313 patients (30%), including 140 with diabetes (with or without metabolic syndrome) and 173 who had metabolic syndrome without diabetes.

RESULTS — Although CAC scores <100 identified a low likelihood (~2%) of ischemia, the presence (versus absence) of metabolic abnormalities (metabolic syndrome or diabetes) was a predictor of more frequent ischemia among patients with CAC scores of 100–399 (13.0 vs. 3.6%, $P < 0.02$) and CAC scores ≥ 400 (23.4 vs. 13.6%, $P = 0.03$). Similar trends were observed when patients with metabolic syndrome and diabetes were considered separately. Multiple logistic regression revealed the odds of MPS ischemia to be 4.3-fold greater per SD of log CAC ($P < 0.001$) and 2.0-fold greater in the presence of metabolic abnormalities ($P < 0.01$).

CONCLUSIONS — Among patients with CAC scores ≥ 100 , metabolic abnormalities, and even metabolic syndrome in the absence of diabetes predicted a higher likelihood of inducible ischemia. These findings suggest the need for assessment of metabolic status when interpreting the results of CAC imaging among patients undergoing such testing because of suspected CAD.

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Abbreviations: ^{99m}Tc, technetium-99m; CAC, coronary artery calcification; CAD, coronary artery disease; CHD, coronary heart disease; EBT, electron beam tomography; MPS, myocardial perfusion scintigraphy; MSCT, multislice computed tomography; SPECT, single-photon emission computed tomography.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Recent studies demonstrate a threshold relationship between the magnitude of coronary artery calcium (CAC), as measured by electron beam tomography (EBT) or multislice computed tomography (MSCT), and the likelihood of inducible myocardial ischemia (1–3). Generally, for CAC scores <400, the frequency of inducible ischemia, as assessed by myocardial perfusion single-photon emission computed tomography (SPECT), is relatively low (1–3). These studies, however, have not shown whether the relationship of CAC scores and myocardial ischemia may be modified by pathophysiological variables. Diabetes and metabolic syndrome are associated with coronary artery disease (CAD) (4), are potent risk factors for cardiac events (5,6), and are growing in prevalence (7,8). Because these metabolic abnormalities are also associated with atherosclerosis, including CAC (9), they may also modify the relationship between atherosclerosis and the likelihood of inducible ischemia. To test this possibility, we evaluated the association between stress-induced myocardial hypoperfusion during stress-rest myocardial perfusion scintigraphy (MPS) and CAC among subjects stratified according to the presence of metabolic abnormalities.

RESEARCH DESIGN AND METHODS

We evaluated 1,043 patients who underwent both dual-isotope stress-rest MPS and CAC scanning by EBT (Imatron C-150 or GE e-Speed; GE-Imatron, South San Francisco, CA) or MSCT (Siemens Volume Zoom; Siemens Medical Systems, Forchheim, Germany) at Cedars-Sinai Medical Center within 3 months of the scan. All patients underwent MPS on a clinical basis. CAC imaging was performed on a physician referral ($n = 509$ patients) or self-referral basis ($n = 50$ patients) or as part of an ongoing research protocol that offered CAC scanning to patients who un-

derwent MPS ($n = 484$ patients). Exclusion criteria included prior coronary artery bypass surgery or percutaneous coronary intervention, previous myocardial infarction, or known valvular heart disease or cardiomyopathy. This research was approved by the Cedars-Sinai Medical Center institutional review board.

Imaging and stress protocol

Patients were injected intravenously at rest with ^{201}Tl (2.5–3.5 mCi depending on patient weight). Rest ^{201}Tl SPECT was initiated 10 min after injection.

Exercise MPS protocol

After rest MPS, symptom-limited treadmill exercise testing was performed using the Bruce protocol in 904 (87%) of the 1,043 study subjects. At near-maximal exercise, a 20- to 30-mCi dose of technetium-99m ($^{99\text{m}}\text{Tc}$) sestamibi was injected (actual patient dose varied with patient weight), and exercise continued for an additional 1 min after injection at peak workload and for an additional 1–2 min at a reduced workload. $^{99\text{m}}\text{Tc}$ sestamibi MPS imaging began 15–30 min after radioisotope injection (10).

Adenosine MPS protocol

This protocol (11) was performed in 137 (13%) of the 1,043 study subjects. Patients were instructed not to consume caffeine products for 24 h before MPS. After rest MPS, pharmacological stress was performed using adenosine infusion ($140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 5–6 min), $^{99\text{m}}\text{Tc}$ sestamibi was injected at the end of the 2nd or 3rd min of infusion for the 5- and 6-min infusions, respectively. In patients who could tolerate low-level exercise, low-level treadmill exercise (as an adjunct to adenosine infusion) was performed at 0–10% grade and 1–1.7 mph. MPS was initiated ~60 min after the end of the adenosine infusion in patients who did not exercise and 15–60 min after injection in those with adjunctive exercise.

SPECT acquisition protocol

MPS imaging was performed as previously described (10). The MPS studies were performed on multidetector scintillation cameras using an elliptical 180° acquisition for 60–64 projections at 20 s/projection. For ^{201}Tl , two energy windows were used, including a 30% window centered on the 68- to 80-keV peak and a 10% window centered on the 167-

keV peak. For $^{99\text{m}}\text{Tc}$ sestamibi SPECT, a 15% window centered on the 140-keV peak was used, and images were obtained in both supine and prone positions. For the supine rest and stress MPS studies, gated SPECT was performed, obtaining 8–16 frames/cycle. Images were acquired using a 64×64 image matrix and were subject to quality control measures as previously described (10). No attenuation or scatter correction was used.

SPECT interpretation

A semiquantitative visual interpretation was performed using 20 segments for each image set. Segments were scored by blinded experienced observers using a five-point scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, and 4 = absence of detectable tracer uptake in a segment) (10).

Scintigraphic indexes

The summed stress and rest scores were obtained by adding the scores of the 20 segments of the respective images (10). The sum of the differences between each of the 20 segments from these images was defined as the summed difference score, representing the amount of ischemia. Each of these variables incorporates the extent and severity of perfusion defects, which independently add prognostic information (12). The summed difference score was converted to percent myocardium ischemia according to a published algorithm. “Ischemic” and “moderately to severely ischemic” MPS studies were defined by ≥ 5 and $\geq 10\%$ of the myocardium, respectively (10). Technically, adenosine infusion does not commonly induce myocardial ischemia per se, but the presence and magnitude of relative hypoperfusion identified during adenosine MPS is roughly equivalent to that induced during maximal exercise (13–17). Thus, we used the term “inducible ischemia” to represent both the ischemia induced during exercise testing and the zones of potential ischemia that are identified during adenosine infusion.

Calcium scan protocol and interpretation

The imaging protocol involved an experienced licensed radiologic technician acquiring a single scan on each patient, consisting of ~30–40 3-mm slices or 2.5-mm slices for electron beam tomog-

raphy and MSCT, respectively. Foci of CAC were identified and scored by an experienced technician, blinded to both patient characteristics and the MPS results, using semiautomatic commercial software on a NetraMD workstation (ScImage, Los Altos, CA) by detection of at least three contiguous pixels (voxel size = 1.03 mm^3) of peak density >130 Hounsfield units (HU) within a coronary artery, with scoring verified by an experienced cardiologist. The software calculated lesion-specific scores as the product of the area of each calcified focus and peak computed tomography number (scores: 1 = 131–199 HU, 2 = 200–299 HU, 3 = 300–399 HU, 4 = ≥ 400 HU). These were summed across all lesions identified within the left main, left anterior descending, left circumflex, and right coronary arteries to provide arterial-specific calcium scores, and across arteries to provide the total CAC score.

Historical and other clinical variables

As part of our historical query, each patient was questioned regarding chest symptoms, divided into four chest pain categories (asymptomatic, nonanginal chest pain, atypical angina, and typical angina) (18–19), shortness of breath, and medication use. Patients were also questioned regarding the following coronary risk factors: 1) family history of early coronary heart disease (male primary relative <55 years of age, female <65 years of age); 2) diabetes; 3) hypertension; and 4) current smoking. Diabetes was defined according to either self-report with medication usage or a fasting glucose level of ≥ 126 mg/dl. In addition, fasting glucose measures, systolic and diastolic blood pressure, use of antihypertensive medication, and lipid profile measures (total cholesterol, HDL cholesterol, and triglycerides) were available. Weight and height were measured, with BMI calculated as weight (kilograms)/height (meters squared). Electrocardiographic ischemia was defined as ST segments ≥ 1 mm horizontal or downsloping or ≥ 1.5 mm upsloping at 80 ms after the one point.

The presence of the metabolic syndrome was defined using modified National Cholesterol Education Program criteria (20) based on having at least three of the following: 1) BMI $\geq 30 \text{ kg/m}^2$; 2) fasting glucose ≥ 110 mg/dl; 3) hyperten-

Table 1—Study population characteristics by metabolic status

Parameters	No metabolic abnormality	Metabolic syndrome patients*	Diabetic patients	P value
n	730	173	140	
Age (years)	58.6 ± 10	55.1 ± 11	59.0 ± 10	0.0002
Female	248 (34)	47 (27)	45 (32)	0.23
Hypertension	257 (35)	91 (53)	90 (64)	<0.0001
Hypercholesterolemia	448 (61)	121 (70)	98 (70)	0.03
Smoking	42 (6)	9 (5)	12 (9)	0.39
Family history	136 (19)	45 (26)	23 (16)	0.05
Chest pain symptoms	433 (59)	107 (62)	94 (67)	0.21
Asymptomatic	297 (41)	66 (38)	46 (33)	
Nonanginal	68 (9)	8 (5)	13 (9)	
Atypical angina	300 (41)	81 (47)	63 (45)	
Typical angina	28 (4)	10 (6)	6 (4)	
Shortness of breath	37 (5)	8 (5)	12 (9)	0.20
BMI (kg/m ²)	25.7 ± 4	31.0 ± 5	30.3 ± 6	<0.0001
Resting heart rate (bpm)	65.7 ± 11	69.7 ± 11	71.8 ± 13	<0.0001
Resting systolic blood pressure (mmHg)	135.6 ± 19	141.1 ± 16	142.4 ± 19	<0.0001
Rest diastolic blood pressure (mmHg)	79.0 ± 9	80.8 ± 10	80.1 ± 9	0.05
Framingham risk score	7.3 ± 6	9.7 ± 8	20.6 ± 2	<0.0001
Log (CAC + 1)	3.9 ± 3	3.5 ± 3	4.1 ± 3	0.18
Summed difference score ≥4	43 (6)	19 (11)	14 (10)	0.03

Data are means ± SD or n (%). *Includes all metabolic syndrome patients without diabetes.

sion, antihypertensive medication usage, systolic blood pressure ≥130 mmHg, or diastolic blood pressure ≥85 mmHg; 4) HDL <40 mg/dl if male or <50 mg/dl if female; or 5) fasting triglycerides ≥150 mg/dl. Diabetes was based on use of antidiabetic medication or fasting glucose ≥126 mg/dl. Those designated as having a metabolic abnormality included those with metabolic syndrome and/or diabetes.

Statistical analyses

ANOVA or the χ^2 test of proportions was used initially to compare demographic and risk factor characteristics, as well as mean Framingham risk scores (percent likelihood of a coronary heart disease [CHD] event in 10 years), log of coronary calcium scores (+1), and the proportion with a positive MPS result (summed difference score ≥4) among those with diabetes, metabolic syndrome without diabetes, or neither condition and across referral groups. The prevalence of an abnormal MPS was compared across calcium score categories (0, 1–99, 100–399, and ≥400) among those with and without a metabolic abnormality (met-

abolic syndrome or diabetes) and among those with metabolic syndrome without diabetes and those with diabetes, as compared with those with neither condition.

Multiple logistic regression was performed to assess whether CAC and the presence of a metabolic abnormality examined as a composite variable including diabetes, as well as the number of metabolic syndrome risk factors (one to two, three, and four to five) and diabetes compared with the absence of metabolic syndrome risk factors, were independently associated with the likelihood of an abnormal MPS result after taking into account risk factors (age, sex, total cholesterol, and smoking, which are not components of the definition for metabolic syndrome) and the presence of symptoms.

RESULTS— Among our 1,043 patients, 730 (70%) had no metabolic abnormality and 313 (30%) had metabolic abnormalities. Among these latter 313 patients, 140 had diabetes, including 88 (63%) patients with both diabetes and metabolic syndrome and another 52 diabetic patients (37%) who did not have

metabolic syndrome. These 140 diabetic subjects were analyzed as one metabolic subgroup, and the 173 patients who had metabolic syndrome but without diabetes constituted our separate metabolic syndrome subgroup for each of our analyses. Comparison of our three patient cohorts (Table 1) revealed that the diabetic and metabolic syndrome patients had more hypertension, history of hypercholesterolemia, and higher BMI, resting heart rate, and systolic blood pressure measurements than the patients without metabolic abnormalities. These patients also had more inducible ischemia by MPS but similar CAC scores compared with the patients without metabolic abnormalities.

Frequency of ischemia according to CAC score and metabolic status

In those with negative or low CAC scores (<100), the prevalence of an ischemic MPS remained low (<3%) regardless of the presence or absence of a metabolic abnormality (Fig. 1A). Among those with scores of 100–399, the presence of metabolic abnormality was associated with a threefold greater likelihood of an ischemic MPS study. Similarly, when CAC scores were ≥400, the frequency of an ischemic MPS study was significantly higher among those with versus those without metabolic abnormalities. Similar trends were noted when patients were divided according to the type of metabolic abnormality (diabetes or metabolic syndrome) (Fig. 1B).

Assessments according to the source of patient referral

The separate analysis of patients according to the source of referral revealed the physician-referred and self-referred patients to be very similar to each other according to all clinical variables. However, these referred patients differed from our research patients in being less likely to be female, having a higher frequency of hypercholesterolemia by history, and having a lower frequency of chest pain symptoms ($P < 0.0001$ for each variable). The referred patients were also older ($P < 0.001$), but the counterbalance among these risk factors resulted in similar mean Framingham risk scores for the referred and research patients. By virtue of being referred for MPS on the basis of their CAC scores, the referred patients also had

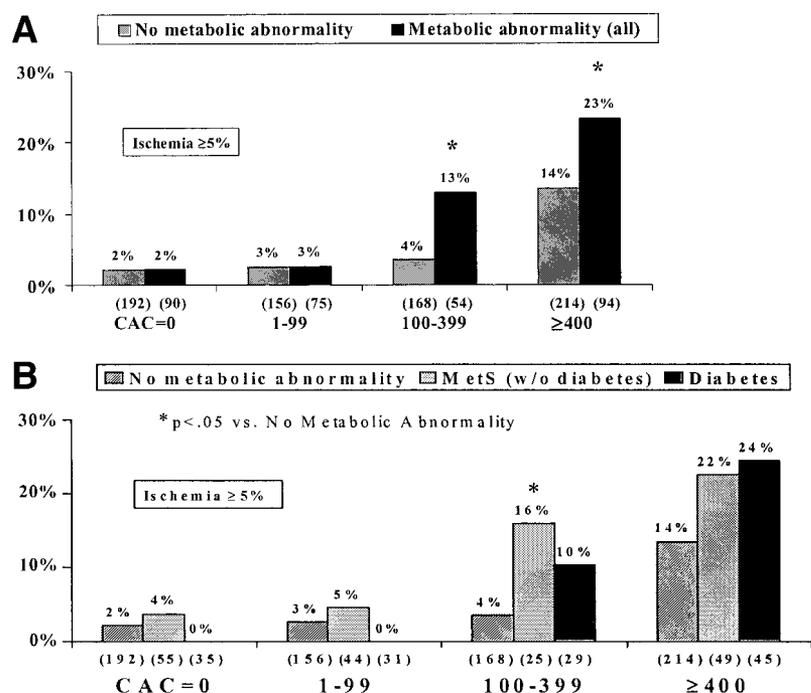


Figure 1—Frequency of myocardial ischemia during MPS across four coronary calcium score categories (0, 1–99, 100–399, and ≥400). A: Patients with metabolic abnormality versus those without metabolic abnormality. **P* < 0.05 for patients with CAC scores of 100–399 and for those with CAC scores ≥400. B: Patients with metabolic abnormality without diabetes versus those with diabetes. **P* < 0.05 compared with patients with no metabolic abnormality.

higher mean CAC scores than the research patients (*P* < 0.0001).

Regardless of these differences, the tendency of metabolic abnormalities to be associated with a higher likelihood of inducible myocardial ischemia for CAC scores ≥100 appeared to be present among both the referred patients and the research patients. For example, for those with a CAC score of 100–399, referred patients with versus those without metabolic abnormalities had a 6.3 vs. 0.9% frequency of ischemia by MPS; for the research patients, these frequencies were 21.1 and 10.6%, respectively (NS, however, due to smaller sample sizes within stratified analyses).

Multivariate predictors of inducible myocardial ischemia

Multivariable logistic regression analysis (Table 2) revealed that three variables, log CAC, the presence of chest pain symptoms (odds ratio [OR] = 2.9, *P* < 0.001), and the presence of metabolic abnormalities (2.0, *P* = 0.008), were all independently associated with the presence of myocardial ischemia. When metabolic abnormalities were divided according to the number of metabolic risk factors or

diabetes, those with three and those with four to five metabolic risk factors continued to show significant adjusted ORs for the prediction of myocardial ischemia (4.8, *P* = 0.049 and 10.9, *P* = 0.005, respectively).

Table 2—Adjusted odds of stress-induced myocardial ischemia by multiple logistic regression analyses

	Odds ratio (95%CI)	<i>P</i> value
Model 1: metabolic abnormalities (combining metabolic syndrome and diabetes)		
Log (CAC score) per SD	4.30 (2.70–6.86)	<0.001
Chest pain symptoms	2.88 (1.67–4.97)	<0.001
Metabolic abnormalities	1.98 (1.20–3.28)	0.008
Model 2: analysis by number of metabolic syndrome risk factors and diabetes		
Log (CAC score) per SD	4.11 (2.60–6.51)	<0.001
Chest pain symptoms	2.94 (1.69–5.09)	<0.001
One or two risk factors	2.99 (0.70–12.83)	0.141
Three risk factors	4.80 (1.01–22.86)	0.049
Four or five risk factors	10.93 (2.09–57.19)	0.005
Diabetes	4.55 (0.98–21.07)	0.053

Data are also adjusted for age, sex, cholesterol, and smoking. Number with ischemia/total for stratum: model 1, metabolic abnormalities (33 of 309) vs. no metabolic abnormalities (referent) (43 of 730); model 2, one or two risk factors (41 of 605), three risk factors (11 of 128), four or five risk factors (8 of 45), and diabetes (14 of 136) vs. no risk factors (2 of 125). Because of missing cholesterol levels in four individuals, the total sample size is 1,039.

CONCLUSIONS— Our findings indicate that the presence of metabolic abnormalities increases the likelihood of observing myocardial ischemia in association with atherosclerosis, as assessed by CAC imaging. For example, in patients with CAC scores in the “intermediate” range of 100–399, the odds of inducible ischemia by MPS were threefold higher among patients with versus patients without metabolic abnormalities. Similarly, the presence of metabolic abnormalities increased the observed prevalence of inducible ischemia among patients with CAC scores ≥400. However, for CAC scores <100, the presence of metabolic abnormalities was unrelated to ischemia. This is consistent with prior studies showing inducible myocardial ischemia to be uncommon among patients with CAC scores <100 (1–3).

We also assessed the separate relationships of diabetes and metabolic syndrome to the likelihood of inducible myocardial ischemia among patients with intermediate and high CAC scores. Both types of metabolic abnormality showed nearly equivalent frequencies for inducible myocardial ischemia among patients with CAC scores ≥100. These results are of interest with respect to the controversy surrounding the cardiac risk associated with metabolic syndrome. Although diabetes is currently considered a “CHD risk equivalent” and automatically assigned to high-risk status, metabolic syndrome is

associated with a wide spectrum of estimated risk for CHD (21). Our results are consistent with previous findings indicating that metabolic syndrome, even if not accompanied by diabetes, is still associated with an excess risk of mortality from cardiovascular disease in the U.S. population (6).

Our multivariate analysis revealed that the presence of metabolic abnormalities provided additional independent information to our potent anatomic measurement of atherosclerosis, CAC, for the prediction of inducible myocardial ischemia, whereas standard coronary risk factors (age, sex, family history, total cholesterol, and smoking) did not. Moreover, the presence of metabolic abnormalities was associated with increased odds of inducible ischemia even after adjusting for age, sex, other CAD risk factors, and coronary calcium. In addition, the OR for inducible ischemia increased as the “burden” or number of metabolic syndrome risk factors increased, thus supporting the notion that the components of the metabolic syndrome may be most potent when presented in combination, as has been shown for the prediction of cardiovascular and total mortality (5).

Although the likelihood of inducible myocardial ischemia is roughly associated with the extent of angiographic disease, the relationship is not tight (22). This is because factors other than anatomy govern the pathophysiology leading to myocardial ischemia. Similarly, the relationship between CAC, a measure of atherosclerosis, and the presence of myocardial ischemia is also apparently highly variable. For instance, in our experience, only 20% of patients with CAC scores >1,000 manifest inducible ischemia by MPS (1). A wide variety of mediators could potentially influence the relationship between atherosclerosis and inducible myocardial ischemia. These include factors affecting endothelial dysfunction, platelet and other coagulation factors, estrogen and other endocrine factors, sympathetic tone, and inflammatory and other processes that may affect the functional integrity of the coronary plaque. Presumably, metabolic abnormalities increase the propensity for inducible ischemia in the presence of atherosclerosis through one or more of these mediating processes, but further study is needed to study these potential interrelationships.

Like stress test procedures, CAC imaging has recently been shown to be a potent predictor of future adverse cardiac events (23–27). Thus, CAC imaging may represent an additional and potentially synergistic tool for risk-stratifying patients with suspected CAD. However, the clinical role of CAC imaging relative to stress testing remains unclear. Recent studies suggest that for CAC scores ≥ 400 , the likelihood of inducible ischemia begins to increase exponentially (1–3). Thus, a logical argument can be made for referring patients with such CAC scores for subsequent stress testing. By contrast, because patients with CAC scores of 100–400 have only an “intermediate” risk for inducible ischemia, the appropriate course for clinical follow-up in such patients is more in doubt. Our study is the first to systematically assess how clinical factors may influence the relationship between CAC scores and inducible myocardial ischemia. Our study indicates that clinical patients can be more effectively stratified into high- and low-risk groups for manifesting myocardial ischemia by analyzing patients’ metabolic profile in relation to CAC. This assessment may prove to be particularly useful among patients presenting with CAC scores in the intermediate range.

Our study had a number of important limitations. First, the mixed referral source of our patient population was an important limitation. Our study population included both clinically referred and research patients who differed according to certain CAD risk factors, chest pain symptoms, and mean CAC scores. A trend toward higher frequencies of ischemia in association with specific CAC/metabolic status combinations was seen for our research versus referral cohorts. This may reflect a confounding effect associated with the higher frequency of chest pain symptoms that was observed in our research cohort, as well as the potential effect of other clinical variables. However, regardless of cohort, the presence of metabolic abnormalities was associated with a higher frequency of ischemia at CAC scores of 100–399 or ≥ 400 . Further prospective study is needed to determine what factors besides metabolic abnormalities influence the relationship between CAC and inducible ischemia. For this reason, caution should be exerted in defining a fixed CAC threshold by which patients with metabolic abnormalities should be

referred for MPS. However, this limitation does not negate our general finding that metabolic abnormalities increase the likelihood of inducible ischemia for patients with CAC scores ≥ 100 . Second, we combined diabetic subjects with and without metabolic syndrome into one group for our statistical analyses, but it would have been preferable, had our sample size permitted, to assess these two diabetic subgroups separately. Third, because our patients were only recently studied, sufficient time to perform adequate follow-up of our patient cohort has not yet occurred. Such follow-up would be useful for assessing whether the associations noted between CAC scores and metabolic factors as they relate to the prediction of myocardial ischemia are also generalizable to the prediction of adverse cardiac events.

Our results suggest that the measurement of metabolic factors should be incorporated routinely into the clinical interpretation of CAC results when evaluating the need to refer patients with suspected CAD for cardiac stress testing.

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