Diabetes, the Metabolic Syndrome, and Angiographic Progression of Coronary Arterial Disease in Postmenopausal Women

Philip B. Mellen, William T. Cefalu, David M. Herrington

Objective—Although the metabolic syndrome (MS) is associated with increased cardiovascular risk, its relationship with atherosclerotic progression is less well defined. We sought to determine whether the MS predicts angiographic progression of coronary heart disease in a cohort of postmenopausal women.

Methods and Results—A total of 309 postmenopausal women entered the Estrogen Replacement and Atherosclerosis trial, of whom 248 underwent baseline angiography and completed follow-up angiography after an average of 3.2 years. Women were identified as having type 2 diabetes mellitus (T2DM) or the MS (National Cholesterol Education Panel diagnostic criteria). In adjusted models, participants with T2DM and the MS had greater angiographic progression [change in minimal diameter (ΔMD): −0.15] than women without T2DM or the MS (ΔMD: −0.08; P<0.05) or with MS alone (ΔMD: −0.07; P<0.005); there was no difference in progression by MS status in women without T2DM (P=0.54). In adjusted logistic regression models, T2DM predicted coronary heart disease events [odds ratio, 2.79 (95% CI, 1.29 to 6.02)], and the MS demonstrated a similar trend [odds ratio, 1.98 (95% CI, 0.90 to 4.33)].

Conclusions—Among postmenopausal women with coronary heart disease, the presence of diabetes predicted disease progression, but the MS did not. (Arterioscler Thromb Vasc Biol. 2006;26:0-0.)

Key Words: PLEASE ■ SUPPLY ■ KEY ■ WORDS ■ XXXX

Type 2 diabetes mellitus (T2DM) has long been recognized as a significant risk factor for coronary heart disease (CHD) and has been acknowledged as a CHD equivalent.1 In recent years, there has been increased interest in the clustering of abnormal glucose metabolism and obesity with other cardiovascular risk factors. Originally referred to by Reaven as “Syndrome X,”2 the intermediate phenotype represented by the constellation of abdominal obesity, insulin resistance or impaired glucose regulation, hypertension, and dyslipidemia [with elevated triglycerides and low high-density lipoprotein (HDL) cholesterol] is now known as the metabolic syndrome (MS). Both overt diabetes3,4 and the MS5–11 are associated with increased risk of cardiovascular events and death. However, it remains unclear whether these associations with clinical events result from an effect on the progression of atherosclerosis, a consequence of changes in stability of existing plaques, or a result of other changes that might facilitate the development of an acute thrombotic event. More data are needed on the relationship of diabetes and the MS with progression of anatomically defined atherosclerosis to clarify the mechanisms underlying their association with CHD.

The Estrogen Replacement and Atherosclerosis (ERA) trial was a randomized, controlled trial that evaluated the effect of hormone replacement therapy on angiographic progression of atherosclerosis. The study design12 and primary results13 have been published previously. We sought to evaluate the role of diabetes and the MS in the progression of coronary atherosclerosis in this cohort of postmenopausal women with established heart disease.

Methods

Study Population and Follow-Up

A total of 309 women were enrolled from 5 clinical sites between January 1996 and December 1997. Participants were postmenopausal women with coronary artery disease documented by >1 epicardial stenoses of the luminal diameter of ≥30%. Exclusion criteria included known or suspected breast or endometrial cancer, previous or planned coronary artery bypass surgery, history of deep venous thrombosis or pulmonary embolism, symptomatic gallstones, elevated liver enzymes, fasting triglyceride level >400 mg/dL, serum creatinine >2 mg/dL, >70% stenosis of the left main coronary artery, uncontrolled hypertension, or uncontrolled diabetes.

At baseline, participants completed questionnaires about health status, medical history, and cardiovascular risk factors before undergoing clinical examination and quantitative coronary angiography. Smoking status was defined as having smoked cigarettes within the last 100 days. Resting blood pressure was determined by taking 3 measures after the subject had been seated comfortably for 5 minutes and averaging the latter 2. Anthropometric measurements included...
height, weight, waist circumference, and hip circumference. Fasting lipids measurements were obtained from all of the participants. Women without a history of diabetes underwent a 75-gm oral glucose tolerance test.

After study entry, participants returned for follow-up examinations at one of the clinical sites after 3 months, 6 months, and every 6 months thereafter until the study conclusion. At these visits, participants were questioned about interval hospitalizations. Hospital discharge summaries were obtained for each hospitalization, and suspected cardiovascular events were documented by hospital records (based on admission/discharge notes, cardiac enzymes, electrocardiograms, and cardiac tests/ procedures) and verified by an independent adjudicator using a classification strategy drawn from the Heart and Estrogen/Progestin Replacement Study. A similar process was used to ascertain events if the ERA clinic was informed of a participant’s death.

Diabetes and the MS
Women were considered to have T2DM if they met any of the following criteria: self-reported history of adult onset diabetes, current use of insulin or oral glucose-lowering medications, fasting glucose of \( \geq 126 \text{ mg/dL} \), or 2-hour postchallenge glucose of \( \geq 200 \text{ mg/dL} \) on the oral glucose tolerance test. Using the National Cholesterol Education Panel (NCEP) definition, the MS was defined by meeting 3 of the following 5 criteria: waist circumference \( \geq 88 \text{ cm} \); fasting glucose of \( \geq 100 \text{ mg/dL} \) without diabetes; systolic blood pressure (SBP) \( \geq 130 \text{ mm Hg} \); diastolic blood pressure \( \geq 85 \text{ mm Hg} \); or current use of antihypertensive medications; fasting triglycerides \( \geq 150 \text{ mg/dL} \); or HDL cholesterol \( < 50 \text{ mg/dL} \). The lower threshold of fasting glucose (which had formerly been \( \geq 110 \text{ mg/dL} \)) was based on recent recommendations of the American Diabetes Association and the American Heart Association. Additional analyses used the World Health Organization criteria to define the MS.

Angiography
Complete details of the angiographic method have been published previously. Briefly, standardized baseline and follow-up quantitative coronary angiographic data were available for 248 of the 309 randomized subjects followed over a mean (\( \pm \text{SD} \)) of 3.2 (\( \pm 0.6 \)) years. Review and analysis of the paired films were performed using a previously validated system of cine projectors (SME-3500; Sony) and software (QCA Plus; Sanders Data Systems). The reference, minimum and average luminal diameters, and the degree of stenosis were assessed in 10 proximal epicardial segments. Angiographic analyses were performed by operators who were blinded to patient information and the temporal sequence of films.

Statistical Analysis
Participants were categorized by the presence or absence of the MS and T2DM, creating 4 groups. Baseline demographic and laboratory data were compared across groups using ANOVA and \( \chi^2 \). The primary outcome of interest was progression of coronary atherosclerosis as defined by change in the minimal vessel diameter (\( \text{MD} \)) within each coronary segment, determined by (follow-up minimal diameter) – (baseline minimal diameter), with negative values representing atherosclerotic progression. We evaluated the change in minimal diameter using generalized linear mixed models, accounting for repeated measures within subjects, adjusting for baseline minimal diameter, location of the coronary segment, age, race, clinical site, estrogen treatment, lipid-lowering medication, time between baseline and follow-up angiogram, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, and early follow-up angiography. Additional analyses adjusted for the base model, as well as SBP, cigarette use, and total cholesterol (full model). Logistic regression models, adjusted for age, race, clinical site, study arm, and lipid-lowering medications (base model), were used to evaluate a composite clinical outcome of any CHD event (nonfatal myocardial infarction, fatal myocardial infarction, coronary revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty), or hospitalization for unstable angina). Additional logistic regression models accounted for the base model covariates, as well as SBP, smoking, and total cholesterol (full model).

Results
The mean age of the cohort was 65.5 ± 7.1 years, and the mean body mass index was 29.8 ± 7.7 kg/m² (Table 1). Ninety-eight women (40%) were classified as having T2DM and the MS, whereas only 8 (3%) had T2DM but not the MS.

### TABLE 1. Baseline Characteristics of Women with Follow-Up Angiography, by T2DM and MS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall % (n) or mean ± SD (n)</th>
<th>DM (−)/MS (−) % (n) or mean ± SD (n)</th>
<th>DM (−)/MS (+) % (n) or mean ± SD (n)</th>
<th>DM (+)/MS (−) % (n) or mean ± SD (n)</th>
<th>DM (+)/MS (+) % (n) or mean ± SD (n)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of total, n</td>
<td>248</td>
<td>217 (64)</td>
<td>35.4 (88)</td>
<td>3.2 (8)</td>
<td>39.5 (98)</td>
<td>0.32</td>
</tr>
<tr>
<td>Age, y</td>
<td>65.5 (7.1)</td>
<td>65.2 (7.3)</td>
<td>65.9 (6.9)</td>
<td>67.5 (8.2)</td>
<td>65.2 (7.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>83.1 (206)</td>
<td>89.7 (52)</td>
<td>90.1 (109)</td>
<td>90.1 (109)</td>
<td>65.2 (45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black</td>
<td>12.9 (32)</td>
<td>6.9 (4)</td>
<td>6.6 (8)</td>
<td>6.6 (8)</td>
<td>29.0 (20)</td>
<td>0.98</td>
</tr>
<tr>
<td>Other</td>
<td>4.0 (10)</td>
<td>3.5 (2)</td>
<td>3.3 (4)</td>
<td>3.3 (4)</td>
<td>5.8 (4)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74.2 (184)</td>
<td>41.4 (24)</td>
<td>85.1 (103)</td>
<td>85.1 (103)</td>
<td>82.6 (57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>65.6 (162)</td>
<td>72.4 (42)</td>
<td>65.8 (79)</td>
<td>65.8 (79)</td>
<td>59.4 (41)</td>
<td>0.31</td>
</tr>
<tr>
<td>Lipid-lowering medications</td>
<td>35.1 (87)</td>
<td>36.2 (21)</td>
<td>34.7 (42)</td>
<td>34.7 (42)</td>
<td>34.8 (24)</td>
<td>0.98</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.8 ± 7.7</td>
<td>24.2 ± 3.9</td>
<td>30.5 ± 9.4</td>
<td>25.7 ± 3.7</td>
<td>32.8 ± 6.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>93.2 ± 15</td>
<td>79.1 ± 10.4</td>
<td>92.3 ± 11.2</td>
<td>81.0 ± 5.1</td>
<td>102.9 ± 14.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>133.6 ± 17.3</td>
<td>126.5 ± 17.2</td>
<td>133.4 ± 17.8</td>
<td>126.9 ± 21.2</td>
<td>138.1 ± 15.3</td>
<td>0.002</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>74.0 ± 8.5</td>
<td>71.7 ± 8.6</td>
<td>74.5 ± 8.2</td>
<td>66.8 ± 7.6</td>
<td>76.6 ± 8.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>217.9 ± 42.5</td>
<td>212.9 ± 32.2</td>
<td>220.5 ± 44.4</td>
<td>189.1 ± 21.9</td>
<td>220.8 ± 46.4</td>
<td>0.31</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>44.5 ± 11.9</td>
<td>53.6 ± 12.4</td>
<td>41.0 ± 8.1</td>
<td>58.6 ± 15.4</td>
<td>41.3 ± 10.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>192.7 ± 106.3</td>
<td>128.4 ± 76.8</td>
<td>212.5 ± 97.3</td>
<td>103.4 ± 34.0</td>
<td>218.3 ± 114.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>103.8 ± 23.4</td>
<td>94.0 ± 11.7</td>
<td>99.3 ± 14.5</td>
<td>99.3 ± 14.5</td>
<td>144.9 ± 61.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P for comparison across diabetes/metabolic syndrome category. DBP indicates diastolic blood pressure.
Angiographic progression of coronary disease: diabetes and the metabolic syndrome. MS, metabolic syndrome; DM, type 2 diabetes mellitus.

Eighty-eight women (35%) met the NCEP diagnostic criteria for the MS alone. Although there were significant differences across the groups by race, obesity, SBP, HDL, triglycerides, and fasting glucose, there were no differences by age, total cholesterol, use of lipid-lowering medications, or smoking status.

There was no difference in angiographic progression (change in minimal diameter, \( \Delta MD \)) between women with the MS and without T2DM (\( \Delta MD: -0.07 \pm 0.03 \)) and those with neither (\( \Delta MD: -0.08 \pm 0.03; P=0.54 \); Figure 1). Conversely, women with T2DM and the MS had greater progression (\( \Delta MD: -0.15 \pm 0.03 \)) than women with the MS alone (\( P<0.05 \)) or neither the MS nor T2DM (\( P=0.005 \)). These findings were attenuated after additional adjustment for smoking, cholesterol, and SBP \( \text{T2DM(+)/MS(+)} \) versus \( \text{T2DM(-)/MS(+)} \), \( P<0.005 \); \( \text{T2DM(+)/MS(+)} \) versus \( \text{T2DM(-)/MS(-)} \), \( P=0.07 \). When comparing all of the women with T2DM to those without T2DM in the full model, those with T2DM had significantly greater progression (\( \Delta MD: -0.07 \pm 0.03 \) versus \(-0.14 \pm 0.03 \text{ mm}; P=0.005 \)). Analyses using the World Health Organization criteria for the MS were qualitatively similar (data not shown).

With respect to the CHD composite clinical end point, individuals with diabetes and the MS had significantly more events than those without diabetes or the MS \( \text{[odds ratio (OR), 2.79 (95\% CI, 1.29 to 6.02), base model]} \) (Table 2). Although women with the MS alone appeared to have increased risk of clinical events, this result was not statistically significant \( \text{[OR, 1.98 (95\% CI, 0.90 to 4.33)]}. \) The ORs were attenuated after additional adjustment for smoking, cholesterol, and SBP but remained similar in magnitude.

## Table 2. Odds of CHD Event* by DM or the MS

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>No. Events</th>
<th>%</th>
<th>OR†</th>
<th>95% CI</th>
<th>OR‡</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (−)/MS (−)</td>
<td>69</td>
<td>11</td>
<td>16%</td>
<td>1</td>
<td>(referent)</td>
<td>1</td>
<td>(referent)</td>
</tr>
<tr>
<td>DM (−)/MS (+)</td>
<td>110</td>
<td>30</td>
<td>27%</td>
<td>1.98</td>
<td>0.90 to 4.33</td>
<td>1.92</td>
<td>0.86 to 4.30</td>
</tr>
<tr>
<td>DM (+)/MS (−)</td>
<td>9</td>
<td>4</td>
<td>44%</td>
<td>4.55</td>
<td>1.02 to 20.25</td>
<td>4.24</td>
<td>0.94 to 19.25</td>
</tr>
<tr>
<td>DM (+)/MS (+)</td>
<td>121</td>
<td>41</td>
<td>34%</td>
<td>2.79</td>
<td>1.29 to 6.02</td>
<td>2.91</td>
<td>1.30 to 6.47</td>
</tr>
</tbody>
</table>

*Nonfatal myocardial infarction, fatal myocardial infarction, revascularization, or hospitalization for unstable angina.
†Adjusted for race, age, clinical site, treatment arm, and lipid-lowering medications (base model).
‡Adjusted for base model, smoking, cholesterol, and SBP.

Discussion

We found that diabetes predicted angiographic progression of coronary atherosclerosis and clinical cardiovascular events in postmenopausal women with coronary artery disease. Conversely, the MS did not predict progression, but there was a trend toward increased clinical events in women with the MS. These observations, taken in the context of existing knowledge, may provide insights into the pathophysiology of cardiovascular risk along the continuum of the MS and type 2 diabetes.

Prior studies have observed the association between diabetes and angiographic progression of coronary atherosclerosis.\(^{18–22}\) The MS has been associated with incident CHD and CHD mortality.\(^{5–11}\) and, although the MS and insulin resistance have been associated with atherosclerosis in cross-sectional studies,\(^{23–26}\) the association between the MS and atherosclerotic progression is less clear. Bonora et al\(^{27}\) found an association between the MS and progression of carotid atherosclerosis, a CHD surrogate, in the Bruneck cohort. Conversely, in the Women’s Angiographic Vitamin and Estrogen trial (WAVE), an angiographic study involving a cohort of postmenopausal women with coronary artery disease, the presence of the MS was not significantly associated with angiographic progression.\(^{28}\) However, women in the WAVE trial with the MS did experience significantly more cardiac events. Similarly, we noted a trend toward increased events in women with the MS, in contrast with the absence of such a trend with respect to progression.

These observations could reflect the differing mechanisms by which altered glucose homeostasis influences cardiovascular events. Whereas the MS may play a limited role in accelerating atherosclerotic progression, it may significantly increase the risk of vascular events through prothrombotic or inflammatory mechanisms.\(^{29–31}\) The Women’s Ischemic Syndrome Evaluation study, an observational study of cardiovascular outcomes in women with angiographically defined coronary disease, found that the MS was predictive of cardiovascular events only in women with significant atherosclerotic disease.\(^{32}\) The ERA cohort consisted exclusively of women with established coronary atherosclerosis, and, thus, this may corroborate a model in which the clinical impact of the MS lies in the altered hemostasis and increased inflammation superimposed on preexisting atherosclerosis rather than on accelerated atherosclerotic progression.

Although the NCEP noted that the MS is characterized by a prothrombotic and proinflammatory state, the diagnostic criteria do not reflect these components of the syndrome.
(NCEP). Additional efforts to elucidate the mechanism of risk in the MS may lead to the incorporation of inflammatory and hemostatic markers (eg, C-reactive protein, plasminogen activator inhibitor 1, or fibrinogen) into future diagnostic criteria. A better understanding of the pathophysiology of the MS could then lead to more effective treatment paradigms. Although current recommendations focus on lifestyle interventions (weight loss and increased physical activity) or risk factor management (glucose, blood pressure, and lipid control), future studies may demonstrate the importance of targeting inflammatory and coagulation pathways in these patients.

Several aspects of this study provide a unique opportunity to evaluate heart disease in older women. This study permitted a direct assessment of coronary atherosclerotic disease progression. The ERA study used QCA, which has been used to follow disease progression in both interventional and observational settings.33–36 Furthermore, atherosclerotic progression as described by serial angiography predicts subsequent clinical events.37,38 An additional strength of this study is its female cohort. The ERA study was a prospective randomized, controlled trial evaluating the effects of postmenopausal hormone replacement on atherosclerotic progression. Many of the studies evaluating the MS and clinical cardiovascular outcomes have included only men5,6,8,9 or have noted a relative paucity of events among women compared with men.11,13,14,40 Recent data from the National Health and Nutrition Examination and Survey (1999–2000) reveal that older women (≥60 years) have the highest prevalence of the MS (56%).41 illustrating the importance of investigating the effects of this process in this population.

Our study has several limitations. First, as a post hoc analysis, it may only generate or support hypotheses. Furthermore, the composite clinical end point was a secondary outcome, and conclusions drawn from this measure must be made with caution. Although there was a trend toward increased events in individuals with the MS alone, our study was not powered to make inferences with confidence about predictors of clinical outcomes. Similarly, the number of women with T2DM but without the MS was small, limiting our ability to examine the importance of the presence or absence of other metabolic risk factors in individuals with T2DM.

The restricted cohort of patients (postmenopausal women) limits the generalizability of our findings. Yet, as noted above, older women bear the greatest burden of diabetes and the MS and deserve greater study as an at-risk population. The inclusion of only women with established CHD additionally limits the generalizability of our findings. Future studies, such as the Multiethnic Study of Atherosclerosis,42 may use noninvasive measures of coronary atherosclerosis (eg, electron beam computed tomography) to follow atherosclerotic progression in cohorts without clinically evident CHD.

In conclusion, diabetes predicted angiographic progression of coronary artery disease in postmenopausal women, but the MS did not. However, women with the MS had a trend toward clinical cardiovascular events. This may reflect the importance of mechanisms other than atherosclerotic progression, such as a proinflammatory or prothrombotic state, in the heart disease risk associated with the MS.

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References


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