The Metabolic Syndrome, Its Component Risk Factors, and Progression of Coronary Atherosclerosis

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**Background:** The mechanism that confers adverse cardiovascular prognosis in patients with the metabolic syndrome (MetS) remains unclear. We sought to investigate the association of MetS and its component risk factors with progression of coronary atherosclerosis.

**Methods:** We performed a systematic review of 3459 patients who participated in 7 clinical trials that monitored coronary atheroma progression with intravascular ultrasonography. Patients with or without MetS were compared with regard to clinical characteristics, coronary atheroma burden at baseline, and change on serial evaluation. Relationships between plaque progression (≥5% increase in percent atheroma volume [PAV]), MetS, and its component risk factors were investigated.

**Results:** The metabolic syndrome was highly prevalent and was associated with greater progression of PAV (+0.51%±0.23% vs +0.23%±0.24%; P=.003). Multivariable analysis showed that MetS was associated with a greater likelihood of undergoing progression of PAV (adjusted odds ratio [OR], 1.25; 95% confidence interval [CI], 1.05-1.48; P=.01). When the individual components were used in the model instead of MetS, hypertriglyceridemia (OR, 1.26; 95% CI, 1.06-1.49; P=.008) and a body mass index of 30 or higher (1.18, 1.00-1.40; P=.05) predicted progression of PAV. However, after adjusting for its individual components, MetS was no longer an independent predictor (OR, 1.04; 95% CI, 0.79-1.37; P=.79).

**Conclusion:** Although accelerated disease progression is observed in the setting of MetS, this is owing to the presence of individual component risk factors rather than to the presence of the syndrome itself.

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Occurrences of Thrombosis,10 REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering),11 ACTIVATE (Acyl-Coenzyme A:Cholesterol Acyltransferase Intravascular Atherosclerosis Treatment Evaluation),14 ASTEROID (a Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden),12 ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by Coenzyme Ester Transfer Protein Inhibition and High-Density Lipoprotein Elevation),13 PERISCOPE (Comparison of Pioglitazone vs Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes),16 and STRADIVARIUS (Effect of Rimonabant on Progression of Atherosclerosis in Patients With Abdominal Obesity and Coronary Artery Disease).17 These were clinical trials that used serial IVUS examination to assess the impact of intensive lipid lowering, antihypertensive therapy, acyl-coenzyme A:cholesterol acyltransferase inhibition, cholesteryl ester transfer protein inhibition, oral glucose-lowering agents, and an endocannabinoid type 1 receptor antagonist on the progression of coronary atherosclerosis. All patients were required to have coronary artery disease, defined as having at least 1 lumen with narrowing of greater than 20% in a major epicardial coronary artery on a diagnostic coronary angiogram performed for a clinical indication.

ACQUISITION AND ANALYSIS OF IVUS IMAGES

The acquisition and analysis of ultrasonic images have been described in detail previously.10-17 In brief, after anticoagulation and administration of intracoronary nitroglycerin, an imaging catheter containing a high-frequency ultrasound transducer (30-40 MHz) was inserted as far as distally possible within a coronary artery. The target vessel for imaging was required to have a segment at least 30 mm long that contained no lumen with narrowing of greater than 30%, had not undergone previous revascularization, and was not considered to be the culprit vessel for a previous myocardial infarction. Continuous ultrasonographic imaging was acquired during withdrawal of the catheter (pullback) through the segment of artery at a constant rate of 0.5 mm/s. Images were stored on videotape and subsequently digitized for analysis in a single core laboratory by individuals who were blinded to the clinical characteristics and treatment status of the patients. Matching arterial segments were defined from the images acquired at the baseline and follow-up studies on the basis of the anatomic location of proximal and distal side branches (fiduciary points). Images spaced precisely 1 mm apart in the segment of interest were selected for analysis. The leading edge of the lumen and the external elastic membrane (EEM) were defined by manual planimetry. The plaque area was defined as the difference in area occupied by the lumen and EEM borders. The total atheroma volume (TAV) was calculated by summation of the plaque area as calculated by the following equation for each measured image and subsequently normalized to account for differences in segment length between subjects:

\[
TAV_{\text{Normalized}} = \frac{\sum (\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\text{No. of Images in Pullback} \times \text{Median No. of Images in Cohort}}
\]

The percent atheroma volume (PAV) was calculated by the following equation as the proportion of vessel wall volume occupied by atherosclerotic plaque:

\[
PAV = \frac{\sum (\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\sum (\text{EEM}_{\text{area}})} \times 100
\]

VOLUMES OCCUPIED BY THE LUMEN AND EEM WERE SIMILARLY CALCULATED BY SUMMATION OF THEIR RESPECTIVE AREAS IN EACH MEASURED IMAGE AND SUBSEQUENTLY NORMALIZED TO ACCOUNT FOR DIFFERENCES IN SEGMENT LENGTH BETWEEN PATIENTS.

Patients were stratified according to the presence or absence of MetS at baseline, as defined by the National Cholesterol Education Program’s Adult Treatment Panel III criterion,18 and by a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or more. The following BMI of 30 or higher, triglyceride levels of 150 mg/dL or greater, low levels of high-density lipoprotein cholesterol (HDL-C) (<40 mg/dL in men and <50 mg/dL in women), elevated fasting glucose (≥100 mg/dL or a diagnosis of diabetes mellitus), and high systolic or diastolic blood pressure (≥130/85 mm Hg or current use of antihypertensive medication). (To convert triglycerides to millimoles per liter, multiply by 0.0113; HDL-C to millimoles per liter, multiply by 0.0259; and glucose to millimoles per liter, multiply by 0.0559.)

Patients with or without MetS were compared with regard to clinical characteristics, the extent of coronary atherosclerosis at baseline, and their serial changes. In addition, the percentage of images containing plaque and calcification were investigated to evaluate differences between groups with regard to the diffuse pattern and degree of calcification of disease, respectively.

STATISTICAL ANALYSES

All analyses were conducted using SAS statistical software (version 9.2; SAS Institute Inc, Cary, North Carolina). Demographic data are expressed in percentages for categorical variables and compared using the χ² statistic. Continuous laboratory data are expressed as means±SD and compared with a standard t test for factors with a normal distribution or expressed as median and interquartile range and compared with the Wilcoxon rank sum test for factors that are nonnormally distributed. Changes in atheroma burden and vascular dimensions on a continuous scale were evaluated using an analysis of variance model for random effects with the baseline value as a covariate, classification group (MetS or no MetS) as a factor, and trial as a random effect to account for the heterogeneity between the different studies. A multivariable logistic regression quantified the relative odds of undergoing substantial plaque progression (defined as a percentage increase in PAV ≥5%) associated with MetS after adjusting for age, sex, race, baseline low-density lipoprotein cholesterol (LDL-C) level, statin use, and study. Separate adjusted models were generated for each component of MetS, and odds ratios (ORs) were calculated for the patients having MetS with or without the component compared with the reference group (no MetS). In addition, each of the components of MetS were forced together into a multivariable logistic model to assess the relative odds of plaque progression for each component in the presence of the others. A 2-sided P<.05 was considered statistically significant.

BASELINE CHARACTERISTICS

Patient characteristics are summarized in Table 1. More than half of the patients (57.8%) met the criteria for MetS at baseline. The prevalence of components of MetS in both patient groups is illustrated in the Figure. Patients with MetS were younger (57.3±9.2 vs 58.5±9.7 years; P<.001) and more likely to be female (32.3% vs 25.1%; P<.001). Patients with MetS were less likely to be treated with stat-

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MetS up are given in /H9252 converting enzyme inhibitors (62.2% vs 45.0%; squared); MetS, metabolic syndrome.

The degrees of risk factor control at baseline and follow-up are given in Table 3. Despite a high percentage of non–HDL-C (144.9±44.4 vs 131.2±40.6 mg/dL; P<.001) and more likely to receive β-blockers (79.1% vs 72.8%; P<.001) and angiotensin-converting enzyme inhibitors (62.2% vs 45.0%; P<.001).

The baseline degree of component risk factor distribution. Atheroma burden and vessel wall dimensions and their percentage change in patients with and without MetS are provided in Table 3. Despite a high percentage of non–HDL-C (144.9±44.4 vs 131.2±40.6 mg/dL; P<.001) and more likely to receive β-blockers (79.1% vs 72.8%; P<.001) and angiotensin-converting enzyme inhibitors (62.2% vs 45.0%; P<.001).

The degree of risk factor control at baseline and follow-up are given in Table 3. Predictably, each diagnostic criterion of MetS was more prevalent in patients with MetS (P<.001). Patients with MetS also had higher baseline levels of non–HDL-C (144.9±44.4 vs 131.2±40.6 mg/dL; P<.001). During the course of the studies, the observed decrease in LDL-C was less (−0.5%±0.2%; 95% CI, −0.2% to 0.2%; P=.003) and less regression in TAV (−0.2%±0.1%; 95% CI, −0.5% to 0.2%; P=.003) at baseline.

SERIAL CHANGES OF ATHEROSCLEROTIC BURDEN AND VASCULAR DIMENSIONS

Changes in atheroma burden and vessel wall dimensions during serial evaluation are given in Table 3. Despite a high rate of medical therapy use, patients with MetS demonstrated accelerated progression of PAV (+0.51%±0.23% vs +0.23%±0.24%; P=.003) and less regression in TAV.

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Table 3. Baseline and Serial Changes of Atheroma Burden and Vascular Dimensions in Patients With and Without MetS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MetS (n=1998)</th>
<th>No MetS (n=1461)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent atheroma volume</td>
<td>38.7 (9.0)</td>
<td>38.5 (9.0)</td>
<td>.57</td>
</tr>
<tr>
<td>Total atheroma volume, mm³</td>
<td>193.6 (85.6)</td>
<td>188.5 (80.0)</td>
<td>.19</td>
</tr>
<tr>
<td>Atheroma volume in most-</td>
<td>62.6 (29.5)</td>
<td>61.3 (27.9)</td>
<td>.19</td>
</tr>
<tr>
<td>diseased 10-mm segment, mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atheroma volume in least-</td>
<td>43.6 (26.2)</td>
<td>42.7 (25.1)</td>
<td>.36</td>
</tr>
<tr>
<td>diseased 10-mm segment, mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM volume, mm³</td>
<td>496.1 (176.2)</td>
<td>484.7 (160.1)</td>
<td>.21</td>
</tr>
<tr>
<td>Lumen volume, mm³</td>
<td>302.4 (114.1)</td>
<td>296.2 (103.9)</td>
<td>.35</td>
</tr>
<tr>
<td><strong>Serial change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent atheroma volume</td>
<td>0.51 (0.23)</td>
<td>0.23 (0.24)</td>
<td>.003</td>
</tr>
<tr>
<td>Total atheroma volume, mm³</td>
<td>−2.3 (1.7)</td>
<td>−3.4 (1.7)</td>
<td>.07</td>
</tr>
<tr>
<td>Atheroma volume in most-</td>
<td>−2.3 (9.8)</td>
<td>−3.3 (9.8)</td>
<td>.005</td>
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<td>diseased 10-mm segment, mm³</td>
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<tr>
<td>Atheroma volume in least-</td>
<td>0.6 (7.6)</td>
<td>0.01 (7.3)</td>
<td>.03</td>
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<tr>
<td>diseased 10-mm segment, mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with substantial</td>
<td>27.2</td>
<td>22.2</td>
<td>.001</td>
</tr>
<tr>
<td>progression, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with substantial</td>
<td>17.7</td>
<td>20.6</td>
<td>.03</td>
</tr>
<tr>
<td>regression, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEM volume, mm³</td>
<td>−12.0 (39.4)</td>
<td>−11.7 (37.5)</td>
<td>.70</td>
</tr>
<tr>
<td>Lumen volume, mm³</td>
<td>−9.8 (31.6)</td>
<td>−7.9 (29.4)</td>
<td>.40</td>
</tr>
</tbody>
</table>

Abbreviations: EEM, external elastic membrane; MetS, metabolic syndrome.

Substantial progression is defined as an increase in percent atheroma volume of 5% or greater.

Substantial regression is defined as a decrease in percent atheroma volume of 5% or greater.

(−2.3±1.7 vs −3.4±1.7 mm³; P=.07), although the latter failed to meet statistical significance. Patients with MetS were more likely to demonstrate substantial atheroma progression (≥5% increase in PAV, 27.2% vs 22.2%; P=.001) and less likely to demonstrate substantial regression (≥5% decrease in PAV, 17.7% vs 20.6%; P=.03). The baseline and serial changes of EEM and lumen volumes were similar in patients with and without MetS.

INDEPENDENT PREDICTORS OF DISEASE BURDEN AND PROGRESSION

Table 4 provides the odds of having substantial atheroma progression for those with MetS, with or without the individual components, compared with those without MetS. Individuals with MetS, including the components of elevated BMI or hypertriglyceridemia, tended to have the highest odds of progression (OR, 1.32; 95% confidence interval [CI], 1.10-1.58 and 1.31, 1.10-1.58, respectively).

In a multivariable model adjusting for age, sex, race, baseline LDL-C level, and baseline statin use, having MetS demonstrated a greater likelihood for substantial progression (OR, 1.25; 95% CI, 1.05-1.48; P=.01) (Table 5). When the individual components were used in the adjusted model instead of the syndrome, hypertriglyceridemia (P=.008) and a BMI of 30 or higher (P=.05) were again shown to be independent predictors of substantial progression of PAV (Table 5). Baseline C-reactive protein levels were not an independent predictor in any of the models (data not shown). When MetS and its individual components were
considered in the model together, MetS as a cluster was not an independent predictor (OR, 1.04; 95% CI, 0.79-1.37; \( P = .79 \)), and the only component that remained significant was hypertriglyceridemia (1.23, 1.02-1.49; \( P = .03 \)).

Further multivariable analysis that considered the change in PAV as a continuous outcome variable showed that elevated glucose levels (\( P = .002 \) and hypertriglyceridemia (\( P < .001 \)), but not MetS (\( P = .15 \)), were independent predictors for progression (data not shown).

**COMMENT**

In this pooled analysis of prospective atherosclerosis progression/regression IVUS trials that included 3459 patients with established coronary artery disease, we examined the association of MetS and its component risk factors with plaque progression. Metabolic syndrome was highly prevalent (57.8%) in this cohort and was associated with higher rates of disease progression. However, multivariable analysis showed that the excess plaque progression appeared to be driven more by its individual risk factors. These results have important implications for understanding the relationship between MetS and cardiovascular disease. A major impetus for developing the concept of MetS involved the observation of a clustering of risk factors for coronary heart disease and diabetes mellitus in patients with abdominal obesity. However, it remains to be unequivocally established whether MetS is a distinct pathologic entity or simply represents an association of risk factors. Debate continues to be supported by the observation that the adverse outcome appears to be driven by the presence of individual risk factors.\(^4^,\(^7^,\(^9\)\) As a result, it remains to be demonstrated that the impact of the syndrome exceeds that of the sum of its individual components. We used atherosclerosis imaging to characterize the association between MetS and atherosclerotic disease progression. The finding of more progression and less regression of disease in patients with MetS on univariate analysis confirms previous observations from studies that used carotid intima-media thickness.\(^2^0^,\(^2^1\)

However, to our knowledge, no previous imaging study has compared the relative contribution of MetS and its individual components with disease progression. Notably, multivariable analysis showed that accelerated disease progression was more likely to be driven by individual risk factors. Although each of the components predicted greater disease progression, hypertriglyceridemia and elevated BMI had the highest hazard ratios for atheroma progression. These findings provide a mechanistic link between the burden of atherosclerosis and reported outcome data. A study based on Third National Health and Nutrition Examination Survey data has found that, among MetS components, hypertriglyceridemia has the strongest relation to prevalent myocardial infarction and stroke in patients with MetS.\(^2^2\) Moreover, Miller et al.\(^2^3\) demonstrated that patients receiving statin therapy after acute coronary syndrome, for whom triglyceride levels while receiving therapy were less than 150 mg/dL, had a lower risk of recurrent coronary heart disease events independent of the level of LDL-C.

The finding that hypertriglyceridemia independently predicted disease progression supports an increasing body of evidence demonstrating that fasting hypertriglyceridemia is an established cardiovascular risk factor.\(^2^4^\) This has been extended to the observations of triglyceride measurements obtained using samples collected in the nonfasting state.\(^2^7^\) The variability in these findings between the fasting and nonfasting samples may also reflect differences in dietary fat and carbohydrate intake, potentially confounding the association to a greater degree. The finding that elevated triglyceride levels predict disease progression and cardiovascular risk, even in patients with LDL-C levels considered to be normal, may result from both the atherogenicity of triglyceride-rich remnant particles and effects on the relative functionality of circulating LDL-C and HDL-C particles.\(^3^0^,\(^3^1\) These observations also suggest that a more aggressive approach to management of even mild triglyceride elevations should be integrated into risk-reduction strategies.

The additional finding that obesity is an independent predictor of disease progression warrants further comment. The presence of central adiposity is commonly encountered in patients with MetS. An abdominal distribution of adipose tissue is associated with a number of factors that are likely to have a detrimental influence on the artery wall, including dysregulation of metabolic factors, activation of inflammatory cascades, and potentially direct effects of adipocytokines.\(^3^2\) It is therefore not surprising that anthropometric factors consistent with abdominal obesity are associated with an adverse cardiovascular outcome. Accordingly, targeting the abdominally obese patient for aggressive preventive measures may be of greater utility than the identification of MetS. Abdominal adiposity may also be the source of targets for new therapies. Although the use of the endocannabinoid receptor antagonist rimonabant did not slow progression of coronary atherosclerosis, the strategy did appear to be beneficial in abdominally obese patients with hypertriglyceridemia.\(^1^0\) This further underscores the interaction between obesity and the development of an atherogenic dyslipidemic phenotype in promoting cardiovascular risk.

The current findings do not diminish the importance of other risk factors previously reported to be associated with disease progression. In particular, LDL-C remains an important promoter of atherosclerosis formation and propagation. The high prevalence of MetS in the current cohort—which is more typically associated with an atherogenic dyslipidemic phenotype—and the high rate of statin therapy use are likely to influence the relationship between LDL-C and disease progression. This is consistent with the observation that the absence of statin therapy remains an independent predictor of disease progression. Similarly, the importance of diabetes mellitus, even after controlling for associated risk factors, underscores the severity of that disease process in the setting of disordered glucose homeostasis beyond the insulin resistance commonly encountered in patients with MetS.

The results do not diminish the importance of the other MetS components. When each component was considered individually in combination with MetS, a greater chance of progression was observed. This supports the importance of hyperglycemia, hypertension, and low HDL-C level as risk factors. Each of these factors remains a potential target for cardiovascular prevention in
these patients. Nevertheless, a more robust association was observed between atheroma progression and baseline hypertriglyceridemia and elevated BMI levels. This underscores the finding that hypertriglyceridemia and elevated BMI levels were stronger predictors of progression on multivariable analysis. In addition, the analysis reflects associations with baseline measurements. It is also possible that changes in some factors, such as HDL-C level, may be more important predictors of progression than their baseline levels, as previously reported in statin-treated patients.33

A number of caveats with regard to the current analysis should be noted. All patients had established coronary artery disease on an angiogram performed for a clinical indication. As a result, it is unknown whether the same findings can be extrapolated to asymptomatic patients in the primary prevention setting. Although the data resulted from pooling of multiple clinical trials, all trials recruited similar patients and the coronary imaging was performed and analyzed according to standardized criteria as set forth by a single core laboratory. No data were collected with regard to the composition of atherosclerotic plaque. This may have an important influence on the propensity to undergo plaque rupture. The relationship between the burden and progression of coronary atherosclerosis and clinical outcome also requires ongoing investigation.

In summary, although accelerated disease progression is observed in patients with MetS, this appears to be largely driven by individual component risk factors rather than by the presence of the syndrome itself. This provides further support for the concept that conferring a diagnosis of MetS highlights a patient with multiple atherogenic risk factors. In particular, hypertriglyceridemia and possibly obesity in these patients provide important targets for potential therapeutic intervention to more effectively reduce cardiovascular risk.

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REFERENCES

The Metabolic Syndrome as a Cluster of Risk Factors

Is the Whole Greater Than the Sum of Its Parts?

From the conception of MetS, much debate has continued regarding the recognition of MetS as a real syndrome and whether it is an informative clinical tool. Supposedly, the MetS combination of 3 of its 5 components (hypertriglyceridemia, hyperglycemia, hypertension, low HDL-C level, and greater waist circumference/adiposity) should not only be helpful in identifying cardiovascular disease (CVD) risk but also represent symptoms of an underlying disease or condition.

Two main questions now persist: (1) whether MetS improves prediction and better characterizes people at risk of CVD rather than simply identifies the presence of the individual component risk factors, and (2) whether the syndrome possesses an underlying pathophysiologic characteristic or is merely an aggregated post hoc collection of correlated cardiovascular risk factors.

In seeking an answer to the first question, Bayturun et al conducted a pooled analysis from 7 clinical trials. They compared the effects of MetS and its individual components on coronary plaque progression, defined as an increase of 5% or greater in PAV measured by IVUS. Notably, although an association between MetS and plaque progression was initially observed, the association disappeared when further simultaneously adjusted for the individual components. These results indicate that MetS does not predict coronary plaque progression beyond the independent risk contributions of its individual components.

This is in line with multiple studies examining whether MetS is a better predictor of CVD and type 2 diabetes mellitus than the individual risk factors. Bruno et al showed that identifying MetS in diabetic subjects does not predict more than do the individual components in an 11-year survival cohort. Wilson et al showed that the individual components of MetS predict CVD and type 2 diabetes equally as well as MetS does. Consistent with their findings, Sundstrom et al also found that MetS did not predict cardiovascular mortality independently of its individual components. Moreover, because each of the MetS components is already part of routine clinical assessment and because treatment strategies are available for the individual risk factors rather than for MetS, it is unclear whether the diagnosis of MetS can improve treatment strategies. One positive scenario is that, for patients with subclinical cardiovascular disease who are not eligible for drug treatment, the diagnosis of MetS may help motivate the patients to make lifestyle changes that improve prediction and better characterize people at risk.