Epidemiology

Obesity, Insulin Resistance, and the Metabolic Syndrome
Determinants of Endothelial Dysfunction in Whites and Blacks

A.A. Lteif, MD; K. Han, MD; K.J. Mather, MD

Background—Insulin resistance is strongly associated with obesity and other components of the metabolic syndrome (MS). The relative importance of these components in the determination of endothelial function is unknown. Furthermore, there is conflicting evidence about whether ethnic differences exist in the relative importance of these components in regard to other cardiovascular outcomes. We evaluated the contributions of insulin resistance, obesity, and the other components of the MS to impaired endothelial function.

Methods and Results—The relationships of the MS components (as defined according the National Cholesterol Education Program) and insulin resistance (estimated using the homeostasis model) with endothelium-dependent vasodilation were examined in 42 white and 55 black subjects. Endothelium-dependent vasodilatation was assessed as the increment in leg blood flow (measured by thermodilution) after exposure to methacholine chloride. Waist circumference, glucose, blood pressure, and insulin resistance distributions did not differ between ethnic groups; blacks in our sample had higher HDL cholesterol (1.31 versus 1.09 mmol/L; P<0.001) and lower triglyceride levels (1.01 versus 1.37 mmol/L; P=0.005) than white subjects. In the absence of the MS, black subjects exhibited reduced endothelium-dependent vasodilatation compared with white subjects (P=0.005), and both groups demonstrated significantly worse endothelial function when the MS was present (maximal increase in leg blood flow: blacks: 107±9% MS absent, 53±16% MS present; whites: 163±16% MS absent, 54±18% MS absent; P=0.007, MS absent versus present; P=NS for interaction of ethnicity and MS). Multivariable regression analysis examining relationships of endothelial function with the 5 MS components (analyzed as continuous variables) revealed independent relationships only with waist circumference (P=0.01) and systolic blood pressure (P=0.02). Waist circumference was no longer independently associated after adding insulin resistance to the modeling (P=0.02 for log of homeostasis model index of insulin resistance, P=0.02 for systolic blood pressure). Ethnicity still exerted an independent effect on endothelial function after accounting for the above components (P=0.04 for an additional effect of ethnic status on endothelial function), with an ethnic difference in the effect of insulin resistance on endothelial function (P=0.046 for interaction of ethnicity and log of homeostasis model index of insulin resistance).

Conclusions—These findings suggest that insulin resistance and systolic blood pressure are the principal determinants of endothelial dysfunction in the MS and that there are ethnic differences in the relative importance of these factors. These differences may imply different benefits from treatments targeting blood pressure or insulin resistance in different ethnic groups. (Circulation. 2005;112:32-38.)

Key Words: endothelium ■ insulin resistance ■ metabolic syndrome ■ obesity

Obesity and the metabolic syndrome (MS) are associated with impaired endothelium-dependent vasodilation (EDV). Insulin resistance, measured with oral euglycemic hyperinsulinemic clamp protocols, is closely related to endothelial dysfunction. Insulin resistance is postulated to be the common underlying pathogenic link between the various components of the MS and may explain the presence of the MS even in nonobese subjects. These interrelationships suggest that measures of insulin resistance should perhaps be included with other measures of obesity- and MS-associated risks for cardiovascular outcomes. Comparatively, few data are available on the value of this approach.

Insulin resistance was found to improve the association between MS and coronary artery calcification. In the Women’s Health Initiative, insulin resistance was a key component of risk factor modeling to explain cardiovascular disease outcomes. The interrelationships of insulin resistance, the MS, and endothelial function have not been previously reported.

Relatively little information is available about ethnic differences in the relationship between insulin sensitivity and cardiovascular outcomes. In the Insulin Resistance Atherosclerosis Study (IRAS), the intrinsic associations of insulin resistance and other MS components did not differ across...

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ethnicities. Although associations of subclinical atherosclerosis with insulin resistance and other MS components were seen in this observational study, no ethnic differences have been reported. In other studies, the prevalence of the MS among blacks appears to be similar to that in other ethnic groups. Despite this finding, endothelial function has been reported to be impaired in blacks compared with weight-matched white subjects. Therefore, it is unclear whether the impact of the MS variables on various outcome parameters, including endothelial function, is uniform across ethnicity.

In light of these questions, we hypothesized that the relationship of the MS components with endothelial function would be dependent on insulin resistance and that this relationship would be present in both black and white subjects. We undertook a cross-sectional evaluation of the relationships of insulin resistance and the components of the MS with direct in vivo measurements of endothelial function, specifically evaluating these relationships in black compared with white subjects.

Methods

Patients/Data Set

Nondiabetic subjects entered into our database of vascular function measurements from 1999 to 2004 were included in these analyses. Subjects were community-dwelling volunteers who elected to participate in one of our ongoing protocols involving vascular function measurements. These studies recruit subjects across the spectrum of body habitus. We have not routinely studied subjects with frankly elevated blood pressure or lipid levels; therefore, such subjects are not overrepresented in our study population. Volunteers for our studies of vascular function routinely undergo screening measurement of fasting lipid profiles and oral glucose tolerance testing. Diabetes mellitus, either previously diagnosed or discovered with screening oral glucose tolerance testing, was an exclusion criterion for this analysis. Subjects were categorized prospectively as lean or obese according to body mass index (female cutpoint, 28 kg/m²; male cutpoint, 26 kg/m²). Ethnicity was self-reported by the participants. All studies were approved by the local Institutional Review Board, and all subjects gave written informed consent. All procedures were performed in accordance with institutional guidelines.

Measurements included in the analysis included anthropomorphic measurements performed within 1 week of the vascular study, and blood pressure and biochemical measurements were performed immediately before the vascular study. Weight was measured on a single stationary hospital-grade scale calibrated yearly. Height was measured with a single wall-mounted stadiometer. Percentage body fat was measured by dual energy x-ray absorptiometry or water measurements from 1999 to 2004 were included in these analyses. Subjects were community-dwelling volunteers who elected to participate in one of our ongoing protocols involving vascular function measurements. These studies recruit subjects across the spectrum of body habitus. We have not routinely studied subjects with frankly elevated blood pressure or lipid levels; therefore, such subjects are not overrepresented in our study population. Volunteers for our studies of vascular function routinely undergo screening measurement of fasting lipid profiles and oral glucose tolerance testing. Diabetes mellitus, either previously diagnosed or discovered with screening oral glucose tolerance testing, was an exclusion criterion for this analysis. Subjects were categorized prospectively as lean or obese according to body mass index (female cutpoint, 28 kg/m²; male cutpoint, 26 kg/m²). Ethnicity was self-reported by the participants. All studies were approved by the local Institutional Review Board, and all subjects gave written informed consent. All procedures were performed in accordance with institutional guidelines.

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The data collected with these studies included duplicate fasting insulin and glucose measurements (separated by 10 minutes) before initiation of the vascular study. These values were used to calculate the homeostasis model index of insulin resistance (HOMA-IR). HOMA-IR has been found to closely relate to formal measurements of insulin sensitivity using hyperinsulinemic euglycemic clamp procedures and has proved useful in epidemiological studies as an index of insulin sensitivity.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III cutpoints for the presence or absence of the various components of the MS were used for analyses of the associations of these features, alone and in combination, with endothelial function. The MS was considered present if ≥3 of these features were present.

Assays

Blood for serum glucose determinations was put in untreated polypropylene tubes and centrifuged with an Eppendorf microcentrifuge (Brinkman). The glucose concentration of the supernatant was then measured by the glucose oxidase method with a glucose analyzer (model 2300, Yellow Springs Instruments). Blood for determination of plasma insulin was collected in heparinized tubes, processed immediately, and frozen at −20°C. Insulin determinations were made with a dual-site radioimmunoassay specific for human insulin and with cross-reactivity with proinsulin <0.2% (Linco). The lower detection limit is 0.56 pmol/L, and in our laboratory, the interassay and intra-assay coefficients of variation are 4.1% and 2.6%, respectively. Standard methodologies for cholesterol and triglyceride determinations were used for assays performed through our the clinical laboratory of the local hospital.

Endothelial Function

All vascular studies were performed after an overnight fast, with subjects in a supine position in a quiet, temperature-controlled room. A 6F sheath (Cordis Corp) was placed into the right femoral vein to allow the insertion of a custom-designed 5F double-lumen thermolysis catheter (Baxter Scientific, Edwards Division) to measure leg blood flow (LBF). The right femoral artery was cannulated with a 5.5F double-lumen catheter to allow simultaneous infusion of substances and invasive blood pressure monitoring via a vital signs monitor (Spacelabs). Baseline LBF and mean arterial pressure measurements were obtained after ≥30 minutes of rest after the insertion of the catheters. Femoral vein thermodilution curves were used to measure LBF rates, calculated by integration of the area under the curve, with a cardiac output computer (model 9520A, American Edwards Laboratories). At baseline, 24 LBF measurements were obtained at ≥30-second intervals. This was followed by measurements of the LBF response to graded intrafemoral arterial infusions of the endothelium-dependent vasodilator methacholine chloride (5, 10, and 15 µg/min). Beginning 2 minutes after initiation of each infusion rate, 10 LBF measurements were obtained at ≥30-second intervals. The mean of these 10 measurements was taken as the response at each step, and the percent increase in LBF relative to baseline was calculated for each subject. These measures were used as integrated measurements of endothelial function in the correlation analyses with the various baseline measures discussed above. These responses are specifically inhibited by coinfusion of inhibitors of nitric oxide synthase such as Nω-nitro-L-arginine, confirming their utility in assessing endothelium-dependent vasodilator responses. This method has variability characteristics superior to other commonly used measures of endothelial function, with within-subject coefficients of variation on the order of 10%.

Statistical Analysis

Statistical analyses were performed with JMP version 5.1 (SAS Institute). The 97 nondiabetic subjects studied in this interval participated in 162 leg line studies; to take advantage of the noise-averaging effect of including multiple measurements within individuals, random-effects modeling was used to account for these repeated measures. One-way ANOVA was used to compare the effect of categorical variables on endothelial function. Univariate analyses evaluated the isolated relationships of each of the continuous variables assessed with endothelial function. Simultaneous multivariate analyses were used to explore the concurrent associations of these variables with endothelial function. Two-sided P values of P<0.05 were taken as statistically significant. HOMA-IR was normalized with a logarithmic transformation before inclusion in...
TABLE 1. Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Whites</th>
<th>Blacks</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36.4</td>
<td>34.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>31/11</td>
<td>35/20</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>20.9</td>
<td>28.4</td>
<td>16.5-40.3</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>71.5</td>
<td>75.9</td>
<td>10.0</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.09</td>
<td>1.31</td>
<td>0.33</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.50</td>
<td>2.58</td>
<td>0.71</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.2</td>
<td>5.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.37</td>
<td>1.01</td>
<td>0.39</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.7</td>
<td>2.8</td>
<td>1.8</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>116.7</td>
<td>127.7</td>
<td>12.8</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>71.5</td>
<td>75.9</td>
<td>10.0</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.26</td>
<td>4.36</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.1</td>
<td>29.2</td>
<td>6.1</td>
</tr>
<tr>
<td>Fat, %</td>
<td>26.6</td>
<td>27.1</td>
<td>11.9</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>79.0</td>
<td>82.9</td>
<td>10.8</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>68.3</td>
<td>70.9</td>
<td>49.7</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>13.6</td>
<td>12.7</td>
<td>11.2-14.2</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

parametric analyses, and values presented reflect the inverse transformation of the results from these analyses. Except when repeated-measures analysis for the dose-response to methacholine is presented, the percent increase in LBF to the maximal dose of methacholine was used as the endothelial function end point. Age and basal (unstimulated) blood flow were important confounders of the relationships under study; therefore, these variables were included in all multivariable analyses as covariates, in addition to the random effect for repeated measures within individuals.

Results

The characteristics of the study population are reported in Table 1. Notable differences between the white and black subjects studied included higher HDL cholesterol levels and lower triglyceride levels among black subjects. These differences were statistically significant but not large on the clinical scale. Modest differences in body mass index and systolic blood pressure did not reach the significance threshold. Of note with regard to the present analysis, the 2 ethnic groups did not differ in measures of insulin, glucose, or HOMA-IR. The prevalence of the MS was similar in both ethnic groups (whites, 6 of 42, 14.3% [95% CI, 9.6 to 19.0]; blacks, 7 of 55, 12.7% [95% CI, 11.2 to 14.2]; P=NS; Table 2). There were also no ethnic differences in the prevalence of each MS component (Table 2).

EDV was impaired in black compared with white subjects (Figure; P=0.03 by repeated-measures ANOVA including all subjects, P=0.005 comparing only subjects without the MS). Both groups demonstrated significantly worse endothelial function when the MS was present (maximal increase in LBF: blacks: 107±9% MS absent, 53±16% MS present; whites: 163±16% MS absent, 54±18% MS absent; P=0.007, MS absent versus present; P=NS for interaction of ethnicity and MS).

These relationships were essentially unchanged when adjusted for age and basal LBF in multivariable linear regression analyses (model incorporating MS and ethnicity, r²=0.64, P<0.001; MS β coefficient, 38.8; P=0.006; and ethnicity β coefficient, 28.4; P=0.007). Adding logHOMA-IR to this model removed the independent effect of the MS, leaving insulin resistance and race as the independent variables (r²=0.67, P<0.001; logHOMA-IR β coefficient, 93.6; P=0.002; ethnicity β coefficient, 27.5; P=0.009).

We analyzed the contributions of the individual components of the MS to endothelial dysfunction using continuous variables rather than the simple categorical designations provided by Adult Treatment Panel III cutpoints. All analyses were adjusted as above. The MS components that were individually associated with impaired EDV were as follows: waist: r=−0.33, P<0.0001; systolic blood pressure: r=−0.29, P=0.002; and triglycerides: r=0.19, P=0.02. Insulin resistance (ie, logHOMA-IR) was also significantly associated by univariate analysis (r=−0.34, P<0.0001). Results from multivariable linear regression analysis modeling of all of these features (adjusted as above) using all study subjects are presented in Table 3. When only the defined MS variables (model 1) are considered, waist and systolic blood pressure were independently related to EDV. Adding insulin resistance to the model (model 2) removed the contribution of waist circumference, suggesting that waist circumference was serving as a surrogate...
measure of the effect of insulin resistance on EDV. Expanding the modeling to include ethnicity (model 3) revealed an additional, independent effect of ethnicity on EDV. An interaction effect for ethnicity by logHOMA-IR was significant (β=58.1, \( P=0.046 \)), but the interaction of ethnicity by systolic blood pressure was not. Including gender as a covariate did not alter the results of these analyses.

Table 4 presents the results of analyzing model 2 within the ethnicity subgroups. The white subjects exhibited largely the same relationship as seen for all subjects combined (Table 2), namely a dominant contribution of logHOMA-IR, but the effect of systolic blood pressure was not significant in these subjects. In contrast, among black subjects, the dominant correlate of impaired EDV was systolic blood pressure, with no important independent effect of logHOMA-IR. As with the modeling for the entire study population, waist circumference did not contribute importantly to the determination of impaired EDV in either subgroup when the concurrent effects of these other variables were considered.

In light of the reduced sample sizes in these subgroup analyses, we considered whether the loss of significance, particularly for insulin resistance among the black subjects, was an artifact of reduced statistical power caused by reduced sample size. Therefore, a retrospective power calculation using the apparent effect sizes and observed variability of these variables was performed. With the present data, we had an ≈7% chance of showing an independent relationship between logHOMA-IR and EDV in this subgroup; conversely, if such a relationship existed, because of the minimal apparent effect size, we would have required a sample size of ≈1300 subjects. Among whites, the retrospective power calculation suggested that we had an ≈12% chance of showing an independent relationship of systolic blood pressure with EDV and would have required a sample size of ≈320 to distinguish the apparent effect size given the observed variability. In both cases, therefore, these are not questions of a borderline loss of power resulting from sample size issues.

**Discussion**

We have reported 2 novel findings in this analysis of the cross-sectional determinants of impaired EDV. First, in analysis of the complete study population, the addition of the HOMA index of insulin resistance (a simple combination of fasting blood glucose and insulin levels) removed the independent contribution of waist circumference in the determination of endothelial dysfunction, suggesting that the effects of the central obesity are mediated by insulin resistance. Second, ethnicity was found to be an important independent determinant of endothelial function, with worse endothelial function among black than white subjects and a reduced effect of insulin resistance to further worsen endothelial function among black subjects.

**Insulin Resistance, MS, and Impaired Endothelial Function**

Insulin resistance is thought to underlie the MS,27 and epidemiological analyses suggest that measures of insulin resistance are an integral component of assessing the presence of the MS.9,21,28,29 It is therefore logical to assume that adding an assessment of insulin resistance to the NCEP-defined MS might alter the apparent contributions of the syndrome components to a given vascular outcome. Insulin resistance and the components of the MS have previously been reported to associate individually with measurements of
EDV. The present study used multivariable analysis to consider the simultaneous, mutually adjusted impact of these factors. Insulin resistance was found to exert an important effect on endothelial function and appeared to account for the contribution of central obesity to EDV. Conversely, waist circumference appeared to serve as a surrogate measure of the effect of insulin resistance on EDV.

A similar effect of using the HOMA index of insulin resistance with the NCEP-defined MS has been found in evaluations of coronary calcification scores as the vascular outcome.6 In studies of cardiovascular event rates and survival, the effect of insulin resistance measures is less apparent,19,30–32 and it is not clear that there will be an incremental effect of insulin resistance beyond assessment of other MS components as data on “hard” cardiovascular outcomes becomes available.33 Endothelial function is related to cardiovascular outcomes,34–36 but it is not necessarily true that the determinants of vascular status in the short term (ie, physiological function) will carry the same weights over the long term. These differences in the additional contribution of insulin resistance to the MS components in predicting a variety of vascular outcomes might therefore reflect true differences in vascular biology. It is equally possible, however, that differing time courses of the effects of each variable or other unidentified modifying factors are obscuring the relationship of insulin resistance to vascular outcomes over longer time frames.

There is general acceptance that the measurement of short-term physiological responses of the vasculature represents a useful, accessible window into vascular biology. The past decade has seen considerable effort expended on the use of such proximate or alternative end points in assessing the effects of a variety of interventions. In this setting, the present result implies that measurement of insulin resistance should be included in the metabolic assessment of cardiovascular risk associated with obesity and the MS.

**Impaired Vascular Responses in Blacks**

Ethnic differences in the prevalence of the MS and of its constituent components have been described.37 In the NHANES III data set, no ethnic differences in the patterns of principal component factor analysis associated with the NCEP-defined MS were seen,12 suggesting that the interrelationship of the NCEP-defined factors is comparable across ethnicities. A similar analysis in the IRAS cohort found that both direct and surrogate measures of insulin resistance were integral to the “metabolic” factor in principal component analysis,9 but again, no differences across ethnicity were seen in these associations. These studies suggest that the biology governing the interrelationships of the factors comprising the MS is similar across ethnicities.

Differences in vascular biology across ethnicities have long been recognized. Blacks, for example, have been found to have an increased risk of macrovascular events at comparable levels of blood pressure and lipid levels.38 Subclinical atherosclerosis is increased among blacks after adjustment for major cardiovascular disease risk factors and insulin sensitivity.39 Consistent with our findings, normotensive blacks have been found to have worse EDV than normotensive white subjects.14,16 Also, black subjects exhibited comparable coronary blood flow responses to endothelium-dependent vasodilators but had an augmented corrective response to coinfusion with L-arginine.15 However, indexes of arterial elasticity were not found to differ between blacks and whites in subjects across the range of hypertension severity.40 Very few molecular studies have been undertaken to explore these differences. In one report, differences in the populations of receptors for endothelin (a proatherosclerotic vascular hormone) across ethnicity were seen.41 Overall, the present finding is consistent with studies demonstrating ethnic differences in other vascular end points, but the reasons for these differences remain obscure.

In a combined analysis of the Cardiovascular Health Study and the Atherosclerosis Risk in Communities study, the impact of traditional cardiovascular risk factors on cerebrovascular and cardiovascular atherosclerosis was found to differ by age and gender.42 The present findings suggest that the metabolic determinants of endothelial function differ between black and white subjects. This is a novel finding for which there are few confirmatory data. In the Women’s Health Initiative, the association of obesity with cardiovascular disease in postmenopausal women was lost among blacks, whereas the relationship between blood pressure and CVD was stronger among black than white women.7 This important question has implications for the impact of therapeutic interventions and warrants further study.

**Study Limitations**

Our study population consisted of volunteer subjects rather than a true population-based sample. The factors leading to participation are presumably equal across subgroups of the study population, so comparisons within the main study population are likely valid. It is less clear, however, that these subjects are clearly representative of the general population; thus, some caution must be used when our results are generalized.

The observations made between ethnic subgroups of our population necessarily involved reductions in sample size, raising concerns about loss of statistical power. However, as detailed in the Results section, when the apparent relationships of insulin resistance and systolic blood pressure with EDV segregated into white and black subjects, respectively, the reason was not borderline power but rather weak effect sizes. We are therefore confident that this observation is robust within our data set.

The various protocols that contributed baseline data to this analysis did not include measurements of any of the host of novel inflammatory cardiovascular risk factors currently being investigated as markers of cardiovascular disease. These questions are clearly relevant and will be addressed prospectively in further studies in our laboratory.

**Conclusions**

The NCEP-defined MS is strongly associated with the presence of endothelial dysfunction in black and white subjects. By multivariate analysis, the association of waist circumference with endothelial dysfunction appeared to depend principally on insulin resistance, and the dominant determinants of endothelial function across our whole study population...
were insulin resistance and systolic blood pressure. The relative importance of these components differed by ethnic subgroup, with a difference specifically in the worsening of endothelial function as a result of insulin resistance. These findings suggest that there are ethnic differences in vascular biology as it relates to EDV. This possibility warrants further study in specific ethnic subgroups because it may imply that different approaches to therapy are needed in black and white patients.

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References


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