Prediction of Type 2 Diabetes Mellitus With Alternative Definitions of the Metabolic Syndrome

The Insulin Resistance Atherosclerosis Study

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Background—In addition to predicting cardiovascular disease (CVD) morbidity and mortality, the metabolic syndrome is strongly associated with the development of type 2 diabetes mellitus (DM), itself an important risk factor for CVD. Our objective was to compare the ability of various metabolic syndrome criteria (including those recently proposed by the International Diabetes Federation), markers of insulin resistance (IR) and inflammation, and impaired glucose tolerance (IGT) in the prediction of DM and to determine whether various proposed modifications to the National Cholesterol Education program (NCEP) metabolic syndrome definition improved predictive ability.

Methods and Results—We examined 822 subjects in the Insulin Resistance Atherosclerosis Study aged 40 to 69 years who were nondiabetic at baseline. After 5.2 years, 148 individuals had developed DM. IGT, metabolic syndrome definitions, and IR markers all significantly predicted DM, with odds ratios ranging from 3.4 to 5.4 (all \( P < 0.001 \)), although there were no significant differences in the areas under the receiver operator characteristic (AROC) curves between the definitions. Modifying or requiring obesity, glucose, or IR components in NCEP-defined metabolic syndrome did not significantly alter the predictive ability of the definition under AROC curve criteria (all \( P > 0.05 \)). Similarly, although IR and inflammation variables were significantly associated with incident DM when included in multivariate models with NCEP-defined metabolic syndrome (all \( P < 0.01 \)), expanding the definition by adding these variables as components did not significantly alter the predictive ability of the definition under AROC curve criteria (all \( P > 0.05 \)).

Conclusions—The International Diabetes Federation and NCEP metabolic syndrome definitions predicted DM at least as well as the World Health Organization definition, despite not requiring the use of oral glucose tolerance testing or measures of IR or microalbuminuria. Modifications or additions to the NCEP metabolic syndrome definition had limited impact on the prediction of DM. (Circulation. 2005;112:3713-3721.)

Key Words: metabolic syndrome ■ diabetes mellitus ■ insulin ■ epidemiology ■ inflammation

The metabolic syndrome, which refers to a cluster of cardiovascular disease (CVD) risk factors, has generated a great deal of recent interest in both the research and lay literature.\(^1\) \(^-\) \(^3\) The metabolic syndrome is highly prevalent,\(^4\) and individuals with the syndrome are at significantly increased risk of cardiovascular morbidity and mortality.\(^5\) In addition, the metabolic syndrome is an especially strong predictor of incident type 2 diabetes mellitus (DM),\(^6\) \(^-\) \(^9\) itself an important risk factor for CVD. The World Health Organization (WHO)\(^10\) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)\(^11\) have published criteria for defining the metabolic syndrome, and these definitions are increasingly being applied in clinical and epidemiological research. Recently, the International Diabetes Federation (IDF) published a “worldwide” metabolic syndrome definition based on recommendations from a consensus workshop of its Epidemiology Task Force.\(^12\) The WHO, NCEP, and IDF definitions similarly emphasize dyslipidemia and hypertension, although they differ in a number of respects, including usage in the WHO definition of microalbuminuria and the requirement of postchallenge hyperglycemia or insulin resistance (IR), and the requirement in the IDF definition of central obesity (defined by use of waist circumference, with ethnicity-specific cutoffs for certain groups).

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Both the WHO and NCEP definitions have been shown to be strong predictors of the development of DM in prospective studies in diverse populations, including Mexican Ameri-
methods.

Methods

Study Subjects

The Insulin Resistance Atherosclerosis Study (IRAS) is a multicenter, observational, epidemiological study of the relationships between IR, CVD, and its known risk factors in different ethnic groups and varying states of glucose tolerance. The design and methods of this study have been described in detail in previous publications. Briefly, the study was conducted at 4 clinical centers. At centers in Oakland and Los Angeles, Calif, non-Hispanic whites and blacks were recruited from Kaiser Permanente, a nonprofit health maintenance organization. Centers in San Antonio, Tex, and San Luis Valley, Colo, recruited non-Hispanic whites and Hispanic Americans from 2 ongoing population-based studies (the San Antonio Heart Study and the San Luis Valley diabetes study). A total of 1625 individuals participated in the baseline IRAS examination (56% women), which occurred between October 1992 and April 1994. Subjects with inflammatory diseases were excluded, and those who were ill on the day of the examination were rebooked for another day. The IRAS protocol was approved by local institutional review committees, and all participants provided written informed consent.

After an average of 5.2 years (range 4.5 to 6.6 years), follow-up examinations of this cohort were conducted according to the baseline protocol. The response rate was 81%, and those who attended the follow-up examination were similar to those who did not attend in terms of ethnicity, sex, baseline glucose tolerance status (normal glucose tolerance versus IGT), and body mass index (BMI; all comparisons \( P > 0.32 \)). Five hundred thirty-seven subjects had DM at baseline and were excluded. A higher proportion of Hispanic and black subjects had baseline diabetes than did non-Hispanic whites (34% and 38% versus 29%, overall \( P = 0.01 \)), although there were no significant ethnic differences in missing data on baseline metabolic variables or follow-up diabetes status. The present report includes information on 822 individuals who were nondiabetic at baseline and for whom information was available on metabolic variables of interest and follow-up glucose tolerance status.

Clinical Measurements and Procedures

The IRAS protocol required 2 visits, 1 week apart, of \( \sim 4 \) hours each. Subjects were asked before each visit to fast for 12 hours, to abstain from heavy exercise and alcohol for 24 hours, and to refrain from smoking the morning of the examination. During the first visit, a 75-g oral glucose tolerance test was administered, with glucose tolerance status classified by WHO criteria. During the second visit, insulin sensitivity and insulin secretion were determined with a frequently sampled intravenous glucose tolerance test, with 2 modifications to the original protocol. First, an injection of regular insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the accurate computation of insulin sensitivity across a broad range of glucose tolerance. Second, a reduced sampling protocol (with 12 rather than 30 samples) was used for efficiency given the large number of participants.

The repeatability of \( S_I \) has been demonstrated in a subsample of the IRAS cohort, and the estimate of \( S_I \) from this modified protocol has been validated against “gold standard” measures of IR from the hyperinsulinemic euglycemic clamp technique.

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. BMI was calculated as weight/height\(^2\) (in kg/m\(^2\)) and was used as an estimate of overall adiposity. Waist and hip girths were measured as described previously.

Duplicate measures were made according to a standardized protocol, and averages were used in the analysis. Resting blood pressure (systolic and fifth-phase diastolic) was recorded with a standard mercury sphygmomanometer after a 5-minute rest. The average of the second and third measurements was used. Ethnicity was assessed by self-report.

Laboratory Procedures

Glucose concentration was determined by standard methods as described previously. Insulin levels were measured with the dextran-charcoal radioimmunoassay, which has a 19% external coefficient of variation. This assay displays a high degree of cross-reactivity with proinsulin. Plasma lipid and lipoprotein concentrations were determined from fasting plasma samples at the central IRAS laboratory (Medlantic Research Institute, Washington DC) with the Lipid Research Clinics methodology. Urinary albumin and creatinine concentrations were assessed in a random morning spot urine sample by procedures described previously.

CRP was measured with an in-house ultrasensitive competitive immunnoassay (antibodies and antigens from Calbiochem, La Jolla, Calif), with an interassay coefficient of variation of 8.9%. The homeostasis model assessment (HOMA) and the quantitative insulin sensitivity check (QUICKI) indices were calculated, as described previously.

The definition of metabolic syndrome was proposed by the WHO, NCEP-ATP III, and the IDF. Under the WHO criteria (1999 revision), the metabolic syndrome in subjects with glucose intolerance (either impaired fasting glucose or IGT) was defined as the presence of 2 or more of the following risk factors: arterial blood pressure \( \geq 140/90 \) mm Hg; triglycerides \( \geq 150 \) mg/dL and/or HDL cholesterol \( < 35 \) mg/dL (men) or \( < 39 \) mg/dL (women); waist-hip ratio \( > 0.9 \) (men) or \( > 0.85 \) women and/or BMI \( > 30 \) kg/m\(^2\); and albumin/creatinine ratio (\( \geq 30 \) mg/g).

Metabolic syndrome in subjects with normal glucose tolerance was defined as the presence of 2 or more of the above-listed risk factors, in addition to IR, which was defined in the present study as the highest quartile of fasting insulin concentration among subjects with normal glucose tolerance. Under the NCEP-ATP III criteria, metabolic syndrome was defined as the presence of 3 or more of the following risk factors: abdominal obesity (waist circumference \( > 102 \) cm [men] or \( > 88 \) cm [women]); triglycerides \( \geq 150 \) mg/dL; HDL cholesterol \( < 40 \) mg/dL (men) or \( < 50 \) mg/dL (women); blood pressure \( \geq 130/85 \) mm Hg; and fasting glucose \( \geq 110 \) mg/dL. To meet the criteria for IDF metabolic syndrome, subjects must have had central obesity (waist circumference \( > 94 \) cm in men and \( \geq 80 \) cm in women) plus any 2 of the following factors: triglycerides \( \geq 150 \) mg/dL; HDL cholesterol \( < 40 \) mg/dL (men) or \( < 50 \) mg/dL (women); blood pressure \( > 130/85 \) mm Hg; and fasting glucose \( \geq 100 \) mg/dL. For all definitions, subjects taking antihypertensive medication were considered to have hypertension.
To determine whether modifications or additions to existing NCEP criteria improved prediction of DM, we assessed several modified versions of NCEP metabolic syndrome. For the following 8 modifications, 3 of 5 disorders were required for diagnosis of metabolic syndrome: (1) reduction of the fasting glucose cutpoint to ≥100 mg/dL; (2) use of IGT in place of fasting glucose ≥110 mg/dL as the glucose component; (3) use of IGT or fasting glucose ≥110 mg/dL for the glucose component; (4) reduction of waist circumference cutpoint to >94 cm (men) or >80 cm (women); (5) use of BMI >30 kg/m² in place of original NCEP waist circumference cutpoints for the obesity component; (6) IR defined as the lowest quartile of QUICKI required for diagnosis; (7) IR defined as the lowest quartile of SI for required for diagnosis; and (8) IGT required for diagnosis. For the following 2 modifications, the number of disorders needed for diagnosis was reduced from 3 to 2 because of the requirement in the modified definition of 1 of the original disorders: (1) fasting glucose ≥110 mg/dL required; and (2) waist circumference >102 cm (men) or >88 cm (women) required.

We next assessed the impact of IR (lowest quartiles of QUICKI or SI) or inflammation (recently proposed CRP cutpoints described above) markers as additional components in revised NCEP metabolic syndrome definitions. Because the addition of these criteria resulted in an increase from 5 to 6 candidate disorders, we assessed the prediction of diabetes under the requirement of either 3 of 6 components or 4 of 6 components. Finally, we assessed the hypertriglyceridemic waist definition of Lemieux and colleagues and the triglycerides/HDL ratio ≥3 definition of McLaughlin and colleagues, 2 recently proposed classifications of increased metabolic disease risk.

Statistical Analyses

The distributions of continuous variables were assessed and transformations used as appropriate. Baseline means and SDs, medians and interquartile ranges, or proportions were presented by follow-up DM status. t Tests or χ² tests were used to assess the significance of differences.

Associations between baseline metabolic risk definitions and DM at follow-up were examined by logistic regression analysis. Model calibration was assessed with Hosmer and Lemeshow tests of goodness of fit; statistically significant χ² statistics from this test indicate poor model fit. In these models, the dependent variable was incident DM, and the independent variables of interest were baseline metabolic syndrome status (using WHO, NCEP-ATP III, IDF, hypertriglyceridemic waist, or triglycerides/HDL definitions), IGT, CRP categories described above, IR indices, or IGT. Each independent variable was examined separately, with adjustment for age, sex, ethnicity, and clinical center; ORs, 95% CIs, and population attributable risk percents (PAR%) were presented. The predictive ability of adapted versions of the NCEP-defined metabolic syndrome based on modifications of existing glucose or obesity components or the addition or requirement of IR or CRP components (described above) was compared with the original NCEP metabolic syndrome definition. Our objective in these analyses was to assess the degree to which the modified NCEP definitions improved the classification of subjects in terms of their diabetes status at follow-up (ie, prediction). Differences in the ability of these models to classify subjects as such were assessed by comparing the areas under the receiver operating characteristic (AROC) curves, with the significance of the differences calculated with the DeLong algorithm. The AROC curve, which is analogous to the concordance index, ranges from 0.5 to 1.0 and is the probability that in a randomly selected case-control pair, the case has a higher value of the criterion variable.

Results

In addition to being older, subjects who had developed diabetes at the follow-up examination had higher baseline levels of total and abdominal adiposity and higher concentrations of insulin, triglyceride, and CRP, as well as lower insulin sensitivity and HDL concentrations. In addition, a greater proportion had IGT and were positive at baseline for various metabolic syndrome definitions, including WHO, NCEP, and IDF definitions (Table 1). After adjustment for age, sex, ethnicity, and clinical center (demographic variables), IGT and the WHO, IDF, and NCEP definitions of the metabolic syndrome each predicted the 5-year incidence of diabetes, with IGT having the strongest magnitude of association, followed by NCEP metabolic syndrome (Figure). There were no significant interactions of ethnicity on the associations of IGT, NCEP metabolic syndrome, or IDF metabolic syndrome with risk of diabetes (all interaction probability values >0.28), although ethnicity modified the
association between WHO metabolic syndrome and diabetes risk (interaction $P=0.02$), with a stronger association among non-Hispanic whites than among blacks or Hispanic Americans (Figure). In separate models adjusted for demographic variables, IGT had the strongest magnitude of association with development of diabetes at follow-up and the largest AROC curve, followed closely by QUICKI Q1 (first quartile among subjects with normal glucose tolerance), HOMA Q4 (fourth quartile among subjects with normal glucose tolerance; not shown), and the WHO, NCEP, and IDF metabolic syndrome definitions (Table 2). There were no significant differences in the AROC curves between these variables. $S_i$, Q1, hypertriglyceridemic waist, triglycerides/HDL ratio $\geq 3.0$, and CRP at recommended cutpoints had weaker magnitudes of association and significantly lower AROC curves than IGT (all $P<0.05$; Table 2). Although $S_i$, Q1 did not perform as well as QUICKI Q1 and HOMA Q4, $S_i$ treated as a continuous variable predicted DM as well as IGT (data not shown). PAR% was highest for IGT and CRP $\geq 1$ and lowest for hypertriglyceridemic waist.

When we adapted the NCEP metabolic syndrome definition using modifications of existing glucose or obesity components or by adding or requiring IR components, it had limited impact on the prediction of DM (Table 3). When we lowered fasting glucose or waist cutpoints or substituted or included IGT for or with fasting glucose, it increased the prevalence of the syndrome and the PAR% but had only a limited impact on the magnitude of the association with incident DM and predictive ability according to AROC curve criteria. If we required the presence of glucose or IR compo-

### TABLE 2. Association of IGT, Indices of IR, CRP, and Various Metabolic Syndrome Definitions With Incident Diabetes Among IRAS Subjects Who Were Nondiabetic at Baseline

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Prevalence</th>
<th>OR (95% CI)*</th>
<th>PAR%</th>
<th>H-L $\chi^2$</th>
<th>AROC Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT</td>
<td>33.2</td>
<td>5.42 (3.60–8.17)</td>
<td>58.47</td>
<td>12.60</td>
<td>0.72</td>
</tr>
<tr>
<td>QUICKI (Q1)</td>
<td>36.0</td>
<td>4.29 (2.86–6.42)</td>
<td>54.22</td>
<td>14.60</td>
<td>0.71</td>
</tr>
<tr>
<td>$S_i$ (Q1)</td>
<td>37.6</td>
<td>2.96 (2.01–4.37)</td>
<td>42.43</td>
<td>3.45</td>
<td>0.67†</td>
</tr>
<tr>
<td>NCEP metabolic syndrome</td>
<td>27.5</td>
<td>4.14 (2.79–6.16)</td>
<td>46.34</td>
<td>3.49</td>
<td>0.69</td>
</tr>
<tr>
<td>WHO metabolic syndrome</td>
<td>34.4</td>
<td>3.68 (2.48–5.45)</td>
<td>47.97</td>
<td>7.66</td>
<td>0.68</td>
</tr>
<tr>
<td>IDF metabolic syndrome</td>
<td>39.5</td>
<td>3.40 (2.28–5.06)</td>
<td>48.67</td>
<td>7.96</td>
<td>0.68</td>
</tr>
<tr>
<td>TG/HDL $\geq 3.0$</td>
<td>40.7</td>
<td>2.50 (1.67–3.74)</td>
<td>37.91</td>
<td>4.27</td>
<td>0.64‡</td>
</tr>
<tr>
<td>Hypertriglyceridemic waist</td>
<td>18.4</td>
<td>2.51 (1.68–3.75)</td>
<td>21.74</td>
<td>7.89</td>
<td>0.64‡</td>
</tr>
<tr>
<td>CRP $\geq 1$ mg/L</td>
<td>69.6</td>
<td>3.05 (1.81–5.12)</td>
<td>58.79</td>
<td>3.22</td>
<td>0.63‡</td>
</tr>
<tr>
<td>CRP $\geq 3$ mg/L</td>
<td>29.0</td>
<td>1.83 (1.23–2.74)</td>
<td>19.40</td>
<td>9.97</td>
<td>0.60§</td>
</tr>
</tbody>
</table>

$H-L \chi^2$ indicates Hosmer and Lemeshow goodness-of-fit test; Q1, first quartile among subjects with normal glucose tolerance; and TG, triglyceride. Note that $P>0.10$ for all Hosmer and Lemeshow goodness-of-fit tests.

*OR adjusted for age, sex, clinical center, and ethnicity.

†$P<0.05$; ‡$P<0.01$; §$P<0.0001$ vs AROC curve for IGT.
nents, it reduced syndrome prevalence and PAR% and increased the magnitude of the association with follow-up DM, although these changes did not have a significant impact on AROC curves (Table 3).

Multiple logistic regression was used to assess associations of IR and inflammation variables with risk of incident diabetes when included in models with NCEP metabolic syndrome (Table 4). The NCEP metabolic syndrome variable remained significantly associated with diabetes development in all models. Measures of IR (either QUICKI Q1 or SI Q1) were significantly associated with diabetes development, and their inclusion slightly reduced the magnitude of association of metabolic syndrome. CRP categories were significantly associated with diabetes, although there was relatively limited impact on the magnitude of the metabolic syndrome variable in these models.

Adapting the NCEP metabolic syndrome definition by adding IR or inflammation components and requiring 3 of 6 criteria for metabolic syndrome diagnosis increased the prevalence of the syndrome and PAR% in all cases (Table 5). The addition of an IR component had mixed effects: The use of QUICKI Q1 had little effect, whereas the use of SI Q1 increased the magnitude of the association and the AROC curve (slightly and nonsignificantly). The addition of CRP at

### Table 3. Association of Modified NCEP Metabolic Syndrome Definitions With Incident Diabetes Among IRAS Subjects Who Were Nondiabetic at Baseline: Evaluating the Effect of Glycemia, Abdominal Obesity, and IR Criteria as Either Modified or Required Components

<table>
<thead>
<tr>
<th>Independent Variable (NCEP MetS Modification)</th>
<th>Prevalence, %</th>
<th>OR (95% CI)*</th>
<th>PAR%</th>
<th>H-L χ²</th>
<th>AROC Curve†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original NCEP definition</td>
<td>27.5</td>
<td>4.14 (2.79–6.16)</td>
<td>46.34</td>
<td>3.49</td>
<td>0.69</td>
</tr>
<tr>
<td>Modifications to glucose and obesity components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. FPG &gt;100 mg/dL</td>
<td>35.9</td>
<td>3.84 (2.59–5.69)</td>
<td>50.48</td>
<td>4.40</td>
<td>0.69</td>
</tr>
<tr>
<td>2. IGT in place of IFG</td>
<td>33.1</td>
<td>4.53 (3.03–6.79)</td>
<td>53.88</td>
<td>7.72</td>
<td>0.70</td>
</tr>
<tr>
<td>3. IGT or IFG</td>
<td>35.2</td>
<td>4.80 (3.19–7.22)</td>
<td>57.22</td>
<td>8.67</td>
<td>0.71</td>
</tr>
<tr>
<td>4. Waist &gt;94 cm (men) or &gt;80 cm (men)</td>
<td>37.0</td>
<td>3.33 (2.25–4.94)</td>
<td>46.30</td>
<td>4.31</td>
<td>0.67</td>
</tr>
<tr>
<td>5. BMI &gt;30 kg/m² in place of waist</td>
<td>26.3</td>
<td>4.36 (2.93–6.48)</td>
<td>46.91</td>
<td>4.52</td>
<td>0.69</td>
</tr>
<tr>
<td>Requiring glucose or obesity components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Elevated FPG required</td>
<td>10.7</td>
<td>5.10 (3.12–8.34)</td>
<td>30.49</td>
<td>10.74</td>
<td>0.66</td>
</tr>
<tr>
<td>7. IGT required</td>
<td>14.1</td>
<td>5.45 (3.77–8.32)</td>
<td>38.55</td>
<td>6.72</td>
<td>0.68</td>
</tr>
<tr>
<td>8. Elevated waist required</td>
<td>19.4</td>
<td>3.59 (2.37–5.45)</td>
<td>33.44</td>
<td>3.39</td>
<td>0.66</td>
</tr>
<tr>
<td>Requiring IR components‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. QUICKI Q1 required</td>
<td>14.9</td>
<td>5.58 (3.56–8.73)</td>
<td>40.56</td>
<td>3.02</td>
<td>0.68</td>
</tr>
<tr>
<td>10. S Q1 required</td>
<td>17.7</td>
<td>4.49 (2.92–6.90)</td>
<td>38.18</td>
<td>5.48</td>
<td>0.67</td>
</tr>
</tbody>
</table>

MetS indicates metabolic syndrome; H-L χ², Hosmer and Lemeshow goodness-of-fit test; FPG, fasting plasma glucose; IFG, impaired fasting glucose; and Q1, first quartile among subjects with normal glucose tolerance.

*OR adjusted for age, gender, ethnicity, and clinical center.
†There were no significant differences between the AROC curve of the original NCEP MetS definition and the AROC curves of any of the modified versions of the definition presented in the Table. Note that P>0.22 for all Hosmer and Lemeshow goodness-of-fit tests.
‡Either QUICKI Q1 or S Q1 required, and 3 of 5 of the original NCEP disorders required for diagnosis.

### Table 4. Association of NCEP MetS With Risk of Incident Diabetes Among IRAS Subjects Who Were Nondiabetic at Baseline, With Addition of IR and Inflammation Markers to the Model

<table>
<thead>
<tr>
<th>Model</th>
<th>Independent Variable*</th>
<th>OR (95% CI)*</th>
<th>P</th>
<th>H-L χ²</th>
<th>AROC Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NCEP metabolic syndrome</td>
<td>4.14 (2.79–6.16)</td>
<td>&lt;0.0001</td>
<td>3.49</td>
<td>0.69</td>
</tr>
<tr>
<td>2.</td>
<td>NCEP metabolic syndrome</td>
<td>3.01 (1.97–4.62)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>QUICKI Q1</td>
<td>2.46 (1.59–3.79)</td>
<td>&lt;0.0001</td>
<td>5.94</td>
<td>0.72</td>
</tr>
<tr>
<td>3.</td>
<td>NCEP metabolic syndrome</td>
<td>3.30 (2.18–5.00)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S Q1</td>
<td>2.13 (1.41–3.22)</td>
<td>0.0003</td>
<td>4.60</td>
<td>0.72</td>
</tr>
<tr>
<td>4.</td>
<td>NCEP metabolic syndrome</td>
<td>3.55 (2.36–5.34)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP 1–3 mg/L</td>
<td>2.20 (1.25–3.87)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP &gt;3 mg/L</td>
<td>2.52 (1.38–4.59)</td>
<td>0.003</td>
<td>5.93</td>
<td>0.71</td>
</tr>
</tbody>
</table>

MetS indicates metabolic syndrome; H-L χ², Hosmer and Lemeshow goodness-of-fit test; Q1, first quartile among subjects with normal glucose tolerance.

*Adjusted for age, gender, ethnicity, and clinical center. Models 2–4 show multivariate results. ORs for NCEP metabolic syndrome and the other variable listed are adjusted for each other as well as for covariates.

Note that P>0.65 for all Hosmer and Lemeshow goodness-of-fit tests.
subjects according to incident diabetes, as assessed with inflammation through the addition of these variables as components of diabetes development in multivariable models that included and inflammation variables were significantly associated with had little effect on diabetes prediction. Similarly, although IR component in the NCEP definition of metabolic syndrome requiring glucose and obesity components or requiring an IR predictive than IGT. In addition, we found that modifying or recommended cutpoints slightly decreased the magnitude of association with DM but had little effect on AROC curves in most cases and reduced AROC curves at lower cuts. Requiring 4 of 6 components for metabolic syndrome diagnosis under these conditions decreased the prevalence of the syndrome in all cases and PAR% in the majority of cases (Table 5). The addition of an IR component increased the magnitude of association with DM but had no effect on AROC curves. The addition of CRP at recommended cutpoints slightly increased the magnitude of association with DM but had little effect on AROC curves in most cases and reduced AROC curves substantially at higher cuts.

Discussion

In the present study, we found that various definitions of the metabolic syndrome, as well as IGT and markers of IR and inflammation, significantly predicted the 5-year incidence of type 2 DM. Although the magnitude of the association with diabetes was strongest for IGT, there were no significant differences in the AROC curves between the various categorizations, except for the first quartile of S_hypertaglyceridemic waist, triglycerides/HDL \( \geq 3.0 \), and CRP at recommended cutpoints, all of which were significantly less predictive than IGT. In addition, we found that modifying or requiring glucose and obesity components or requiring an IR component in the NCEP definition of metabolic syndrome had little effect on diabetes prediction. Similarly, although IR and inflammation variables were significantly associated with diabetes development in multivariable models that included NCEP metabolic syndrome, modification of the NCEP definition through the addition of these variables as components did not result in significant improvement in classification of subjects according to incident diabetes, as assessed with AROC curves.

Both the WHO and NCEP metabolic syndrome definitions have previously been shown to be strong and consistent predictors of DM in a number of populations, including Mexican Americans, non-Hispanic whites, Native Americans, and middle-aged Finnish and Scottish men. Similarly, others have shown that multivariate models that used conventional metabolic syndrome traits treated as continuous variables or multivariate models that used scores from factor analyses of these variables also predicted DM. The present observation that IGT was not significantly better in predicting DM than metabolic syndrome definitions is consistent with the work of Stern et al, who have reported that combinations of conventional clinical cardiovascular variables do as well as IGT in predicting DM. In addition, in multivariate models, NCEP metabolic syndrome remained a significant predictor of DM after adjustment for indices of IR or CRP, which suggests that metabolic syndrome increases the risk of incident diabetes through mechanisms that are at least partially independent of IR or chronic subclinical inflammation. In contrast, the relatively poorer predictive ability of hypertriglyceridemic waist and triglycerides/HDL \( \geq 3.0 \) may be due to the fact that these definitions contain too few core metabolic syndrome variables. Notwithstanding this, these simple definitions may be of value in predicting CVD, although this issue is not examined in the present report.

Excess visceral adipose tissue is associated with a more detrimental metabolic profile than excess subcutaneous adipose tissue, an observation that has led to the widespread use of waist circumference (a surrogate measure of visceral adipose tissue) in epidemiological analyses and various metabolic syndrome characterizations. The present analysis demonstrated, however, that the use of BMI in place of waist circumference in the NCEP metabolic syndrome definition

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**TABLE 5.** Modified NCEP MetS Definitions and Associations With Incident Diabetes Among IRAS Subjects Who Were Nondiabetic at Baseline: Evaluating the Effect of Revising the Definition to Include IR and Inflammation Markers, With MetS Requiring Either 3 of 6 or 4 of 6 Components

<table>
<thead>
<tr>
<th>Independent Variable (NCEP MetS Modification)</th>
<th>Prevalence, %</th>
<th>OR (95% CI)*</th>
<th>PAR%</th>
<th>H-L ( \chi^2 )</th>
<th>AROC Curve†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Original NCEP definition</td>
<td>27.5</td>
<td>4.14 (2.79–6.16)</td>
<td>46.34</td>
<td>3.49</td>
<td>0.69</td>
</tr>
<tr>
<td>3 of 6 criteria required</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. QUICKI Q1 as a component</td>
<td>34.5</td>
<td>4.06 (2.74–6.04)</td>
<td>51.35</td>
<td>2.13</td>
<td>0.70</td>
</tr>
<tr>
<td>3. S_hypertaglyceridemic waist as a component</td>
<td>39.5</td>
<td>4.80 (3.17–7.25)</td>
<td>60.02</td>
<td>3.83</td>
<td>0.72</td>
</tr>
<tr>
<td>4. CRP ≥1 mg/L as a component</td>
<td>47.5</td>
<td>3.87 (2.54–5.90)</td>
<td>57.69</td>
<td>2.04</td>
<td>0.69</td>
</tr>
<tr>
<td>5. CRP &gt;3 mg/L as a component</td>
<td>36.4</td>
<td>3.43 (2.32–5.08)</td>
<td>51.09</td>
<td>1.76</td>
<td>0.68</td>
</tr>
<tr>
<td>4 of 6 criteria required</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. QUICKI Q1 as a component</td>
<td>17.7</td>
<td>5.46 (3.57–8.34)</td>
<td>44.12</td>
<td>3.78</td>
<td>0.69</td>
</tr>
<tr>
<td>7. S_hypertaglyceridemic waist as a component</td>
<td>20.0</td>
<td>5.04 (3.32–7.65)</td>
<td>44.69</td>
<td>9.52</td>
<td>0.69</td>
</tr>
<tr>
<td>8. CRP ≥1 mg/L as a component</td>
<td>24.5</td>
<td>4.84 (3.23–7.25)</td>
<td>48.47</td>
<td>7.51</td>
<td>0.70</td>
</tr>
<tr>
<td>9. CRP &gt;3 mg/L as a component</td>
<td>17.4</td>
<td>4.91 (3.19–7.56)</td>
<td>40.49</td>
<td>3.96</td>
<td>0.67</td>
</tr>
</tbody>
</table>

MetS indicates metabolic syndrome; H-L \( \chi^2 \), Hosmer and Lemeshow goodness-of-fit test; and Q1, first quartile among subjects with normal glucose tolerance.

*Adjusted for age, gender, ethnicity, and clinical center.
†There were no significant differences between the AROC curve of the original NCEP MetS definition and the AROC curves of any of the modified versions of the definition presented in the table.

Note that \( P=0.30 \) for all Hosmer and Lemeshow goodness-of-fit tests.
had almost no impact on diabetes prediction, a finding that may be due to the fact that the waist is an indirect measure of visceral adipose tissue. Although waist circumference is more strongly correlated with direct measures of visceral adipose tissue than other anthropometric indices, this measure nevertheless contains a substantial degree of misclassification. Furthermore, in a previous report from the IRAS, it was reported that the association between S1 and waist circumference was slightly weaker among blacks than among other ethnic groups, albeit the differences did not reach statistical significance. In that study, the fasting insulin and waist association was statistically weaker in blacks than in non-Hispanic whites. However, we found that there was no difference in diabetes prediction when BMI was used in lieu of waist in separate analyses by ethnic group (data not shown). Additionally, it is notable that the prediction of diabetes with NCEP metabolic syndrome definitions (with either waist circumference or BMI) was stronger among blacks than among the other ethnic groups, although the interaction was not statistically significant (Figure). We determined minimum waist circumference, measured at the natural indentation or at a level midway between the iliac crest and the lower edge of the rib cage if no natural indentation was present. The slight difference in measurement location from ATP III recommendations (above the superior iliac spine) is unlikely to have materially altered our results.

Few studies have directly compared the WHO and NCEP metabolic syndrome definitions, and the results have been inconsistent, with the WHO definition having a stronger magnitude of association with DM and better sensitivity among middle-aged Finnish men and Pima Indians, with better specificity only among the latter. In contrast, the NCEP definition had a larger AROC curve among Mexican Americans and Non-Hispanic whites in the San Antonio Heart Study. It is notable that in most of these studies, modifications of the WHO metabolic syndrome definition were used owing to the unavailability of either albumin/creatinine ratio or postchallenge glucose concentrations. In the present study, we used an unmodified WHO metabolic syndrome definition, which allowed for a direct comparison with the NCEP definition. Our results showed that the magnitude of the association with DM, as well as the AROC curve, was slightly (but not significantly) stronger under the NCEP metabolic syndrome definition than under either the WHO or IDF definitions.

The WHO, NCEP, and IDF metabolic syndrome definitions differ in the inclusion of postchallenge hyperglycemia and measures of IR, and thus there is interest in whether these differences influence the prediction of diabetes. In addition, since the publication of the WHO and NCEP criteria for metabolic syndrome, a number of modifications to the criteria for the glucose and obesity components have been proposed, including the reduction of glucose and weight or waist cutpoints or, in the case of NCEP, the use of BMI in lieu of waist circumference. In the present study, we found that modifications to the NCEP metabolic syndrome definition, including the requirement of IR or IGT, or the modification of glucose or obesity criteria, did not significantly improve the predictive ability of the definition using AROC curve criteria. Hanson et al have reported that the requirement of IGT or IR in metabolic syndrome definitions is a major determinant of the prediction of diabetes in the Pima Indians. These results are not directly comparable to those reported here given differences in the analytic approach and ethnic composition of the population under study. Pima Indians have high prevalence rates of obesity, IGT, and IR, and these latter disorders may be more important determinants of DM in this population than in Hispanics, non-Hispanic whites, and blacks. In addition, we found that requiring central obesity, through the application of either the new IDF criteria or the modification of the NCEP criteria, did not significantly alter the prediction of diabetes.

Our conclusions to this point about modifications to and comparisons between various metabolic syndrome definitions have been made under the assumptions of AROC curve analysis, in which classification of subjects with regard to outcome is the primary focus with false-positives and false-negatives given equal weight. Although diabetes prediction with the NCEP metabolic syndrome definition did not improve substantially through the modification or requirement of postchallenge glucose components, the prevalence of the syndrome decreased under these modifications. This feature can be considered advantageous in situations in which cost and time efficiency are paramount, including the identification of participants for enrollment in diabetes prevention trials or treatment for the prevention of DM using expensive interventions.

A number of previous studies have reported that CRP predicts type 2 DM independently of traditional risk factors. Furthermore, in the present study, we found that CRP treated as a categorical variable (CRP 1 to 3 mg/L and >3 versus ≤1 mg/L) was significantly associated with incident diabetes in a multivariate model that also included the NCEP metabolic syndrome. These findings have important implications for diabetes etiology in that they suggest that the association of metabolic syndrome with diabetes development is not entirely explained by subclinical inflammation. Our observation that a CRP categorization of ≤1 to ≤ 3 mg/L was predictive of diabetes independent of metabolic syndrome suggests that protection from DM may be restricted to relatively low levels of subclinical inflammation. Furthermore, our multivariate results are similar to those by Sattar et al, who reported the enhancement of prognostic information for diabetes with the addition of CRP to multivariate models that included NCEP metabolic syndrome. This and similar findings for incident CVD have inspired proposals to modify the NCEP metabolic syndrome definition by adding CRP as a new component, although no previous study has formally tested the impact of modifying the definition in this way on prediction of DM. We found that actual modification of the NCEP definition to include new CRP components did not have any affect on the prediction of DM as assessed by differences in AROC curves. This observation highlights possible limitations of the OR in identifying variables that can be considered useful in discriminating between who will and will not develop an outcome of interest. As has been pointed out elsewhere, only

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extremely strong measures of association translate into improvements in classification accuracy.

In conclusion, IGT, IR, and various metabolic syndrome definitions appear to be useful for identifying subjects at risk for DM. The NCEP or IDF metabolic syndrome definitions may be especially useful given that their prediction of DM is similar to that for WHO metabolic syndrome and IGT, they do not interact with ethnicity, and they do not require an oral glucose tolerance test or measures of insulin or microalbuminuria and thus are simpler to define in field and clinical settings. It is also possible that the NCEP or IDF metabolic syndrome definitions may be superior predictors of CVD, although this issue was not explored in the present report.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

It has been known for some time that both type 2 diabetes mellitus and cardiovascular disease are characterized and predicted by a common set of risk factors, including central obesity, dyslipidemia, hypertension, hyperglycemia, and insulin resistance. A number of organizations have adopted the term “metabolic syndrome” to refer to this risk factor cluster, and standard criteria for defining the syndrome have been proposed. Although these proposed definitions share common elements, including dyslipidemia and hypertension, they differ in their emphasis on insulin resistance, postchallenge hyperglycemia, or central obesity. In addition, modifications to these standard definitions have recently been suggested, including lowering glucose and/or obesity cutpoints, replacing anthropometric measures of central adiposity with body mass index, and/or adding high-sensitivity C-reactive protein, a marker of subclinical inflammation. The objective of our study was to compare how various metabolic syndrome definitions predicted the development of type 2 diabetes mellitus and to determine whether proposed modifications outlined above actually improved predictive ability. Our results showed that the metabolic syndrome was a strong and significant predictor of diabetes mellitus regardless of the definition used. Simpler definitions that used variables routinely collected in clinical practice predicted diabetes as well as the more complicated definitions that used measures of insulin resistance, microalbuminuria, and/or postchallenge glucose concentration. Modifying these definitions by lowering the glucose or obesity cutpoints or substituting body mass index for anthropometric measures had little impact on diabetes prediction. In addition, although insulin resistance and C-reactive protein were significantly related to diabetes development in multivariate regression models, the addition of these variables to metabolic syndrome definitions did not improve diabetes prediction. Our results suggest the metabolic syndrome, defined using routine clinical information, identifies individuals at high risk for progression to diabetes mellitus.
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