Critical Evaluation of Adult Treatment Panel III Criteria in Identifying Insulin Resistance With Dyslipidemia

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OBJECTIVE — The goal of this study was to evaluate the efficacy of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) in identifying insulin resistance.

RESEARCH DESIGN AND METHODS — This study included 74 nondiabetic Caucasians who were evaluated for insulin resistance and risk factors associated with the metabolic syndrome. Glucose disposal rate (GDR) was measured by hyperinsulinemic-euglycemic clamp and was used to quantify insulin resistance. Sensitivity and specificity of ATP III criteria in detecting insulin resistance were calculated for various cutoffs of GDR.

RESULTS — Insulin resistance was associated with increased waist circumference, fasting glucose, blood pressure, triglycerides, and decreased levels of HDL cholesterol. Only 12.2% of study subjects met ATP III criteria for metabolic syndrome, and ATP III criteria exhibited low sensitivity for detecting insulin resistance. Although high in specificities (>90%), the sensitivities of ATP III criteria ranged only between 20 and 50% when insulin resistance was defined as various GDR cutoff values below 10 to 12 $mg \cdot kg^{-1} \cdot min^{-1}$. The larger number of subjects who were insulin resistant but did not meet ATP III criteria were found to have an adverse cardiovascular disease risk profile, including higher BMI, waist circumference, fasting glucose, triglycerides, and an unfavorable lipoprotein subclass profile determined by nuclear magnetic resonance compared with insulin-sensitive individuals (i.e., increased large VLDL, increased small LDL, and decreased large HDL particle concentrations).

CONCLUSIONS — ATP III criteria have low sensitivity for identifying insulin resistance with dyslipidemia in nondiabetic individuals who are at increased risk for cardiovascular disease and diabetes. More sensitive criteria should be developed for clinical assessment of metabolic and cardiovascular disease risk relevant to the metabolic syndrome.

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Abbreviations: ATP III, Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; GDR, glucose disposal rate; IGT, impaired glucose tolerance; NMR, nuclear magnetic resonance; ROC, receiver operating characteristic.

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

See accompanying editorial, p. 1011.

The metabolic syndrome is associated with increased risk of both atherosclerosis and type 2 diabetes (1,2). The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) established criteria for diagnosing the syndrome (3). Individuals with three or more of five abnormalities, including abdominal obesity, elevated blood pressure, elevated serum triglycerides, decreased HDL cholesterol, and elevated fasting glucose, were considered as having the syndrome. Clinically, the intention was that these criteria would identify individuals for intensified management of risk and surveillance for cardiovascular disease. Although empirical data provide some foundation for the guidelines, the ATP III acknowledged that recommendations are based on the panel's best judgment even when there were no direct data available and advocated for further studies (3).

Accumulating evidence strongly indicates that insulin resistance is the common pathogenic factor for the individual components of the metabolic syndrome and explains the trait cluster (1,2,4–6). Thus, in the context of the metabolic syndrome, investigators have suggested that insulin resistance is the common denominator in the development of both type 2 diabetes (1) and atherosclerosis (7). In the current study, we evaluated the accuracy of ATP III criteria in identifying insulin resistance, measured by hyperinsulinemic-euglycemic clamp. Our study also assessed cardiovascular disease risk factors in insulin-resistant individuals who did not meet ATP III criteria.

RESEARCH DESIGN AND METHODS

— We studied 74 nondiabetic subjects with clinical characteristics shown in Table 1. These subjects answered advertisements placed in the metropolitan newspaper, and those individuals satisfying inclusion/exclusion criteria were sequentially recruited and studied. All subjects were allowed to equilibrate on a weight-maintenance diet

Table 1—*Clinical characteristics and Pearson correlations between glucose disposal rate and each continuous variable in 74 subjects*

Variables	Mean ± SD	*r*	*P*
Age (years)	35.7 ± 11.2	−0.2	0.05
Male (%)	46.0		
BMI (kg/m^2)	26.9 ± 4.7	−0.3	0.00
Waist circumference (cm)	88.4 ± 12.0	−0.5	<0.00
Abdominal obesity (%)	27.0		
Systolic blood pressure (mmHg)	116.5 ± 11.9	−0.2	0.04
Diastolic blood pressure (mmHg)	65.8 ± 9.7	−0.3	0.00
Abnormal blood pressure (%)	17.6		
Triglycerides (mg/dl)	112.2 ± 64.4	−0.4	<0.00
Abnormal triglycerides (%)	18.9		
HDL (mg/dl)	40.6 ± 10.8	0.2	0.03
Abnormal HDL (%)	73.0		
Fasting glucose (mg/dl)	86.9 ± 8.0	−0.4	<0.00
Abnormal glucose (%)	0		
Impaired glucose tolerance (%)	22.7		
Fasting insulin (pmol/l)	37.1 ± 23.4	−0.5	<0.00
Glucose disposal rate (mg · kg^{-1} · min^{-1})	13.7 ± 3.3	1.0	
Insulin resistance (%)			
GDR <11	18.9		
GDR <12	33.8		
GDR <13	40.5		

(28–32 kcal · kg^{-1} · day^{-1}) consisting of 50% carbohydrate, 30% fat, and 20% protein. They were then admitted to the General Clinical Research Center where, throughout the study, they remained active and the isocaloric diet was maintained. Weight had to be stable (±3%) for at least 3 months before the study. None of the study subjects engaged in regular exercise. Cardiovascular, renal, hepatic, and thyroid disease were absent in all individuals. No subjects were ingesting any pharmacological agents known to affect carbohydrate homeostasis. Individuals with diabetes were excluded from the current analysis. Protocols were approved by the Medical University of South Carolina Institutional Review Board, and informed consent was obtained from every subject.

Insulin sensitivity measurement

In vivo insulin sensitivity was assessed using the euglycemic-hyperinsulinemic glucose clamp technique as previously described (8,9). After a 12-h fast, a catheter was inserted into the brachial vein to administer insulin, glucose, and KPO_4. A dorsal hand vein was cannulated in a retrograde manner and kept in a warming device (65°C) to provide arterialized venous blood for sampling. For maximally stimulating glucose uptake and suppressing hepatic glucose production, regular insulin (Humulin; Eli Lilly, Indianapolis, IN) was administered at a rate of 200 mU · m^{-2} · min^{-1}, producing a mean steady-state insulin concentration of 3,480 ± 138 pmol/l that is maximally effective for stimulating glucose uptake into skeletal muscle. Plasma glucose was clamped at 5.0 mmol/l for at least 3 h, and maximal glucose uptake for each individual was calculated from the mean glucose infusion rate over the final three 20-min intervals. Whole-body glucose uptake was calculated on the basis of the glucose infusion rate corrected for changes in the glucose pool size, assuming a distribution volume of 19% body weight and a pool fraction of 0.65. Glucose uptake was normalized per kilogram of lean body mass (excluding bone mass) determined by dual-energy X-ray absorptiometry to yield the glucose disposal rate (GDR) per kilogram of lean body mass. Lower GDR values indicate greater insulin resistance.

Nuclear magnetic resonance lipoprotein subclass measurement

Fasting blood for the nuclear magnetic resonance (NMR) lipoprotein subclass profile was obtained from the same draw as the conventional lipid panel. Venipuncture did not involve intravenous fluids or heparin administration. For the NMR-lipoprotein subclass profile, serum was isolated from blood at 4°C by prompt centrifugation (3,000 rpm, 20 min) after blood clotting and stored at −80°C until assay. The NMR lipoprotein profile was determined using a 400-MHz proton NMR analyzer at LipoScience (Raleigh, NC). Spectra of each sample were acquired in duplicate at 47°C, and the lipid methyl group signal envelope at 0.8 ppm were deconvoluted to give the particle concentrations and mean diameter size of 16 lipoprotein subclasses (10). The NMR lipoprotein subclass profile technique has been described previously in detail (10–13), and also previously we have described our approach for analyzing and presenting these data (13).

Other measurements

HDL cholesterol levels were measured by a colorimetric oxidase technique and triglycerides measured by a colorimetric glycerophosphate technique using Vitos autoanalyzers (Johnson and Johnson, Rochester, NY). Plasma glucose was measured by the glucose oxidase method using a glucose analyzer (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH). Serum insulin levels were measured using an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany).

ATP III criteria for identification of insulin resistance

ATP III guidelines (3) recommended that clinical diagnosis of the insulin resistance syndrome require the presence of three or more of the following components: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), elevated blood pressure level (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg), elevated triglycerides (≥150 mg/dl), decreased HDL cholesterol (<40 mg/dl in men and <50 mg/dl in women), and elevated fasting glucose (110–125 mg/dl).

Statistical analyses

The maximally insulin-stimulated GDR was used as the "gold standard" measure of insulin resistance. GDR was analyzed as a continuous variable and as a dichotomized variable to classify people as either insulin resistant (true cases) or insulin sensitive (noncases). As a continuous

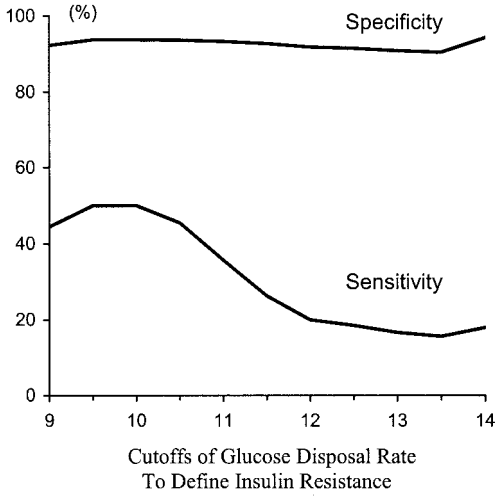

Figure 1—*Sensitivities and specificities of the ATP III criteria. Various cut points for GDR were used to classify insulin resistance such that insulin-resistant individuals had values below the cut point. ATP III criteria: the presence of three or more of five abnormalities, including abdominal obesity (waist circumference >102 cm in men and >88 cm in women), elevated blood pressure level (systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg), elevated triglycerides (>150 mg/dl), decreased HDL cholesterol (<40 mg/dl in men and <50 mg/dl in women), and elevated fasting glucose (110–125 mg/dl).*

variable, Pearson correlation analysis was performed to examine the relationships between GDR and other continuous variables, such as age, BMI, waist circumference, blood pressure, lipids/lipoproteins, and NMR lipoprotein subclass measures.

Analyzed as a dichotomized variable, observed GDRs were used to evaluate the predictive validities of ATP III criteria in identifying insulin resistance. There is no established level of GDR by which to define insulin resistance. Therefore, arbitrary cut points ranging from 9 to 14 mg · kg^{-1} · min^{-1} were examined. Individuals having GDR lower than the cutoff were defined as insulin-resistant subjects. The specificity and sensitivity of ATP III criteria for identifying insulin resistance were then calculated at each GDR value in the defined range. Sensitivity, specificity, positive predictive value, and negative predictive value of predicting insulin resistance were also calculated for different numbers (e.g., ≥1, ≥2, etc.) of abnormal risk factors considered in the ATP III criteria. In this latter analysis, GDR <12 mg · kg^{-1} · min^{-1} was defined as insulin resistance. The overall predictive accuracy was evaluation by area under the receiver operating characteristic (ROC) curve analysis (14). An area under the ROC curve of 1.0 indicates perfect classification of cases (insulin resistant) and noncases (insulin sensitive), whereas 0.5 means that the classification is not better than chance.

RESULTS — Table 1 summarizes the clinical characteristics of participants and the Pearson correlations between continuous variables and maximally insulin-stimulated GDR. Mean values were 36 years for age (range 18–58 years), 26.9 kg/m^2 for BMI, 88.4 cm for waist circumference, and 13.7 mg · kg lean $mass^{-1}$ · min^{-1} for GDR, and the sex composition was 46% male. No participant had impaired fasting glucose between 110 and 125 mg/dl in this study, and there were no patients with diabetes by design. However, 12 patients (16.4% of total) met criteria for impaired glucose tolerance (IGT) (15) on the basis of a 2-h glucose level during oral glucose tolerance test. The component traits of the metabolic syndrome, i.e., waist circumference, fasting glucose, blood pressure, triglycerides, and HDL cholesterol, all correlated significantly with GDR. Fasting insulin was also highly correlated with GDR. As in our previous report (13), GDR significantly inversely correlated with large VLDL particle concentration, average VLDL size, and total and small to intermediate LDL particle concentration and positively correlated with large LDL particle concentration, average LDL size, large HDL particle concentration, and average HDL size (data not shown). In total, 12.2% of subjects met ATP III criteria for the metabolic syndrome.

To evaluate the accuracy of ATP III criteria in predicting which individuals were insulin resistant, we calculated the sensitivity and specificity of these criteria using maximally stimulated GDR as the measure of insulin resistance (Fig. 1). Sensitivity and specificity were calculated for various cutoffs of GDR ranging from 9 to 14 mg · kg^{-1} · min^{-1}, below which levels individuals were deemed to be insulin resistant. The sensitivity for using ATP III criteria to predict insulin resistance was highest at a GDR cutoff of 9.5–10 mg · kg^{-1} · min^{-1} in which sensitivity was 50% and specificity was ~94%. At a GDR cutoff of 11 mg · kg^{-1} · min^{-1}, the sensitivity was 36% and fell rapidly to 20% as cutoff values were increased to 12 mg · kg^{-1} · min^{-1}, whereas the specificity remained high (>90%).

Current ATP III criteria require three or more out of five risk factors for identification of the metabolic syndrome. We examined how the predictive value for insulin resistance changed when the stringency of ATP III criteria were altered by requiring the presence of one to four risk factors for diagnosis, as shown in Table 2. We observed that there are tradeoffs between sensitivity and specificity and between positive predictive value and negative predictive value as stringency was relaxed or strengthened. It appears that using two or more abnormal risk factors for diagnosis yielded the best balance optimizing both sensitivity and specificity. Using the number of risk factors required for diagnosis to construct an ROC curve, the area under the curve was 0.65, indicative of a less than desirable predictive value for insulin resistance. When abnormal fasting insulin, defined as >42 pmol/l (7 μU/ml), was incorporated as a risk factor that could contribute to the total number of abnormalities, area under the ROC curve increased to 0.73.

The poor sensitivity of ATP III criteria for identifying insulin resistance could indicate that a significant number of people are insulin resistant but do not exhibit the metabolic syndrome trait complex. To explore this possibility, we assessed cardiovascular risk factors, including NMR lipoprotein subclass parameters associated with insulin resistance (13) in three groups of subjects: those who met ATP III criteria ($ATP\ III^+$), insulin-resistant individuals (GDR <12 mg · kg^{-1} · min^{-1}) who did not meet ATP III criteria ($ATP\ III^-$), and those who were $ATP\ III^-$ and insulin sensitive (GDR ≥12 mg · kg^{-1} · min^{-1}) (Table 3). Approximately one-third (20 of 65) of subjects who did not meet ATP III criteria were insulin resistant. Importantly, compared with the insulin-sensitive subgroup, these $ATP\ III^-$ insulin-resistant subjects had significantly worse cardiovascular disease risk factors, including significantly greater mean BMI, waist circumference, triglycerides, and fasting glucose. They also had

Table 2—*Sensitivity, specificity, positive predictive value, and negative predictive value of various definitions in predicting insulin resistance*

Number of abnormal factors	Sensitivity	Specificity	Positive predictive value	Negative predictive value
≥1	84	16	34	67
≥2	64	76	57	80
≥3	20	92	56	69
≥4	4	98	50	67

Insulin resistance is defined as glucose disposal rate <12 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}. Abnormal factors considered in the ATP III criteria are abdominal obesity, elevated blood pressure level, elevated triglycerides, decreased HDL cholesterol, and elevated fasting glucose.

unfavorable NMR lipoprotein subclass measures such as increased large VLDL concentration and VLDL size, increased total LDL concentration (mainly due to an increment in small to intermediate LDL particles), decreased LDL particle size, and decreased large HDL particles, and HDL size (all $P < 0.05$) (Table 3 and Fig. 2). In addition, 20% of the insulin-resistant subjects who did not meet ATP III criteria had IGT (by 2-h glucose criteria). Hence, ATP III criteria failed to identify many insulin-resistant individuals who have an adverse cardiovascular disease risk profile, including dyslipidemia as manifested by the NMR lipoprotein subclass analysis.

CONCLUSIONS — The present study demonstrates that ATP III criteria have low sensitivity for predicting insulin resistance, the primary factor in the pathogenesis of the metabolic syndrome. Importantly, insulin-resistant individuals who did not meet ATP III criteria were still characterized by metabolic and cardiovascular disease risk factors and an unfavorable lipoprotein subclass profile, including increased large VLDL, increased small LDL, and decreased large HDL particle concentrations. Because these risk factors are components of the core trait cluster of the metabolic syndrome, we conclude that ATP III criteria would fail to identify many individuals at increased risk of future diabetes and cardiovascular disease. This detracts from the value of ATP III criteria as a screening paradigm where high sensitivity is desirable.

In the Third National Health and Nutrition Examination Survey, 23.8% of Caucasians and 21.6% of African Americans satisfied ATP III criteria for the metabolic syndrome (16). This survey included individuals with type 2 diabetes, almost all of whom would be classified as having insulin resistance. Because ~11% of U.S. adults have diabetes (diagnosed plus undiagnosed) (17), the prevalence of

Table 3—*Characteristics of subjects who met ATP III criteria, insulin-resistant subjects who did not meet ATP III criteria, and insulin-sensitive subjects*

Variables	ATP III$^+$	ATP III$^-$	
		Insulin resistant	Insulin sensitive
n	9	20	45
Age (years)	45.6 ± 7.8	37.2 ± 11.0	33.0 ± 10.9
BMI (kg/m^2)	33.6 ± 3.1*	28.2 ± 4.5	24.9 ± 3.5*
Waist circumference (cm)	104.2 ± 11.0*	93.8 ± 9.3	82.8 ± 9.0*
Abdominal obesity (%)	89.9*	30.0	13.3
Systolic blood pressure (mmHg)	123.4 ± 14.1	117.2 ± 10.5	114.8 ± 11.8
Diastolic blood pressure (mmHg)	72.4 ± 10.5	66.5 ± 8.7	64.2 ± 9.5
Abnormal blood pressure, (%)	55.6*	10.0	13.3
Triglycerides (mg/dl)	220.7 ± 88.6*	125.6 ± 55.0	84.6 ± 29.5*
Abnormal triglycerides (%)	77.8*	25.0	4.4*
HDL (mg/dl)	34.4 ± 5.7	38.5 ± 11.2	42.8 ± 11.0
Abnormal HDL (%)	100.0	70.0	68.9
Fasting glucose (mg/dl)	90.7 ± 5.5	91.7 ± 8.2	84.0 ± 7.0*
Impaired glucose tolerance (%)	25.0	20.0	13.3
Glucose disposal rate (mg $\cdot$ kg^{-1} $\cdot$ min^{-1})	11.1 ± 3.8	10.6 ± 1.4	15.6 ± 2.2*
NMR profile (selected)			
Large VLDL concentration (nmol/l)	6.5 ± 4.1	3.9 ± 4.1	1.4 ± 1.8*
VLDL size (nm)	56.7 ± 8.1	54.4 ± 10.1	48.2 ± 8.7*
Total LDL concentration (nmol/l)	1,696 ± 469	1,431 ± 424	1,155 ± 287*
Large LDL concentration (nmol/l)	353 ± 283	479 ± 379	620 ± 321
Small to intermediate LDL (nmol/l)	1,332 ± 489	938 ± 533	523 ± 280*
LDL size (nm)	20.4 ± 0.6	20.6 ± 0.7	21.2 ± 0.5*
Large HDL concentration (μmol/l)	2.3 ± 1.8	4.3 ± 3.3	7.1 ± 3.3*
HDL size (nm)	8.5 ± 0.2	8.6 ± 0.3	9.0 ± 0.4*

Data are means ± SD, unless otherwise indicated. ATP$^+$, met ATP criteria; ATP$^-$, did not meet ATP III criteria. *$P < 0.05$ compared with persons who did not meet ATP III criteria (ATP III$^-$) and who were insulin resistant with glucose disposal rate <12 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}.

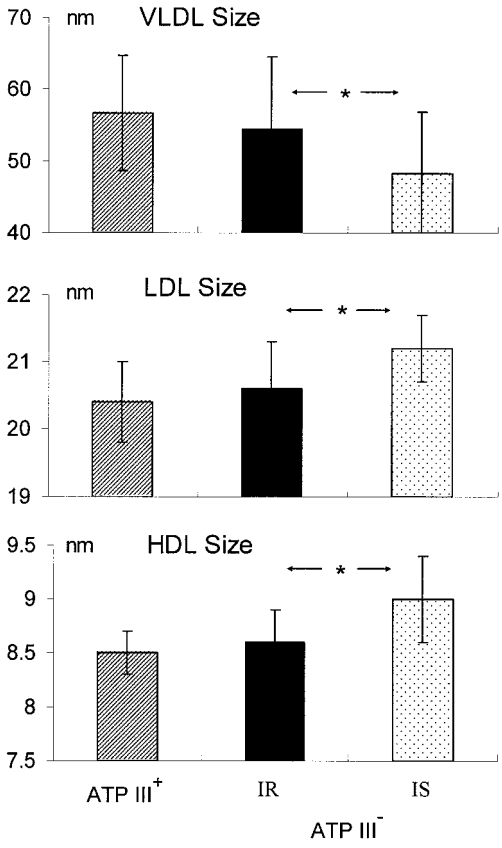

Figure 2—*Mean lipoprotein particle sizes in individuals who met ATP III criteria (ATP III$^+$) and those who did not meet ATP III criteria (ATP III$^-$) and who were insulin resistant (IR) or insulin sensitive (IS). Insulin resistant is defined as GDR $<12\ mg \cdot kg^{-1} \cdot min^{-1}$, and insulin sensitive is defined as GDR $\geq 12\ mg \cdot kg^{-1} \cdot min^{-1}$. Error bars are standard deviations. *P < 0.05 in the two groups comparison.*

the metabolic syndrome in nondiabetic individuals would be considerably reduced below 21.6–23.8% in this survey. In the current study, 12.2% of our sample of nondiabetic individuals was found to have the syndrome by ATP III criteria, a prevalence rate that is comparable with the predicted prevalence among nondiabetic individuals in Third National Health and Nutrition Examination Survey. Our data suggest that ATP III criteria exhibit low sensitivity and that the true prevalence of increased cardiovascular risk associated with insulin resistance may be ~39%, which is the proportion of subjects in both the ATP III$^+$ group and the insulin-resistant group who fail to satisfy ATP III criteria.

It was also evident that the mean age in the ATP III$^-$/insulin-resistant subgroup was younger than in the ATP III$^+$ subgroup, even though both groups were comparable in their degree of insulin resistance. Predictably, the risk factor parameters in the ATP III$^-$/insulin-resistant group would worsen in severity as these individuals aged, and several would convert to an ATP III$^+$ status. Thus, ATP III criteria were unable to identify the increase in metabolic and cardiovascular disease risk in these individuals, especially at a younger age when risk factor intervention would be advantageous.

ATP III uses fasting glucose concentration as one of its criteria. The majority of patients who meet criteria for IGT will do so on the basis of elevated blood glucose values at the 2-h time point after the glucose challenge and not as a result of fasting hyperglycemia (17). Consistent with this observation, there were 12 individuals with IGT (i.e., elevated 2-h glucose values) in the current study who also had fasting glucose in the normal range (i.e., <110 mg/dl). Individuals with IGT will be insulin resistant as a group and have a proclivity for the metabolic syndrome (1,2). Therefore, the use of fasting glucose instead of the 2-h postchallenge glucose, although relatively convenient, will diminish sensitivity for identification of insulin resistance.

Our data also emphasize that ATP III criteria can fail to identify individuals with an adverse lipoprotein subclass profile by relying on the conventional lipid panel (i.e., total cholesterol, triglycerides, and HDL cholesterol). It has been recognized that major lipoprotein classes are heterogeneous with respect to particle size and density. Subclasses of particles based on composition and size exist within VLDL, LDL, and HDL lipoprotein classes and can be variably associated with cardiovascular disease risk (11,12) and insulin resistance (13), including high concentrations of small dense LDL particles. The relationship between specific lipoprotein subclasses and risk for atherosclerosis or coronary heart disease (11,12,18,19), as well as the relationship between lipoprotein subclasses and insulin resistance (13,20,21), has been investigated in multiple studies.

The metabolic syndrome trait cluster may vary by race or ethnicity. Previous studies (22) have indicated that African Americans are more insulin resistant than Caucasians yet paradoxically exhibit lower triglyceride and higher HDL cholesterol levels. By uniformly applying the same values for triglycerides and HDL cholesterol, ATP III criteria may even more profoundly under diagnose insulin resistance in African Americans. Along these lines, some authors have advocated that thresholds for elevated serum triglycerides may be too high for coronary heart disease risk assessment in African Americans (23,24). Our own preliminary data suggest that the metabolic syndrome trait cluster is compositionally different in African Americans and that the ATP III criteria exhibit even lower sensitivity for identification of insulin resistance than in Caucasians (Y.L., S.K., S.S., P.W., A.H., A.J.J., R.L.K., W.T.G., unpublished data). These considerations explain why only Caucasians are included for analyses in the current study. The participants of the current study were from a single institute and may not represent the overall general population in the U.S. Studies are needed involving multigeographies and institutes with larger sample size and specifically address these issues in multiracial and ethnic groups.

Since Reaven (25) first introduced a term for the Insulin Resistance Syndrome in 1988, new factors have been attributed to the syndrome as we better understand underlying mechanisms. This process invites an ongoing re-examination of improved diagnostic schemes for the syndrome, which ultimately must be tested in a prospective manner against future outcomes. In the end, these studies will enhance the ability of the clinician to

identify and manage risk and prevent metabolic and cardiovascular diseases.

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