Correspondence Between the Adult Treatment Panel III Criteria for Metabolic Syndrome and Insulin Resistance

JUSTO SIERRA-JOHNSON, MD, MS[1]
BRUCE D. JOHNSON, PHD[1]
THOMAS G. ALLISON, PHD, MPH[1]
KENT R. BAILEY, PHD[2]
GARY L. SCHWARTZ, MD[1]
STEPHEN T. TURNER, MD[1]

OBJECTIVE — The aim of the present study was to assess the diagnostic accuracy of the Adult Treatment Panel III (ATP-III) definition of the metabolic syndrome in identifying insulin-resistant individuals and to explore alternative approaches to improve identification of insulin-resistant individuals among asymptomatic adults from the general population.

RESEARCH DESIGN AND METHODS — The sample consisted of 256 non-Hispanic white subjects without treated hypertension or diabetes, from the Rochester (Minnesota) Heart Family Study (123 men and 133 women; aged 20–60 years). Frequently sampled intravenous glucose tolerance tests were performed in all subjects. The reference standard for insulin resistance was determined by Bergman's minimal model; insulin resistance was defined as an insulin sensitivity index $<2 \times 10\ \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$. Component metabolic syndrome measures included blood pressure determined by sphygmomanometer; fasting serum triglycerides, HDL cholesterol, and glucose concentrations determined enzymatically; and waist circumference determined by tape measure.

RESULTS — By ATP-III criteria, the prevalence of metabolic syndrome was 15.6% (16.3% in men and 15.1% in women; $P = 0.465$). The presence of metabolic syndrome had low sensitivity to identify insulin resistance (45% in men and 39% in women; sex difference, $P = 0.137$) but high specificity (93% in men and 95% in women; sex difference, $P = 0.345$). Based on the area under the receiver operating characteristic curve (AUC) constructed by counting metabolic syndrome components as recommended by ATP-III, diagnostic accuracy was fair (AUC = 0.797 in men and 0.747 in women). When component metabolic syndrome measures were considered as quantitative traits rather than dichotomized, use of waist circumference alone, rather than counting metabolic syndrome components, improved diagnostic accuracy for insulin resistance (in men, AUC = 0.906, $P = 0.001$; in women, AUC = 0.822, $P = 0.10$).

CONCLUSIONS — Application of the ATP-III metabolic syndrome criteria provides good specificity but low sensitivity to screen asymptomatic white adults for insulin resistance. Measuring just waist circumference is simpler and may provide greater accuracy for identifying insulin resistance.

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The metabolic syndrome is a cluster of coronary heart disease (CHD) risk factors including high blood pressure, dyslipidemia, hyperglycemia, and central obesity that are associated with decreased ability of insulin to stimulate glucose disposal on peripheral target tissues, referred to as insulin resistance (1). Insulin resistance may be a fundamental metabolic disorder associated with aging and obesity that drives abnormal levels of blood pressure, lipids, and glucose and may increase risk for CHD events (2). Some evidence suggests that measures of insulin resistance may make an additional, i.e., independent, contribution to prediction of CHD risk after consideration of component measures of the metabolic syndrome (3). These observations suggest that there may be additional, unidentified pathways through which insulin resistance influences cardiovascular risk. Insulin resistance can be identified under controlled circumstances by various methods including euglycemic clamp, homeostasis model assessment, and the minimal model (4).

Data from the third National Health and Nutrition Examination Survey suggest that >20% of the U.S. adult population, i.e., up to 47 million Americans, meet the criteria for the metabolic syndrome (5). The criteria proposed by the third report of the National Cholesterol Education Program-Adult Treatment Panel III (ATP-III) are the most current and widely used in the U.S. to identify the metabolic syndrome and require three or more of following components: high waist circumference, high fasting glucose value, low HDL cholesterol level, high triglyceride level, and high blood pressure (6). Components of the metabolic syndrome were selected by ATP-III not only because they tend to cluster together, but also because they occur more commonly in insulin-resistant individuals who may be at increased CHD risk beyond that indexed by LDL cholesterol levels. The ATP-III guidelines for identification of the metabolic syndrome were proposed to create a secondary target for intervention and reduction of CHD risk. Although the ATP-III states in its executive summary that the metabolic syndrome is closely linked to insulin resistance (6), measurements of insulin sensitivity directly were not recommended, due to the laborious and time-consuming methods required. However, metabolic syndrome is widely believed to be a reliable method of identifying insulin-resistant individuals.

Given the increasing prevalence of obesity, identification of individuals with the metabolic syndrome and insulin resistance would appear to be an important

From the [1]Divisions of Nephrology and Hypertension and Cardiovascular Diseases, Department of Internal Medicine, Rochester, Minnesota; and the [2]Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic and Foundation, Rochester, Minnesota.

Address correspondence and reprint requests to Stephen T. Turner, MD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. E-mail: sturner@mayo.edu.

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Abbreviations: ATP-III, Adult Treatment Panel III; AUC, area under the curve; CHD, coronary heart disease; FSIVGTT, frequently sampled intravenous glucose tolerance test; GCRC, General Clinical Research Center; RFHS, Rochester Family Heart Study; ROC, receiver operating characteristic.

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

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aspect of CHD prevention. The aim of the present study was to assess the diagnostic accuracy of the ATP-III definition of the metabolic syndrome in identifying insulin-resistant individuals and to explore alternative approaches to improve identification of insulin-resistant individuals. To accomplish this, we studied a well-characterized sample of 256 asymptomatic subjects from the white non-Hispanic population of Rochester, Minnesota, in which insulin resistance was determined by application of Bergman's minimal model to serial measurements of glucose and insulin obtained during a frequently sampled intravenous glucose tolerance test (FSIVGTT).

RESEARCH DESIGN AND METHODS

The sample consisted of 256 asymptomatic adults (133 men and 123 women) who had previously participated in the Rochester Family Heart Study (RFHS) or were spouses, siblings, or offspring of previous RFHS participants. The RFHS cohort included 3,974 members of three-generation pedigrees who were ascertained through households with children enrolled in the schools of Rochester, Minnesota, in 1984 (7), without regard to the health status of family members. Recruitment for the present study required that individuals were between the ages of 20 and 60 years and were not taking any medications that could affect lipid or carbohydrate metabolism. No pregnant or lactating women were recruited. The study protocol was approved by the Institutional Review Board of the Mayo Clinic and was carried out in accordance with institutional guidelines after each participant signed a consent form.

Each participant underwent an initial evaluation that included blood sampling, a review of prior medical history (including use of medications), physical examination that included measurements of blood pressure by random zero sphygmomanometer, height by wall stadiometer, weight by electronic scale, and waist and hip circumferences by tape measure (all recorded by trained personnel). The examining physician administered a standardized medical questionnaire and recorded the subjects' responses as part of this evaluation. The blood pressure measurements were taken after subjects sat quietly for at least 5 min, and averages of the three readings were used in the analyses. Blood was drawn after an overnight fast of at least 8 h, and samples were placed on the ice immediately and centrifuged within 1 h, after which serum and plasma were separated, frozen, and stored at −80°C until assays were performed. Waist circumference was measured with the subject standing upright; the examiner, positioned at the right of the subject, made an imaginary horizontal mark just above the uppermost lateral border of the right iliac crest and crossed it with a vertical mark on the midaxillary line. The measuring tape was placed in a horizontal plane around the abdomen at the level of this marked point; the plane of the tape was parallel to the floor and the tape was snug but did not compress the skin. The measurement was made at normal, minimal inspiration. Hip circumference was defined as being the widest circumference over the buttocks and below the iliac crest. To obtain an accurate measurement, measurements were made at several positions and the widest circumference was recorded. Subjects underwent dual-energy X-ray absorptiometry scanning (DPX-IQ; Lunar Radiation, Madison, WI) for body composition assessment (body fat percentage) at the General Clinical Research Center (GCRC). Blood was drawn after an overnight fast (at least 8 h) for measurement of plasma glucose and lipid (total cholesterol, triglycerides, and HDL cholesterol) concentrations. Subjects were required to discontinue any prescription medications known to influence blood pressure, plasma lipids, or glucose. Two of the subjects had a previous history of drug-treated hypertension, but these medications were withdrawn at least 4 weeks before study participation. However, none of the subjects had a previous history of diabetes and none was previously treated with antidiabetic medications.

Metabolic syndrome definition

The metabolic syndrome definition was determined by the categorical ATP-III criteria. The following cutoff points were used: waist circumference >102 cm (>40 inches) in men and >88 cm (>35 inches) in women; HDL cholesterol <40 mg/dl in men and <50 mg/dl in women; triglycerides ≥150 mg/dl in both sexes; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg in both sexes; and fasting glucose ≥110 mg/dl in both sexes (1).

Diet at the GCRC

Subjects consumed a controlled, high-carbohydrate diet to increase insulin sensitivity for 6 days before the FSIVGTT (8). The diet consisted of ~55% carbohydrate, 30% fat, 15% protein; daily, the diet contained 1 g of calcium, 150 mmol of sodium, and 90 mmol of potassium per 2000 kcal with sufficient kilocalories to maintain weight. The meals were prepared in the metabolic kitchen of the GCRC, where participants ate two of their three meals each day.

The FSIVGTT

On the morning of day 7 between 7 and 9 A.M. after an overnight fast, an intravenous catheter was placed in each of the subjects' forearms—one for bolus injections of glucose and tolbutamide and the other for rapid, repeated blood sampling for measurement of glucose and insulin concentrations. After baseline samples, a bolus of glucose (0.3 g/kg body weight) was injected over a 60-s period. Blood was then sampled 36 times over the next 180 min, with an initial frequency of 1 sample per min. Twenty minutes after the glucose bolus, a single dose of tolbutamide was injected (100–300 mg) to elicit a secondary insulin response, which facilitates estimation of insulin resistance in subjects with impaired endogenous insulin release.

Minimal model

The reference standard for insulin resistance was determined by Bergman's minimal model. Consistent with previous literature, insulin resistance was defined as an insulin sensitivity index (S_i) below the lowest quartile for nondiabetic subjects in this study, i.e., $S_i < 2.0 \times 10$ $\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$ (9,10).

Statistical analysis

Data were summarized by calculating means ± SD for quantitative variables and percentages for categorical variables. Each individual was assessed for the presence of the metabolic syndrome using data collected on waist circumference, blood pressure, and fasting plasma concentrations of HDL cholesterol, glucose, and triglycerides. Using the ATP-III definition of the metabolic syndrome described above, we calculated the sensitivity, specificity, and positive predictive value of detecting insulin resistance defined as stated above. Receiver operating characteristic (ROC) curves were constructed to provide a graphical representation of the relationship between false-positive (i.e., 1 − specificity) and true-positive (sensitivity) detection rates for the counting of categorical metabolic syndrome components. In addition, ROC curves were constructed for

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each quantitative trait underlying the component measures. A standard way to evaluate diagnostic accuracy is by calculating the area under the ROC curve, and the optimum value for each quantitative measure can be defined by the value on the ROC curve closest to the upper left corner of the graph, using the formula: square root of $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$. To determine whether the areas under the curve (AUC) obtained using different predictors were significantly different, we used the method of Delong et al. (11).

In each sex, multiple linear regression was used to identify metabolic syndrome component measures that made additional contributions to the prediction of S_i after adjustment for age. Predictor variables were selected in a forward stepwise fashion with standardized variable entry (0.05) and elimination (0.10) criteria. The utility of the additional predictive measures was assessed by comparing R^2 values of a full model that included the additional predictor with a reduced model that did not. All analyses were conducted using the statistical software JMP, 5.0 version (12).

Table 1—*Descriptive characteristics*

	Pooled	Men	Women
n	256	123	144
Variables			
Age (years)	39.1 ± 12.2	38.1 ± 12.3	39.9 ± 12.1
Height (cm)	172 ± 8.9	178 ± 5.9	165 ± 6.4*
Weight (kg)	79.4 ± 16.1	85.6 ± 12.9	73.6 ± 16.5*
BMI (kg/m^2)	26.7 ± 5.01	26.7 ± 3.7	26.7 ± 5.9
Hip circumference	106.1 ± 10	104.4 ± 7.1	107.6 ± 12*
% body fat	31.3 ± 11	23.7 ± 6.7	38.4 ± 10*
Metabolic syndrome components			
Waist circumference (cm)	86 ± 13	91 ± 11	82 ± 13*
High waist prevalence	61 (24)	23 (19)	38 (28)
Fasting glucose (mg/dl)	93 ± 10	95 ± 10	91 ± 10*
High glucose prevalence	14 (5)	8 (6)	6 (4)
Triglycerides (mg/dl)	111 ± 61	124 ± 68	99 ± 51*
High triglyceride prevalence	50 (19)	32 (26)	18 (13)*
HDL cholesterol	41 ± 12	36 ± 9	45 ± 12*
Low HDL cholesterol prevalence	182 (71)	90 (73)	92 (69)
Systolic blood pressure (mmHg)	114 ± 13	115 ± 12	113 ± 13
Diastolic blood pressure (mmHg)	71 ± 9	72 ± 9	70 ± 9
High blood pressure prevalence	42 (16)	23 (19)	19 (14)
Minimal model			
S_i ($\times 10^{-4} \cdot \text{min}^{-1} \cdot \text{mU}^{-1} \cdot \text{ml}^{-1}$)	3.67 ± 2.6	3.70 ± 2.7	3.64 ± 2.5
Insulin resistance prevalence	69 (26)	31 (26)	38 (27)

Data are means ± SD or *n* (%). *$P < 0.05$ for difference between sexes.

RESULTS — The sample was composed of 123 men and 133 women between the ages of 20 and 60 years (mean ± SD 39.1 ± 12 years). On average, men were significantly taller and heavier and had larger waist circumference, glucose values, and triglyceride concentrations and lower HDL cholesterol concentrations than women (Table 1). Overall, 69 of the 256 (26%) subjects were insulin resistant based on having S_i values $<2 \times 10^{-4}\ \text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$. Mean S_i did not differ significantly between sexes nor did the prevalence of insulin resistance (26% in men, 27% in women; $P = 0.348$). Based on the ATP-III criteria, the prevalence of the metabolic syndrome was 15.6% and did not differ significantly between sexes (16.2% in men and 15.1% in women; $P = 0.465$).

Diagnostic accuracy of the metabolic syndrome to identify insulin resistance

Sensitivity of the metabolic syndrome to identify insulin resistance was 42% (45% in men and 39% in women; $P = 0.137$) and specificity was 94% (93% in men and 95% in women; $P = 0.345$) (Table 2). Sensitivity and 1 − specificity are plotted in Fig. 1 as functions of the number of components of the metabolic syndrome. Sensitivity could be improved to 70% (from 42%) by requiring only two metabolic syndrome components at the expense of decreasing specificity to 78% (from 94%). Diagnostic accuracy of counting metabolic syndrome components, judged by the AUC, was 0.768 (0.797 in men and 0.747 in women).

Improving diagnostic accuracy

We constructed ROC curves of each metabolic syndrome component to identify optimum values to identify insulin resistance (Table 3). By using these optimum values as cut points for the predefined metabolic syndrome components, overall diagnostic accuracy of counting components, judged by the AUC, was improved to 0.847 in men (from 0.797; $P = 0.18$) and to 0.787 in women (from 0.747; $P = 0.43$). However, the AUC for waist circumference alone considered as a quantitative trait was greater in both men (0.906; $P = 0.001$) and women (0.822; $P = 0.10$) and equivalent to counting metabolic syndrome components when the sexes were pooled (0.813). Triglyceride concentration was the only other single component that provided greater overall diagnostic accuracy than counting the metabolic syndrome components. However, the AUC for triglyceride concentrations alone (0.806 in men and 0.806 in women) was less than that for waist circumference or for counting optimum value components.

To further evaluate the predictive utility of quantitative levels of component measures of the metabolic syndrome, we conducted multiple variable linear regres-

Table 2—*Test characteristics of the ATP-III metabolic syndrome criteria to screen for insulin resistance*

	Pooled	Men	Women
n	256	123	133
Sensitivity	29/69 (42)	14/31 (45)	15/38 (39)
Specificity	176/187 (94)	86/92 (93)	90/95 (95)
Positive predictive value	29/40 (72)	14/17 (82)	15/23 (65)
Negative predictive value	176/216 (81)	86/103 (83)	90/113 (79)

Data are *n* (%).

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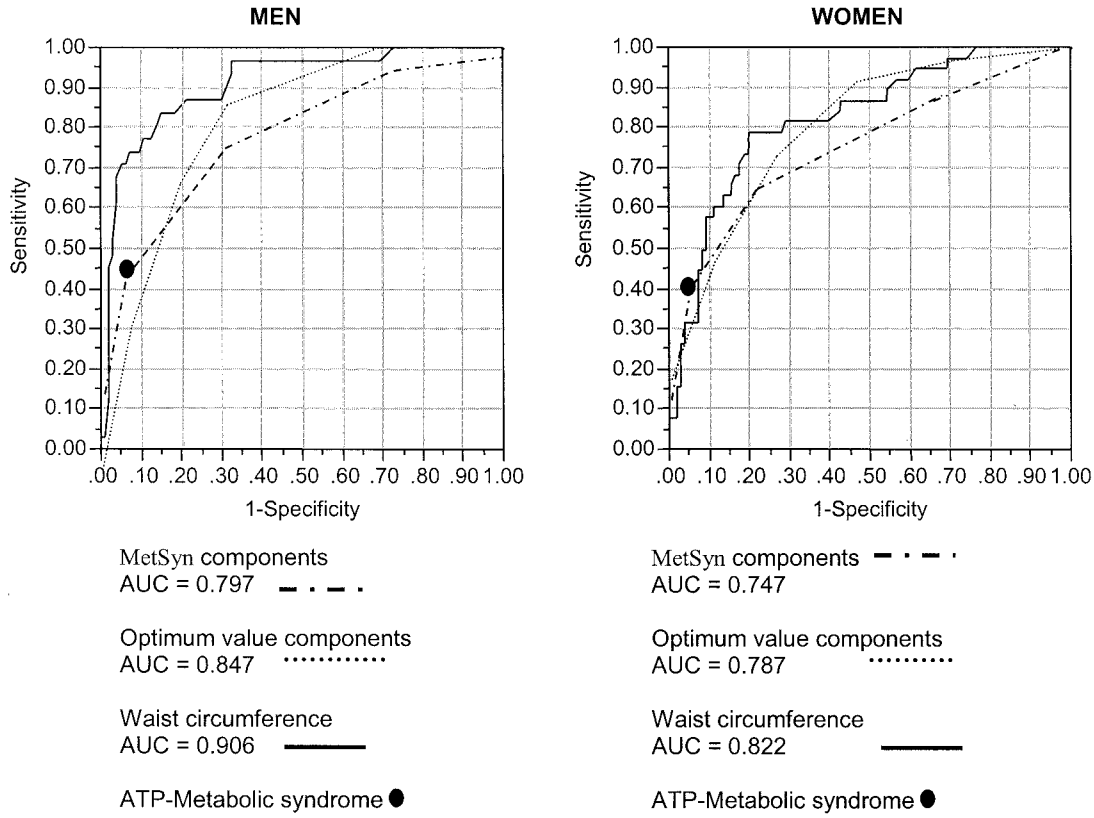

Figure 1—*ROC curves with the number of components of the current ATP-III definition of the metabolic syndrome (MetSyn), the number of optimum value components, and waist circumference.*

sion analyses in which the outcome variable was quantitative level of insulin sensitivity ($\log S_I$). In men, waist circumference was the only metabolic syndrome component to enter the model as an additional predictor of $\log S_I$ after controlling for age. Waist circumference accounted for an additional 39% of the interindividual variation in $\log S_I$ (model R^2 = 0.47, P = 0.001). In women, after we controlled for age, not only waist circumference but also triglycerides and fasting glucose entered the model as additional predictors of $\log S_I$, together accounting for 43% of the interindividual variation of $\log S_I$ (model $R^2 = 0.44$, $P = 0.001$). However, waist circumference accounted for most of the additional variation in $\log S_I$ explained by the latter model (i.e., 34%).

CONCLUSIONS — In this study of asymptomatic subjects from the white non-Hispanic population of Rochester, Minnesota, insulin resistance was determined by the minimal model technique under standardized conditions of diet and activity. Our findings confirm that the ATP-III criteria for the metabolic syndrome are an insensitive but fairly specific method to identify subjects with insulin resistance (13). The individual component measures of the metabolic syndrome, as defined by ATP-III, vary both in terms of their prevalences and in their relationships to insulin resistance. Moreover, cut point values for each quantitative metabolic syndrome component measure that optimized diagnostic accuracy for insulin resistance in our sample from the general Caucasian population differed from those recommended by ATP-III. A single measure of central obe-

Table 3—*Recommended and optimum values for each single component using ROCs*

	Pooled		Men		Women	
Single components	AUC	Optimum value	AUC	Optimum value	AUC	Optimum value
n	256		123		133	
High waist circumference (cm)	0.813	—	0.906	92	0.822	82
High triglycerides	0.794	111	0.806	124	0.806	99
Low HDL cholesterol	0.680	—	0.732	36	0.690	45
High fasting glucose (mg/dl)	0.698	93	0.696	96	0.723	91
High systolic BP (mmHg)	0.592	114	0.627	115	0.572	113
High diastolic BP (mmHg)	0.629	71	0.638	73	0.622	70

BP, blood pressure.

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sity, waist circumference, alone appeared to provide greater overall diagnostic accuracy than counting metabolic syndrome components as advocated by ATP-III guidelines.

The notion that the metabolic syndrome is a cluster of related abnormalities that commonly occur among pre-diabetic, insulin-resistant individuals was first brought forward by Reaven in 1988 (14). According to this conceptualization, insulin resistance is considered to be an underlying pathophysiologic disturbance that not only contributes to glucose intolerance, dyslipidemia, and hypertension but also may make an additional, independent contribution to CHD risk. However, the ATP-III panel did not recommend routine measurement of insulin resistance or include assessment of insulin resistance per se as identifying criterion for the metabolic syndrome, primarily because of the laborious, time-consuming methods required to measure insulin sensitivity.

Previous studies

To our knowledge, only two previous reports have assessed the relationship between the ATP-III criteria and a measure of insulin resistance. In a small nondiabetic sample, Liao et al. (13) compared component metabolic syndrome measures to insulin resistance measured by hyperinsulinemic-euglycemic clamp in 74 unselected Caucasian individuals. They reported that ATP-III criteria have low sensitivity to identify insulin resistance among nondiabetic subjects. Also in a nondiabetic sample, Cheal et al. (15) compared each individual component of the metabolic syndrome to insulin resistance determined by a modified insulin suppression test (steady-state plasma glucose concentration) in 443 subjects who were selected from a database of individuals who had participated in metabolic studies over the previous 10 years. They reported that the ATP-III criteria for metabolic syndrome do not provide a sensitive approach to identify insulin-resistant individuals and that measures of obesity and dyslipidemia are more useful predictors. However, this study did not measure waist circumference but instead used BMI as a measure of obesity in the definition of metabolic syndrome. Moreover, the sample selection criteria effectively leave the population of inference unknown. The estimated overall prevalence of the metabolic syndrome in their sample was higher than that in ours by almost 5% (20.5 versus 15.6%), and this increase in prevalence, seen especially in women (22.6% compared with 15.1% in our sample) might be explained by the use of BMI instead of waist circumference as a measure of obesity.

Relationship between the ATP-III criteria and insulin sensitivity

The relationship between the presence of the metabolic syndrome by ATP-III criteria and insulin resistance is not perfect and suffers mostly from lack of sensitivity. Depending upon the screening objective, more sensitive criteria may be desirable. For example, recognizing that insulin resistance may be the underlying metabolic disorder contributing to increased cardiovascular risk (6), reducing the number of required ATP-III components from three to two would provide greater sensitivity to identify individuals at increased risk. It is also apparent that the relationship of each metabolic syndrome component to insulin resistance differs greatly among the recommended ATP-III components. Waist circumference and triglyceride concentrations appeared to have the greatest diagnostic accuracy for insulin resistance, whereas blood pressure, glucose value, and HDL cholesterol concentration had lesser predictive utility. Our results suggest that simple measurement of just waist circumference may provide greater overall diagnostic accuracy than counting categorical components of the metabolic syndrome. That is, use of additional measures beyond waist circumference added essentially nothing to either sensitivity or specificity in the identification of insulin-resistant individuals.

Study limitations

A limitation of this study is that the results may only be strictly applicable to healthy Caucasians without type 2 diabetes. The FSIVGTT analyzed by the minimal model technique in the present study is not perfectly correlated with estimates of $\log S_i$ from the euglycemic clamp, which is the gold standard for measuring insulin sensitivity. However, application of the minimal model to measurements of glucose and insulin obtained during a FSIVGTT provides well-correlated estimates of $\log S_i$ and is more feasible for epidemiologic studies (9).

In summary, application of the ATP-III metabolic syndrome criteria provides good specificity but low sensitivity for screening asymptomatic white adults for insulin resistance. Measuring just waist circumference is simpler and may provide greater accuracy for identification of insulin resistance.

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