Use of Metabolic Markers To Identify Overweight Individuals Who Are Insulin Resistant

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Background: **Insulin resistance is more common in overweight individuals and is associated with increased risk for type 2 diabetes mellitus and cardiovascular disease. Given the current epidemic of obesity and the fact that lifestyle interventions, such as weight loss and exercise, decrease insulin resistance, a relatively simple means to identify overweight individuals who are insulin resistant would be clinically useful.**

Objective: **To evaluate the ability of metabolic markers associated with insulin resistance and increased risk for cardiovascular disease to identify the subset of overweight individuals who are insulin resistant.**

Design: **Cross-sectional study.**

Setting: **General clinical research center.**

Patients: **258 nondiabetic, normotensive overweight volunteers.**

Measurements: **Body mass index; fasting glucose, insulin, lipid and lipoprotein concentrations; and insulin-mediated glucose disposal as quantified by the steady-state plasma glucose concentration during the insulin suppression test. Overweight was defined as body mass index of 25 kg/m^2 or greater, and insulin resistance was defined as being in the top tertile of steady-state plasma glucose concentrations. Receiver-operating characteristic curve analysis was used to identify the best markers of insulin resistance; optimal cut-points were identified and analyzed for predictive power.**

Results: **Plasma triglyceride concentration, ratio of triglyceride to high-density lipoprotein cholesterol concentrations, and insulin concentration were the most useful metabolic markers in identifying insulin-resistant individuals. The optimal cut-points were 1.47 mmol/L (130 mg/dL) for triglyceride, 1.8 in SI units (3.0 in traditional units) for the triglyceride–high-density lipoprotein cholesterol ratio, and 109 pmol/L for insulin. Respective sensitivity and specifity for these cut-points were 67%, 64%, and 57% and 71%, 68%, and 85%. Their ability to identify insulin-resistant individuals was similar to the ability of the criteria proposed by the Adult Treatment Panel III to diagnose the metabolic syndrome (sensitivity, 52%, and specificity, 85%).**

Conclusions: **Three relatively simple metabolic markers can help identify overweight individuals who are sufficiently insulin resistant to be at increased risk for various adverse outcomes. In the absence of a standardized insulin assay, we suggest that the most practical approach to identify overweight individuals who are insulin resistant is to use the cut-points for either triglyceride concentration or the triglyceride–high-density lipoprotein cholesterol concentration ratio.**

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Recent reports (1) indicate that more than 50% of the U.S. population is overweight (body mass index [BMI] $\geq$ 25 kg/m^2), with approximately 20% designated as obese (BMI $\geq$ 30 kg/m^2). Because overweight is important in the genesis of type 2 diabetes mellitus and cardiovascular disease (CVD), the absolute number of Americans in this category is disturbing. The gravity of the problem is accentuated in light of the report that only approximately 50% of physicians polled provided weight loss counseling (2) and that pharmacologic treatment of weight loss is not being used appropriately in overweight persons (3).

Reluctance to assign weight control programs a high priority might be decreased if identifying overweight or obese individuals at greatest risk for adverse health consequences were possible, particularly if weight loss would significantly attenuate the risk. In this context, it is necessary to begin by emphasizing that the prevalence of insulin resistance is increased in patients with type 2 diabetes mellitus, essential hypertension, and CVD and that insulin resistance and compensatory hyperinsulinemia have been shown to be independent predictors of all 3 clinical syndromes (4–9). Since obese individuals tend to be insulin resistant and become more insulin sensitive with weight loss (10), an obvious approach to identify individuals who would most benefit from weight loss is to measure insulin-mediated glucose disposal. However, direct measures of insulin-mediated glucose disposal are not clinically practical.

On the other hand, overweight persons are also at increased risk for glucose intolerance, and the higher the plasma glucose or insulin concentrations in nondiabetic persons, the more likely that the persons are insulin resistant (4, 11). Thus, differences in fasting plasma glucose or insulin concentrations might be useful to identify insulin-resistant persons. These persons also have a characteristic dyslidemia (4), and measuring these variables might also help identify insulin resistance. For example, plasma triglyceride and high-density lipoprotein (HDL) cholesterol levels are independently associated with insulin resistance (12) and are independent predictors of CVD (13, 14). In addition, the plasma concentration ratio of total cholesterol to HDL cholesterol is well recognized as a predictor of CVD (15) and is also highly correlated with insulin resistance (16). A less commonly considered CVD risk factor is the ratio of triglyceride to HDL cholesterol, despite the observation that the triglyceride–HDL cholesterol ratio is as significant a predictor of CVD as are the ratios of low-density lipoprotein (LDL) cholesterol to HDL cholesterol or total cholesterol to HDL cholesterol (17). A more recent study showed that persons in the highest tertile of the triglyceride–HDL cholesterol ratio had increased CVD

risk in the absence of the 4 conventional risk factors, whereas those in the lowest tertile had decreased risk in the presence of the same 4 risk factors (18).

Although obese individuals tend to be insulin resistant, hyperinsulinemic, glucose intolerant, and dyslipidemic, not all overweight or obese individuals are insulin resistant, nor do they all have the characteristic disturbances in glucose or lipid metabolism (19–23). Furthermore, not all CVD risk factors improve with weight loss, and the metabolic benefits associated with weight loss are largely confined to overweight or obese individuals with these abnormalities at baseline (20–23). Given the relative ease of measuring plasma glucose, insulin, and lipid concentrations, and their importance as both CVD risk factors and manifestations of insulin resistance, we attempted to develop a simple clinical approach using these measurements to identify overweight or obese individuals who are both insulin resistant and at greatest risk for CVD.

Context

Insulin resistance is associated with adverse outcomes, such as cardiovascular disease and type 2 diabetes mellitus. The insulin suppression test, the gold standard method of diagnosing insulin resistance, is cumbersome to administer. A simple method to identify persons with insulin resistance would be useful.

Contribution

In a group of overweight individuals, 3 easily measured variables (triglyceride levels, the ratio of triglyceride to high density lipoprotein [HDL] cholesterol levels, and insulin concentration) identified insulin-resistant individuals with sensitivities of 57% to 67% and specificities of 68% to 85%.

Implications

Triglyceride levels, the triglyceride–HDL cholesterol ratio, and insulin concentration are imperfect but practical methods for identifying overweight persons who are insulin resistant and at greatest risk for complications.

–The Editors

METHODS

The study sample consisted of 258 persons with a BMI of 25 kg/m^2 or greater, classified as overweight or obese by National Institutes of Health (24) and World Health Organization criteria (25). Participants were drawn from a large database of 490 healthy volunteers who have participated in research studies in the past 10 years. These studies typically used newspaper advertisements to identify persons without known disease to participate in our efforts to define the relationship between insulin resistance and metabolic abnormalities. According to their medical histories, study participants did not have major chronic medical illnesses, including CVD, and were not taking any medication known to influence insulin resistance or lipid metabolism (such as corticosteroids and lipid-lowering drugs). No clinically significant abnormalities were found during physical examination; participants were not anemic, had normal liver and kidney function, and were nondiabetic on the basis of plasma glucose concentrations in response to a standard oral glucose challenge (26).

The 258 individuals included 127 men and 131 women with a mean age (±SD) of 50 ± 16 years (range, 19 to 70 years) and a mean BMI (±SD) of 29.2 ± 3.2 kg/m^2 (range, 25.0 to 39.1 kg/m^2). Most participants were white (87%); the remaining participants were Asian American (9%), Hispanic (3%), or African American (1%).

Insulin-mediated glucose disposal was estimated by a modification (27) of the insulin suppression test introduced and validated by our research group (28, 29). We have used this approach for more than 35 years to measure insulin action, and results are highly correlated ($r > 0.9$) with the more commonly used euglycemic, hyperinsulinemic clamp approach (29). After an overnight fast, intravenous catheters are placed in each of the patient's arms. A 180-minute infusion of somatostatin (250 μg/h), insulin (179 μmol/m^2 per min^{-1}), and glucose (13.3 mmol/m$^{2-2}$ per min) is administered into 1 arm. Blood samples are collected from the other arm every 30 minutes initially and at 10-minute intervals from 150 to 180 minutes of the infusion to determine the steady-state plasma insulin and glucose concentrations. Since steady-state plasma insulin concentrations are similar for all participants, the steady-state plasma glucose concentration directly measures the insulin's ability to mediate disposal of the infused glucose load; the higher the steady-state plasma glucose concentration, the more insulin resistant the patient. Blood samples were obtained before the insulin suppression test to measure plasma glucose (30), insulin (31), and lipid and lipoprotein (32–34) levels by methods that were identical during the period of study.

We have found that insulin's ability to stimulate glucose disposal varied continuously in a sample of 490 healthy persons (35), precluding an objective definition of an individual as being insulin sensitive or insulin resistant. However, in 2 prospective studies (8, 9), we showed that CVD and glucose intolerance or type 2 diabetes developed to a statistically significantly greater degree in one third of the healthy sample that was the most insulin resistant (that is, the tertile with the highest steady-state plasma glucose concentrations). On the basis of these considerations and for the purposes of this analysis, we used as an operational definition of insulin resistance a steady-state plasma glucose concentration in the upper tertile of the distribution of the original 490 healthy volunteers.

Because of possible interaction between metabolic markers, sex, and menopausal status of women, we performed logistic regression analysis for predicting insulin resistance that included the best metabolic marker, sex, menopausal status, and all interaction terms. Since there

were no significant interactions, men and women, regardless of their menopausal status, were considered together in subsequent analyses.

Clinical utility of metabolic markers to identify individuals in the most insulin-resistant tertile was evaluated by constructing receiver-operating characteristic (ROC) curves, which depict the relationship between true-positive (sensitivity) and false-positive (1 − specificity) test results for each diagnostic marker. Markers for which a relative increase in sensitivity is matched by a similar increase in false-positive results are represented by a diagonal line and are of less clinical use. Metabolic markers considered were fasting plasma concentrations of glucose, insulin, triglyceride, cholesterol, and HDL cholesterol, as well as the cholesterol–HDL cholesterol ratio and the triglyceride–HDL cholesterol ratio. Areas under the ROC curves were compared using the method of Hanley and McNeil (36). The metabolic markers of insulin resistance that were statistically significantly better performers were selected for cut-point analysis to identify specific values that would be useful in predicting insulin resistance.

The cut-points diagnostic of the top tertile of steady-state plasma glucose were based on the formula $M = ws + (1 - w) \times p$, where w = prevalence of disease (top tertile steady-state plasma glucose), s = sensitivity, and p = specificity (37). According to this equation, the cut-point identified is the value that maximizes M, which represents the optimal combination of sensitivity and specificity for the study sample, based on the prevalence of disease (insulin resistance). We determined the sensitivity, specificity, positive predictive value, positive likelihood ratio, and negative likelihood ratio for cut-points chosen. The positive likelihood ratio is the true-positive rate divided by the false-positive rate; the negative likelihood ratio is the true-negative rate divided by the false-negative rate.

For purposes of comparison, we determined the ability of the Adult Treatment Panel III (ATP III) criteria, which have been proposed by the National Cholesterol Education Program (38) for diagnosis of the metabolic syndrome, to identify insulin resistance. These criteria specify that the metabolic syndrome is present if 3 or more of the following criteria are met: waist circumference greater than 102 cm in men and greater than 88 cm in women, serum triglyceride concentration of 1.69 mmol/L (150 mg/dL) or more, serum HDL cholesterol concentration less than 1.03 mmol/L (40 mg/dL) in men and less than 1.29 mmol/L (50 mg/dL) in women, blood pressure of 130/85 mm Hg or greater or therapy with antihypertensive medication, and fasting plasma glucose level of 6.11 mmol/L (110 mg/dL) or greater. Since we did not measure waist circumference for most of our participants, we substituted a BMI of 25 kg/m^2 or greater for women and 29 kg/m^2 or greater for men, values that provided the same prevalence of the metabolic syndrome in the third National Health and Nutrition Examination Survey as did use of waist circumference (Ford E. Personal communication).

Data are expressed as means (±SD), and the areas under the ROC curve are expressed as SEs. Comparison of continuous variables across steady-state plasma glucose tertiles used 1-way analysis of variance with Tukey correction for several comparisons; categorical data (sex) were compared with chi-square analysis. Sensitivity, specificity, and positive predictive values were calculated by using 2 × 2 tables. Likelihood ratios were calculated as the ratios of sensitivity – (1 − specificity) (positive likelihood ratio) and (1 − sensitivity) – specificity (negative likelihood ratio). Statistical analyses were performed by using SAS software, version 8.0 (SAS Institute, Inc., Cary, North Carolina); STATA, version 7.0 (Stata Corp., College Station, Texas), was used to compare areas under the ROC curves. *P* values less than 0.05 were considered statistically significant.

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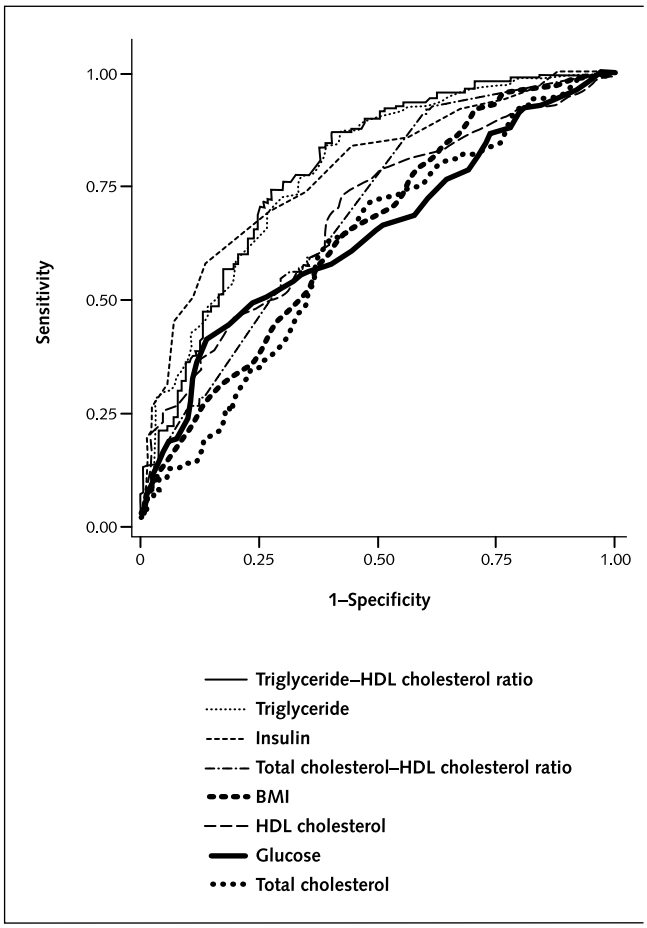
Table 1. **Demographic and Metabolic Characteristics of Overweight or Obese Participants in Steady-State Plasma Glucose Tertiles***

Variable	Tertile of Steady-State Plasma Glucose			*P* Value†
	Low (*n* = 44)	Middle (*n* = 85)	High (*n* = 129)	
Steady-state plasma glucose level, *mmol/L* (*mg/dL*)	3.8 ± 0.2 (68.5 ± 3.6)	7.9 ± 0.2 (142.3 ± 3.6)	13.8 ± 0.2 (248.6 ± 3.6)	<0.001
Age, *y*	47 ± 12	51 ± 12	51 ± 13	>0.2
Women/men, *%/%*	57/43	49/51	50/50	>0.2
BMI, *kg/m^2*	27.5 ± 2.4	28.6 ± 2.8	30.2 ± 3.5	0.006
Fasting glucose level, *mmol/L* (*mg/dL*)	5.0 ± 0.6 (90.1 ± 10.8)	5.2 ± 0.6 (93.7 ± 10.8)	5.4 ± 0.6 (97.3 ± 10.8)	0.04
Fasting insulin level, *pmol/L* (*μU/mL*)	65 ± 7 (9.0 ± 1.0)	79 ± 7 (11.1 ± 1.0)	129 ± 7 (18.1 ± 1.0)	0.01‡
Triglyceride level, *mmol/L* (*mg/dL*)	1.0 ± 0.06 (88.6 ± 5.32)	1.4 ± 0.07 (124.04 ± 6.2)	1.9 ± 0.08 (168.34 ± 7.09)	0.005
Cholesterol level, *mmol/L* (*mg/dL*)	4.9 ± 0.1 (189.2 ± 3.9)	5.0 ± 0.1 (193.1 ± 3.9)	5.2 ± 0.1 (200.8 ± 3.9)	>0.2
HDL cholesterol level, *mmol/L* (*mg/dL*)	1.4 ± 0.05 (54.1 ± 1.93)	1.2 ± 0.03 (46.3 ± 1.16)	1.1 ± 0.03 (42.5 ± 1.16)	0.2§
Triglyceride–HDL cholesterol ratio, *SI units* (*traditional units*)	1.07 ± 0.06 (1.8 ± 0.10)	1.72 ± 0.12 (2.89 ± 0.20)	2.4 ± 0.12 (4.03 ± 0.20)	<0.001
Total cholesterol–HDL cholesterol ratio	3.7 ± 0.2	4.4 ± 0.1	4.8 ± 0.1	>0.2§

* Values expressed with plus/minus signs are means ± SD. BMI = body mass index; HDL = high-density lipoprotein.
† One-way analysis of variance with Tukey adjustment for multiple comparisons.
‡ Significant differences between tertiles 1 vs. 3 and 2 vs. 3 only.
§ Significant differences between tertiles 1 vs. 2 and 1 vs. 3 only.

Figure. **Receiver-operating characteristic curves for metabolic markers of insulin resistance.**



Comparison, in individuals with body mass index (*BMI*) of 25 kg/m^2 or greater, of relationships between rates of true-positive test results (sensitivity) and false-positive test results (1 − specificity) for plasma concentrations of fasting triglyceride–high-density lipoprotein (*HDL*) cholesterol ratio, triglyceride, insulin, cholesterol–HDL cholesterol ratio, BMI, HDL cholesterol, glucose, and total cholesterol.

RESULTS

Table 1 presents the demographic and metabolic characteristics of the 258 overweight or obese participants, stratified according to steady-state plasma glucose. Fifty percent of the overweight or obese individuals were in the most insulin-resistant tertile and 17% were in the most insulin-sensitive tertile. Age and sex distribution of the overweight or obese individuals did not vary as a function of steady-state plasma glucose tertile. However, with the exception of plasma cholesterol concentration, every other metabolic marker of CVD was accentuated in proportion to the degree of insulin resistance. Furthermore, with the exception of the HDL cholesterol concentration and the cholesterol–HDL cholesterol ratio, the CVD risk factors were statistically significantly greater in the upper than in the middle steady-state plasma glucose tertile.

The **Figure** shows the ROC curves for all potential metabolic markers evaluated. For insulin and triglyceride concentrations and the triglyceride–HDL cholesterol ratio, incremental increases in true-positive rates (sensitivity) are associated with relatively smaller increases in false-positive rates (1 − specificity) as compared with the other curves, represented by the slope of the curves. In contrast, the curves for cholesterol concentration, HDL cholesterol concentration, cholesterol–HDL cholesterol ratio, BMI, and plasma glucose concentration have greater increases in false-positive rates (1 − specificity) for incremental increases in sensitivity and are of lesser diagnostic utility. **Table 2** presents the areas under the ROC curves rank-ordered. The greatest areas were for triglyceride concentration, triglyceride–HDL cholesterol ratio, and insulin concentration. These areas were statistically significantly greater than those of the other 5 markers.

While logistic regression modeling showed no interaction between sex, menopausal status, and predictive ability of the markers for insulin resistance, ROC curves were also constructed for the subgroups to confirm the lack of interaction. Indeed, the area under the ROC curve for triglyceride did not statistically significantly differ between sexes, between pre- and postmenopausal women, or between either of these subgroups of women and men. The area under the ROC curve for the triglyceride–HDL cholesterol ratio was statistically significantly greater for postmenopausal women compared with men and premenopausal women, but did not differ between women and men or between premenopausal women and postmenopausal women. Thus, further analyses considered all subgroups by sex and menopausal status together.

Determination of the optimal cut-point (using maximization, *M*) to identify insulin resistance for these markers yielded the following values: triglyceride–HDL cholesterol ratio of 1.8 SI units (3.0 traditional units) or greater, triglyceride concentration of 1.47 mmol/L (130 mg/dL) or greater, or fasting insulin concentration of 108 pmol/L or more. **Table 3**, which is rank-ordered according to maximum number of insulin-resistant persons identified, shows

Table 2. **Comparison of Area under the Receiver-Operating Characteristic Curves for Metabolic Markers of Insulin Resistance***

Marker	Area under the ROC Curve ± SE (95% CI)
Triglyceride–HDL cholesterol ratio†	0.781 ± 0.029 (0.724–0.837)
Triglyceride level†	0.780 ± 0.029 (0.722–0.835)
Insulin level†	0.778 ± 0.029 (0.722–0.834)
Total cholesterol–HDL cholesterol ratio‡	0.687 ± 0.032 (0.624–0.750)
BMI§	0.680 ± 0.033 (0.615–0.745)
HDL cholesterol level‡	0.641 ± 0.034 (0.573–0.709)
Glucose level‡	0.638 ± 0.034 (0.570–0.705)
Cholesterol level‡	0.609 ± 0.035 (0.540–0.678)

* BMI = body mass index; HDL = high-density lipoprotein; ROC = receiver-operating characteristic.
† Triglyceride–HDL cholesterol ratio, triglyceride level, and insulin level were statistically significantly better than other markers.
‡ $P < 0.05$.
§ $P = 0.06$.

Table 3. **Comparison of Triglyceride Level, Triglyceride–High-Density Lipoprotein Cholesterol Ratio, Fasting Insulin Level, and Adult Treatment Panel III Guidelines for Predicting Top Tertile of Steady-State Plasma Glucose Level in Men and Postmenopausal Women***

Marker	Patients in Top Tertile	Patients Not in Top Tertile	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	Positive Predictive Value
	n		%				%
Triglyceride level ≥ 1.47 mmol/L (130 mg/dL)	87	38	67 (59–75)	71 (62–78)	2.30 (1.71–3.07)	0.46 (0.35–0.61)	70
Triglyceride level < 1.47 mmol/L (130 mg/dL)	42	91					
Triglyceride–HDL cholesterol ratio ≥ 1.8 (3.0)	82	41	64 (55–71)	68 (60–76)	2.00 (1.51–2.66)	0.53 (0.41–0.69)	67
Triglyceride–HDL cholesterol ratio < 1.8 (3.0)	47	88					
Insulin level ≥ 108 pmol/L (≥15 μU/mL)	74	19	57 (49–66)	85 (78–90)	3.89 (2.51–6.05)	0.50 (0.40–0.62)	80
Insulin level < 108 pmol/L (<15 μU/mL)	55	110					
Met ATP III criteria	67	19	52 (43–60)	85 (78–90)	3.60 (2.26–5.52)	0.56 (0.47–0.68)	78
Did not meet ATP III criteria	62	112					

* ATP = Adult Treatment Panel; HDL = high-density lipoprotein; LR = likelihood ratio.

the results of applying these values to the study sample of overweight or obese persons. Of the 258 participants, 125 had triglyceride concentrations greater than the cut-point, 87 of whom were in the top tertile of insulin resistance (positive predictive value, 70%). Nearly as many individuals (n = 123) exceeded the triglyceride–HDL cholesterol ratio cut-point, 82 of whom were in the top tertile of insulin resistance (positive predictive value, 67%). Use of the plasma insulin criteria decreased sensitivity but increased positive predictive value; 93 participants exceeded the diagnostic cut-point, 74 of whom were in the top tertile of insulin resistance (positive predictive value, 80%). **Table 3** shows the ability of the ATP III criteria to identify overweight or obese persons who are insulin resistant. Eighty-six individuals met the ATP III criteria, 67 of whom were insulin resistant (positive predictive value, 78%); these values are similar to those seen with fasting insulin concentration. The positive likelihood ratio values indicate that the odds of insulin resistance increased by 2.0- to 3.6-fold if the test result was positive (as compared with the whole study sample). This ratio was greatest for insulin concentration, followed by ATP III criteria, triglyceride concentration, and triglyceride–HDL cholesterol ratio. The negative likelihood ratios indicate the extent to which the odds of insulin resistance decrease if the test result is negative. These odds decreased most for triglyceride concentration, followed by insulin, triglyceride–HDL cholesterol concentration ratio, and ATP III criteria.

DISCUSSION

Our goal was to develop a relatively simple approach that used metabolic markers associated with both insulin resistance and increased CVD risk (6, 7, 11–19) to identify overweight or obese persons who were insulin resistant. Early identification of high-risk patients might lead to earlier, more successful interventions, such as weight loss or prevention of further weight gain. Before addressing the clinical implications of our findings, we should clearly enunciate the 4 general principles that form the conceptual framework of our study. Most fundamental is the fact that not all overweight or obese persons are insulin resistant (19–23). A corollary to this basic postulate is that the metabolic abnormalities that increase CVD risk in overweight or obese individuals are seen primarily in persons who are also insulin resistant (19–23), a view that was confirmed in a recently published study of more than 300 persons (39). In addition, a large body of evidence shows that insulin resistance or compensatory hyperinsulinemia, and the manifestations of these abnormalities of insulin metabolism, statistically significantly increases CVD risk (6–9, 13, 14, 16–19). Finally, while few large prospective studies have evaluated the effect of intentional weight loss on clinical events, many studies show reduction in CVD risk factors (40), which are most pronounced in the insulin-resistant subgroup (21, 22, 41).

Resistance to insulin-mediated glucose disposal is distributed continuously throughout the general population (35), and there is no absolute criterion with which to classify individuals as being insulin resistant or insulin sensitive. For this analysis, we classified an individual as insulin resistant if he or she was in the upper tertile for steady-state plasma glucose. This decision was based on the results of 2 prospective studies that evaluated the relationships between upper, middle, and lower steady-state plasma glucose tertile and untoward outcomes. In 1 study (8), 1 of 7 apparently healthy, middle-aged individuals in the highest steady-state plasma glucose tertile at baseline had a documented cardiovascular event within 5 years. In another study (9), in which CVD, glucose intolerance, hypertension, stroke, and cancer were the end points, 36% of the individuals in the highest steady-state plasma glucose tertile had 1 or more documented events within an average of 6.3 years. In contrast, no end point occurred in the lowest steady-state plasma glucose tertile. In both studies, untoward events occurred in the middle steady-state plasma glucose tertile but occurred less often than in the upper one third. Although the decision to define the tertile with the highest steady-state plasma glucose values as insulin resistant could be viewed as somewhat arbitrary, it is not inconsistent with various published data. For example, in a prospective study

that used plasma insulin concentrations as a surrogate estimate of insulin resistance, 25% of the unselected sample of factory workers with the highest insulin levels had statistically significant increases in the development of states of glucose intolerance, hypertension, and CVD (7). Our choice of the upper steady-state plasma glucose tertile as the operational definition for sufficient insulin resistance to be at increased risk for an adverse outcome, rather than the upper plasma insulin quartile, was based on the premise that a specific measure of the abnormality in question was preferable to a surrogate estimate.

The observation that highlights the potential clinical utility of our analysis is that more than 50% of the apparently healthy participants were overweight or obese by accepted criteria (24, 25). It seems unlikely that our current health care system is prepared to initiate intensive efforts at changing lifestyle in more than half of the U.S. population. Furthermore, only 129 of the overweight or obese persons were also identified as insulin resistant (positive predictive value, 50%) (**Table 1**). In other words, if all 258 obese or overweight persons in the study sample had lost weight, only 50% would have statistically significantly improved insulin sensitivity and associated CVD risk factors.

The results in **Table 1** highlight the untoward metabolic consequences of the approximately 50% of the overweight or obese persons in the upper steady-state plasma glucose tertile. In addition, **Table 1** points out that 17% of the overweight or obese individuals were insulin sensitive and did not have the associated metabolic consequences, and, on the basis of our previous findings (20–23), it is unlikely that any measurement would change statistically significantly with weight loss (20–23). Thus, it seems reasonable to argue that having a relatively simple way to identify overweight or obese persons who were insulin resistant and at greatest risk for CVD would be clinically beneficial. We believe that the results in **Tables 2** and **3** demonstrate that the use of the fasting plasma triglyceride concentration, the plasma triglyceride–HDL cholesterol ratio, or fasting plasma insulin concentration offers a reasonable degree of clinical utility. Of these alternatives, the plasma insulin concentration is the metabolic marker most closely related to insulin resistance. For example, the ability of the pancreas to maintain a state of hyperinsulinemia prevents the development of type 2 diabetes mellitus in insulin-resistant individuals (4). Furthermore, we have shown (35) in 490 nondiabetic persons that insulin-mediated glucose disposal and fasting plasma insulin concentration were significantly correlated ($r = 0.60$; $P < 0.001$). More recently, we demonstrated (42) in the same 490 individuals (including normal weight, overweight, and obese participants) that the ability of fasting plasma insulin concentrations to identify insulin-resistant individuals (upper steady-state plasma glucose tertile) was similar to that of the current study, which was limited to overweight or obese individuals (sensitivity, 66%; specificity, 83%). On the other hand, absence of a standardized insulin assay significantly hampers the clinical utility of plasma insulin concentrations to identify insulin-resistant persons. Thus, the absolute values used in this study cannot necessarily be translated to any other sample using a different assay method. It seems evident that a standardized insulin assay would be significantly clinically useful, and there is no intellectual reason why this cannot be accomplished in the future.

Although less closely related physiologically to insulin resistance than the plasma insulin concentration, our use of the plasma triglyceride and the triglyceride–HDL cholesterol ratio to identify insulin-resistant individuals also had a degree of sensitivity and specificity similar to that of the plasma insulin concentration. In addition, these metabolic markers are recognized to increase CVD risk (13–19), as well as to be associated with insulin resistance and compensatory hyperinsulinemia (4, 12). Furthermore, their sensitivity and specificity seem to be reasonably similar to the ATP III criteria in identifying insulin-resistant individuals. Although the plasma triglyceride and the triglyceride–HDL cholesterol ratio seemed similar in their ability to identify insulin-resistant individuals, the relatively more consistent association between low HDL cholesterol level and CVD makes the triglyceride–HDL cholesterol ratio a clinically appealing marker for CVD risk in addition to insulin resistance. Thus, if the goal is to identify those insulin-resistant individuals who are at risk for CVD, this marker may offer some advantage over the others.

Our findings have several limitations. First, the study sample was primarily white, and the ability of the same metabolic markers or cut-points to predict insulin-resistance in overweight individuals of other ethnicities is unproven. For example, a different marker or different cut-point for a marker identified in this paper might best predict insulin resistance in African Americans and yet another in Southeast Asians. It is also possible that the relationship between BMI and metabolic derangements differs according to ethnicities; therefore, optimal prediction of both insulin-resistance and cardiac risk requires study in specific ethnic subgroups. Second, the sensitivity and specificity of the markers studied could be better. On the other hand, use of the more complicated ATP III criteria to identify insulin-resistant persons was even less sensitive and only slightly more specific than the criteria presented. Perhaps one of the most important points of this paper is that the ATP III criteria do predict insulin resistance with reasonable specificity, although they miss more than half of insulin-resistant individuals who might benefit from targeted interventions to prevent CVD and type 2 diabetes mellitus. Relative differences in sensitivity and specificity largely reflect the diagnostic cut-point chosen, which in the case of this analysis was done mathematically, considering 1) the relatively high prevalence of disease (insulin resistance) and 2) an even harm-to-benefit ratio, indicating that the harm resulting from the diagnosis of true- and false-positive rates is not greater than the benefit of treating both

the true- and false-positive rates. As applies to the current analysis, the primary intervention in individuals identified will consist of lifestyle changes, such as weight loss, preventing weight gain, or exercise, which will benefit those correctly identified, and either benefit or have a neutral effect on those falsely identified. For example, obesity has many health-related implications, such as gallbladder disease, respiratory depression, and osteoarthritis, that are not known to be related to insulin resistance or hyperinsulinemia (43) and may be minimized with weight loss.

In conclusion, more than half of the U.S. population is overweight or obese, which has led to a medical problem of enormous magnitude. The results of our study suggest that approximately half of these individuals have clinically significant insulin resistance. The ability to identify those overweight or obese individuals who are insulin resistant could help health care professionals be more successful in bringing about lifestyle interventions, such as weight loss, by focusing their efforts more intensively on the smaller number of such individuals who are at greatest risk for CVD. In that context, use of the cut-points of plasma triglyceride concentration or triglyceride–HDL cholesterol ratio described in this paper is relatively simple, is based on changes in lipid metabolism known to increase CVD risk, and seems to be at least as effective as other alternatives that have been proposed to accomplish this goal.

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COMMENTARY

The goal of testing is to identify overweight or obese persons who are insulin resistant to focus extra attention on helping them lose weight. The question to be asked of any measure of insulin resistance is whether the results would change management strategy. Put in probabilistic terms, would the results alter the probability of insulin resistance enough to change management? To form this judgment, Bayes' theorem is used to calculate the post-test probability of insulin resistance. Bayes' theorem requires the pretest odds of insulin resistance and the likelihood ratio for the tests of insulin resistance.

In the present study, 50% of patients had a steady-state plasma glucose level high enough to define them as insulin resistant. Thus, the pretest probability of insulin resistance was 50% (1:1 odds), meaning that a physician caring for an overweight or obese person should be uncertain whether the patient is insulin resistant.

The main result of this study is the likelihood ratios of the tests for insulin resistance (**Table 3**). According to Bayes' theorem (post-test odds = pretest odds × likelihood ratio), the positive likelihood ratio tells us how much the odds of insulin resistance increase when the result is above the cut-points shown in **Table 3**. The positive likelihood ratio for the triglyceride level is 2.30, which means that the post-test odds are 1:1 × 2.30, or 2.30:1, which corresponds to a probability of 70% that the patient is insulin resistant. Given the likelihood ratio's 95% CI of 1.71 to 3.07, the post-test probability could be as low as 63% and as high as 75% (although these extreme values aren't likely to occur).

A pretest probability of 50% and a post-test probability of 70% mean that the physician is fairly uncertain that the patient has insulin resistance. Likewise, when the triglyceride level is below the cut-point, the post-test probability is 1:1 × 0.46 or 1:2.17 (a probability of 32%). So, irrespective of the triglyceride result, the physician is nowhere near a certain diagnosis of insulin resistance. Does this result imply that the test has no value for managing the obese patient? No. If the results are negative, one must make a major effort at weight loss for 3 patients to have an effect on 1 insulin-resistant patient. If the results are positive, one must treat approximately 1.5 patients to affect 1 insulin-resistant patient. A positive test result reduces the number of overweight patients necessary to treat to help an insulin-resistant patient.

How do the extra measurements (fasting triglyceride and serum glucose level, serum cholesterol level, blood pressure, and BMI) outlined in the ATP III criteria help the clinician in diagnosing insulin resistance? The likelihood ratio for the ATP III criteria was 3.60 if patients satisfied the criteria and 0.56 if they did not. The post-test probabilities corresponding to these test results were 78% and 36%, respectively, which implies considerable diagnostic uncertainty. If the test results are positive, one would have to treat 1.25 overweight patients to affect 1 insulin-resistant patient, slightly fewer than the number needed to treat to affect 1 insulin-resistant patient than if only the serum triglyceride level had been used for classification.

This analysis suggests that these tests won't help make a firm diagnosis of insulin resistance in this mixed sample of overweight and obese healthy people. The pretest probability of insulin resistance may have been sufficiently high in the obese patients to make a firm diagnosis after a positive test result, but the authors did not provide this information. The test results do separate the patients into groups with substantially different probabilities of insulin resistance: one in which most patients are not insulin resistant, so that an all-out effort at weight reduction would have a modest return, and the other in which most treated patients would be insulin resistant and likely to benefit. Although these tests don't greatly change the probability of insulin resistance, they are likely to be useful in selecting patients for intense weight reduction efforts.

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