Is There a Simple Way to Identify Insulin-Resistant Individuals at Increased Risk of Cardiovascular Disease?

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The goal of this study was to evaluate the ability of various routine measures of lipoprotein metabolism to identify patients who were insulin resistant and dyslipidemic, and therefore, at increased risk of cardiovascular disease. For this purpose, insulin resistance was quantified by determining the steady-state plasma glucose concentration during the insulin suppression test in 449 apparently healthy patients. The low-density lipoprotein (LDL) particle diameter and subclass phenotype were measured by gradient gel electrophoresis in 1,135 patients. Pearson's correlation coefficients and receiver-operating characteristic curves were used to evaluate measures of lipoprotein metabolism as potential markers of insulin resistance and LDL phenotype. The results indicated that the ratio of the plasma concentrations of triglyceride to high-density lipoprotein cholesterol was the best predictor of insulin resistance and LDL particle diameter. The optimal triglyceride/high-density lipoprotein cholesterol ratio for predicting insulin resistance and LDL phenotype was 3.5 mg/dl; a value that identified insulin-resistant patients with a sensitivity and specificity comparable to the criteria currently proposed to diagnose the metabolic syndrome. The sensitivity and specificity were even greater for identification of patients with small, dense, LDL particles. In conlusion, a plasma triglyceride/high-density lipoprotein cholesterol concentration ratio ≥3.5 provides a simple means of identifying insulin-resistant, dyslipidemic patients who are likely to be at increased risk of cardiovascular disease. (Am J Cardiol 2005;96:399–404)

Insulin resistance and a related lipid abnormality, small, dense, low-density lipoprotein (LDL) cholesterol, are associated with an increased risk of cardiovascular disease.[1–6] The triglyceride (TG)/high-density lipoprotein (HDL) cholesterol ratio, which is often elevated in insulin-resistant patients, has also been shown to predict cardiovascular events independently.[7,8] The present analysis was initiated to test the hypothesis that the TG/HDL cholesterol concentration ratio, in addition to its link to increased cardiovascular disease risk, would provide a simple and useful approach to identify insulin-resistant patients, as well as the presence of small, dense LDL particles. To address this issue, we combined data available to the investigators from Stanford University School of Medicine (insulin resistance), Lawrence Berkeley National Laboratory (LDL particle diameter and phenotype), and the Universities of California at San Francisco and Los Angeles (LDL particle diameter and phenotype).

Methods

The experimental subjects were healthy patients who had volunteered for a variety of clinical studies in response to advertisements in local newspapers. Three study populations were included in the analyses. The Stanford population consisted of 449 healthy volunteers recruited from communities in the vicinity of Palo Alto, California, who were on an ad-lib diet; the San Francisco/Los Angeles population consisted of 456 patients recruited by clinics at the University of California, San Francisco, and the University of California, Los Angeles, who were also on an ad-lib diet; and the Berkeley population included 689 subjects sampled after 3 to 6 weeks on a defined weight-stable diet containing (as a percentage of daily calories) 20% to 24% fat, 15% to 16% protein, and 60% to 65% carbohydrate. All 3 groups were primarily of white ancestry (>75%). During the initial screening visit, blood samples were obtained from all volunteers after a 12-hour overnight

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Dr. Krauss was supported by a grant from the National Dairy Council, Rosemont, Illinois. Drs. Krauss, Waters, Saad, and Simon were supported by Grant U01-HL6975, Drs. McLaughlin, Reaven, Abbasi, and Ms. Lamendola were supported by Grant RR000070, and Dr. McLaughlin was supported by Grant RR16071-01 from the National Institutes of Health, Bethesda, Maryland. The funding sources had no role in the design, conduct, or manuscript preparation for this study.

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doi:10.1016/j.amjcard.2005.03.085

Table 1
Demographic and lipoprotein characteristics of three study populations

Variable	Stanford; Ad-Lib Diet (n = 449)	San Francisco/Los Angeles; Ad-Lib Diet (n = 456)	Berkeley; Defined Diet* (n = 689)
Age (yrs)	48 ± 13	56 ± 13	42 ± 11
Men/women	47%/53%	49%/51%	89%/11%
Body mass index (kg/m^2)	26.3 ± 4.3	27.5 ± 5.9	25 ± 3.1
Total cholesterol (mg/dl)	189 ± 35	213 ± 36	178 ± 36
Triglyceride (mg/dl)	120 ± 71	118 ± 64	135 ± 102
HDL cholesterol (mg/dl)	50 ± 13	55 ± 16	41 ± 10
LDL cholesterol (mg/dl)	115 ± 30	134 ± 34	111 ± 31
Non–HDL cholesterol (mg/dl)	139 ± 37	160 ± 40	137 ± 36

Data presented as mean ± SD.
* Eucaloric diet with 20% to 24% fat, 15% to 16% protein, and 60% to 65% carbohydrate.

Table 2
Correlation with steady-state plasma glucose concentration: fasting insulin and lipoprotein concentrations

Variable	r	p Value
Insulin*	0.60	<0.001
Triglyceride/HDL cholesterol*	0.60	<0.001
Triglyceride*	0.57	<0.001
Cholesterol/HDL cholesterol	0.43	<0.001
HDL cholesterol*	−0.40	<0.001
Non–HDL cholesterol	0.35	<0.001
LDL cholesterol	0.18	<0.001

* Log transformed.

fast. All participants were in good general health, with fasting plasma glucose concentrations <126 mg/dl and normal liver and kidney function, who were not taking any drug known to affect carbohydrate or lipid metabolism. The institutional review boards at all sites approved the respective studies, and all subjects gave written, informed consent.

Insulin-mediated glucose disposal was quantified by a modification[9] of the insulin suppression test.[10,11] In brief, after an overnight fast, octreotide was administered at 25 μg/hour in a solution containing 2.5% (weight/volume) human serum albumin by an infusion pump to suppress endogenous insulin secretion. Simultaneously, insulin and glucose were infused at 25 mU/m^2/min and at 240 mg/m^2/min, respectively. Blood was sampled at 10-minute intervals from 150 to 180 minutes, and then averaged to obtain the steady-state plasma glucose and insulin concentrations achieved during the infusion. Because the steady-state plasma insulin concentrations were comparable in all patients qualitatively and quantitatively, and the glucose infusion rate was identical, the magnitude of the resultant steady-state plasma glucose concentration provided a specific and quantitative measure of insulin-mediated glucose disposal; the greater the concentration, the more insulin resistant the patient. Subjects were considered insulin resistant or insulin sensitive if their steady-state plasma glucose concentrations were in the top or bottom tertile, respectively, of the distribution of these values as described in a population of 490 healthy patients.[12]

Fasting plasma insulin concentrations were measured by radioimmunoassay.[13] Lipid and lipoprotein concentrations were measured by previously described methods.[6,14–19] The LDL peak particle diameter was determined by nondenaturing gradient gel electrophoresis, and the LDL subclass phenotype B was determined from gradient gel electrophoresis by previously published criteria.[17–19]

Because of non-normal distributions, insulin, TG, HDL cholesterol, and the TG/HDL cholesterol ratio were log transformed for tests of statistical significance. The results are presented as the mean (of the non–log-transformed values) ± SD. Pearson's correlations were performed on potential markers (lipid and lipoprotein concentrations) of insulin resistance and LDL particle diameter. Stepwise multiple linear regression analysis was conducted with all lipid and lipoprotein markers, as well as age and body mass index, as predictors of insulin resistance and LDL particle diameter. Comparison of the predictive ability was done using receiver-operating characteristic curves for each marker with respect to (1) identification of insulin resistance and (2) LDL-phenotype B. The optimal cutpoint was determined for the TG/HDL cholesterol ratio with respect to predicting insulin resistance or LDL phenotype B using maximization of M,[20] with the following formula: $M = ws + (1 - w) \times p$, where w is the prevalence of disease (insulin resistance or LDL phenotype B) in the study sample, s is the sensitivity, and p is the specificity. For purposes of comparison, we also determined the ability of the criteria proposed by the Adult Treatment Panel III for the diagnosis of the metabolic syndrome[21] to identify insulin resistance, as defined above. Because we did not have waist circumference measurements for most of our subjects, we substituted a body mass index of ≥25.0 kg/m^2 for women and ≥29.0 kg/m^2 for men, values that provided the same prevalence of the metabolic syndrome in the Third National Health and Nutrition Examination Survey population as did the use of the waist circumference.[4] Analyses were performed using Statistical Analysis Systems, version 8.0 (SAS Institute, Cary, North Carolina) and, for comparison of the area under the receiver-operating characteristic curves, STATA, version 8.2 (College Station, Texas).

Table 3
Relation between lipoprotein variables and low-density lipoprotein peak particle diameter

Lipoprotein Variable	San Francisco/Los Angeles Ad-Lib Diet		Berkeley Defined Diet	
	Particle Diameter	p Value	Particle Diameter	p Value
TG/HDL cholesterol*	−0.77	<0.0001	−0.77	<0.0001
Triglyceride*	−0.73	<0.0001	−0.72	<0.0001
HDL cholesterol*	0.59	<0.0001	0.60	<0.0001
Cholesterol/HDL cholesterol	−0.58	<0.0001	−0.63	<0.0001
Non–HDL cholesterol	−0.30	<0.0001	−0.34	<0.0001
LDL cholesterol	−0.06	NS	−0.01	NS

* Log transformed.

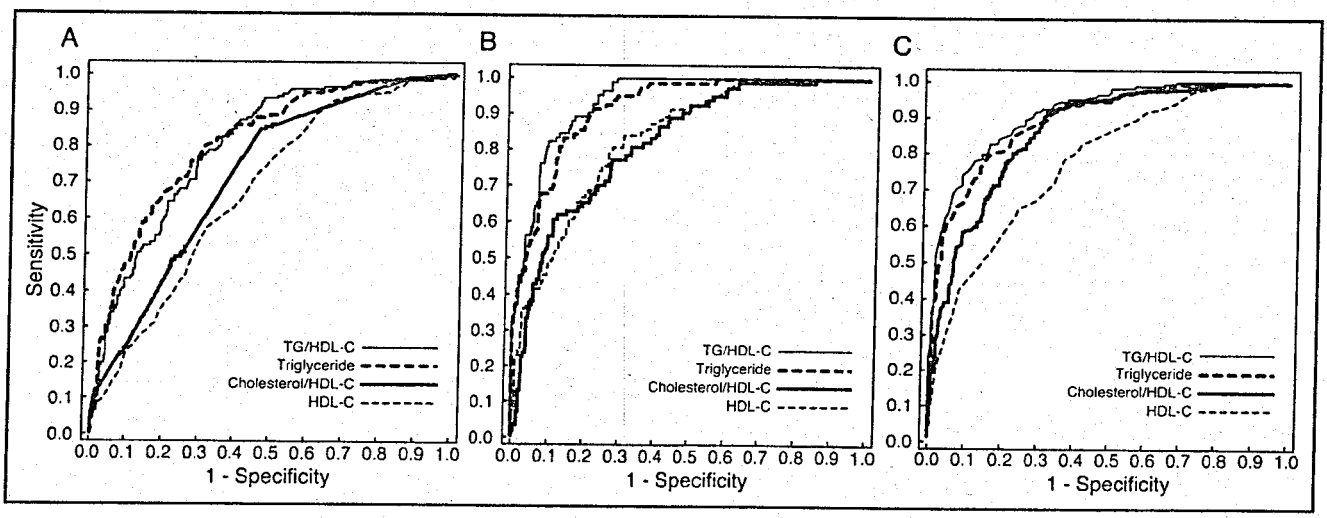

Figure 1. Receiver-operating characteristic curves of the TG/HDL cholesterol (HDL-C) ratio, triglyceride, cholesterol/HDL cholesterol ratio, and HDL cholesterol concentrations for prediction of insulin resistance in the *(A)* Stanford population, LDL phenotype B in *(B)* San Francisco/Los Angeles ad-lib diet population, and *(C)* Berkeley defined diet population.

Results

Table 1 lists the demographic and metabolic characteristics of the 3 study populations; age, gender, and body mass index were relatively comparable, with the exception that the Berkeley group on the defined diet was predominantly men.

The fasting plasma insulin concentration is considered a useful surrogate estimate of insulin action.[12,22] Table 2 compares the relation between a specific measure of insulin-mediated glucose disposal (steady-state plasma glucose concentration) and fasting plasma insulin concentration, as well as between the steady-state plasma glucose concentration and various aspects of lipoprotein metabolism. The r values are ranked in order of the magnitude of the relation. It was clear that the correlation between the degree of insulin resistance and the TG/HDL cholesterol concentration ratio was equal to that between the degree of insulin resistance and the fasting insulin concentrations. The correlation between TG and insulin resistance was nearly as strong. Furthermore, the relations between these 2 markers and the steady-state plasma glucose concentration were substantially closer than any of the other measures of lipoprotein metabolism.

Table 3 presents the relation between lipoprotein variables and LDL peak particle diameter. As in Table 2, the lipoprotein variables are listed in order of the magnitude of their relation with the LDL peak particle diameter. These data are similar to those seen in Table 2, in that the TG/HDL cholesterol concentration ratio was most closely related to the LDL peak particle diameter, followed by the relation between the plasma TG concentration and the LDL particle peak diameter. As with the measure of insulin resistance, the LDL particle peak diameter and HDL cholesterol and the cholesterol/HDL cholesterol concentration ratio were moderately related, and the non–HDL cholesterol and LDL cholesterol concentrations were most weakly related to the LDL peak particle diameter.

Stepwise linear regression analysis was performed to further evaluate the relation between the various measures of lipoprotein metabolism and insulin resistance and LDL particle diameter. The TG/HDL cholesterol ratio entered the model first when applied to all 3 study populations, and was the only significant ($p < 0.001$)

Table 4
Areas under receiver-operating characteristic curves (c values) and 95% confidence intervals

Lipoprotein Variable	Stanford Ad-Lib Diet	San Francisco/Los Angeles Ad-Lib Diet	Berkeley Defined Diet
Triglyceride/HDL cholesterol	0.84* (0.80–0.88)	0.94*† (0.92–0.96)	0.91*† (0.89–0.93)
Triglyceride	0.83* (0.79–0.87)	0.92* (0.90–0.95)	0.90* (0.88–0.92)
Cholesterol/HDL cholesterol	0.76 (0.72–0.80)	0.82 (0.79–0.88)	0.87 (0.84–0.89)
HDL cholesterol	0.72 (0.67–0.77)	0.83 (0.78–0.87)	0.78 (0.74–0.81)

* $p < 0.001$ compared with c value for cholesterol/HDL cholesterol and HDL cholesterol.
† $p < 0.001$ compared with c value for triglycerides.

Table 5
Sensitivity and specificity of triglyceride/HDL cholesterol concentration ratio ≥3.5 for identifying insulin resistance (Stanford) and small dense LDL phenotype (San Francisco/Los Angeles and Berkeley) compared with Adult Treatment Panel III criteria for identifying insulin resistance in Stanford population

Variable Predicted	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Insulin resistance (Stanford criteria)	47	88	66	77
Small, dense LDL phenotype (San Francisco/Los Angeles ad-lib diet)	79	85	82	83
Small, dense LDL phenotype (Berkeley defined diet)*	71	91	88	78
Metabolic syndrome (Adult Treatment Panel III criteria)	46	92	75	77

* No analysis by gender because small number of women in population.
NPV = negative predictive value; PPV = positive predictive value.

independent predictor of insulin resistance and the LDL particle diameter.

The ability of the 4 lipoprotein variables that were most closely related to the steady-state plasma glucose concentration and LDL peak particle diameter to predict insulin resistance and LDL phenotype B were evaluated by receiver-operating characteristic curve analysis. These results are shown in Figure 1, and the c values for these 4 variables are shown in Table 4. In line with the Pearson correlations shown in Tables 2 and 3, the areas (c) under the receiver-operating characteristic curves were greatest for the TG/HDL cholesterol concentration ratio and TG concentration in the Stanford population, and the c values for the markers were significantly greater statistically than those for the cholesterol/HDL cholesterol concentration ratio and HDL cholesterol. The receiver-operating characteristic curves were essentially identical in the San Francisco/Los Angeles and Berkeley populations, with the TG/HDL cholesterol ratio a significantly better predictor statistically than the next best marker, plasma TG, in these 2 groups ($p = 0.04$ and $p = 0.009$, respectively). The areas under the receiver-operating characteristic curves were significantly lower statistically for the cholesterol/HDL cholesterol and HDL cholesterol concentration in the San Francisco/Los Angeles and Berkeley populations. For all 3 populations and for all markers, the comparison of the area under the receiver-operating characteristic curves by gender revealed no statistically significant differences.

On the basis of these data and the previous observation that the plasma TG and HDL cholesterol concentrations are independently related to insulin resistance,[16] the TG/HDL cholesterol concentration ratio was deemed to be preferable to TG alone as the best predictor of insulin resistance and LDL phenotype B, and a ratio of 3.5 was determined to be the most useful cutpoint. The sensitivity, specificity, and positive and negative predictive power of the TG/HDL cholesterol ratio as a predictor of insulin resistance and LDL phenotype B are shown in Table 5. For the sake of comparison, the Adult Treatment Panel III criteria for the metabolic syndrome were applied as a predictor of insulin resistance. The results in Table 5 showed that the TG/HDL cholesterol ratio is comparable to the Adult Treatment Panel III criteria in predicting insulin resistance, and even better in predicting the LDL phenotype B in 2 separate populations who were on different diets. The positive likelihood TG/HDL cholesterol ratio for the Stanford, San Francisco/Los Angeles, and Berkeley populations was 3.9, 9.3, and 8.1, respectively.

Discussion

The present study was initiated in an effort to find a simple approach to identify apparently healthy patients who were insulin resistant and at an increased risk of cardiovascular disease and other clinical syndromes related to this defect in insulin action. The results presented support the view that a plasma TG/HDL cholesterol concentration ratio ≥3.5 may well provide such information.

Perhaps the most surprising finding was the observation

that the TG/HDL cholesterol ratio was as closely associated with the specific measure of insulin-mediated glucose disposal as was the fasting plasma insulin concentration—a surrogate estimate of insulin action that has been widely used to study the relation between insulin resistance and various clinical syndromes. Mathematic manipulations of fasting plasma glucose and insulin concentrations, aimed at providing a better estimate of insulin sensitivity, such as Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI), provide values for insulin resistance that are essentially identical to the information gained by simply measuring the fasting plasma insulin concentration.[12,23] The conclusion that the TG/HDL cholesterol concentration ratio provides an estimate of insulin sensitivity that is as useful as any other surrogate estimate used for this purpose depends on the specificity of the method used to quantify insulin-mediated glucose disposal. The insulin suppression test has been validated and used for 30 years,[10–12] and it has provided considerable information concerning the relation between insulin resistance and human disease.[23,24] It also is highly correlated ($r > 0.9$) with measurements of insulin-mediated glucose disposal by the euglycemic, hyperinsulinemic clamp technique.[12] Thus, it seems reasonable to conclude that the greater the TG/HDL cholesterol concentration ratio, the more insulin resistant the patient, and that this value provides an estimate of insulin sensitivity that is as accurate as the fasting plasma insulin concentration and the other surrogate estimates that use measures of fasting plasma glucose and insulin concentration to assess insulin action.

In addition to being as useful a surrogate estimate of insulin sensitivity as is the fasting plasma insulin concentration, the TG/HDL cholesterol concentration ratio has other advantages. At the simplest level, measures of plasma lipid concentrations are standardized to a much greater degree than are assays of fasting plasma insulin concentration, so the possibility of finding a specific numeric value that would have clinical utility throughout the country is much greater in the case of the TG/HDL cholesterol ratio. Of greater significance is the TG/HDL cholesterol concentration ratio not only provides an estimate of insulin resistance, but also identifies patients who have an atherogenic lipoprotein profile that puts them at increased cardiovascular disease risk.

The lipoprotein phenotype that characterizes insulin-resistant/hyperinsulinemic patients consists of a high plasma TG and low HDL cholesterol concentration, smaller and denser LDL particles, and an increase in the postprandial accumulation of remnant lipoproteins.[24] In addition to being associated with insulin resistance, this lipoprotein phenotype is also associated with increased cardiovascular disease. Although plasma TG and HDL cholesterol concentrations are routinely measured, this is not the case for the LDL particle diameter or postprandial remnant concentrations. However, the results of the present study have confirmed a previous report of the existence of a strong relation between the TG/HDL cholesterol ratio and LDL peak diameter,[25] and the results in Table 5 indicate that a TG/HDL cholesterol concentration ratio ≥ 3.5 predicts the presence of the small dense LDL phenotype (LDL phenotype B) with high sensitivity and specificity. Thus, by measuring plasma TG and HDL cholesterol concentrations, and calculating their ratio, it is possible to gain insight into 3 of the 4 changes in lipoprotein metabolism that increase cardiovascular disease risk in insulin-resistant patients.

Although the TG/HDL cholesterol ratio is a significant predictor of insulin resistance, the actual value of this ratio that would be most useful to identify insulin-resistant patients is not as straightforward as it is for the LDL phenotype. Specifically, values for insulin-mediated glucose disposal vary continuously throughout the population,[12] so an objective way to classify a patient as either insulin resistant or insulin sensitive is not available. However, we have shown in prospective studies that the tertile of the general population with the greatest steady-state plasma glucose concentrations is at significantly greater risk of developing a variety of adverse outcomes, including cardiovascular disease.[26,27] Using this operational definition of insulin resistance, we found that a TG/HDL cholesterol concentration ratio ≥ 3.5 identified insulin-resistant patients with a reasonable degree of sensitivity and specificity.

Finally, because the plasma TG concentration performs almost as well as does the TG/HDL cholesterol concentration ratio in identifying insulin-resistant patients with smaller and denser LDL particles, it could be argued that its measurement offers an even simpler way to identify patients at increased cardiovascular risk. However, neither its relation to insulin nor the LDL particle diameter was as strong as that of the TG/HDL cholesterol ratio, and, in the case of the LDL phenotype (Table 4), the difference was statistically significant. Furthermore, when placed in the stepwise linear regression model, with either the steady-state plasma glucose concentration or the LDL particle diameter, the TG/HDL cholesterol ratio always entered first. Finally, because TG and HDL cholesterol were independently related to insulin resistance,[16] the TG/HDL cholesterol ratio also appears to offer a more physiologically relevant choice, with a solitary high plasma TG convention more likely to result from abnormalities unrelated to insulin resistance.

Acknowledgment: We acknowledge the assistance of Patricia Blanche, BS, Laura Holl, BA, and Joseph Orr, BA, in performing the lipid and lipoprotein analyses.

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