Insulin Resistance and Triglycerides

Charles J. Glueck, MD, Naseer A. Khan, MD,* Muhammad Umar, MD,* Muhammad S. Uppal, MD,* Waqas Ahmed, MD,* John A. Morrison, PhD,† Naila Goldenberg, MD,* and Ping Wang, PhD**

Abstract: In 1385 adults with primary untreated hyperlipidemia and in a population study of 339 adults (Princeton Follow-up Study [PFS]), we hypothesized that homeostasis model assessment (HOMA) insulin resistance (IR) was a significant explanatory variable for triglycerides (TG) and that IR rose in a stepwise fashion, independent of age, race, sex, and body mass index (BMI), whereas TG categories rose from less than 150 to 150 to 200, to 200 to 500, and to more than 500 mg/dL. A third hypothesis was that TG, BMI, and the ratio of TG to high-density lipoprotein cholesterol (TG/HDL-C) were significant explanatory variables for IR and that IR was inversely associated with HDL-C quintiles and positively associated with non–HDL-C quintiles. By stepwise multiple regression with age, race, sex, BMI, and IR as explanatory variables, in the 1385 patients, positive explanatory variables for TG included BMI (partial $R^2 = 1.3\%$, $P < 0.0001$), sex (men higher, partial $R^2 = 1.1\%$, $P = 0.0001$), and IR (partial $R^2 = 0.4\%$, $P = 0.012$). In the 339 PFS subjects, positive explanatory variables for TG were IR (partial $R^2 = 11.4\%$, $P < 0.0001$), race (whites higher, partial $R^2 = 2.1\%$, $P = 0.005$), and sex (men higher, partial $R^2 = 1.4\%$, $P = 0.019$). After adjusting for age, race, sex, and BMI, in 1385 patients, HOMA IR rose while TG categories rose, with least square means of 2.64 for the TG category less than 150 mg/dL, 3.27 for 150 to 200 mg/dL, 3.85 for 200 to 500 mg/dL, and 4.12 for more than 500 mg/dL. Similarly, in the PFS, while TG categories rose, the least square means of HOMA IR rose, with 1.68 for the TG category less than 150 mg/dL, 2.34 for 150 to 200 mg/dL, and 3.03 for 200 to 500 mg/dL. Body mass index, TG, and TG/HDL-C were significant explanatory variables for IR. Homeostasis model assessment IR is a significant, potentially reversible explanatory variable for TG in patients referred because of hyperlipidemia and in population subjects.

Key Words: insulin, insulin resistance, triglycerides, HDL cholesterol, cardiovascular disease

(*J Investig Med* 2009;57: 874–881)

Insulin resistance (IR) has an effect on the modulation of plasma insulin, triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) concentrations, independent of generalized abdominal or physical endurance capacity.[1] In whites, a TG level of 130 mg/dL or higher and a TG to HDL-C ratio of 3 or higher predict IR in individuals with a body mass index (BMI) of 25 kg/m^2 or higher, but in African Americans,[2] TG levels and TG/HDL-C ratio are not reliable markers of IR. Nonfasting[3–5] and fasting hypertriglyceridemia (HTG)[6–9] is an independent risk factor for coronary heart disease (CHD), particularly for women. In the prospective Bruneck population study, HOMA IR independently predicted incident cardiac events.[10]

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[11] recently identified TG levels lower than 150 mg/dL as normal, 150 to 200 mg/dL as borderline high, 200 to 500 mg/dL as high, and 500 mg/dL or higher as very high. In the current report, we studied 1385 patients referred for diagnosis and treatment of primary untreated hyperlipidemia, 816 patients with a TG level of 150 mg/dL or higher, and a free-living population study of 364 adults (the Princeton Follow-up Study [PFS]). We hypothesized that HOMA IR was a significant explanatory variable for TG9,[12–24] and that IR rose in a stepwise fashion, independent of age, race, sex, and BMI, whereas TG categories[10] rose from less than 150 mg/dL to 150 to 200 mg/dL, to 200 to 500 mg/dL, and to more than 500 mg/dL. A third hypothesis was that TG, BMI, and TG/HDL-C ratio were significant explanatory variables for IR and that IR was inversely associated with HDL-C quintiles and positively associated with non–HDL-C quintiles.

MATERIALS AND METHODS

Study Design

The study followed protocols approved by the institutional review board with signed informed consent.

Cases

After an overnight fast, blood was drawn for cholesterol, TG, and HDL-C tests, along with glucose, insulin, renal, thyroid, and liver function tests, in 2392 patients consecutively referred to the Cholesterol Center from September 27, 1987, to June 12, 2007, for diagnosis and treatment of hyperlipidemia (Table 1). A detailed written history was taken regarding prescription drug use, weekly alcohol intake, diabetes, and fasting hyperglycemia (Table 1). Referral to a regional lipid diagnosis and treatment center reflected a selection bias in the patient group to hyperlipidemia. To assess an untreated patient cohort also free of major causes of secondary hyperlipidemia, a subset of 1385 patients was focused on, with exclusions including using statin and/or TG-lowering drugs, a fasting glucose level of 126 mg/dL or higher, 6 or more drinks of alcoholic beverages per week, 10-mg/d or more prednisone, a hemoglobin A1C score of 7 or higher, hypothyroidism, exogenous estrogen use, and uremia (Table 1).

Princeton Family Study Subjects

To assess relationships between IR, TG, and TG/HDL-C in a healthy, free-living population sample, we studied 364 adults from the PFS,[25] a 25- to 30-year follow-up study of lipids, lipoproteins, and metabolic syndrome in former student participants in the National Heart, Lung, and Blood Institute Lipid Research Clinics Prevalence Study (1973–1976) in a suburban Cincinnati school district. Twenty-two PFS subjects with a fasting blood glucose level of 126 mg/dL or higher and 3 with missing BMI entries were excluded from the data analyses, leaving 339 subjects (Table 2).

From the *Cholesterol Center, Jewish Hospital of Cincinnati; †Division of Cardiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.
Received December 14, 2008, and in revised form August 12, 2009.
Accepted for publication August 14, 2009.
Reprints: Charles J. Glueck, MD, Cholesterol Center, ABC Bldg, 3200 Burnet Ave, Cincinnati, OH 45229. E-mail: glueckch@healthall.com.
Supported in part by the Lipoprotein Research Fund and the Medical Research Funds of the Jewish Hospital of Cincinnati.

ISSN: 1081-5589
DOI: 10.231/JIM.0b013e3181bca9d2

TABLE 1. Exclusions From the 2392 Patients Referred for Diagnosis and Treatment of Hyperlipidemia to Provide a Cohort of 1385 Patients With Primary Untreated Hyperlipidemia

Exclusionary Conditions	Yes	No
Statin use	622	1770
Glucose level ≥ 126 mg/dL	319	2073
Prescribed use of TG	301	2091
≥6 drinks of alcoholic beverages per week	46	2346
Steroids use	24	2368
Hemoglobin A1C score ≥ 7	15	2377
Hypothyroid	11	2381
Estrogen use	5	2387
Uremia	1	2391
Any of the above 9 conditions	1007	1385

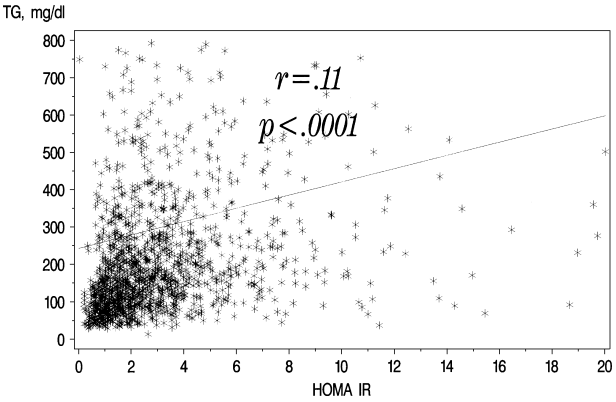

FIGURE 1. Correlation between the TGs (milligrams per deciliter) and HOMA IR in the 1385 adult patients with primary untreated hyperlipidemia (Pearson *r*).

Laboratory and Clinical Measures

Throughout the duration of the study, insulin, lipid, and glucose levels were measured after an overnight fast (≥8 hours) by the same methods for the patients and for the PFS subjects. Insulin was measured by a competitive protein-binding radioimmunoassay. Glucose was measured by a glucose oxidase method with the Hitachi 704 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). Between-batch coefficients of variation were 9% for insulin and 4% for glucose. Homeostasis model assessment IR,[26] which correlates with estimates of IR measured by the euglycemic clamp technique, was used as an index of IR.[26] Although the HOMA IR measure is less accurate than the euglycemic clamp method, in large epidemiological studies, it is a reasonable alternative to the complicated clamp method that requires continuous intravenous administration of insulin and glucose for 3 hours for estimation of insulin sensitivity.[27] Blood lipids were measured in Centers for Disease Control and Prevention-standardized laboratories.[25]

Height, weight, and blood pressure were systematically measured. A fasting serum insulin level was identified as high for levels equal to or more than the laboratory 97.5th percentile, blood glucose was identified as high by the American Diabetes Association criteria if it is 126 mg/dL or higher,[28] and obesity was identified by the criteria of Flegal et al.,[29] with a BMI of 25 to 30 kg/m^2 or higher as overweight, 30 to 40 kg/m^2 or higher as obese, and 40 kg/m^2 or higher as severe obesity.

Statistical Analysis

All statistical analyses were performed using SAS (version 9.1) (SAS Institute, Cary, NC).

Sample size calculations were based on the primary hypothesis of the study that IR and TG were correlated, using the data on correlations of IR to TG ($r = 0.267$) of Moro et al.[30] With $\alpha = 0.05$ and $\beta = 0.8$, 107 subjects would be required.

Scatter plots were constructed to assess relationships between HOMA IR and TG in the 1385 patients (Fig. 1) and in the 339 PFS subjects (Fig. 2). Regression lines were displayed (Figs. 1 and 2).

The patients and the PFS population subjects[25] were categorized into the 4 NCEP ATP III[11] fasting TG categories

TABLE 2. Characteristics of the 1385 Patients Referred for Diagnosis and Treatment of Primary Hyperlipidemia and of the 339 PFS Subjects From a Free-Living Suburban School Population (After Exclusions of 22 Subjects With a Fasting Blood Glucose level ≥ 126 mg/dL, 3 Subjects Without Entry BMI; Original Total Cohort, 364)

	1385 Patients, Mean (SD), Median (Interquartile Range)	339 PFS Subjects, Mean (SD), Median (Interquartile Range)	*P*
Age, yr	50 (13), 51 (42–59)	47 (13), 41 (37–59)	<0.0001, Wilcoxon
Race	White, 1296 (94%)	White, 232 (68%)	$X^2 = 170.8$
	Black, 51 (4%); other, 38 (3%)	Black, 107 (32%)	$P < 0.0001$
Sex	Female, 674 (49%)	Female, 168 (50%)	$X^2 = 0.087$
	Male, 711 (51%)	Male, 171 (50%)	$P = 0.77$
BMI, kg/m^2	30.0 (6.1), 29.2 (25.7–33.2)	28.1 (6.3), 27.1 (23.7–31.4)	<0.0001, Wilcoxon
TC, mg/dL	222 (66), 214 (179–253)	193 (42), 188 (168–216)	<0.0001*
TG, mg/dL	301 (531), 175 (106–307)	133 (99), 101 (69–174)	<0.0001*
HDL-C, mg/dL	Female, 52 (16), 50 (41–60)	Female, 51 (13), 51 (42–58)	0.21*
	Male, 41 (22), 39 (32–46)	Male, 42 (14), 39 (32–49)	
LDL, mg/dL	130 (46), 126 (98–157)	120 (35), 117 (96–142)	0.0018*
Insulin, μ/mL	13.7 (13.4), 10.2 (6.1–16.8)	9.1 (7.3), 6.8 (4.5–11.1)	<0.0001*
HOMA IR	3.30 (3.26), 2.41 (1.44–4.03)	2.00 (1.78), 1.40 (0.91–2.39)	<0.0001*

**P* values were for comparisons adjusted for age, race, sex, and BMI.

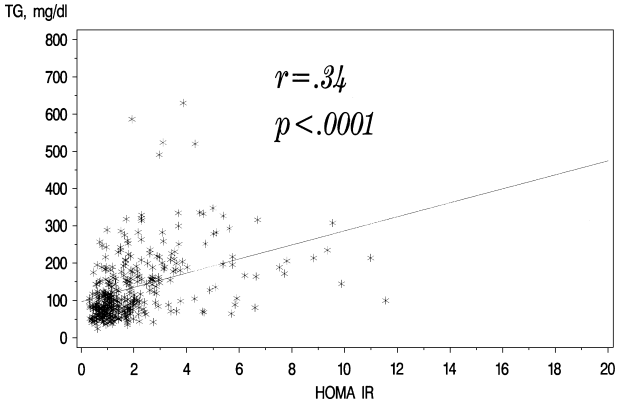

FIGURE 2. Correlation between TGs (milligrams per deciliter) and HOMA IR in the 339 adults in the free-living population study (PFS; Pearson *r*).

(normal, <150 mg/dL; borderline high, 150–200 mg/dL; high, 200–500 mg/dL; and very high, ≥500 mg/dL; Table 6). The patients and the PFS subjects were also characterized by race- and sex-specific HDL-C and non–HDL-C quintiles (Tables 7 and 8). The Jonckheere-Terpstra nonparametric test for ordered differences among classes was used to test the association of HOMA IR with the 4 TG categories (Table 6), the HDL-C quintiles (Table 7), and the non–HDL-C quintiles (Table 8).

Stepwise regression was used with TG as the dependent variable, and age, race, sex, BMI, and HOMA IR were used as explanatory variables in the 1385 patients with untreated primary hyperlipidemia and in the 339 PFS subjects (Table 3).

TABLE 3. Significant Explanatory Variables for TG in the 1385 Patients Referred for Diagnosis and Therapy of Primary Hyperlipidemia and in the 339 Free-Living PFS Subjects

Group	n	Significant Explanatory Variables	*P*	Partial R^2, %
Stepwise regression, TG = age + race + sex + BMI + IR				
Patients	1385	BMI	+, <0.0001	1.3
		Sex (F = 0, M = 1)	+, 0.0001	1.1
		IR	+, 0.012	0.4
PFS	339	IR	+, <0.0001	11.4
		Race (W = 1, B = 0)	+, 0.0050	2.1
		Sex (F = 0, M = 1)	+, 0.019	1.4
Separated by sex, stepwise regression, TG = age + race + BMI + IR				
Patients, Female	674	BMI	+, 0.047	0.6
Patients, male	711	BMI	+, 0.0021	3.0
		Age, yr	−, 0.029	0.6
		IR	+, 0.031	0.6
PFS, female	168	IR	+, <0.0001	17.6
		Age, yr	+, 0.0001	6.9
		Race (W = 1, B = 0)	+, 0.029	2.2
PFS, male	171	IR	+, 0.0002	8.1

B indicates black; F, female; M, male; W, white.

TABLE 4. Significant Explanatory Variables for IR in the 1385 Patients Referred for Diagnosis and Therapy of Primary Hyperlipidemia and in the 339 Free-Living PFS Subjects

Group	n	Significant Explanatory Variables	*P*	Partial R^2, %
Stepwise regression, IR = age + race + sex + BMI + TG				
Patients	1385	BMI	+, <0.0001	14.5
		TG	+, 0.0075	0.4
PFS	339	BMI	+, <0.0001	34.7
		TG	+, <0.0001	3.8
Separated by sex, stepwise regression, IR = age + race + BMI + TG				
Patients, female	674	BMI	+, <0.0001	12.3
Patients, male	711	BMI	+, <0.0001	18.9
		TG	+, 0.044	0.5
PFS, female	168	BMI	+, <0.0001	40.0
		TG	+, <0.0001	6.9
PFS, male	171	BMI	+, <0.0001	34.4
		TG	+, 0.034	1.7

To assess whether TG or TG/HDL-C were significant explanatory variables for IR and whether TG or TG/HDL-C were surrogate markers for HOMA IR, stepwise regression was used with HOMA IR as the dependent variable, and age, race, sex, TG (or TG/HDL-C), and BMI were used as explanatory variables in the 1385 patients and in the 339 PFS subjects (Tables 4 and 5).

Analysis of variance was used to compare HOMA IR with the TG categories after adjusting for age, race, sex, and BMI (Fig. 3).

To assess the relationships of HOMA IR and TG to BMI categorized by 25 or less, 25 to 30, 30 to 40, and 40 kg/m^2 or higher, analysis of variance was used with adjustment for age, race, and sex; least square means and SEs of IR (Fig. 4) and TG (Fig. 5) were displayed.

To control for false positives related to multiple comparisons in Figures 3 to 5, Hochberg-Benjamini[31] adjusted *P* values

TABLE 5. Significant Explanatory Variables for IR in the 1385 Patients Referred for Diagnosis and Therapy of Primary Hyperlipidemia and in the 339 Free-Living PFS Subjects

Group	n	Significant Explanatory Variables	*P*	Partial R^2, %
Stepwise regression, IR = age + race + sex + BMI + TG/HDL				
Patients	1385	BMI	+, <0.0001	14.5
		TG/HDL	+, 0.0005	0.8
PFS	339	BMI	+, <0.0001	34.7
		TG/HDL	+, <0.0001	4.3
Separated by sex, stepwise regression, IR = age + race + BMI + TG/HDL				
Patients, female	674	BMI	+, <0.0001	12.3
		TG/HDL	+, 0.0061	1.0
Patients, male	711	BMI	+, <0.0001	18.9
		TG/HDL	+, 0.034	0.5
PFS, female	168	BMI	+, <00001	40.1
		TG/HDL	+, <00001	8.9
PFS, male	171	BMI	+, <0.0001	34.4
		TG/HDL	+, 0.025	1.9

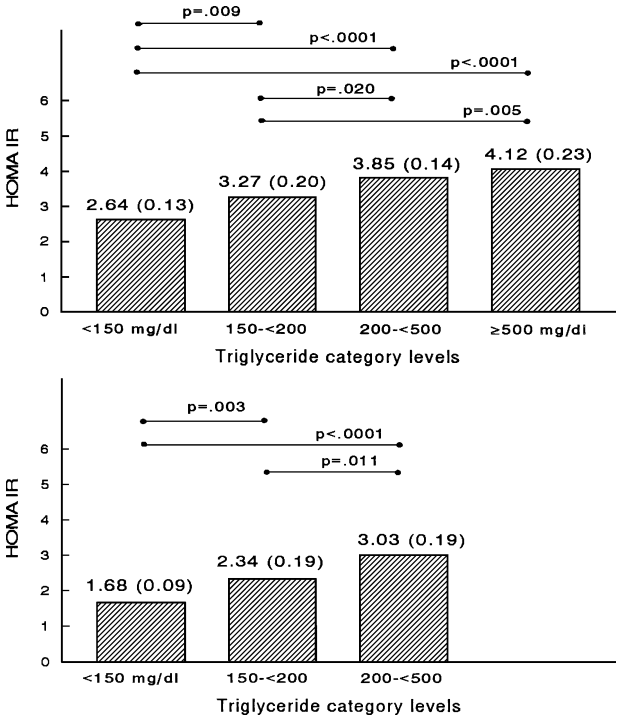

FIGURE 3. Least square mean HOMA IR (SE) among the TG categories[10] after covariance adjusting for age, race, sex, and BMI. Upper panel, The 1385 adult patients with primary untreated hyperlipidemia; lower panel, the 339 adults in a free-living population study (PFS).

were checked. All of the *P* values shown in Figures 3 to 5 were significant below the Hochberg-Benjamini threshold.

RESULTS

Patients and PFS Subjects

After exclusions to rule out secondary causes of HTG, and excluding patients with statin and TG-lowering drug use, the Cholesterol Center patient cohort was reduced from 2392 to 1385 patients with primary untreated hyperlipidemia (Table 1). The characteristics of these 1385 patients and the 339 PFS subjects are displayed in Table 2. The patients differed from the PFS subjects for total and low-density lipoprotein (LDL) cholesterol, TG, and fasting serum insulin levels and HOMA IR (Table 2).

In the 1385 patients with primary untreated hyperlipidemia, HOMA IR was positively correlated with TG ($r = 0.11$, $P < 0.0001$; Fig. 1). The R^2 for the direct correlation between IR and TG was 0.012, so that a 1.2% variation of TG is explained by IR (Fig. 1). There was a closer IR/TG correlation ($r = 0.34$, $P < 0.0001$) in the PFS subjects ($R^2 = 0.116$), so that an 11.5% variation of TG is explained by IR (Fig. 2).

The least square mean (SE) HOMA IR rose in patients in step with the TG categories, with the highest adjusted IR in patients with a TG level of 500 mg/dL or higher, and in the PFS subjects with a TG level of 200 to 500 mg/dL (Fig. 3). There were only 5 PFS subjects with a TG level of 500 mg/dL or higher.

In the 1385 patients with primary untreated hyperlipidemia, significant explanatory variables for TG included BMI, sex (TG higher in men), and IR (Table 3). In the PFS cohort, IR was a significant explanatory variable, as was race (TG level higher in whites) and sex (TG level higher in men; Table 3). Although statistically significant in the patient group ($P = 0.012$), the partial R^2 of IR as an explanatory variable for TG was 0.4%, whereas it was 11.4% ($P < 0.0001$) in the PFS subjects (Table 3).

In the stepwise regression models run separately for men and women, BMI was the only significant explanatory variable for TG in female patients and was the most significant variable in male patients (Table 3). In the PFS cohort, IR was the most significant explanatory variable for TG in women and the only significant variable in men (Table 3).

In both patients and in the PFS cohort, BMI was the major predictive variable for IR, with TG being a significant but much less important explanatory variable (Table 4). When the regression model was run separately for men and women, BMI was the most significant explanatory variable for IR, but TG was a significant but less important variable in male patients and in male and female PFS subjects (Table 4).

With IR as the dependent variable and TG/HDL-C, age, race, sex, and BMI as the explanatory variables (Table 5), BMI was the predominant explanatory variable, with TG/HDL-C also significant but much less important in both the patients and the PFS subjects.

After categorizing by BMI, patients and PFS subjects had a progressive increase in IR as BMI categories rose (after covariance adjusting for age, sex, and race; Fig. 4).

The NCEP ATP III criteria[11] for an elevated TG level (≥150 mg/dL) captured 815 (59%) of 1385 patients with primary untreated hyperlipidemia and 109 (32%) of 339 of the free-living PFS sample (Table 6). In both the patient and the PFS

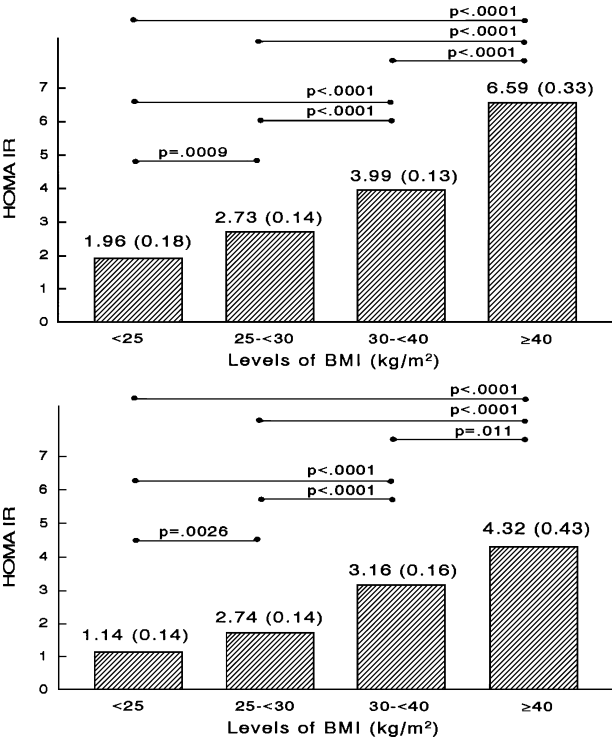

FIGURE 4. Least square mean HOMA IR (SE) among the BMI categories[29] after covariance adjusting for age, race, and sex. Upper panel, the 1385 adult patients with primary untreated hyperlipidemia; lower panel, the 339 adults in a free-living population study (PFS).

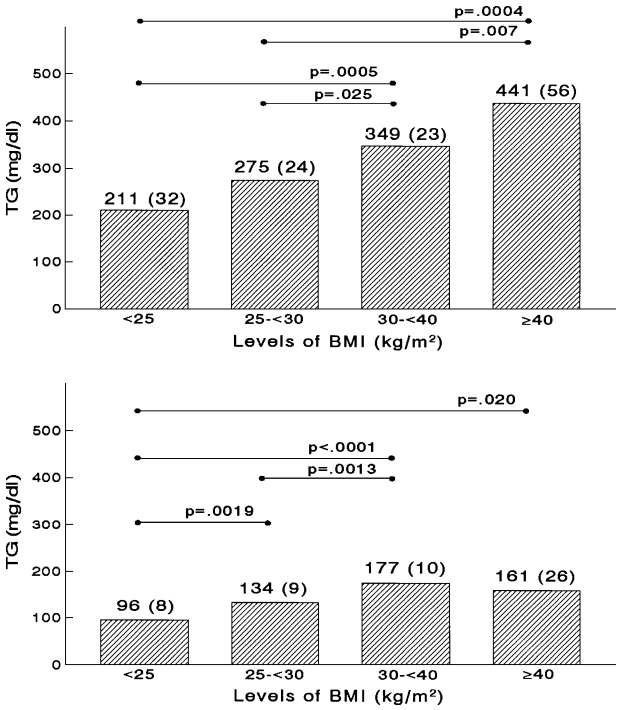

FIGURE 5. Least square mean TG (SE) among the BMI categories[29] after covariance adjusting for age, race, and sex. Upper panel, the 1385 adult patients with primary untreated hyperlipidemia; lower panel, the 339 adults in a free-living population study (PFS).

cohorts, the percentage of subjects with a HOMA IR equal to or more than the 97.5th percentile for healthy subjects in our center (5.54) rose with TG category (Table 6).

After categorizing by BMI, the patients and the PFS subjects had increasing TG levels while BMI categories rose (Fig. 5).

In both the patient and PFS cohorts, the percentage of patients with a HOMA IR equal to or more than the 97.5th percentile for healthy subjects in our center fell as the HDL-C quintile increased (Table 7).

In both the patient and the PFS cohorts, the percentage of patients with a HOMA IR equal to or more than the 97.5th percentile for healthy subjects in our center rose with non–HDL quintiles (Table 8).

DISCUSSION

In our current study, both in patients referred for diagnosis and treatment of primary hyperlipidemia and in healthy free-living subjects, IR was a significant, independent, explanatory variable for TG. However, IR was a much stronger independent predictor of TG (11.4%) in the PFS cohort than in the patient cohort (0.4%). For the direct correlation between IR and TG in patients, 1.2% of the TG was explained by IR compared with 11.5% for the PFS cohort. We speculate that the weaker relationship of IR to TG in the patient cohort reflects other competing variables more likely to be concentrated in the patient cohort including obesity, a significant independent predictor of TG in the patient but not PFS cohort, and genetic contributions to HTG,[32–40] much more frequent in the patient than in PFS cohort. Because patients and PFS subjects with a fasting serum glucose level of 126 mg/dL or higher were excluded from our analyses, the high IR portion of the present study population is enriched with individuals with high insulin relative to glucose.

TABLE 6. Distribution of HOMA IR by TG Categories in the 1385 Patients Referred for Diagnosis and Therapy of Primary Hyperlipidemia and in the 339 Free-Living PFS Subjects

	TG Level				
Group, n (%)	**<150 mg/dL**	**150–200 mg/dL**	**200–500 mg/dL**	**≥500 mg/dL**	**All**
Patients	570 (41)	211 (15)	427 (31)	177 (13)	1385 (100)
With HOMA IR ≥ 5.54 by TG category	41 (7)	30 (14)	77 (18)	47 (26)	195 (14)
	Jonckheere-Terpstra $Z = 7.03$, $P < 0.0001$				
PFS	230 (68%)	51 (15%)	53 (16%)	5 (1.5%)	339 (100)
With HOMA IR ≥ 5.54 by TG category	6 (3)	5 (10)	8 (15)	0 (0)	19 (6)
	Jonckheere-Terpstra $Z = 3.53$, $P = 0.0004$				

TABLE 7. Distribution of HOMA IR by HDL Quintiles in the 1385 Patients Referred for Diagnosis and Therapy of Primary Hyperlipidemia and in the 339 Free-Living PFS Subjects

	HDL Quintiles (Race and Sex Specific)					
Group, n (%)	**Bottom 20%**	**20%–40%**	**40%–60%**	**60%–80%**	**Top 20%**	**All**
Patients	282 (20)	276 (20)	287 (21)	277 (20)	263 (19)	1385 (100)
With HOMA IR ≥ 5.54 by HDL quintiles	69 (24)	54 (20)	36 (13)	23 (8)	13 (5)	195 (14)
	Jonckheere-Terpstra $Z = -7.58$, $P < 0.0001$					
PFS	67 (20)	64 (19)	72 (21)	70 (21)	66 (19)	339 (100)
With HOMA IR ≥ 5.54 by TG category	6 (9)	6 (9)	5 (7)	0 (0)	2 (3)	19 (6)
	Jonckheere-Terpstra $Z = -2.41$, $P = 0.016$					

TABLE 8. Distribution of HOMA IR by Non-HDL Quintiles in the 1385 Patients Referred for Diagnosis and Therapy of Primary Hyperlipidemia and in the 339 Free-Living PFS Subjects

	Non-HDL Quintiles (Race and Sex Specific)					
Group, n (%)	**Bottom 20%**	**20%–40%**	**40%–60%**	**60%–80%**	**Top 20%**	**All**
Patients	272 (20)	282 (20)	277 (20)	278 (20)	276 (20)	1385 (100)
With HOMA IR ≥ 5.54 by non-HDL quintiles	26 (10)	37 (13)	42 (15)	44 (16)	46 (17)	195 (14)
	Jonckheere-Terpstra $Z = 2.54$, $P = 0.011$					
PFS	64 (19)	72 (21)	67 (20)	69 (20)	67 (20)	339 (100)
With HOMA IR ≥ 5.54 by non-HDL quintiles	1 (2)	2 (3)	3 (4)	6 (9)	7 (10)	19 (6)
	Jonckheere-Terpstra $Z = 2.66$, $P = 0.0077$					

In our current study, as TG categories[11] rose from normal (<150 mg/dL) to borderline high (150–200 mg/dL), to high (200–500 mg/dL), and to very high (>500 mg/dL), IR rose in a stepwise fashion independent of age, race, sex, and BMI. Insulin resistance and TG were significantly correlated. These findings were congruent with previous reports.[10,12–24] Although correlation does not impute causation, we speculate that the uniform associations of IR with TG in the current study may reflect underlying biological directionality, in agreement with many other studies.[1,10,12–24,41–45] Moreover, in keeping with putative biological directionality of IR to TG, decreasing IR reduces TG levels.[15,16,46–51]

In the current study, TG/HDL-C was a significant explanatory variable for IR, consistent with previous reports that IR leads to HTG, low HDL-C, and more small dense LDL molecules, the atherogenic triad.[13,41–45] Laws and Reaven[1] reported that IR modulates plasma insulin, TG, and HDL-C concentrations, independent of BMI, waist-to-hip ratio, or physical endurance capacity. Reaven[13] also reported that IR was associated with increased postprandial accumulation of remnant lipoproteins, elevated plasminogen activator inhibitor activity, and increased levels of adhesion molecules that promote binding of mononuclear cells to the endothelium. Resistance to insulin-mediated glucose uptake has been described as the basic metabolic abnormality both in patients with endogenous HTG and in nonobese subjects with a TG level lower than 175 mg/dL.[52] Plasma glucose, insulin, and TG increase significantly with each tertile of IR.[53]

Insulin resistance is associated with high levels of the TG/HDL-C ratio.[54] Triglyceride[55] and TG/HDL-C ratio[56] are surrogate predictors of IR. McLaughlin et al.[8,9] have reported that TG and TG/HDL-C ratio are closely correlated with IR. In the current study, congruent with previous reports,[8,9,55,56] TG and TG/HDL-C were significant explanatory variables for IR in both the patients and the PFS subjects after covariance adjusting for race, sex, age, and BMI. However, fasting TG and the TG/HDL-C ratio are not reliable markers of IR in African Americans,[57,58] probably because of a lack of effect of IR on postheparin lipoprotein lipase that clears TG.[58]

In 1998, in the Bruneck general population study, Bonora et al.[58] reported that IR was very common, found in 84.2% of patients with high TG and low HDL-C and in 83.9% of patients with non–insulin-dependent diabetes. After a 15-year follow-up, Bonora et al.[10] subsequently reported that HOMA IR was associated with development of cardiovascular disease, independent of all classic and several nontraditional CHD risk factors, and suggested that reducing IR may be an important approach to reduce CHD risk. In a cross-sectional study of 293 nondiabetic patients referred for diagnosis and treatment of hyperlipidemia, Glueck et al.[59] reported that fasting serum insulin independently and uniformly improved the prediction of arteriosclerotic cardiovascular disease status beyond traditional risk factors and lipid variables. Lawlor et al.[60] have reported independent associations between fasting insulin and stroke and CHD in older women. Lebovitz[61] emphasized that "insulin resistance was a common link between type 2 diabetes and cardiovascular disease." In patients with the IR syndrome, Reaven[13] has proposed that IR imparts cardiovascular risk.

The NCEP ATP III criteria[11] for elevated TG (≥150 mg/dL) captured 59% of 1385 patients with primary untreated hyperlipidemia referred to our center for diagnosis and treatment of hyperlipidemia and 32% of the free-living PFS population sample. This emphasizes the high frequency of HTG in the general free-living population and in patients referred for diagnosis and treatment of hyperlipidemia when the TG cut point[11] of 150 mg/dL or higher is used.

Patients referred for diagnosis and therapy for HTG, as in the current report, often have concomitant hyperinsulinemia, hyperglycemia, obesity, and low HDL-C, major components of the metabolic syndrome,[15] all of which need to be treated. The goals of treatment in patients with high TG and concomitant IR are focused on the reduction of cardiovascular disease risk,[11,42] with concomitant focus on optimal low HDL-C targets.[11]

REFERENCES

1. Laws A, Reaven GM. Evidence for an independent relationship between insulin resistance and fasting plasma HDL-cholesterol, triglyceride and insulin concentrations. *J Intern Med*. 1992;231: 25–30.
2. Sumner AE, Finley KB, Genovese DJ, et al. Fasting triglyceride and the triglyceride–HDL cholesterol ratio are not markers of insulin resistance in African Americans. *Arch Intern Med*. 2005;165:1395–1400.
3. Bansal S, Buring JE, Rifai N, et al. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;298:309–316.
4. McBride PE. Triglycerides and risk for coronary heart disease. *JAMA*. 2007;298:336–338.
5. Nordestgaard BG, Benn M, Schnohr P, et al. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299–308.
6. Austin MA, McKnight B, Edwards KL, et al. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: a 20-year prospective study. *Circulation*. 2000;101:2777–2782.
7. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007;115: 450–458.

8. McLaughlin T, Abbasi F, Cheal K, et al. Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med*. 2003;139:802–809.
9. McLaughlin T, Reaven G, Abbasi F, et al. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? *Am J Cardiol*. 2005;96:399–404.
10. Bonora E, Kiechl S, Willeit J, et al. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in Caucasian subjects from the general population: the Bruneck study. *Diabetes Care*. 2007;30:318–324.
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
12. Aronne LJ. Therapeutic options for modifying cardiometabolic risk factors. *Am J Med*. 2007;120:S26–S34.
13. Reaven GM. Insulin resistance, the insulin resistance syndrome, and cardiovascular disease. *Panminerva Med*. 2005;47:201–210.
14. Glueck CJ, Fontaine RN, Wang P, et al. Metformin reduces weight, centripetal obesity, insulin, leptin, and low-density lipoprotein cholesterol in nondiabetic, morbidly obese subjects with body mass index greater than 30. *Metabolism*. 2001;50:856–861.
15. Orchard TJ, Temprosa M, Goldberg R, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005;142:611–619.
16. Ratner R, Goldberg R, Haffner S, et al. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care*. 2005;28:888–894.
17. Betteridge DJ. Effects of pioglitazone on lipid and lipoprotein metabolism. *Diabetes Obes Metab*. 2007;9:640–647.
18. Franceschini G, Paoletti R. Pharmacological control of hypertriglyceridemia. *Cardiovasc Drugs Ther*. 1993;7:297–302.
19. Sirtori CR, Tremoli E, Sirtori M, et al. Treatment of hypertriglyceridemia with metformin. Effectiveness and analysis of results. *Atherosclerosis*. 1977;26:583–592.
20. Eriksson A, Attvall S, Bonnier M, et al. Short-term effects of metformin in type 2 diabetes. *Diabetes Obes Metab*. 2007;9:483–489.
21. Glueck CJ, Aregawi D, Agloria M, et al. Sustainability of 8% weight loss, reduction of insulin resistance, and amelioration of atherogenic-metabolic risk factors over 4 years by metformin-diet in women with polycystic ovary syndrome. *Metabolism*. 2006; 55:1582–1589.
22. Derosa G, D'Angelo A, Ragonesi PD, et al. Metformin-pioglitazone and metformin-rosiglitazone effects on non-conventional cardiovascular risk factors plasma level in type 2 diabetic patients with metabolic syndrome. *J Clin Pharm Ther*. 2006;31:375–383.
23. Banaszewska B, Duleba AJ, Spaczynski RZ, et al. Lipids in polycystic ovary syndrome: role of hyperinsulinemia and effects of metformin. *Am J Obstet Gynecol*. 2006;194:1266–1272.
24. Betteridge DJ, Verges B. Long-term effects on lipids and lipoproteins of pioglitazone versus gliclazide addition to metformin and pioglitazone versus metformin addition to sulphonylurea in the treatment of type 2 diabetes. *Diabetologia*. 2005;48:2477–2481.
25. Morrison JA, Khoury P, Laskarzewski PM, et al. Intrafamilial associations of lipids and lipoproteins in kindreds with hypertriglyceridemic probands: the Princeton School Family Study. *Circulation*. 1982;66:67–76.
26. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
27. Ferrannini E, Mari A. How to measure insulin sensitivity. *J Hypertens*. 1998;16:895–906.
28. Rijkelijkhuizen JM, Nijpels G, Heine RJ, et al. High risk of cardiovascular mortality in individuals with impaired fasting glucose is explained by conversion to diabetes: the Hoorn study. *Diabetes Care*. 2007;30:332–336.
29. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002;288:1723–1727.
30. Moro E, Gallina P, Pais M, et al. Hypertriglyceridemia is associated with increased insulin resistance in subjects with normal glucose tolerance: evaluation in a large cohort of subjects assessed with the 1999 World Health Organization criteria for the classification of diabetes. *Metabolism*. 2003;52:616–619.
31. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. *Stat Med*. 1990;9:811–818.
32. Hu Y, Ren Y, Luo RZ, et al. Novel mutations of the lipoprotein lipase gene associated with hypertriglyceridemia in members of type 2 diabetic pedigrees. *J Lipid Res*. 2007;48:1681–1688.
33. Jemaa R, Tuzet S, Portos C, et al. Lipoprotein lipase gene polymorphisms: associations with hypertriglyceridemia and body mass index in obese people. *Int J Obes Relat Metab Disord*. 1995;19:270–274.
34. Ko YL, Ko YS, Wu SM, et al. Interaction between obesity and genetic polymorphisms in the apolipoprotein CIII gene and lipoprotein lipase gene on the risk of hypertriglyceridemia in Chinese. *Hum Genet*. 1997;100:327–333.
35. Pasalic D, Sertic J, Kunovic B, et al. Lipoprotein lipase gene polymorphism and lipid profile in patients with hypertriglyceridemia. *Croat Med J*. 2001;42:517–522.
36. Tybjaerg-Hansen A, Nordestgaard BG, Gerdes LU, et al. Genetic markers in the apo AI-CIII-AIV gene cluster for combined hyperlipidemia, hypertriglyceridemia, and predisposition to atherosclerosis. *Atherosclerosis*. 1993;100:157–169.
37. Wen T, Liu L, Nie S. The relationship between apolipoprotein E genotype and hypertriglyceridemia-associated recurrent acute pancreatitis [in Chinese]. *Zhonghua Wai Ke Za Zhi*. 2008;46: 1579–1582.
38. Yamada Y, Matsuo H, Warita S, et al. Prediction of genetic risk for dyslipidemia. *Genomics*. 2007;90:551–558.
39. Chadarevian R, Foubert L, Beucler I, et al. Lipoprotein lipase activity and common gene variants in severely hypertriglyceridemic patients with and without diabetes. *Horm Res*. 2003;60:61–67.
40. Duggirala R, Blangero J, Almasy L, et al. A major susceptibility locus influencing plasma triglyceride concentrations is located on chromosome 15q in Mexican Americans. *Am J Hum Genet*. 2000;66:1237–1245.
41. Zak A, Slaby A. Atherogenic dyslipidemia and the metabolic syndrome: pathophysiological mechanisms [in Czech]. *Cas Lek Cesk*. 2008; 147:459–470.
42. Nesto RW. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. *Am J Cardiovasc Drugs*. 2005;5:379–387.
43. Sparks JD, Sparks CE. Insulin regulation of triacylglycerol-rich lipoprotein synthesis and secretion. *Biochim Biophys Acta*. 1994;1215:9–32.
44. DeFronzo RA. Insulin resistance, hyperinsulinemia, and coronary artery disease: a complex metabolic web. *J Cardiovasc Pharmacol*. 1992;20(suppl 11):S1–S16.
45. Olefsky JM, Farquhar JW, Reaven GM. Reappraisal of the role of insulin in hypertriglyceridemia. *Am J Med*. 1974;57:551–560.
46. Abbasi F, Farin HM, Lamendola C, et al. Pioglitazone administration

decreases cardiovascular disease risk factors in insulin-resistant smokers. *Metabolism*. 2008;57:1108–1114.

47. Abbasi F, Chen YD, Farin HM, et al. Comparison of three treatment approaches to decreasing cardiovascular disease risk in nondiabetic insulin-resistant dyslipidemic subjects. *Am J Cardiol*. 2008;102:64–69.
48. Rachmani R, Bar-Dayan Y, Ronen Z, et al. The effect of acarbose on insulin resistance in obese hypertensive subjects with normal glucose tolerance: a randomized controlled study. *Diabetes Obes Metab*. 2004;6:63–68.
49. Shapiro H, Bruck R. Omega-3 may indirectly reduce hepatocyte triglycerides through modulation of hyperinsulinemia, cytokines and adipocytokines. *Am J Cardiol*. 2007;99:146.
50. Salpeter SR, Buckley NS, Kahn JA, et al. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. *Am J Med*. 2008;121:149.e2–157.e2.
51. Eleftheriadou I, Grigoropoulou P, Katsilambros N, et al. The effects of medications used for the management of diabetes and obesity on postprandial lipid metabolism. *Curr Diabetes Rev*. 2008;4:340–356.
52. Tobey TA, Greenfield M, Kraemer F, et al. Relationship between insulin resistance, insulin secretion, very low density lipoprotein kinetics, and plasma triglyceride levels in normotriglyceridemic man. *Metabolism*. 1981;30:165–171.
53. McLaughlin T, Allison G, Abbasi F, et al. Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. *Metabolism*. 2004;53:495–499.
54. Karelis AD, Pasternyk SM, Messier L, et al. Relationship between insulin sensitivity and the triglyceride-HDL-C ratio in overweight and obese postmenopausal women: a MONET study. *Appl Physiol Nutr Metab*. 2007;32:1089–1096.
55. McAuley KA, Williams SM, Mann JI, et al. Diagnosing insulin resistance in the general population. *Diabetes Care*. 2001;24:460–464.
56. Kannel WB, Vasan RS, Keyes MJ, et al. Usefulness of the triglyceride-high-density lipoprotein versus the cholesterol-high-density lipoprotein ratio for predicting insulin resistance and cardiometabolic risk (from the Framingham Offspring Cohort). *Am J Cardiol*. 2008;101:497–501.
57. Sumner AE, Vega GL, Genovese DJ, et al. Normal triglyceride levels despite insulin resistance in African Americans: role of lipoprotein lipase. *Metabolism*. 2005;54:902–909.
58. Bonora E, Kiechl S, Willeit J, et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. *Diabetes*. 1998;47:1643–1649.
59. Glueck CJ, Lang JE, Tracy T, et al. Contribution of fasting hyperinsulinemia to prediction of atherosclerotic cardiovascular disease status in 293 hyperlipidemic patients. *Metabolism*. 1999;48:1437–1444.
60. Lawlor DA, Fraser A, Ebrahim S, et al. Independent associations of fasting insulin, glucose, and glycated haemoglobin with stroke and coronary heart disease in older women. *PLoS Med*. 2007;4:e263.
61. Lebovitz HE. Insulin resistance—a common link between type 2 diabetes and cardiovascular disease. *Diabetes Obes Metab*. 2006;8:237–249.

