

Triglyceride-to-High-Density-Lipoprotein-Cholesterol Ratio Is an Index of Heart Disease Mortality and of Incidence of Type 2 Diabetes Mellitus in Men

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Background: High triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) impart risk for heart disease. This study examines the relationships of TG/HDL-C ratio to mortality from all causes, coronary heart disease (CHD), or cardiovascular disease (CVD).

Subjects and Methods: Survival analysis was done in 39,447 men grouped by TG/HDL-C ratio cut point of 3.5 and for metabolic syndrome. National Death Index *International Classification of Diseases (ICD-9 and ICD-10)* codes were used for CVD and CHD deaths occurring from 1970 to 2008. Incidence of type 2 diabetes mellitus (DM) according to ratio was estimated in 22,215 men. Triglyceride/HDL-C ratio and cross-product of TG and fasting blood glucose (TyG index) were used in analysis.

Results: Men were followed up for 581,194 person-years. Triglyceride/HDL-C ratio predicted CHD, CVD, and all-cause mortality after adjustment for established risk factors and non-HDL-C. Mortality rates were higher in individuals with a high ratio than in those with a low ratio. Fifty-five percent of men had metabolic syndrome that was also predictive of CHD, CVD, and all-cause mortality. Annual incidence of DM was 2 times higher in men with high TG/HDL-C ratio than in those with a low ratio. Individuals with high TG/HDL-C ratio had a higher incidence of DM than those with a low ratio. The TyG index was not equally predictive of causes of mortality to TG/HDL-C, but both were equally predictive of diabetes incidence.

Conclusions: Triglyceride/HDL-C ratio predicts CHD and CVD mortality as well as or better than do metabolic syndrome in men. Also, a high ratio predisposes to DM. The TyG index does not predict CHD, CVD, or all-cause mortality equally well, but like TG/HDL-C ratio, it predicts DM incidence.

Key Words: TG/HDL-C ratio, CVD mortality, CHD mortality

(*J Invest Med* 2014;62: 345–349)

High levels of plasma triglycerides (TGs) are a risk factor for cardiovascular disease (CVD) regardless of high-density lipoprotein cholesterol (HDL-C) levels.^{1,2} Hypertriglyceridemia is also frequently associated with impaired fasting glucose, impaired

glucose tolerance, insulin resistance, type 2 diabetes mellitus (DM), and metabolic syndrome.^{3,4} Elevated TGs are commonly associated with a lipoprotein phenotype designated “atherogenic dyslipidemia”⁵; this includes reduced HDL-C and increased number of small, dense, low-density lipoproteins.

A TG/HDL-C ratio of 3.5 or greater was reported by McLaughlin et al.⁶ to be highly correlated with insulin resistance and atherogenic dyslipidemia in men; this threshold was also associated with metabolic syndrome. They proposed that the TG/HDL-C ratio provides a simple way to identify insulin-resistant, dyslipidemic patients who are likely to be at increased risk for CVD. More recently, the TG × fasting glucose (TyG index) has been suggested as a new measure of insulin resistance^{7,8}; this index was compared with the TG/HDL-C ratio and found to be similarly correlated with insulin resistance.

In the current study, we examined the impact of the TG/HDL-C ratio, the TyG index, and the metabolic syndrome risk factors on risk of mortality from coronary heart disease (CHD), CVD, and all causes in a cohort of nonobese and relatively healthy men participating in the Cooper Center Longitudinal Study (CCLS). In addition, the relative impact of TG/HDL-C ratio and TyG index as predictors of type 2 DM incidence was examined.

METHODS

The CCLS was originally designed to examine effects of cardiorespiratory fitness on CVD or cancer incidence.⁹ The CCLS participants were mostly college graduates (95% American white or European) who were self-referred or referred by their employers for clinical evaluation. For the current analysis, data collected between 1970 and 2008 were used, and it includes clinical history, physical examination, vital signs, plasma concentration of TGs, cholesterol, lipoprotein cholesterol, and fasting glucose. Analytical methods used have been detailed previously.¹⁰

A total of 39,447 men aged 20 to 90 years were included in the survival analyses. Men were grouped by TG/HDL-C ratio using a cut point of 3.5. Survival analysis was done in men followed from their baseline examination until the date of death for decedents or until December 31, 2008, for survivors. The primary source for mortality surveillance was The National Death Index. Cardiovascular disease death was defined with *International Classification of Diseases, Ninth Revision (ICD-9)* codes (390–449.9) for deaths before 1999 or *International Classification of Diseases, 10th Revision (ICD-10)* codes (I00–I78) for deaths occurring from 1999 to 2008. Briefly, the code list covers diseases of the circulatory system (acute rheumatic fever; chronic rheumatic fever; hypertension; ischemic heart disease; disease of pulmonary circulation; other forms of heart disease; cerebrovascular disease; diseases of the arteries, arterioles, and capillaries; diseases of veins and lymphatics; and other diseases of the circulatory system). Coronary heart disease death was defined with *ICD-9* codes (410.0–414.9 and 429.2)

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Received July 3, 2013, and in revised form August 6, 2013.

Accepted for publication August 6, 2013.

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This study was supported in part by grant UL1TR000451 from the National Center for Advancing Translational Sciences, National Institutes of Health (to S.M.G. and G.L.V.)

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ISSN: 1081-5589

DOI: 10.2310/JIM.0000000000000044

for deaths before 1999 or ICD-10 codes I20–I26 for deaths occurring from 1999 to 2008. The list includes angina pectoris, acute myocardial infarction and subsequent complications, ischemic heart diseases, and pulmonary embolism. Hazard ratios (HRs) were estimated for those with a high ratio of TGs to HDL-C, and results were also compared with the HR estimated for individuals with a high TyG index. The cut point for the TyG index was determined as described in the statistical section.

The CCLS is approved annually by the institutional review board at The Cooper Institute. All participants provided signed informed consent for participation in the CCLS. The data are maintained by The Cooper Institute.

Descriptive parameters are summarized as means \pm SDs. Log transformations were done for parameters with skewed distributions before data modeling. Cut points for high or low levels of parameters were defined using Adult Treatment Panel III criteria for metabolic syndrome.^{11,12} Accordingly, high plasma TG was 150 mg/dL or greater, low HDL-C was less than 40 mg/dL, high blood pressure was 130/85 mm Hg or greater, high fasting blood glucose was 100 mg/dL or greater, high non-HDL-C was 160 mg/dL or greater, and high waist girth was 102 cm or greater. Thresholds for TG/HDL-C were selected to maximize the likelihood ratio χ^2 statistic between those with and without metabolic syndrome.^{11,12} The estimated ratio was 3.5, identical to that proposed by McLaughlin et al.⁶ Analysis of variance was used to compare parameter means at baseline between low and high TG/HDL-C ratio groups. The TyG was calculated, and its relation to mortality was compared with the association of the ratio of TGs to HDL-C. The TyG index cut points were determined in the same manner as the cut points for the TG/HDL-C ratio. The cut point dividing high and low TyG index was 15,346 mg². This value was similar to that found by Abbasi and Reaven.⁷ Metabolic syndrome risk factors included the ATP III criteria of 3 of 5 risks (high TG, low HDL-C, elevated fasting blood glucose, increased blood pressure, and/or increased waist girth).⁴ Cox proportional hazard regressions were used to estimate crude and adjusted HRs. Attained age was used as the time scale in the proportional hazards models so that potentially nonlinear age effects would be absorbed into the baseline hazard function.

Incidence of type 2 DM was estimated for men grouped according to TG/HDL-C ratios. These analyses were conducted among 22,215 individuals who had more than 1 fasting plasma glucose measurement as well as measures of plasma TG and HDL-C as previously detailed.¹⁰ Subjects were subgrouped at baseline according to fasting plasma glucose categories of normoglycemia (fasting glucose 70–99 mg/dL), mild hyperglycemia (100–109 mg/dL), and intermediate hyperglycemia (110–125 mg/dL). For the estimation of incidence of type 2 DM, data were analyzed as detailed previously.¹⁰ Incidence was determined for subgroups of TG/HDL-C or TyG cut points. Briefly, time to incident DM was calculated as the difference in examination year between the first clinic visit and the earliest clinic visit at which the individual had a blood glucose level greater than 125.9 mg/dL or a reported diagnosis of type 2 DM. Exponential survival models were applied to the interval censored data to estimate incidence rates in the glucose subgroups and to compare glucose subgroups within sexes. SAS/STAT software (Cary, NC), version 9.2, was used for all analyses. Finally, the usefulness of the TyG index in prediction of all-cause mortality and in the incidence of type 2 diabetes was compared with the TG/HDL-C ratio.

RESULTS

Men were followed up for 581,194 person-years. Overall, at baseline, 1% of men reported history of type 2 diabetes, and 16% reported personal history of hypertension; 2% had history

of myocardial infarction, and 17% reported to be current smokers. Subjects were subgrouped by cut points of TG/HDL-C of 3.5 (Table 1). Men with high ratio (TG/HDL-C \geq 3.5) had a higher prevalence of obesity defined by body mass index (BMI) or by waist girth. They also had a higher prevalence of high fasting plasma glucose, TGs, and non-HDL-C; reduced HDL-C; and increased blood pressure (Table 1).

Two thousand seven hundred fifty three men died over the period of observation. Kaplan-Meier plots for CHD mortality, CVD mortality, and all-cause mortality are shown in Figures 1A–C, respectively. These data show that CHD and CVD mortality was significantly higher in those with high TG/HDL-C ratio than in those with a low ratio. Significant differences also were noted for all-cause mortality.

The percentage of decedent cases with CHD and CVD comprised 57.4%, and the remainder died of other causes (Fig. 2A). Among decedents from CHD, CVD, and other causes, 50.6%, 46.2%, and 34.5% had mortality associated with a high ratio of TGs to HDL-C, respectively (Fig. 2A). Those with a high ratio of TGs to HDL-C had higher mortality rates per 10,000 person-years than individuals with a low ratio (Fig. 2B).

TABLE 1. Subject Demography and Clinical Characteristics

	TG/HDL-C Ratio	
	<3.5	\geq 3.5
	Mean \pm SD	
n	26,261	13,186
Follow-up, y	14.7 \pm 7.9	14.8 \pm 7.6
Age, y	44.3 \pm 10.0	45.5 \pm 9.3*
BMI, kg/m ²	26.0 \pm 3.6	28.6 \pm 4.2*
% BMI >30 kg/m ²	11.0	28.0
Waist girth, cm	90.3 \pm 15.7	98.1 \pm 16.6
Elevated waist girth, %	14.0	37.0
Fasting plasma glucose, mg/dL	98.5 \pm 13.1	104.7 \pm 25.8*
Plasma glucose \geq 100 mg/dL, %	39.0	53.0*
Plasma TG median, † mg/dL	91 (69–117)	201 (164–261)*
% Plasma TG \geq 150 mg/dL	5.0	84.0*
HDL-C, mg/dL	50.7 \pm 11.3	36.5 \pm 7.3*
Reduced HDL-C, %	14.0	69.0*
TG/HDL-C ratio	1.91 \pm 0.78	7.20 \pm 16.80*
Non-HDL-C, mg/dL	150.0 \pm 36.9	184.2 \pm 41.3*
Non-HDL-C \geq 160 mg/dL, %	36.0	71.0
Systolic blood pressure, mm Hg	120.8 \pm 13.2	124.0 \pm 13.7*
Systolic blood pressure \geq 130 mmHg, %	24.0	33.0*
Diastolic blood pressure, mm Hg	80.6 \pm 9.5	83.8 \pm 9.7*
Diastolic blood pressure \geq 85 mmHg, %	30	42*
% Smokers	15	21*
% DM	1	2*
% Hypertension	13	22*
% Metabolic syndrome (ATP III)	8	55*

*Significantly different from parameters in groups with low TG/HDL-C ratio, $P < 0.0001$.

†Median (25th–75th percentile).

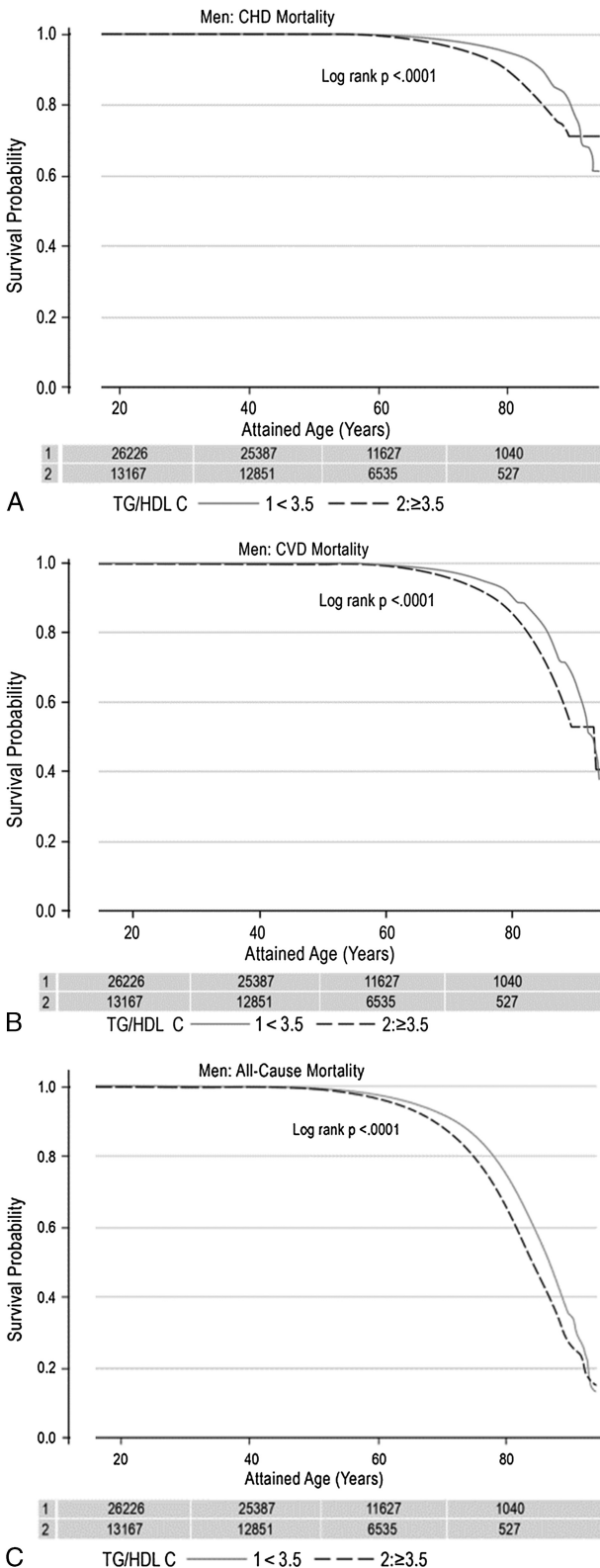


FIGURE 1. Kaplan-Meier survival plots for CHD mortality (A), CVD mortality (B), and all-cause mortality (C) in men grouped by TG/HDL-C ratio of 3.5. Men with a high TG/HDL-C ratio (≥ 3.5) have a higher mortality rate from CHD, CVD, and from all-cause than do men with a low TG/HDL-C ratio (< 3.5). Group 1: low ratio; group 2: high ratio.

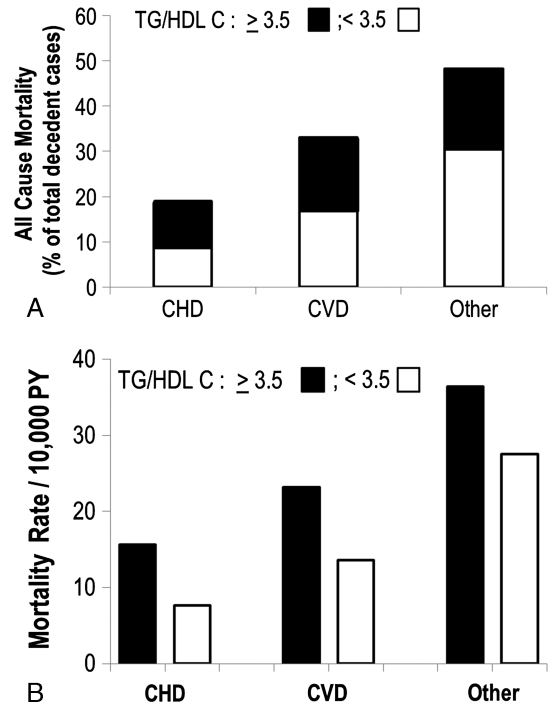


FIGURE 2. Percentage of total mortality cases from CHD, CVD, and other causes (A). Mortality from CHD and CVD comprised 57.4%. The percentage of mortality cases associated with a high ratio of TGs to HDL-C was 50.6% of cases with CHD, 46.2% of cases with CVD, and 34.5% of cases with other mortality causes. The rate of CHD, CVD, and other-cause mortality for those with high ratio was higher than for those with low TG/HDL-C (B). PY indicates patient-years.

A high TG/HDL-C ratio was a strong independent predictor of CHD, CVD, and all-cause mortality (Table 2) before (unadjusted) and after adjustment for age, smoking, BMI, and resting systolic blood pressure, or additional adjustment for non-HDL-C levels. Similarly, the product of TyG was predictive of CHD, CVD, and all-cause mortality before and after adjustments for age, BMI, systolic blood pressure, and smoking (Table 2). Further adjustment for non-HDL-C levels rendered TyG uninformative (Table 2).

Hazard ratio for CHD, CVD, and all-cause mortality was calculated based on the number of metabolic syndrome risk factors as defined by ATP III criteria, that is, 3 or more of 5 risks (increased plasma TGs and/or reduced HDL-C, increased fasting plasma glucose, increased blood pressure and/or increased waist girth) or 3 of 4 risk factors after adjusting for resting blood pressure variance. In the current data set, 9353 men had metabolic syndrome by ATP III criteria. Fifty-five percent of men with a high ratio of TGs to HDL-C and 8% of men with a low ratio had metabolic syndrome.

A cluster of 3 or more of 5 metabolic syndrome risk factors was a strong independent predictor of CHD, CVD, and all-cause mortality (Table 2), and 3 of 4 risk factors, after adjustment for age, BMI, resting blood pressure, and smoking, also were predictive of mortality (Table 2). The usefulness of a cluster of metabolic syndrome risk factors as CHD or CVD predictor failed after additional adjustment for non-HDL-C levels. However, metabolic syndrome risk factor clusters were a significant predictor of all-cause mortality (Table 2) in all analytical models.

In the secondary analysis, there were a total of 22,215 men; 57.5% were normoglycemic, 30.6% were mildly hyperglycemic,

TABLE 2. HRs and 95% Confidence Intervals for Mortality From CHD, CVD, and All-Cause According to TG/HDL-C Ratio and TyG Index

	TG/HDL-C Ratio*	TyG Index†	Metabolic Syndrome (ATP-III)* Risk Factors
	HR (95% Confidence Interval)		
CHD mortality§			
Unadjusted	1.92 (1.64–2.25)‡	1.84 (1.57–2.17)‡	1.75 (1.49–2.21)‡
Age, BMI, RSBP, smoking	1.52 (1.28–1.80)‡	1.46 (1.23–1.74)‡	1.31 (1.09–1.57)‡
Age, BMI, RSBP, smoking, non-HDL-C	1.30 (1.09–1.56)‡	0.83 (0.69–1.00)	1.19 (0.99–1.43)
CVD mortality§			
Unadjusted	1.62 (1.43–1.84)‡	1.64 (1.44–1.86)‡	1.56 (1.37–1.78)‡
Age, BMI, RSBP, smoking	1.30 (1.13–1.48)‡	1.31 (1.15–1.50)‡	1.18 (1.02–1.37)‡
Age, BMI, RSBP, smoking, non-HDL-C	1.15 (1.00–1.33)‡	0.89 (0.77–1.03)	1.11 (0.95–1.28)
All-cause mortality§			
Unadjusted	1.36 (1.26–1.47)‡	1.36 (1.26–1.47)‡	1.33 (1.23–1.44)‡
Age, BMI, RSBP, smoking	1.18 (1.09–1.28)‡	1.16 (1.07–1.26)‡	1.15 (1.05–1.26)‡
Age, BMI, RSBP, smoking, non-HDL-C	1.14 (1.05–1.25)‡	0.89 (0.82–0.97)	1.14 (1.04–1.25)‡

*TG/HDL ratio cut- point is 3.5 or greater.

†The TyG index cut point is 15,346 or greater.

‡Significant HR at *P* < 0.03.

§Adjusted for listed variables.

RSBP indicates resting systolic blood pressure.

and 11.9% had intermediate hyperglycemia. The incidence of type 2 DM in men grouped according to TG/HDL-C ratio or TyG index and subgrouped according to fasting glucose levels was estimated. In men with a low TG/HDL-C ratio (or TyG index), the incidence of type 2 diabetes was higher in the subgroup with mild hyperglycemia (Fig. 3). Similar trends in the incidence of type 2 DM were noted among men with mild hyperglycemia and a high TG/HDL-C ratio. However, the incidence of type 2 diabetes was significantly higher for the groups with a high TG/HDL-C (or TyG index) compared with those with a low ratio (Fig. 3).

DISCUSSION

This study shows that a high TG/HDL-C ratio in men is a predictor of mortality from CHD and CVD. The TG/HDL-C ratio had a significant and higher HR for mortality from CHD and CVD than was found for the TyG index. These 2 measures, TG/HDL-C ratio and TyG index, similarly predicted incidence of type 2 diabetes, but the HR associated with a high TG/HDL-C seems to make the ratio a preferred single parameter of measurement. In this study, we also noted that the HRs for prediction of CHD, CVD, and all-cause mortality were similar for the TG/HDL-C ratio and the metabolic syndrome except when the latter was adjusted for non-HDL-C and other factors (Table 2). The HR associated with a high TG/HDL-C ratio was similar to that previously reported for the metabolic syndrome in the CCLS population.¹³

Most investigators view the TG/HDL-C ratio as an index of insulin resistance based on comparisons of the ratio to measures of insulin resistance.^{6,7} This perspective is supported in part by the work of Laws and Reaven,¹⁴ who provided evidence for the association between a high TG and low HDL-C to resistance to insulin-stimulated glucose uptake by peripheral tissues independently of body habitus and physical fitness. They showed that insulin resistance has an effect on plasma insulin, TGs, and HDL concentrations. Similarly, the ratio of TGs to HDL-C has been compared with the metabolic syndrome to identify insulin resistance.¹⁵ As such, it has been suggested that the ratio represents a simple clinical marker of the metabolic syndrome. Even so, as

shown in this study, only 55% of the CCLS population having an elevated TG/HDL-C ratio also had current criteria for the metabolic syndrome. Thus, the ratio appears to contain useful clinical information for early detection of the metabolic risk.

Several previous investigators have examined the utility of the TG/HDL-C ratio as an atherogenic marker. Hanak et al.¹⁶ found a high correlation between the ratio and low-density lipoprotein phenotype B (atherogenic dyslipidemia). In another study, Dobiášová and Frohlich¹⁷ found that the log of TG/HDL-C correlated strongly with lipoprotein particle size and the esterification rate in apoB-lipoprotein-depleted plasma, another putative atherogenic marker. Furthermore, in another large study, Gaziano

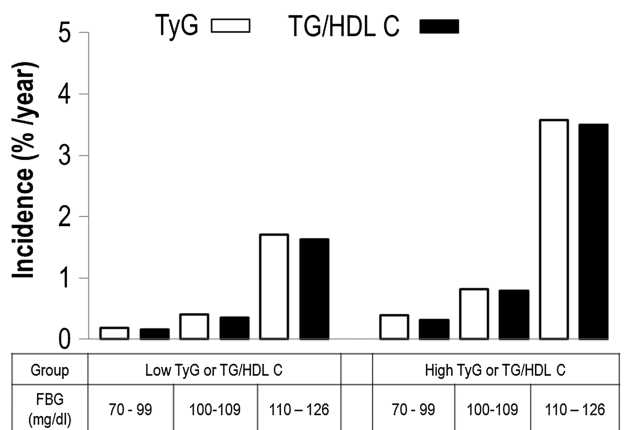


FIGURE 3. Incidence of DM as a function of TyG index (white bars) or TG/HDL-C ratio (black bars). The estimate of type 2 diabetes incidence was similar when determined by either the TyG index or the ratio of TGs to HDL-C. Diabetes incidence was higher in those with a high ratio of TGs to HDL-C (or TyG) than in those with a low cut point. In addition, individuals with a high TG/HDL-C ratio (TyG index) and a fasting glucose in the range of 110 to 125.9 mg/dL had the highest incidence of diabetes. The TyG index and TG/HDL-C ratio provide an index of risk for type 2 DM.

et al.¹⁸ found that the ratio of TGs to HDL was a strong predictor of myocardial infarction. In accord, Salazar et al.¹⁹ reported that an elevated TG/HDL-C ratio is as effective as the metabolic syndrome for predicting the development of CVD. Other studies suggest the potential use of the TG/HDL-C ratio as an atherogenic marker. For example, Urbina et al.²⁰ found that the TG/HDL-C ratio is associated with arterial stiffness in younger persons.

Despite these claims of utility of the TG/HDL-C for identifying a higher risk state, Kannel et al.²¹ questioned whether this ratio is better than the total cholesterol/HDL-C ratio for defining risk for CHD. For the Framingham Heart Study population, these workers found that the TG/HDL-C correlated with insulin resistance (estimated by homeostasis model assessment–insulin resistance) only moderately. Furthermore, these ratios had power to predict CHD only slightly better than did the total cholesterol/HDL-C ratio.

Despite its limitations, the TG/HDL-C ratio has several advantages. A high ratio is suggestive of insulin resistance and metabolic syndrome. Its presence should alert the clinician to the likelihood of a metabolic disorder. A careful evaluation for the presence of the metabolic syndrome is indicated. A high ratio is also a risk factor for CVD. Its presence should lead to a full Framingham risk scoring to determine absolute risk. Although there is overlap between the TG/HDL-C ratio and the metabolic syndrome, almost half of persons with a high ratio did not have the syndrome. Therefore, it independently points to greater risk for CVD. At the same time, the finding of a high ratio calls for more attention to individual metabolic risk factors such as abdominal obesity, hypertension, and dysglycemia.

The finding of a high TG/HDL-C ratio is not a replacement for the metabolic syndrome in clinical practice. Rather, it is a simple number to serve as an alert that a patient is both at increased metabolic risk and cardiovascular risk. Its presence should lead to a more intensive evaluation for these 2 types of risk and, if necessary, to more intensive clinical intervention. It is also important to recognize that TG/HDL-C ratio predicts CHD and CVD mortality for those who have a high ratio independently of the presence of metabolic syndrome and of type 2 DM as shown in the current study.

ACKNOWLEDGMENTS

The authors thank Dr Kenneth H. Cooper for establishing the CCLS, the Cooper Clinic physicians and technicians for collection of baseline data, and The Cooper Institute's data management team for database maintenance.

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