Influence of Triglyceride Concentration on the Relationship Between Lipoprotein Cholesterol and Apolipoprotein B and A-I Levels

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A sample of 2,103 men aged 47 to 76 years from the Québec Cardiovascular Study cohort was examined to quantify the influence of plasma triglyceride (TG) levels on the relationship between plasma lipoprotein cholesterol and either apolipoprotein A-I (apo A-I) or apo B concentrations. Regression analyses between high-density lipoprotein cholesterol (HDL-C) and apo A-I through TG tertiles showed highly significant correlations ($.62 \leq r \leq .75$, $P < .0001$) in all TG tertiles between these 2 variables. The associations for plasma apo B versus low-density lipoprotein cholesterol (LDL-C) and non-HDL-C levels were also studied on the basis of TG concentrations, and correlation coefficients between either LDL-C or non-HDL-C and apo B were essentially similar among TG tertiles ($.78 \leq r \leq .85$ and $.83 \leq r \leq .86$ for LDL-C and non-HDL-C, respectively, $P < .0001$). Regression analyses also showed that lower HDL-C levels were found for any given apo A-I concentration among men in the 2 upper TG tertiles, whereas lower LDL-C concentrations were observed at any given apo B level among subjects in the upper TG tertile. We further investigated whether there were synergistic alterations in the HDL-C/apo A-I and LDL-C/apo B ratios as a function of increasing plasma TG. A significant association was noted between these 2 ratios ($r = .37$; $P < .0001$). Mean HDL-C/apo A-I and LDL-C/apo B ratios were then calculated across quintiles of plasma TG concentrations. Increased TG concentrations were first associated with a reduced HDL-C/apo A-I ratio, followed by a decreased LDL-C/apo B ratio. These results suggest that a relatively modest increase in TG may rapidly alter the relative cholesterol content of HDL particles. Finally, the cholesterol content of the non-HDL fraction appears to be influenced less by TG levels than HDL-C and LDL-C fractions. Thus, the plasma apo B–containing lipoprotein cholesterol level may provide a better index of number of atherogenic particles than the LDL-C concentration, particularly in the presence of hypertriglyceridemia (HTG).

HYPERTRIGLYCERIDEMIA (HTG) is a common feature of the dyslipidemic profile found among patients with ischemic heart disease (IHD).[1-3] However, elevated triglyceride (TG) levels seem to act as an indirect contributor to IHD, since most prospective studies have reported that adjustment for the high-density lipoprotein cholesterol (HDL-C) level eliminated the relationship between TGs and IHD.[4-6] Thus, it has been suggested that the TG-IHD association can be explained to a significant extent by the negative correlation between plasma TG and HDL-C levels,[6,7] since low HDL-C is related to an increased risk of IHD.[5,7-9] However, it has been previously suggested that the presence of HTG may provide relevant clinical information, as this condition frequently underlies other atherogenic metabolic disturbances.[10,11] For instance, elevated TG levels may be the result of increased plasma concentrations of apolipoprotein B (apo B)–associated lipoproteins.

For this reason, it has been suggested that plasma apo B can provide further information in the assessment of IHD risk.[12-15] Although HTG is commonly associated with elevated low-density lipoprotein (LDL) apo B levels,[16-18] LDL cholesterol (LDL-C) levels may often be in the normal range in HTG patients, suggesting alterations in LDL composition. In this regard, HTG has been associated with a greater proportion of small, dense LDL particles.[19-21] In addition, we have recently reported that apo A-I is a poor correlate of plasma TG, as opposed to HDL-C, suggesting important alterations in HDL composition in HTG.[22] Therefore, the main objective of the present study was to examine the relationships between TG and correlates of HDL and LDL composition in a sample of 2,103 men.

SUBJECTS AND METHODS

Study Population

The Québec Cardiovascular Study population and procedures related to its evaluation have been previously described.[23,24] In 1985, 2,443 men agreed to participate in an evaluation of cardiovascular disease risk factors that included an electrocardiogram and a fasting plasma lipid and lipoprotein profile. Lifestyle habits and medical history were documented according to a standardized questionnaire administered by trained nurses. Among 2,443 participants, 288 had IHD and 52 had TG greater than 4.5 mmol/L and were therefore excluded from the present analyses. Thus, the remaining 2,103 men aged 47 to 76 years represent the sample of the present study.

Assessment of Risk Factors

Body weight, height, and resting blood pressure obtained in the sitting position were assessed by research nurses. Two blood pressure measurements were performed within a 5-minute interval, and the mean value was used in the analyses. Information obtained from the questionnaire included the familial and personal history of IHD and diabetes, smoking habits, alcohol consumption, and medication use. Diabetes was considered when men reported the disease or were receiving treatment for it. Diuretics and β-blockers were used in 4% and 8% of men, respectively, whereas hypolipidemics drugs were used in only 2% of men. Although these agents have been shown to have an impact on plasma lipoprotein levels, the exclusion of men on medica-

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tion did not alter the relationships presented herein. Patients under the above-mentioned medication were therefore not excluded from the analyses, to maximize sample size. Alcohol intake was computed from the type of beverage (beer, wine, and spirits) consumed in ounces weekly and standardized as an absolute quantity, with 1 oz of absolute alcohol equivalent to 22.5 g alcohol.

Plasma Lipid and Lipoprotein Measurements

After a 12-hour fast, a blood sample was obtained in the morning with subjects in the sitting position. A tourniquet was used but was released before blood withdrawal into Vacutainer tubes (Becton-Dickinson, Mountain View, CA) containing EDTA. Samples were then processed within 3 hours after blood collection. Plasma was separated by conventional low-speed centrifugation, and cholesterol and TG levels were assessed on an Autoanalazer II (Technicon Instrument, Tarrytown, NY) after extraction of plasma with isopropanol and treatment with zeolite.[25] Plasma HDL-C levels were determined in the supernatant after precipitation of apo B–containing lipoproteins with heparin and manganese chloride,[26] and plasma LDL-C concentrations were estimated using the equation of Friedewald et al,[27] as all men

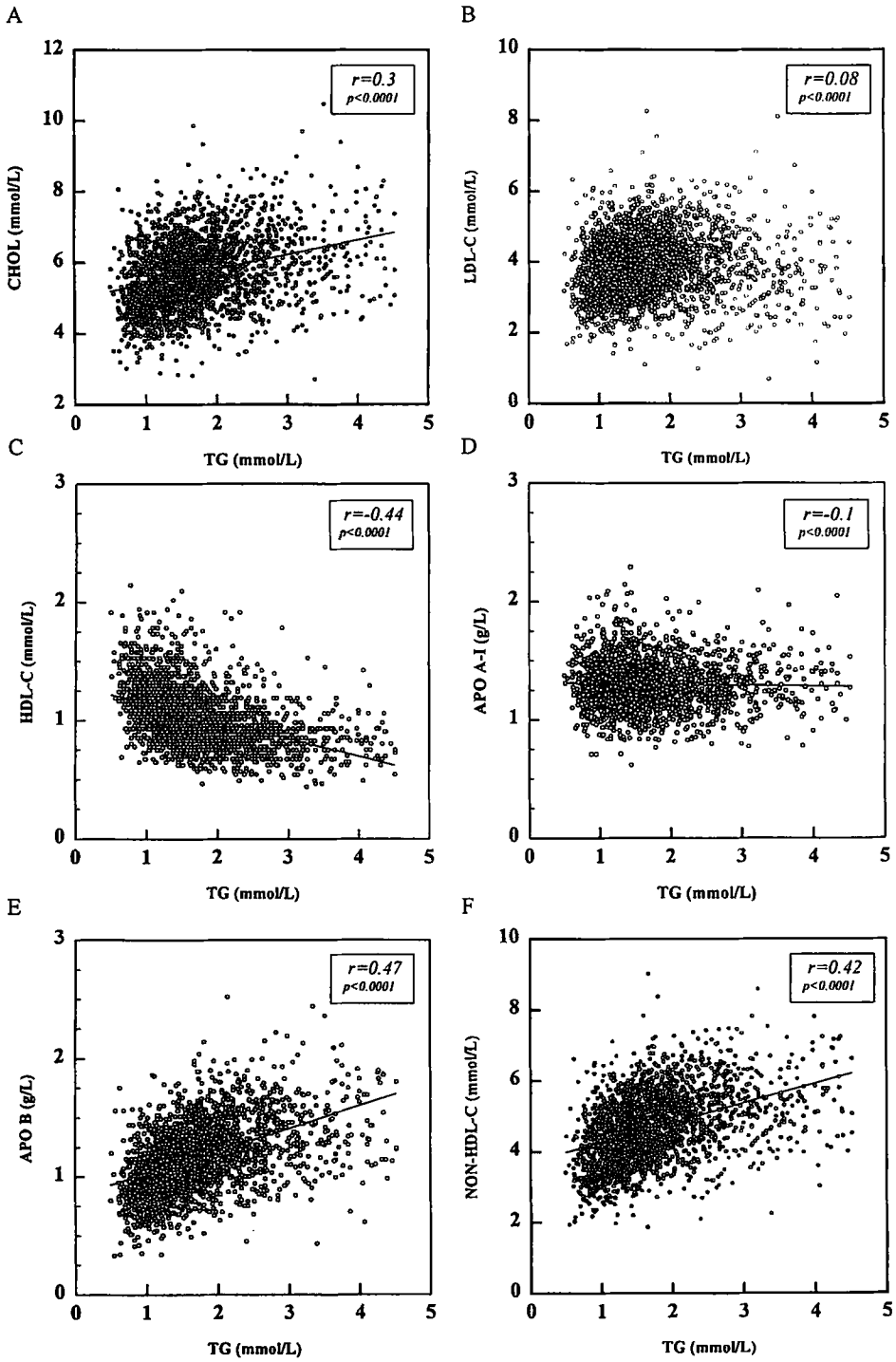

Fig 1. Relationship between (A) total cholesterol (CHOL), (B) LDL-C, (C) HDL-C, (D) apo A-I, (E) apo B, and (F) apo B lipoprotein cholesterol (NON-HDL-C) and TG concentrations in the overall sample of 2,103 men.

considered for the present analyses had TG levels not exceeding 4.5 mmol/L. Plasma apo B and HDL apo A-I concentrations were assessed by the rocket immunoelectrophoretic method of Laurell[28] as previously described.[29] The lyophilized serum standards for apolipoprotein measurements were prepared in our laboratory and calibrated against sera obtained from the Centers for Disease Control (Atlanta, GA). Total cholesterol, HDL-C, TG, and apolipoprotein measurements all had coefficients of variation less than 3%.

Statistical Analyses

Associations between metabolic variables were determined with the Pearson correlation coefficient. Subjects were also subgrouped using the 33rd and 66th percentiles of plasma TG levels. Differences in the characteristics of men within each TG tertile were tested by the General Linear Models (GLM) ANOVA and by chi-square analysis for parametric and nonparametric variables, respectively. Interaction terms were introduced into the GLM to test the interaction between selected variables in modulating the dependent variable of interest. Stepwise multiple regression analysis was also used to quantify the independent contributions of $\log_{10}$-transformed TG and apo A-I levels to the variance of the plasma HDL-C concentration. All statistical analyses were performed with the SAS package (SAS Institute, Cary, NC).

RESULTS

The relationship between each variable of interest and TG is presented in Fig 1. Total cholesterol levels were weakly correlated with TG levels ($r = .30$, $P < .0001$), while no relationship was found between LDL-C and TG levels (Fig 1B). HDL-C concentrations were negatively associated with TG levels ($r = -.44$, $P < .0001$), and a positive association of similar strength was found between both apo B and non-HDL-C and TG concentrations ($r = .47$ and .42, respectively, $P < .0001$). Then, the subjects were divided on the basis of TG tertiles and the characteristics among subgroups were compared (Table 1). No difference was found for age among the 3 TG groups. Increased TGs were associated with a higher body mass index (BMI) and with increased cholesterol/HDL-C ratio, total cholesterol, apo B–associated lipoprotein cholesterol (non-HDL-C), and apo B levels. However, similar LDL-C concentrations were found among the second and third tertiles. Lower HDL-C concentrations were also found as TG levels increased. Subjects with higher TG concentrations had higher systolic/diastolic blood pressure and a greater prevalence of medication use. No difference was found in smoking habits and alcohol consumption, and the trend for a greater prevalence of diabetes in men with high TGs was not significant.

To effectively evaluate the contribution of TG to the relative redistribution of cholesterol among lipoproteins, TG concentrations were divided into quintiles (Fig 2). The relative content of cholesterol associated with the very–low-density lipoprotein fraction increased as a function of TG quintiles. Moreover, there was relatively less cholesterol associated with the HDL fraction as a function of increasing triglyceridemia.

Plasma HDL-C levels were significantly correlated with apo A-I concentrations ($0.62 \leq r \leq .75$, $P < .0001$), but the shared variance between these 2 measurements was moderate (from 36% to 55%; Fig 3B to D). As TG levels increased, lower HDL-C levels were found for any given apo A-I concentration. Stepwise multiple regression analysis showed that 43% of the variance of HDL-C could be explained by the variation in apo A-I concentrations, whereas an additional 17% could be explained by variations in $\log_{10}$-transformed TG levels (Table 2). Figure 4B to D depicts the highly significant relationships ($.78 \leq r \leq .85$, $P < .0001$) between apo B and LDL-C levels,

Table 1. Characteristics of Subjects Classified on the Basis of Tertiles of TG

Characteristic	(1) TG ≤1.3 mmol/L (n = 692)	(2) TG = 1.3-1.9 mmol/L (n = 714)	(3) TG >1.9 mmol/L (n = 697)	P
Age (yr)	56.6 ± 7.2	56.7 ± 6.8	56.3 ± 7.0	.53
BMI (kg/m²)	24.9 ± 3.6	26.4 ± 3.6*	27.2 ± 3.7*†	.0001
TG (mmol/L)	1.04 ± 0.19	1.59 ± 0.17*	2.62 ± 0.62*†	.0001
CHOL (mmol/L)	5.33 ± 0.89	5.73 ± 0.93*	6.09 ± 1.02*†	.0001
LDL-C (mmol/L)	3.67 ± 0.86	3.98 ± 0.89*	4.00 ± 0.98*	.0001
HDL-C (mmol/L)	1.17 ± 0.25	1.02 ± 0.23*	0.90 ± 0.21*†	.0001
Non-HDL-C (mmol/L)	4.15 ± 0.87	4.71 ± 0.89*	5.18 ± 0.98*†	.0001
CHOL/HDL-C	4.71 ± 1.16	5.84 ± 1.39*	7.01 ± 1.68*†	.0001
Apo B (g/L)	0.99 ± 0.25	1.17 ± 0.25*	1.35 ± 0.30*†	.0001
Apo A-I (g/L)	1.33 ± 1.92	1.31 ± 0.21	1.28 ± 0.21*†	.0001
Diabetes (%)‡	3.9	4.5	6.3	.10
Systolic BP (mm Hg)	128 ± 17	130 ± 1*	133 ± 17*†	.0001
Diastolic BP (mm Hg)	79 ± 10	80 ± 11*	83 ± 10*†	.0001
Medication users (%)‡	4.9	8.1	12.8	.001
Smokers (%)‡	10.8	12.6	10.6	.23
Alcohol consumption (oz/wk)	5.84 ± 8.86	5.03 ± 7.5	5.62 ± 7.82	.15

NOTE. Values are the mean ± SD.

Abbreviations: CHOL, total cholesterol; BP, blood pressure.

*Significantly different *v* group 1, †significantly different *v* group 2 by Duncan post hoc test, $P < .05$.

‡Chi-square test used for frequency data, and GLM ANOVA for others.

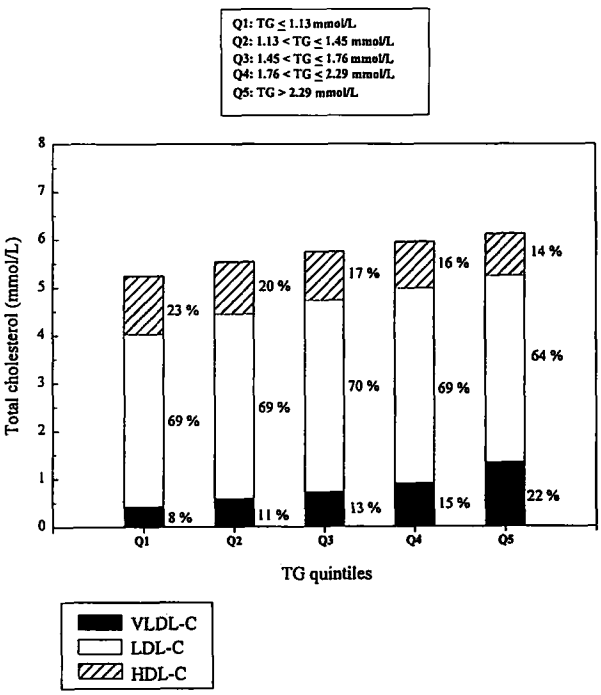

Fig 2. Relative distribution of cholesterol among the various plasma lipoprotein subfractions according to TG quintiles.

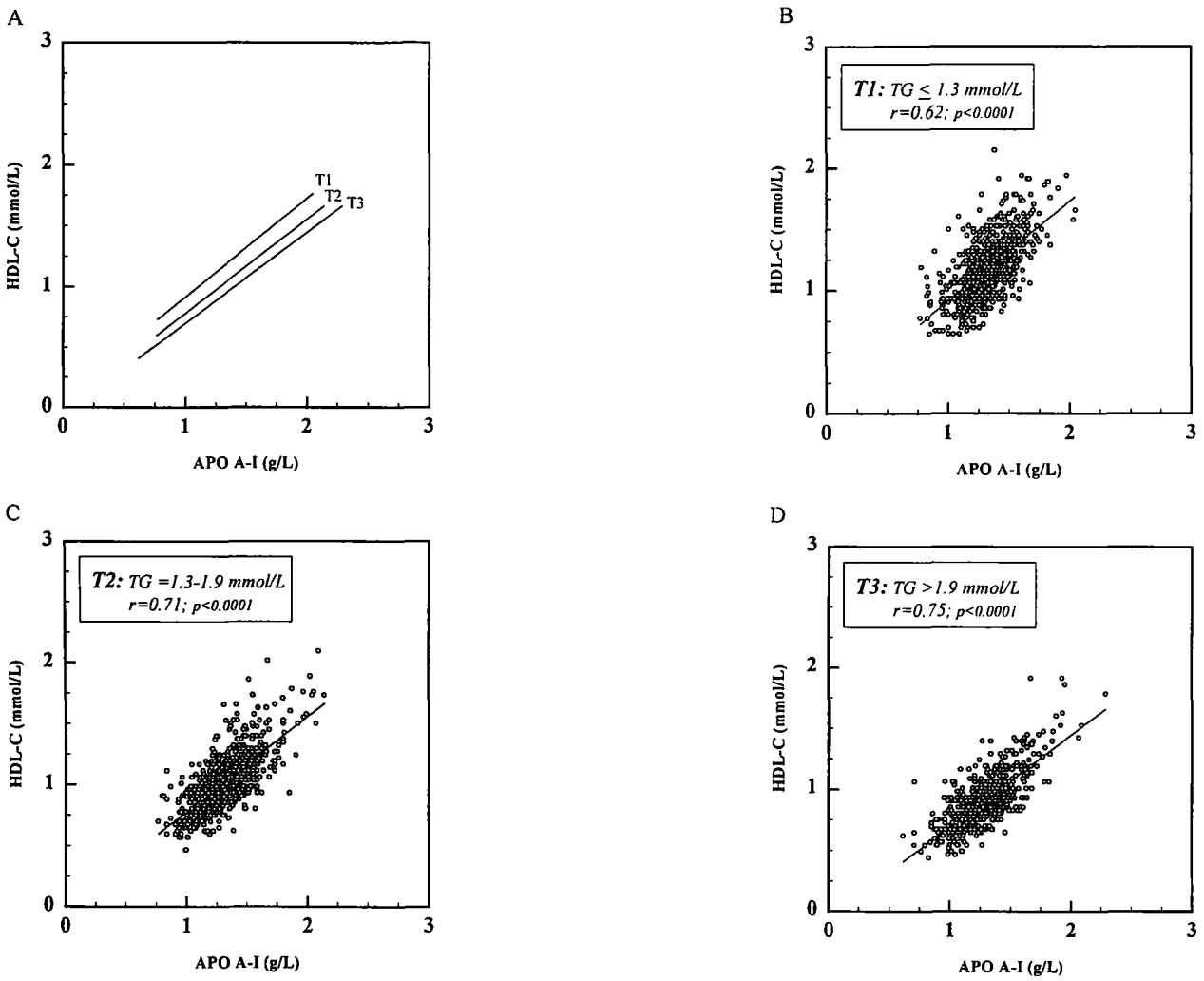

Fig 3. (A) Relationship between HDL-C and apo A-I concentrations among tertiles (T) of TG. (B, C, and D) Relationship between HDL-C and apo B concentrations among tertiles of TG.

and subjects in the third TG tertile were characterized by lower LDL-C levels for any given apo B concentration compared with subjects in the first 2 TG tertiles. Furthermore, the slope of the relationship was different in the third TG tertile, as indicated by a significant interaction term ($P < .0001$). To better appreciate the magnitude of the effect of different TG levels on the relationship of HDL-C to apo A-I, as well as LDL-C to apo B, Table 3 provides an example of the predicted LDL-C or HDL-C concentrations according to given apo B or apo A-I levels among tertiles of TG. Thus, for an apo B or apo A-I level of 1.2 g/L, the predicted LDL-C decreased from 4.27 to 3.62 mmol/L and the predicted HDL-C decreased from 1.08 to 0.85 mmol/L across increasing TG tertiles.

As elevated TG concentrations seemed to alter the relationship between apo A-I and HDL-C levels, as well as the association between apo B and LDL-C levels, we further investigated whether there was an association between these 2 ratios. Figure 5 indicates that there was a positive correlation

Table 2. Contribution of TG and Apo A-I Levels to the Variance in Plasma HDL-C Concentration

Dependent Variable	Independent Variables	Partial (R^2 × 100)	Total (R^2 × 100)	P
HDL-C	ApoA-I	43.2	43.2	<.0001
	TG	16.8	60.0	<.0001

NOTE. Variables included in the analysis were apo A-I and $\log_{10}$-transformed TG levels.

Table 3. Predicted LDL-C or HDL-C Concentrations According to Given Apo B or Apo A-I Levels Among Tertiles of TG

Variable	Regression Equation [$y = m(x) + b$]	Predicted Value
Apo B (1.2 g/L)		LDL-C
T1	$y = 2.93(1.2) + 0.75$	4.27
T2	$y = 2.98(1.2) + 0.50$	4.08
T3	$y = 2.51(1.2) + 0.61$	3.62
Apo A-I (1.2 g/L)		HDL-C
T1	$y = 0.82(1.2) + 0.10$	1.08
T2	$y = 0.78(1.2) + 0.01$	0.95
T3	$y = 0.75(1.2) - 0.05$	0.85

Abbreviation: T, tertile.

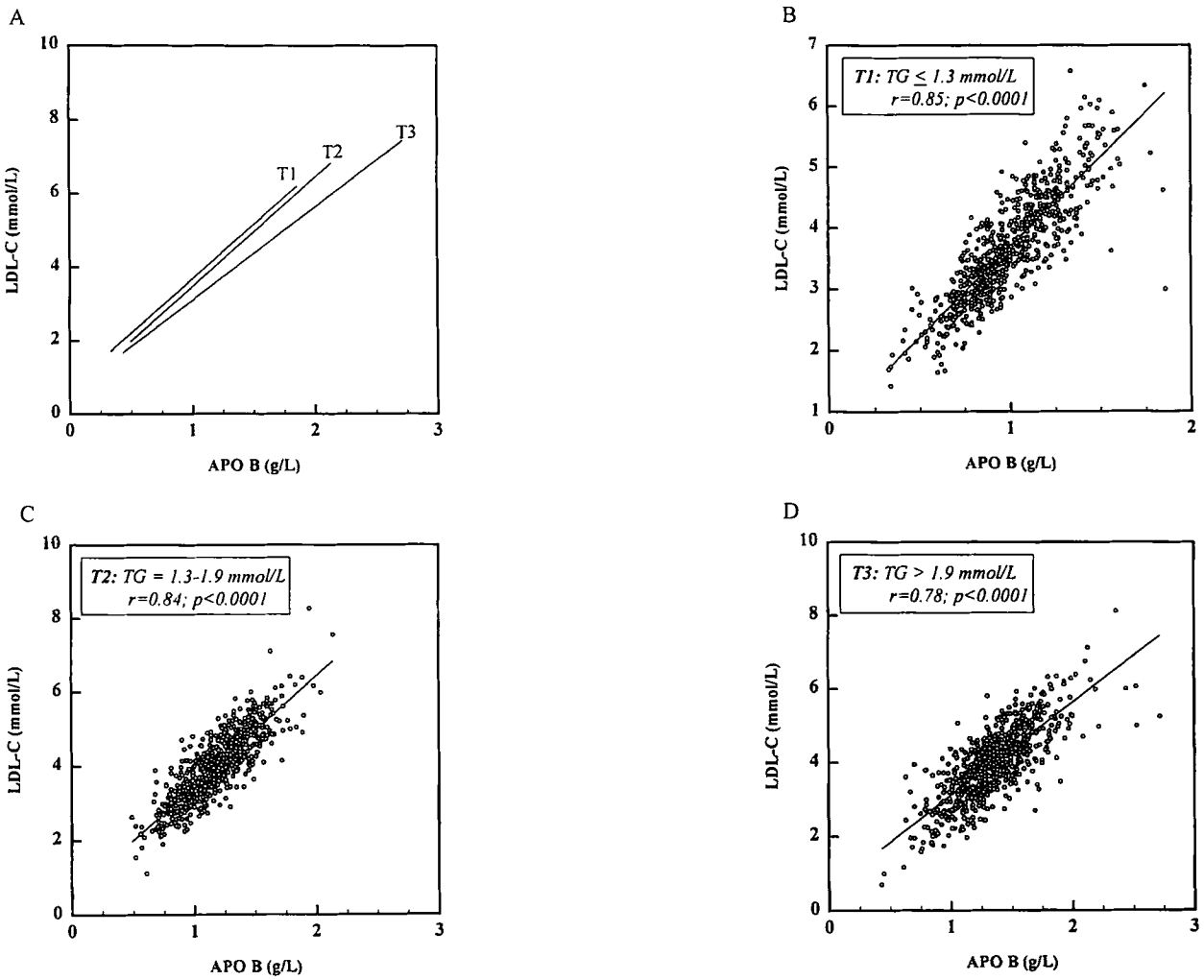

Fig 4. (A) Relationship between LDL-C and apo B concentrations among tertiles of TG. (B, C, and D) Relationship between LDL-C and apo B concentrations among tertiles of TG.

($r = .37$, $P < .0001$) between the HDL-C/apo A-I and LDL-C/apo B ratios. Figure 6A and B indicates that the HDL-C/apo A-I and LDL-C/apo B ratios showed slightly different relationship patterns with TG concentrations. Indeed, the HDL-C/apo A-I ratio progressively decreased across TG quintiles, and men in the third TG quintile were characterized by a 59% decrease in this ratio compared with men in the first quintile. However, the LDL-C/apo B ratio required a more substantial increase in TG (4th quintile) before decreasing by 50%. Finally, Fig 7B to D shows the strong association between non-HDL-C and apo B levels ($.83 \leq r \leq .86$, $P < .0001$). Figure 7A indicates that this relationship was affected less than LDL-C levels by the concomitant variation in TG concentrations. Thus, although a different slope was found in the third TG tertile (interaction term of $P < .001$), similar non-HDL-C levels were found for any given apo B level, irrespective of the variation in plasma TG concentrations.

DISCUSSION

Relationships between triglyceridemia and plasma lipoprotein-lipid levels are already well established in the literature.[10,11] High plasma cholesterol concentrations are known to be associated to a certain extent with higher TG levels, but it is now clear that many metabolic disturbances affecting the distribution of cholesterol among plasma lipoproteins are associated with increased TG levels, leading to the development of other dyslipidemic phenotypes.[24] Our results support those alterations, and the negative relationship between HDL-C and TG levels has been well documented,[6,7] while apo A-I levels seem to be a poor correlate of plasma TG levels, suggesting important alterations in HDL composition in HTG.[22] Moreover, many studies have shown the positive relationship between apo B and TG levels[16-18] and the potential effect of increasing TG on the altered LDL composition, as no association was found between LDL-C and TG levels. Finally, the fact that there was a stronger correlation between apo B-associated lipoprotein cholesterol (non-HDL-C) and TG compared with LDL-C and TG supports the relevance of using this variable (non-HDL-C) in the assessment of IHD risk in HTG patients.

Significant associations have been reported between apo A-I and HDL-C levels,[22,30-32] but the magnitude of this relationship has been found to vary from one study to another. Among the

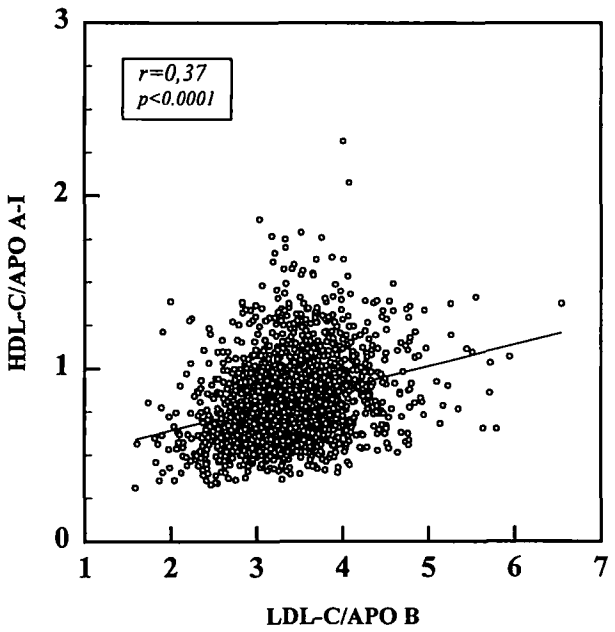

Fig 5. Relationship between the HDL-C/apo A-I and LDL-C/apo B ratio in the overall sample of 2,103 men.

factors that may explain this variation, changes in plasma TG concentrations may partly contribute to the HDL-C variability observed among subjects with similar plasma apo A-I levels. In this regard, Schaefer et al[33] reported that TG levels, as well as the BMI and alcohol intake, contributed significantly to the variability in plasma HDL-C and apo A-I concentrations. Our results indicate that for any given plasma apo A-I concentration, lower HDL-C levels may be observed among subjects with elevated fasting TG concentrations. Numerous metabolic alterations associated with the presence of high TG levels may underlie this reduction in the relative cholesterol content of HDL. The presence of insulin resistance, often associated with abdominal obesity,[34,35] has been related to increased plasma TG, as it reduces the catabolism of TG-rich lipoproteins by altering lipoprotein lipase activity.[36,37]

On the other hand, it is important to point out that HDL composition also can be altered by mechanisms independent of the variation in TG levels. Indeed, stepwise multiple regression analyses showed that 43% of the variance in HDL-C levels could be attributed to the variation in apo A-I concentrations, whereas plasma TG explained a further 17% of the HDL-C variance. Thus, in addition to the contribution of plasma TG to the variation in HDL-C levels, mechanisms modulating apo A-I levels also have a major impact on plasma HDL-C concentrations. In this regard, some studies have characterized HDL subfractions on the basis of apolipoprotein composition such as apo A-I–containing particles (LpA-I) and lipoproteins containing both apo A-I and apo A-II (LpA-I:A-II).[38,39] Among subjects with low HDL-C levels, a preferential reduction of apo A-I in LpA-I particles was noted as compared with LpA-I:A-II particles irrespective of the concomitant variation in TG levels.[38] Moreover, increased apo A-I and apo A-II fractional catabolic rates, one of the mechanisms also contributing to the regulation of apo A-I levels, have been associated with low HDL-C regardless of the presence or absence of HTG.[40,41] Thus, these factors are likely involved in the highly significant relationship that we found between apo A-I and HDL-C levels. However, the results of the present study also suggest that factors related to the modulation of TG concentrations may play a role in the regulation of plasma HDL-C levels.

Higher plasma TG was associated with a substantial reduction in plasma LDL-C for any given apo B concentration, suggesting the presence of smaller LDL particles. Moreover, the

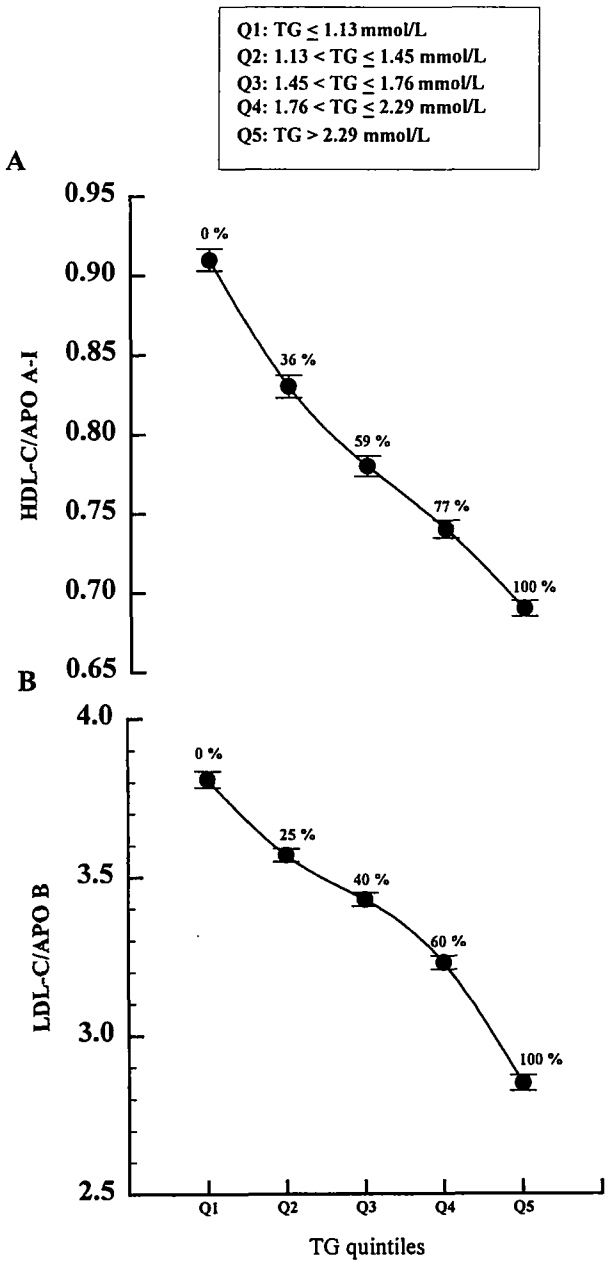

Fig 6. (A) Mean HDL-C/apo A-I ratio among men subgrouped on the basis of TG quintiles. (B) Mean LDL-C/apo B ratio among men subgrouped on the basis of TG quintiles. Mean TG values for each quintile (Q) corresponded to Q1 0.93 mmol/L, Q2 1.30 mmol/L, Q3 1.60 mmol/L, Q4 1.99 mmol/L, and Q5 2.97 mmol/L. Values represent the % difference between the top *v* the lowest quintile.

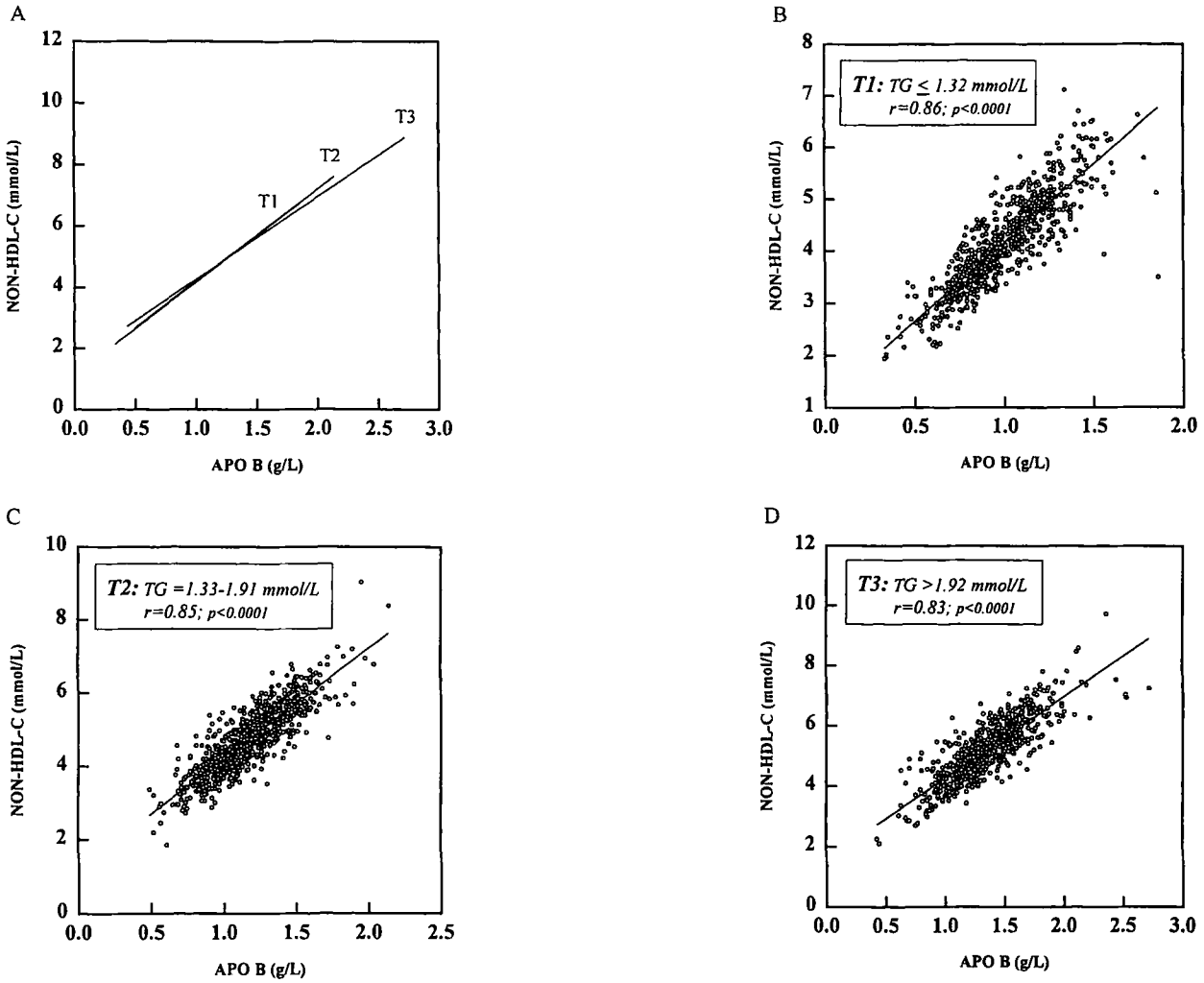

Fig 7. (A) Relationship between NON-HDL-C and apo B concentrations among tertiles of TG. (B, C, and D) Relationship between NON-HDL-C and apo B concentrations among tertiles of TG.

evidence of alterations in LDL composition was further supported by the slightly modified relationship between LDL-C and apo B concentrations observed in the third TG tertile. The presence of small, dense, cholesteryl ester–depleted LDL particles has been associated with the high TG–low HDL-C dyslipidemic state often observed in visceral obesity and in a hyperinsulinemic insulin-resistant condition.[19,20,42,43] However, previous results from our laboratory have indicated that the increased risk of IHD among men with the small, dense LDL phenotype was confined to the subgroup of men with elevated plasma apo B concentrations.[44] This finding is concordant with observations by Tornvall et al,[45] who suggested that both LDL size and LDL particle concentration should be considered in the assessment of IHD risk. It is important to point out that because LDL apo B levels were not assessed in this study, total apo B concentrations were used to examine LDL composition, leading to a slight overestimation of its relative cholesterol content.

The association between the relative cholesterol content of both HDL and LDL (r = .37) suggests that these 2 variables, to a certain extent, vary under similar conditions. However, the different progression of the 2 ratios among TG quintiles further suggests that there was a different pattern in the alteration of HDL and LDL composition caused by elevated TG concentrations. Indeed, the relative cholesterol content of HDL particles appeared to be "sensitive" to a moderate increase in TG levels, whereas LDL composition required higher TG levels in order to be substantially altered. However, it is important to point out that lipid/apolipoprotein ratios are relevant but crude markers of lipoprotein particle size or composition, which are better evaluated by other analytical techniques. Our results support the inverse nonlinear relationship that we previously suggested[10] between HDL-C and TG levels. In the previous study,[10] we reported that major changes in HDL-C concentrations were already observed among subjects with TG less than 2.5 mmol/L, suggesting a substantial reduction in HDL-C content even at moderately increased TG levels.

The results of the present study also suggest that non-HDL-C may be a better predictor of apo B concentrations than LDL-C, as the former may be influenced less by TG concentrations. Elevated TG levels promote the redistribution of cholesteryl

esters among lipoproteins, which may reduce the relative cholesterol content of HDL and LDL but not of all apo B–containing lipoproteins combined. This finding supports the thesis developed by Vega and Grundy,[46] who proposed that the non-HDL-C concentration could provide a crude but clinically relevant estimate of the apo B concentration.

In summary, TG concentrations modify the association between HDL-C and apo A-I, as well as between LDL-C and apo B, to a greater extent than the relationship between apo B and non-HDL-C concentrations. It is therefore proposed that non-HDL-C concentrations may provide a crude estimate of the number of atherogenic particles, which may be more relevant from a clinical standpoint than LDL-C measurements in HTG patients.

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