

Ratio of Triglycerides to HDL Cholesterol Is an Indicator of LDL Particle Size in Patients With Type 2 Diabetes and Normal HDL Cholesterol Levels

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OBJECTIVE— In patients with type 2 diabetes, a normal HDL cholesterol level does not rule out that LDL particles may be small. Although techniques for analyzing LDL subfractions are not likely to be used in clinical practice, a prediction of LDL size based on a regular lipid profile may be useful for assessment of cardiovascular risk.

RESEARCH DESIGN AND METHODS— Sixty patients with type 2 diabetes with acceptable glycemic control and an HDL cholesterol level ≥ 1 mmol/l were recruited after cessation of lipid-altering treatments. LDL size was determined by 2–20% PAGE; patients having small LDL ($n = 30$) were compared with those having intermediate or large LDL ($n = 30$).

RESULTS— Clinical characteristics, pharmacological therapies, lifestyle, and prevalence of diabetes-related complications were similar in both patient groups. LDL size correlated negatively with plasma triglycerides (TGs) ($R^2 = 0.52$) and positively with HDL cholesterol ($R^2 = 0.14$). However, an inverse correlation between the TG-to-HDL cholesterol molar ratio and LDL size was even stronger ($R^2 = 0.59$). The ratio was >1.33 in 90% of the patients with small LDL particles (95% CI 79.3–100) and 16.5% of those with larger LDL particles. A cutoff point of 1.33 for the TG-to-HDL cholesterol ratio distinguishes between patients having small LDL values better than TG cutoff of 1.70 and 1.45 mmol/l.

CONCLUSIONS— The TG-to-HDL cholesterol ratio may be related to the processes involved in LDL size pathophysiology and relevant with regard to the risk of clinical vascular disease. It may be suitable for the selection of patients needing an earlier and aggressive treatment of lipid abnormalities.

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The recent statement from the American Heart Association on diabetes and cardiovascular disease emphasizes the role of lipid abnormalities and the need for early detection of risk factors in insulin-resistant patients with or without diabetes (1). In addition to the results of epidemio-

logical studies, randomized trials have shown that treatments with lipid-altering agents reduce both the levels of lipid risk factors and the occurrence of cardiovascular events, providing good evidence for a causal association in diabetic and nondiabetic patients (2,3). Thus, the assessment of

atherosclerotic risk in patients with type 2 diabetes requires close attention to lipid screening, along with screening for other risk factors. The typical dyslipoproteinemia of type 2 diabetes is characterized by elevated VLDL, small (dense) LDL particles, and decreased HDL (4). The percentage of individuals having small LDL is increased by at least twofold in type 2 diabetes (5). The prevalence of this qualitative abnormality of LDL has been reported to be surprisingly high, even in the absence of the characteristic diabetic dyslipidemia. Thus, up to 45% of patients with low triglyceride (TG) levels and an even higher percentage of patients with borderline hypertriglyceridemia have small LDL, in comparison with 30% in nondiabetic men and $\sim 10\%$ in nondiabetic women (5–8).

Three prospective studies have established that small dense LDL is the best predictor of future coronary artery disease (CAD) in nondiabetic subjects, even after adjustment for confounding by TG, LDL cholesterol, and HDL cholesterol levels (9). Despite an increasing number of publications on this subject, the relationship between LDL size and CAD has not yet been prospectively studied in newly diagnosed diabetic patients. Nevertheless, a prospective study has shown that features usually observed in patients with small LDL (low HDL and HDL2 cholesterol, high VLDL cholesterol, and high total TG and VLDL-TG) were powerful risk indicators for CAD events in patients with type 2 diabetes (10).

Low HDL cholesterol levels are observed in $\sim 45\%$ of patients with type 2 diabetes, mostly in association with hypertriglyceridemia (4). In typical diabetic dyslipidemia, the LDL particles are small in nearly all of the patients with this condition. Therefore, the high cardiovascular risk of such patients is indicated by low HDL cholesterol, which is taken into account by the assessment of usual risk factors. Although small LDL particles are observed more frequently than low HDL cholesterol levels in type 2 diabetes, a normal HDL cholesterol

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Abbreviations: apo, apolipoprotein; CAD, coronary artery disease; FFA, free fatty acid; HL, hepatic lipase; IDL, intermediate-density lipoprotein; TG, triglyceride.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Characteristics of the 60 study patients according to LDL size

| | Small LDL | Intermediate + large LDL | r |
|--|------------------|--------------------------|--------|
| Clinical and biochemical characteristics | | | |
| M/F | 15/15 | 14/16 | |
| Age (years) | 65 ± 9.5 | 66 ± 8.5 | 0.07 |
| Diabetes duration (years) | 15 ± 9 | 13.5 ± 7.5 | -0.18 |
| BMI | 28.9 ± 4.4 | 28.4 ± 5 | -0.22 |
| Waist-to-hip ratio | 0.98 ± 0.06 | 0.98 ± 0.09 | -0.20 |
| Waist girth (cm) | 100 ± 8.4 | 99.6 ± 11.7 | -0.24 |
| Glucose (mmol/l) | 9.9 ± 3.3 | 10.5 ± 3.3 | -0.15 |
| Creatinine (μmol/l) | 83.2 ± 1.1 | 84.1 ± 1.2 | -0.09 |
| HbA _{1c} (%) | 7.8 ± 1.2 | 7.7 ± 1.3 | -0.19 |
| C-peptide after intravenous glucagon (nmol/l) | 0.97 ± 0.40 | 0.83 ± 0.30 | -0.23 |
| Glucose decrement after intravenous insulin (mmol/l) | 1.8 ± 1.0 | 2.5 ± 1.8 | 0.32* |
| Lipase ratio: LPL/HL | 0.45 (0.2–1.4) | 0.46 (0.1–1.1) | 0.12 |
| Fibrinogen (g/l) | 3.9 (3–5.9) | 3.8 (2.7–5.6) | -0.03 |
| Treatments and complications (%) | | | |
| Diet alone | 3 | 3 | |
| Sulfonylurea | 60 | 53 | |
| Metformin | 60 | 57 | |
| Insulin | 47 | 47 | |
| β-Blockers or diuretics | 33 | 23 | |
| 30 < Urinary albumin excretion < 300 mg/g creatinine | 33 | 47 | [1] |
| Urinary albumin excretion >300 mg/g creatinine | 10 | 13 | [1] |
| Vascular disease | 53 | 37 | |
| Background retinopathy | 34 | 40 | |
| Retinal photocoagulation | 13 | 10 | |
| Sensory impairment | 10 | 10 | |
| Absence of reflex | 40 | 23 | |
| Lipids (mmol/l) | | | |
| Triglycerides | 2.3‡ (1.1–4.4) | 1.3 (0.7–2.2) | -0.66‡ |
| Total cholesterol | 6.7 ± 1.3‡ | 5.6 ± 1.0 | -0.35‡ |
| Unesterified cholesterol | 2.5 ± 0.7‡ | 2.0 ± 0.5 | -0.36‡ |
| LDL cholesterol | 4.2 ± 1.1* | 3.6 ± 0.9 | -0.18 |
| HDL cholesterol | 1.2 ± 0.2‡ | 1.4 ± 0.3 | 0.38‡ |
| Phospholipids | 78 ± 14‡ | 67 ± 9 | -0.40‡ |
| HDL triglycerides | 0.15 ± 0.04‡ | 0.11 ± 0.04 | -0.54‡ |
| LDL triglycerides | 0.39 ± 0.12‡ | 0.27 ± 0.07 | -0.41‡ |
| IDL + VLDL cholesterol | 1.34 ± 0.79 ‡ | 0.76 ± 0.46 | -0.42‡ |
| FFAs | 0.71 (0.30–13.8) | 0.66 (0.32–15.0) | -0.19 |
| Lipoproteins, apolipoproteins, and lipid ratios | | | |
| LDL size (nm) | 26.15 ± 0.25‡ | 26.85 ± 0.25 | |
| % HDL2 | 29.5 ± 10* | 38 ± 12 | 0.45‡ |
| apo B (mg/dl) | 129 ± 34‡ | 100 ± 21 | -0.52‡ |
| apo A1 (mg/dl) | 139 ± 20 | 136 ± 17 | 0.15 |
| apo E genotype 23/33/43 (%) | 7/70/23 | 7/68/25 | |
| Lipoprotein(a) >300 mg/l (%) | 40 | 37 | -0.08 |
| Cholesterol/HDL cholesterol | 5.40 ± 1.05‡ | 4.14 ± 1.06 | -0.52‡ |
| TG/HDL cholesterol (mmol) | 2.06 ± 1.02‡ | 0.96 ± 0.41 | -0.70‡ |
| apo B/HDL2 cholesterol (mg) | 8.68 ± 4.11‡ | 5.58 ± 3.54 | -0.46‡ |
| Risk factors and lifestyle (%) | | | |
| Hypertension | 73 | 77 | |
| Smoker >15 years | 43 | 30 | |
| Never-smoker | 47 | 53 | |
| Monounsaturated fatty acid consumption | 70 | 67 | |

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level or a TG level <2.8 mmol/l does not necessarily predict a normal LDL size (5,6). Thus, CAD risk may be underestimated in some patients without typical diabetic dyslipidemia. Because the methods used to characterize LDL are cumbersome and not standardized, they are unlikely to be used in clinical practice. Therefore, a prediction of LDL size based on the information readily available in a standard lipid profile may be more useful for a proper assessment of CAD risk in patients with type 2 diabetes and normal HDL cholesterol levels. The present preliminary data show that the TG-to-HDL cholesterol ratio predicts LDL particle size in patients with type 2 diabetes. The following discussion supports the notion that this ratio is relevant in considering the estimation of CAD risk and the processes involved in LDL size pathophysiology.

RESEARCH DESIGN AND METHODS

Patients

We recruited 64 consecutive patients with type 2 diabetes and HDL cholesterol levels ≥1 mmol/l from the outpatient clinics after obtaining informed consent, as approved by the institutional ethics committee. Four subjects were subsequently excluded from the study because of low HDL cholesterol levels detected after discontinuing lipid-lowering drugs. Type 2 diabetes was defined as diagnosis after the age of 40 years and the absence of ketosis and insulin treatment during the 2 years after the diagnosis. Lipid-lowering drugs were discontinued at least 4 weeks before the beginning of the study. The main exclusion criteria were as follows: any recent illness, change in treatment of diabetes or hypertension during the preceding 3 months, alcohol abuse, hepatic disease, treatment with estrogen or glucocorticoids, impaired thyroid or renal function (creatinine clearance <0.8 ml/s), and HbA_{1c} >10%. The patients' characteristics are shown in Table 1 (vascular disease is defined in the footnote).

Methods

All venous blood samples were obtained after an overnight fast unless otherwise stated. Samples for measuring plasma lipase activities were obtained 10 min after the intravenous administration of 100 U heparin per kg body mass. Insulin sensitivity was assessed by the decrement in plasma glucose 15 min after the intravenous injection of 0.05 U insulin per kg body mass

(11). Pancreatic β -cells were evaluated by measuring plasma C-peptide 10 min after injecting 1 mg glucagon intravenously. A urine sample was collected for a 2-h period to quantify albuminuria (albumin-to-creatinine ratio).

Cholesterol, TGs, and phospholipids were measured using enzymatic methods. Unesterified cholesterol was measured before hydrolysis by cholesterol esterase. HDL cholesterol was measured in the supernatant obtained after precipitation of apoprotein B-containing lipoproteins with Na-phosphotungstate plus $MgCl_2$. Apoprotein A-I and B (Orion Diagnostica, Espoo, Finland) and lipoprotein(a) (Dako, Copenhagen, Denmark) were measured by immunoturbidimetric assay. LDL cholesterol levels were estimated by the equation of Friedewald if TG levels were <4.5 mmol/l. The contents of VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL were measured after ultracentrifugation in a KBr-NaCl density gradient. The plasma concentration of free fatty acids (FFAs) was determined by an enzymatic method (Wako, Richmond, VA) immediately after obtaining the sample. DNA was amplified by the polymerase chain reaction technique and then clived by restriction enzyme *HhaI*, and DNA fragments were separated using migration on polyacrylamide gel to determine apolipoprotein E alleles. HbA_{1c} was measured by high-performance liquid chromatography (normal value $<6\%$). Urinary albumin was determined by immunoturbidimetry (Behring, Marburg, Germany).

The size and distribution of LDL and HDL particles were determined by 2–20% polyacrylamide linear gradient gel electrophoresis of Sudan Black prestained plasma, followed by densitometric scanning at 590 nm. The gels were calibrated with high molecular weight markers of known diameter. The interassay coefficient of variation was 1.8%. LDL was classified into three groups based on the major LDL peak.

Lipase activity in post-heparin plasma was determined by using an emulsion of triolein as the substrate after adding apoprotein CII to the medium. To measure hepatic lipase (HL), incubation was carried out without apoprotein CII in high-salt buffer (NaCl 0.9 mol/l), which inactivates lipoprotein-lipase (LPL). LPL activity was calculated from total lipase and HL activities.

Statistical analysis

Group differences for normally distributed data were analyzed by a Student's *t* test.

Table 1—Continued

| | Small LDL | Intermediate + large LDL | <i>r</i> |
|---------------------------|-----------|--------------------------|----------|
| Lifestyle (%) | | | |
| ≤ 1 drink/week | 47 | 50 | |
| > 2 drinks/day | 7 | 10 | |
| Inactivity | 30 | 30 | |
| Exercise ≥ 10 h/week | 23 | 23 | |

r = linear coefficient of correlation between LDL size and continuous variables. [1] log urinary albumin excretion, *r* = 0.08. **P* < 0.03; †*P* < 0.01; ‡*P* < 0.001. Patients having small LDL particles (≤ 26.4 nm) are compared with those having intermediate and large LDL particles (> 26.4 nm). Normally distributed data are means \pm SD. Other data are medians (95% CI). Clinical characteristics and lifestyle of the patients, prevalence of diabetes-related complications, and treatments were not different between the two groups. Vascular disease included history of myocardial infarction, angina pectoris, stroke, coronary or peripheral revascularizations, and femoral or carotid stenosis $>60\%$. LPL/HL, lipoprotein lipase/hepatic lipase activity.

Nonnormally distributed parameters are shown as the median. Categorical data were compared using the χ^2 test or Fisher's exact test. Continuous variables were fitted to linear, polynomial, or exponential equations by the least-squares method. A *P* value ≤ 0.05 was chosen for statistical significance.

RESULTS

LDL particle size distribution

In a control group of men (*n* = 78; age 30–60 years), the median LDL size was 26.7 nm (range 25.3–28.4) with values of 25.6, 26.2, 27.1, and 27.5 nm for the 10th, 25th, 75th, and 90th percentiles, respectively. For a control group of women (*n* = 109; age 30–60 years), the median was 27.2 nm (range 25.7–28.4), and the corresponding percentile values were 26.3, 26.7, 27.5, and 27.7 nm. LDL subclasses were defined based on the size distribution in control subjects. Values ≤ 26.4 nm were observed in 28% of men and 12% of women (mainly in older women) and defined small LDL particles; values ≥ 27.0 nm were observed in 37% of men and 75% of women and defined large LDL particles; values in the intermediate range (26.5–26.9 nm) were observed in 35% of men and 23% of women and defined intermediate LDL particles.

The mean LDL size was 26.5 ± 0.45 nm in patients (25.4–27.6), with similar values in men (26.5 ± 0.46) and women (26.5 ± 0.41). The prevalence of small, intermediate, and large LDL particles was 50% (30 of 60), 37% (22 of 60), and 13% (8 of 60), respectively. Anthropometric and biochemical characteristics of the 30 patients with small LDL were similar to those of the 30 patients with intermediate or large LDL particles.

LDL subclasses and clinical characteristics

There were no significant differences between patients with type 2 diabetes having small LDL particles and those having larger LDL particles (Table 1). It is noteworthy that age, sex ratio, other anthropometric data, duration of diabetes, lifestyle, and pharmacological therapies were similar in both groups and that the prevalence of diabetes-related complications was high, whereas the glycemic control was fair to good. The average blood pressure was $141 \pm 11/84 \pm 7$ mmHg. Tests requiring intravenous injections were available in 58 of 60 patients. As expected for insulin-resistant patients, the decrement observed in the insulin tolerance test was small but correlated positively with LDL size (*P* < 0.03). Yet, the difference observed when patients with small LDL particles were compared with those with larger LDL particles was insignificant (glucose decrement > 2 mmol/l in 33 vs. 50% and > 2.5 mmol/l in 20 vs. 32%, respectively). An increase in plasma C-peptide > 3 μ g/l after intravenous administration of glucagon was observed in 37 and 25% of the patients in each group, respectively.

Plasma lipids, lipoproteins, and LDL subclasses

The two patient groups differed significantly in regard to the plasma levels of total cholesterol, LDL cholesterol, and apolipoprotein (apo)B, as well as the percentage of HDL₂ of total HDL. However, the overlap of these measurements between the groups was large enough to preclude their usefulness as a biologic surrogate for assessing LDL size in individual patients (Table 1). Figure 1 shows a weak correla-

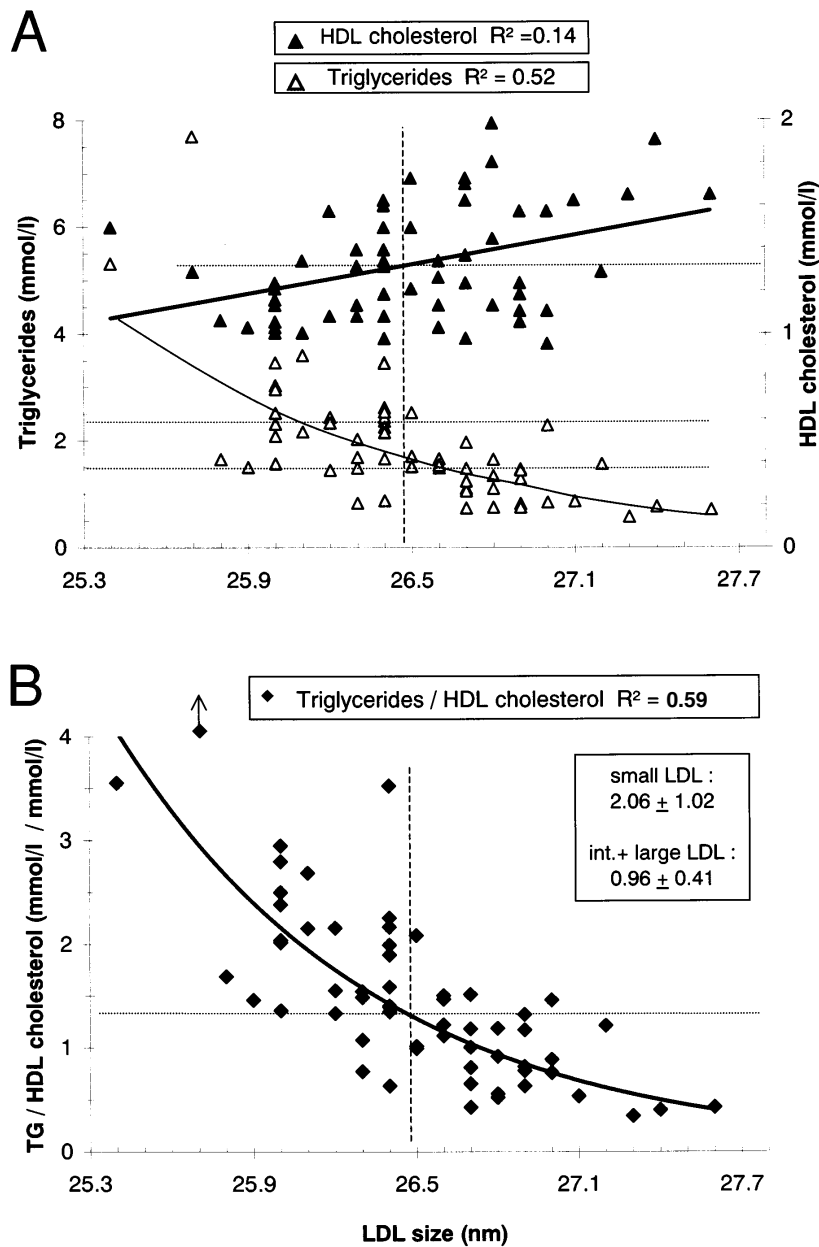


Figure 1—A: Inverse correlations between LDL peak particle diameter and HDL cholesterol (▲, $y = 0.23 \times -4.7$) and between LDL peak particle diameter and fasting TG levels (△, $y = 2E + 10 e^{-0.88x}$). B: Correlation between LDL peak particle diameter and TG-to-HDL cholesterol ratio (lipid values in mmol/l; ◆, $y = 1E + 12 e^{-1.05x}$).

tion between LDL size and HDL cholesterol ($R^2 = 0.145$) and a stronger correlation with fasting TG levels ($R^2 = 0.52$). The chemical composition of each lipoprotein class was consistent with published data. The patient group with small LDL particles had significantly higher IDL- ($P < 0.001$), LDL-, and HDL-TGs, as well as IDL ($P = 0.03$) and IDL + VLDL cholesterol (Table 1). The ratio of TG-LDL to apoB-LDL was significantly higher in the small LDL group

($P = 0.001$) but did not correlate better with LDL size ($r = 0.40$) than LDL-TGs.

Fasting concentrations of FFAs (Table 1) and post-heparin plasma lipase activities (LPL 12 ± 5 and $12 \pm 6 \mu\text{mol} \cdot \text{ml}^{-1} \cdot \text{h}^{-1}$; HL 25 ± 8 and 28 ± 9) were similar in both patient groups. A high prevalence of a lipoprotein(a) concentrations $>300 \text{ mg/dl}$ (12 of 30 and 11 of 30 subjects) and the E4 allele (7 of 30 and 7 of 28 subjects) in both groups should be noted.

TG-to-HDL cholesterol ratio and LDL subclasses

Large or intermediate LDL were not observed when the TG concentration was $>2.6 \text{ mmol/l}$. The TGs, which were significantly higher in the group with small LDL particles, showed a positive correlation with LDL size (Fig. 1). Nevertheless, small LDL particles were observed in many patients ($n = 15$) with TGs $<2.3 \text{ mmol/l}$ —a range common in type 2 diabetic patients. Figure 1 shows that the TG-to-HDL cholesterol ratio correlated more strongly with LDL size ($R^2 = 0.59$) than either triglycerides or HDL cholesterol alone, even in the TG range from 1.5 to 2.3 mmol/l. In this subgroup, LDL size was within 25.8 and 27.2 nm, and the TG levels were not different ($P = 0.27$) between patients having small LDL ($1.81 \pm 0.30 \text{ mmol/l}$; $n = 12$) and large LDL ($1.68 \pm 0.25 \text{ mmol/l}$; $n = 11$). By contrast, the TG-to-HDL cholesterol ratio was significantly higher in patients with small LDL (1.58 ± 0.33 vs. 1.23 ± 0.22 ; $P = 0.007$). To determine the TG-to-HDL cholesterol molar ratio that best distinguishes patients with small LDL from those with intermediate and large LDL, cumulative frequency distributions were plotted as a function of the ratio (Fig. 2). By using the inverse distribution for one of the plots (intermediate and large LDL) and calculating its intersection with the other plot, the resulting TG-to-HDL cholesterol molar ratio (1.33) defines a point separating the two distributions. When this ratio was used, 90% of the patients with small LDL (95% CI 79.3–100) fell above 1.33, and 83.5% of those with intermediate or large LDL fell below. All patients with small LDL and a ratio <1.33 ($n = 3$) as well as those with intermediate or large LDL and a ratio >1.33 ($n = 4$) had LDL sizes within 0.2 nm from the cutoff point of 26.5 nm originally used to define the two patient groups. On the other hand, TG distributions cross at 1.7 mmol/l (data not shown): a TG level $>1.7 \text{ mmol/l}$ is 70% sensitive (95% CI 53.6–86.4) and 84% specific for the detection of small LDL. These data indicate that a TG/HDL cholesterol cutoff point of 1.33 (3 when lipid values are expressed in mg/dl) best distinguishes patients having small LDL than a TG cutoff point of 1.7 mmol/l ($P = 0.02$).

The cholesterol-to-HDL cholesterol ratio, which has been found to be the best simple lipid index to predict CHD risk, and the apo-B-to-HDL2 cholesterol ratio were less well correlated to LDL size than the TG-to-HDL cholesterol ratio (Table 1).

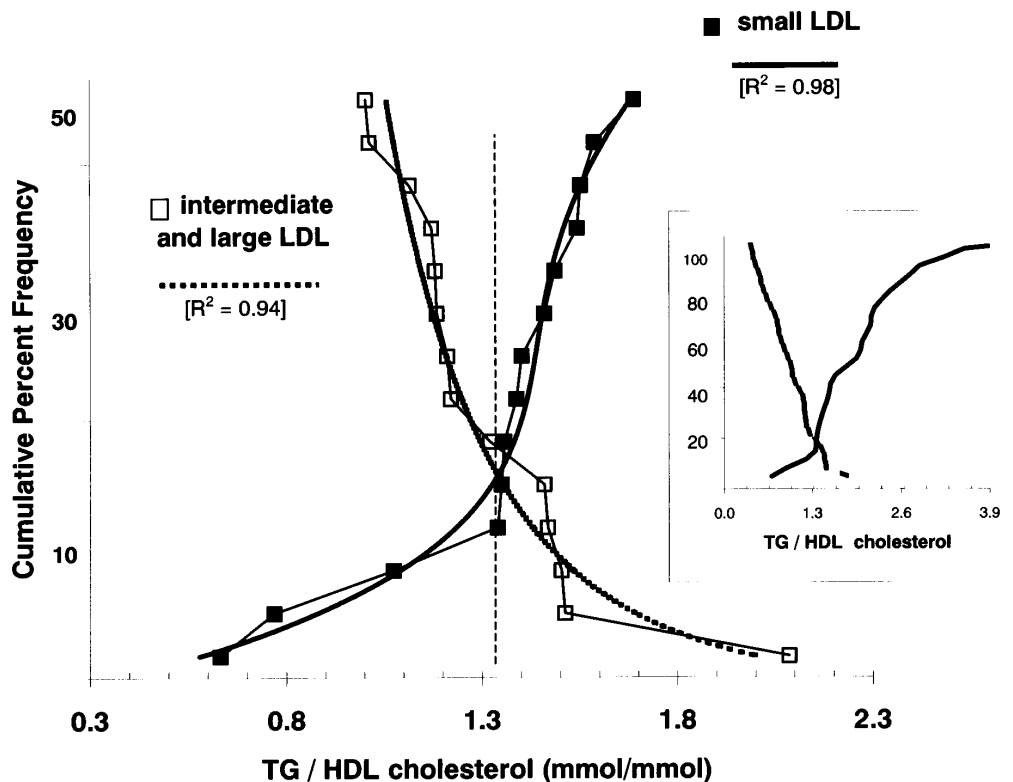


Figure 2—Cumulative distributions of TG-to-HDL cholesterol ratio for patients having large or intermediate (□) and small (■) LDL particles (□ is reversed to indicate the degree of overlap of TG/HDL cholesterol distribution in both LDL size subgroups); the TG/HDL cholesterol distributions cross at 1.33 (lipid values in millimoles per liter). The insert shows cumulative distributions up to 100%.

Nevertheless, in the subgroup of patients with TG levels from 1.5 to 2.3 mmol/l and with LDL size from 25.8 to 27.2 nm, the cholesterol-to-HDL cholesterol ratio was significantly higher in the patients having small ($n = 12$) than in those with larger ($n = 11$) LDL (5.28 ± 0.78 and 4.44 ± 1.21 , respectively, $P = 0.002$). The power of three different parameters—the TG-to-HDL cholesterol ratio, TGs, and the cholesterol-to-HDL cholesterol ratio—for detection of small LDL is shown in Table 2. With increasing sensitivity, the TG-to-HDL cholesterol ratio loses less specificity than the TGs and the cholesterol-to-HDL cholesterol ratio ($P < 0.05$).

CONCLUSIONS— Previous studies have established that LDL particles are small in nearly all subjects with low HDL cholesterol, whereas a normal HDL cholesterol level does not rule out the presence of small LDL particles (4–7). This study is focused on patients with type 2 diabetes having normal HDL cholesterol levels (i.e., ≥ 1 mmol/l), and it shows a wide range of LDL particle size in this patient sample. Because small LDL

particles are observed in 50% of the patients included in this study, our data confirm that LDL particle size is abnormal in a number of diabetic patients with normal HDL cholesterol levels. Because of the sample size and the fact that a selection bias cannot be excluded, these results do not necessarily apply to any population of patients with type 2 diabetes and normal HDL cholesterol levels. One could object that the upper size limit used to define small LDL size in this study is high. Apparent LDL size is clearly method dependent and may be augmented by prestaining plasma lipoproteins with Sudan back and/or the calibration standards chosen. Compared with post-staining with Coomassie blue or calibration using reference LDL preparations of known size, our method results in a shift toward higher values, which is consistent with the mean values and size distribution reported in male and female control subjects (8,12).

BMI, waist-to-hip ratio, and waist circumference were of the magnitude usually observed in patients with type 2 diabetes and did not differ with regard to LDL size group (13,14). Prevalence of high blood

pressure and complications related to diabetes were not different, and any effect of age and sex is excluded because age and sex were also similar in the two groups. The prevalence of vascular disease was high in both groups, but this prevalence could be due to selection bias, because our study population was elderly with a high prevalence of hypertension and nephropathy (75 vs. 50 and 51 vs. 35%, respectively, in the CODIAB study assessing the prevalence rates of complications in France, which included a representative percentage of patients with type 2 diabetes not managed in specialized university centers) (15). Moreover, there was a trend toward an overrepresentation of apo E4 carriers (25 vs. 15% in a non-Scandinavian Caucasian population) and high lipoprotein(a) concentrations in both groups. It is possible that these characteristics have augmented the vascular risk to the extent that the effect of LDL size may have been obscured.

Contrary to previous reports (14, 16–18), the present results do not show that the patients with small LDL were

Table 2—Sensitivity and specificity for the detection of patients having small LDL particles

| Plasma lipids | Cut point | All patients | | Subgroup 1.5 < TG < 2.3 | |
|-----------------------------|-----------|--------------|-------------|-------------------------|-------------|
| | | Sensitivity | Specificity | Sensitivity | Specificity |
| TGs | 1.45 | 90 | 63* | 100 | 0* |
| | 1.70 | 70 | 87 | 55 | 73 |
| | 2.30 | 50 | 93 | 0 | 100 |
| TGs/HDL cholesterol | 1.33 | 90 | 83 | 100 | 64 |
| | 1.48 | 70 | 90 | 55 | 88 |
| | 1.90 | 50 | 97 | 27 | 100 |
| Cholesterol/HDL cholesterol | 4.3 | 90 | 60* | 100 | 55 |
| | 4.7 | 70 | 63* | 64 | 55 |
| | 5.3 | 50 | 83 | 45 | 82 |

*P < 0.05 compared with TG/HDL cholesterol. Power of TGs, TGs/HDL cholesterol, and cholesterol/HDL cholesterol ratios in predicting small LDL particles, for all patients and the patient subgroup having plasma TGs in the critical range (1.5–2.3 mmol/l) is shown.

significantly more insulin resistant. However, both study groups were markedly insulin resistant and the method used to assess insulin sensitivity may be lacking the precision to detect a difference (11). It is unlikely that the results were influenced by environmental factors because the patients were taken off lipid-lowering agents for 4–6 weeks before the beginning of the study, and the percentage of patients treated with metformin, sulfonylurea, insulin, or diet alone was the same within the two groups (19,20). HbA_{1c} levels were not different and were of the magnitude reported in the U.K. Prospective Diabetes Study for intensively treated patients with similar diabetes duration. Moreover, alcohol consumption, dietary monounsaturated fatty acids, and physical activity, which can all modulate LDL size (21,22), were similar in the two groups.

The weak relationship between LDL size and HDL cholesterol, a stronger relationship between LDL size and fasting TG levels, and the presence of small LDL in patients with TG levels >1.65 mmol/l have also been reported in other studies (23,24). However, as usually observed in type 2 diabetes under acceptable glycemic and weight control, the TG levels in ~40% of the patients included in this study were in the range of 1.5–2.3 mmol/l (5,18,20). The LDL particles were small in 12 of these patients and intermediate or large in 11 patients. These data confirm that the prediction of LDL size by the TG level only is not accurate when the TG concentration is moderately increased and the HDL cholesterol level is normal (6,7). By contrast, the present study has shown that LDL size is strongly associated with the TG-to-HDL

cholesterol ratio; the present study has also established a cutoff point (TG-to-HDL cholesterol molar ratio of 1.33), allowing for a minimal degree of overlap between the two LDL size groups.

These results raise two questions. First, why is the ratio of TG to HDL cholesterol a better predictor of LDL size than either parameter alone? It has been firmly established that VLDL concentration assessed by fasting TG levels is a major determinant of LDL size. However, three other mechanisms contribute to transformation of LDL and HDL particles—namely postprandial hypertriglyceridemia, cholesteryl ester transfer protein activity, and hepatic lipase activity. All induce a decrease in HDL and are abnormal in type 2 diabetes (17,25–28). Thus, for a given fasting TG level, a lower HDL cholesterol level suggests that any of these three mechanisms is disturbing lipoprotein metabolism more markedly. Therefore, any given fasting TG level can be associated with a lower HDL cholesterol level and small LDL particles.

The second question relates to the relevance of the TG-to-HDL cholesterol ratio with regard to coronary risk. Three lines of evidence reported in nondiabetic subjects support its use. A case-control study has recently concluded that the ratio of TG to HDL is a strong predictor of myocardial infarction with a risk factor-adjusted relative risk of 16 in the highest versus lowest quartile (unfortunately, the quartile ranges are not indicated) (29). The Copenhagen Prospective Study concluded that there was a clear risk gradient for CAD with increasing TG levels and within each level of HDL cholesterol, including high HDL cholesterol level and TG levels <1.6 mmol/l (30). These

recent data are consistent with those of the Helsinki Heart Study, which previously emphasized the combined effects of HDL cholesterol and TG on CAD incidence (31).

In conclusion, the LDL particles may be small and the risk of CAD increased in patients with type 2 diabetes, even when the HDL cholesterol level is normal and TG level is <2.3 mmol/l. A TG-to-HDL cholesterol molar ratio >1.33 distinguishes the small and large LDL size pattern. This ratio may be used to identify diabetic patients with an atherogenic lipid profile and may be relevant for assessing CAD risk. Especially in newly diagnosed patients, it may be useful for the selection of patients who need aggressive treatment of lipid abnormalities early in the course of diabetes or before the onset of clinical cardiovascular disease.

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