Impact of Postprandial Variation in Triglyceridemia on Low-Density Lipoprotein Particle Size

Patricia Blackburn, Mélanie Côté, Benoît Lamarche, Charles Couillard, Agnès Pascot, Angelo Tremblay, Jean Bergeron, Isabelle Lemieux, and Jean-Pierre Després

The fasting atherogenic dyslipidemia of visceral obesity, which includes the presence of small, dense low-density lipoprotein (LDL) particles, is predictive of an increased risk of coronary heart disease (CHD). It has also been suggested that progression of atherosclerosis may be accelerated in the presence of postprandial hyperlipidemia independently from the fasting dyslipidemic state. Studies have shown that the best predictor of postprandial hyperlipidemia and of the small, dense LDL phenotype is fasting triglyceride (TG) concentration. In the present study, we evaluated the impact of postprandial hypertriglyceridemia on the variation in LDL particle size. Fasting (0 hour) and postprandial changes (2, 4, 6, and 8 hours) in LDL particle size were measured by nondenaturing 2% to 16% polyacrylamide gel electrophoresis in a sample of 49 men (mean age ± SD: 46.6 ± 9.2 years) who underwent a standardized breakfast with a high-fat (64% calories as fat) content. The postprandial increase in TG levels was associated with a transient reduction in LDL particle size, the most substantial reduction being observed 4 hours (−1.0 ± 2.4 Å) after the oral fat load. Although there were strong correlations between TG-rich lipoprotein (TRL)-TG levels and LDL particle size in the fasting state ($r = -0.71$, $P < .0001$) as well as 4 hours after the oral fat load ($r = -0.70$, $P < .0001$), changes in TRL-TG concentrations during the postprandial state (from time 0 to 4 hours) were not associated with changes in LDL particle size during this period ($r = -0.04$, not significant [NS]). However, among subgroups of men matched for similar fasting TRL-TG levels (n = 12), subjects with the highest total area under the curve (AUC) of TRL-TG after the fat load were characterized by smaller LDL particle size at 6 and 8 hours compared with men with the lowest AUC TRL-TG ($P < .02$). Men displaying the highest postprandial AUC TRL-TG were also characterized by the greatest accumulation of visceral adipose tissue (AT) ($P < .05$). These results indicate that the hypertriglyceridemic (hyperTG) state induced by a high-fat meal is associated with a transient reduction in LDL peak particle diameter, which is not proportionate, however, to the level of TG achieved in the postprandial state. Furthermore, despite similar TG levels at baseline, viscerally obese men with an impaired postprandial lipemia had smaller LDL particles at the end of the oral fat load than obese men with a lower accumulation of visceral AT.

THE MEASUREMENT of plasma lipoprotein-lipid levels is common practice to predict coronary heart disease (CHD) risk. For instance, fasting hypertriglyceridemia, the presence of small, dense low-density lipoprotein (LDL) particles, reduced high-density lipoprotein (HDL) cholesterol levels leading to a markedly increased cholesterol/HDL cholesterol ratio, and elevated apolipoprotein (apo) B concentrations are features of an atherogenic dyslipidemic state, which has been found to be associated with a disturbed plasma glucose-insulin homeostasis.[1] In this regard, it has been shown that obesity, especially visceral obesity, was the most prevalent correlate of the atherogenic dyslipidemia, which is a key feature of the insulin resistance syndrome. Thus, this atherogenic dyslipidemia found in viscerally obese individuals contributes to increase CHD risk.[1]

On the other hand, an exaggerated postprandial lipemia has been suggested to be implicated in the development of atherosclerosis.[2] Studies that have examined correlates of an exaggerated postprandial triglyceride (TG) response and of an impaired clearance of TG-rich lipoproteins (TRL), have found that fasting small LDL size, elevated TG levels, as well as a high accumulation of visceral adipose tissue (AT) are all associated with a deteriorated postprandial metabolism.[3,4] A few studies have reported a transient reduction in LDL particle size or changes in LDL composition during an oral fat load.[5-9] For instance, Lupattelli et al[6] have found a significant decrease in LDL particle size occurring 6 hours after an oral fat load in normolipidemic patients with peripheral arterial disease. Similar findings were reported in women with mixed hyperlipidemia.[5] Karpe et al[7] have also underlined the importance of postprandial lipemia in the regulation of LDL particle composition. These results suggested that a postprandial hyperlipidemic state may contribute to the formation of small, dense LDL particles.

Because postprandial lipemia is characterized by a transient hypertriglyceridemic (hyperTG) state and because fasting TG concentration is the best correlate of LDL particle size and of

From the Québec Heart Institute, Laval Hospital Research Center, Ste-Foy, Québec; Lipid Research Center, CHUQ Research Center, CHUL Pavilion, Ste-Foy, Québec; Institute on Nutraceuticals and Functional Foods, Department of Food Sciences and Nutrition and the Division of Kinesiology, Laval University, Ste-Foy, Québec, Canada.

Submitted November 5, 2002; accepted June 5, 2003.

Supported by the Canadian Institutes of Health Research (MOP-14014) and by the Québec Heart and Stroke Foundation. P.B. is a recipient of a studentship from the Fonds de la Recherche en Santé du Québec-Fonds pour la formation de Chercheurs et l'Aide à la Recherche (FRSQ-FCAR Santé); B.L. is chair professor of Nutrition, Functional Foods and Cardiovascular Health from the Canada Research Program at Laval University; C.C. is a research scholar from the FRSQ-CHUQ/CHUL; A.T. holds the Canada Research Chair on Physical Activity, Nutrition and Energy Metabolism; and J.B. is a clinical research scholar from the FRSQ. J-P.D. is chair professor of human nutrition and lipidology, which is supported by Pfizer, Provigo, and the Foundation of the Québec Heart Institute.

Address reprint requests to Jean-Pierre Després, PhD, Director of Research, Québec Heart Institute, Laval Hospital Research Center, 2725, chemin Ste-Foy Pavilion Marguerite-D'Youville, 4th Fl, Ste-Foy, Québec, Canada G1V 4G5.

0026-0495/03/5211-0006$30.00/0

doi:10.1016/S0026-0495(03)00315-9

postprandial lipemia, we investigated whether the presumed reduction in LDL size produced by the induction of a postprandial hyperTG state would lead to a reduction in LDL size that could be comparable to what is observed in a similar hyperTG condition under fasting state.

SUBJECTS AND METHODS

Subjects

Forty-nine men, aged 27 to 63 years (mean age ± SD: 46.6 ± 9.2 years) were recruited from the Québec City metropolitan area by solicitation through the media. Participants were selected on purpose to cover a wide range of body mass index (BMI) values (20.2 to 41.0 kg/m^2). Subjects gave their written consent to participate in the study, which was approved by the Medical Ethics Committee of Laval University. All subjects were healthy, nonsmoking volunteers and were not under treatment for CHD, diabetes, dyslipidemias, or endocrine disorders.

Anthropometric and Body Composition Measurements

Body weight, height,[10] and waist circumference[11] were measured following standardized procedures. Body density was measured by the hydrostatic weighing technique.[12] The mean of 6 measurements was used in calculating percent body fat from body density using the equation of Siri.[13] Fat mass was obtained by multiplying body weight by percent body fat. Abdominal AT accumulation was assessed by computed tomography, which was performed on a Siemens Somatom DRH scanner (Erlangen, Germany) using previously described procedures.[14]

Oral Lipid Tolerance Test

After a 12-hour overnight fast, an intravenous catheter was inserted into a forearm vein for blood sampling. Each participant was given a test meal containing 60 g fat/m^2 body surface area as previously described.[3] The meal consisted of eggs, cheese, toasts, peanut butter, peaches, whipped cream, and milk. Composition of the meal was 64% fat, 18% carbohydrate, and 18% protein. The fatty acid composition of the fat consumed was 39.6% saturated fat, 21.2% monounsaturated fat, and 4.2% polyunsaturated fat leading to a ratio of polyunsaturated fat to saturated fat of 0.11. The test meal was well tolerated by all subjects. After the meal, subjects were not allowed to eat for the next 8 hours, but were given free access to water. Blood samples were drawn before the meal and every 2 hours after the meal over an 8-hour period.

Measurement of LDL Particle Size

LDL peak particle size and integrated LDL particle size were measured under fasting (0 hour) and postprandial conditions (2 hours, 4 hours, 6 hours, and 8 hours). Nondenaturing 2% to 16% polyacrylamide gradient gel electrophoresis was performed on whole plasma kept at −80°C before use by using a modification of procedures previously described.[15-17] All subject samples (0 hour, 2 hours, 4 hours, 6 hours, and 8 hours) were analyzed on the same polyacrylamide gradient gel. LDL particle size was determined on 8 × 8 cm polyacrylamide gradient gels prepared in batches in our laboratory. A volume of 3.5-μL whole plasma samples was applied on lanes in a final concentration of 20% sucrose and 0.25% bromophenol blue and loaded onto the gels. Electrophoresis was performed in a refrigerated cell (10°C to 15°C) for a prerun of 15 minutes at 125 V. This prerun preceded electrophoresis of the plasma samples at 70 V for 20 minutes and at 150 V for 4 hours. Gels were stained for lipids overnight with Sudan black (Lipostain; Paragon electrophoresis system, Beckman, Montréal, Canada) in 55% ethanol. Gels were destained in a 45% ethanol solution, and original gel size was restored in 9% acetic acid, 20% methanol solution. Gels were analyzed by the Imagemaster 1-D Prime computer software (Amersham Pharmacia Biotech, Newcastle, UK). LDL size was extrapolated from the relative migration of 4 plasma standards of known diameters.[16] The estimated diameter for the major peak in each scan was identified as the LDL peak particle size. An integrated (or mean) LDL diameter was also computed by using a modification of the approach described by Tchernof et al.[16] This integrated LDL particle size corresponds to the weighed mean size of all subclasses. It was computed as the sum of the diameter of each LDL subclass multiplied by their relative area. Analysis of pooled plasma standards revealed that measurement of LDL peak and mean particle size was highly reproducible, with an interassay coefficient of variation below 2%.

Fasting and Postprandial Plasma Lipoprotein Concentrations

Plasma was separated immediately after blood collection by centrifugation at 3,000 rpm for 10 minutes at 4°C. Plasma TG and cholesterol concentrations in total plasma were determined enzymatically on a Technicon RA-500 (Bayer, Tarrytown, NY) as previously described.[18] Each plasma sample (4 mL) was then subjected to a 12-hour ultracentrifugation (50,000 rpm) in a Beckman 50.3 Ti rotor (Beckman, Palo Alto, CA) at 4°C, in a 6-mL Beckman Quickseal tube, which yielded 2 fractions: the top fraction containing TRLs (total-TRLs; density (d) < 1.006 g/mL) and the bottom fraction (d > 1.006 g/mL) containing TG-poor lipoproteins. All lipoprotein isolation procedures were completed within 2 to 3 days of the fat load. Fasting total apo B concentration was measured in plasma by the rocket immunoelectrophoretic method of Laurell.[19] The lyophilized serum standard for apo B measurement was prepared in our laboratory and calibrated with reference standards obtained from the Centers for Disease Control (Atlanta, GA).

Postheparin Plasma TG Lipase Activities

Plasma lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) activities were measured on one occasion in subjects after a 12-hour overnight fast, 10 minutes after an intravenous injection of heparin (60 IU/kg body weight). The activity was measured using a modification of the method of Nilsson-Ehle and Ekman[20] as previously described.[21] Lipase activities were expressed as nanomoles of oleic acid released per millimeter of plasma per minute.

Statistical Analyses

Data are expressed as mean ± SD unless stated otherwise. A 1-way analysis of variance (ANOVA) design was used to compare groups with different total areas under the curve (AUCs) of TRL-TG. A posteriori comparisons were performed using the Tukey's technique. The AUC of TRL-TG concentrations were determined by the trapezoid method. Data matched for similar fasting TRL-TG levels with either low or high AUC TRL-TG were analysed with the Student's t test. To analyze TRL-TG, LDL peak particle size, LDL-TG, LDL-cholesterol, and LDL-TG/LDL cholesterol ratio, 2 experimental factors, 1 being subjects (random factor) and the other the serial measurements (0 hour, 2 hours, 4 hours, 6 hours, and 8 hours) (fixed factor) were defined. The latter was analyzed as a repeated-measure factor. Different statistical models were applied to obtain the best-fitted model and likelihood ratio tests were performed among models. Comparisons of Akaike's information criterion for the different models were also obtained.[22] The covariance structure used was an autoregressive one. The selection of the covariance structure was important to obtain valid inferences for fixed effects. The univariate normality assumptions were verified with the Shapiro-Wilk test, and multivariate normality was verified with Mardia tests.[23] Relationships between variables were evaluated using Pearson correlation coefficients. Results were considered significant for P values ≤ .05. Analyses were performed with the statistical package SAS (SAS, Cary, NC).

Table 1. Physical Characteristics and Fasting Metabolic Profile of the Sample of 49 Men

	Means ± SD	Range
Age (yr)	46.6 ± 9.2	27.0-63.0
Body mass index (kg/m^2)	28.3 ± 3.9	20.2-41.0
Fat mass (kg)	23.3 ± 8.3	6.7-44.9
Waist circumference (cm)	96.8 ± 9.3	78.7-116.4
Abdominal adipose tissue areas (cm^2)		
Total	416.6 ± 137.2	73.7-767.0
Visceral	143.1 ± 56.8	38.2-300.0
Subcutaneous	273.5 ± 105.1	35.4-469.8
LDL peak particle size (Å)	259.2 ± 4.2	250.1-270.7
Cholesterol (mmol/L)	5.24 ± 0.74	2.88-6.87
Triglycerides (mmol/L)	1.85 ± 0.83	0.47-3.84
LDL cholesterol (mmol/L)	3.57 ± 0.71	1.48-4.86
HDL cholesterol (mmol/L)	0.98 ± 0.19	0.66-1.43
Apolipoprotein B (g/L)	1.11 ± 0.18	0.70-1.41
Cholesterol/HDL cholesterol	5.55 ± 1.33	2.82-8.04
Postheparin plasma lipase activities		
LPL (nmol · min^{-1} · mL^{-1})	47.0 ± 25.8	10.2-100.6
HTGL (nmol · min^{-1} · mL^{-1})	191.1 ± 81.5	19.9-336.2
HTGL/LPL	6.49 ± 6.17	0.52-26.0
Fasting insulin (pmol/L)	74.4 ± 42.7	1.0-214.0
Fasting glucose (mmol/L)	5.41 ± 0.49	4.80-6.70

NOTE. Data are means ± SD.

Abbreviations: LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase.

RESULTS

Table 1 shows the characteristics of the sample of 49 men. Mean TG concentrations were in the upper normal range (1.85 ± 0.83 mmol/L) and varied between 0.47 to 3.84 mmol/L. Mean LDL peak particle size in the fasting state was 259.2 ± 4.2 Å and ranged from 250.1 to 270.7 Å. Overall, subjects were overweight (BMI >25 kg/m^2)[24] and were characterized by an increased visceral AT accumulation (>130 cm^2).[25] The mean apo B values (1.11 ± 0.18 g/L) were elevated[26] and suggested to be predictive of an overall increase in the risk of CHD.

Postprandial variations in TRL-TG levels and LDL peak particle size among 49 men are presented in Fig 1. The highest TRL-TG values were reached 4 and 6 hours after the high-fat meal (Fig 1A). Moreover TRL-TG concentrations remained elevated 8 hours after the oral fat load and were far from returning to fasting values ($P < .0001$). A concomitant significant decrease in LDL peak particle size was observed 4 hours after the oral fat load ($P < .005$) (Fig 1B). Similar results were found for the integrated LDL particle size (data not shown). Figure 2 shows postprandial variations in LDL-TG (Fig 2A), LDL cholesterol (Fig 2B), as well as LDL-TG/LDL cholesterol ratio (Fig 2C). During the postprandial state, the LDL-TG/LDL cholesterol ratio increased markedly due to an increase in LDL-TG levels accompanied by a concomitant decrease in LDL cholesterol concentrations ($P < .05$). Figure 3 shows that there were significant correlations between LDL peak particle size and TRL-TG levels in the fasting state ($P < .0001$), as well as 4 hours after the fat load ($P < .0001$). However, despite a substantial increase in TG levels 4 hours after the fat meal, the significant decrease in LDL particle size observed at this time point was of smaller magnitude than what would have been predicted on the basis of the TG levels achieved. To further explore this issue, we investigated the relationship between changes in LDL peak particle size and changes in TRL-TG concentrations between 0 and 4 hours, and we found no correlation between the postprandial changes of these 2 variables ($r = -.04$, not significant [NS]) (Fig 4A). Indeed, the mean reduction in LDL peak particle size was −1.0 ± 2.4 Å ($P < .005$) (Fig 4B) compared with an increase of +2.5 ± 1.4 mmol/L ($P < .0001$) for the TRL-TG concentrations between the fasting state and 4 hours after the fat load. Relationships between changes in LDL peak particle size from 0 to 4 hours

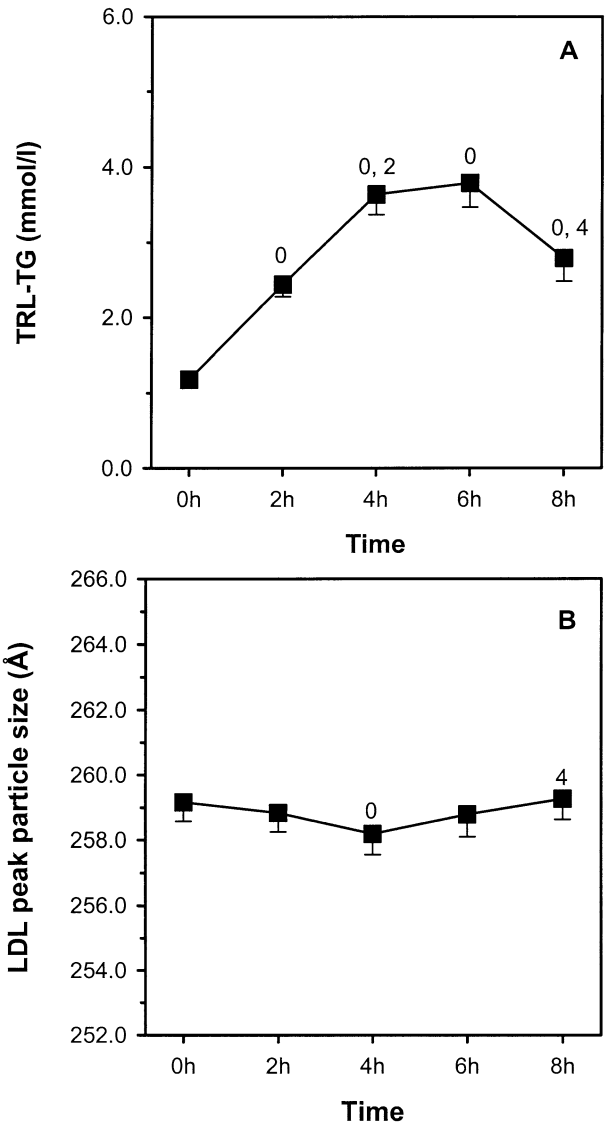

Fig 1. Postprandial variations in (A) TRL-TG and (B) LDL peak particle size in the sample of 49 men. Data are means ± SEM. The significant difference with the corresponding time point is indicated above the standard error ($P < .0001$).

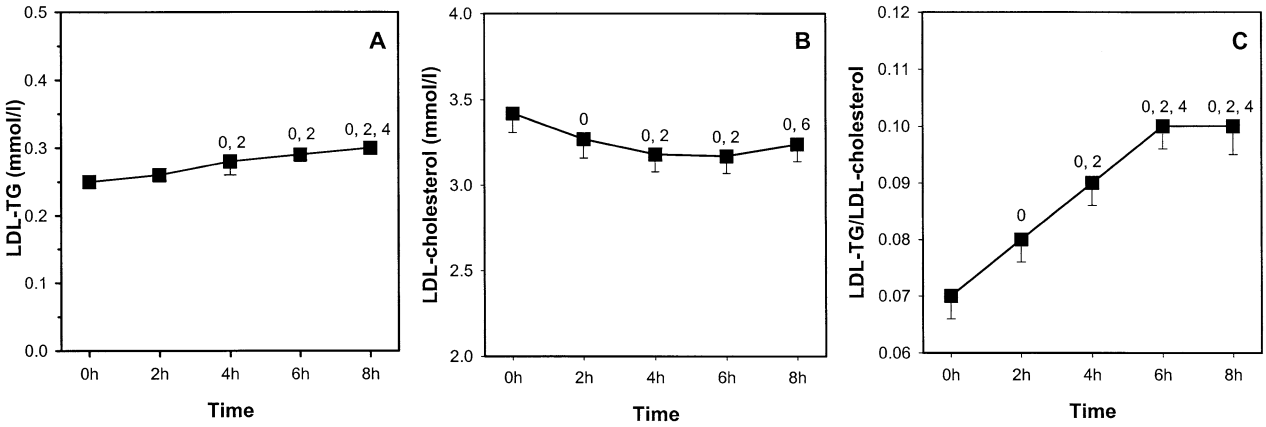

Fig 2. Postprandial variations in (A) LDL-TG levels, (B) LDL cholesterol concentrations, as well as (C) LDL-TG/LDL cholesterol ratio in the sample of 49 men. Data are means ± SEM. The significant difference with the corresponding time point is indicated above the standard error ($P < .03$).

and changes in TRL-TG concentrations from 0 to 2 hours ($r = -.03$, NS) or from 0 to 6 hours ($r = .02$, NS) were also investigated. Again, no correlation was found between the postprandial changes of these 2 variables. Although there was no significant relationship between AUC of TRL-TG and changes in LDL peak particle size from 0 to 4 hours ($r = -.03$, NS), a positive correlation was found between AUC of TRL-TG and AUC of LDL peak particle size ($r = -.76$, $P < .0001$).

To further explore the impact of postprandial TRL-TG concentrations on variations in LDL peak particle size, subjects were divided into 3 groups according to the AUC of TRL-TG. Figure 5 shows the postprandial variation in TRL-TG concentrations (Fig 5A), as well as in the LDL peak particle size (Fig 5B) among men characterized by low (tertile 1), intermediate (tertile 2) or high AUC TRL-TG (tertile 3). Overall, fasting and postprandial LDL peak particle sizes were lower as a function of increasing AUC TRL-TG ($P < .03$). Subjects characterized by the highest AUC TRL-TG also had the lowest LDL peak particle size ($P < .004$) at any time point.

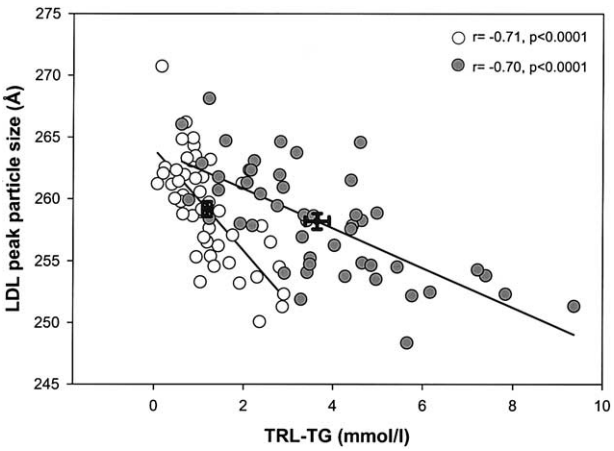

Fig 3. Correlation coefficients between TRL-TG and LDL peak particle size in the fasting state (○) and 4 hours after the fat load (◎) in 49 men. Mean values in LDL peak particle size and in TRL-TG in the fasting state and 4 hours after the fat load are indicated by circles.

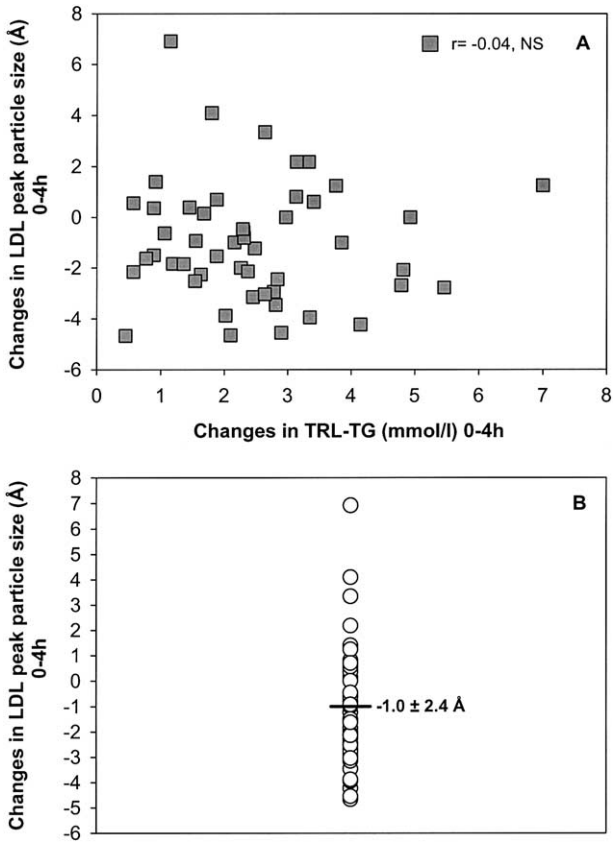

Fig 4. Correlation between changes in (A) LDL peak particle size and changes in TRL-TG between times 0 and 4 hours after the fat load and (B) changes between times 0 and 4 hours in the LDL peak particle size among 49 men (mean change ± SD of mean).

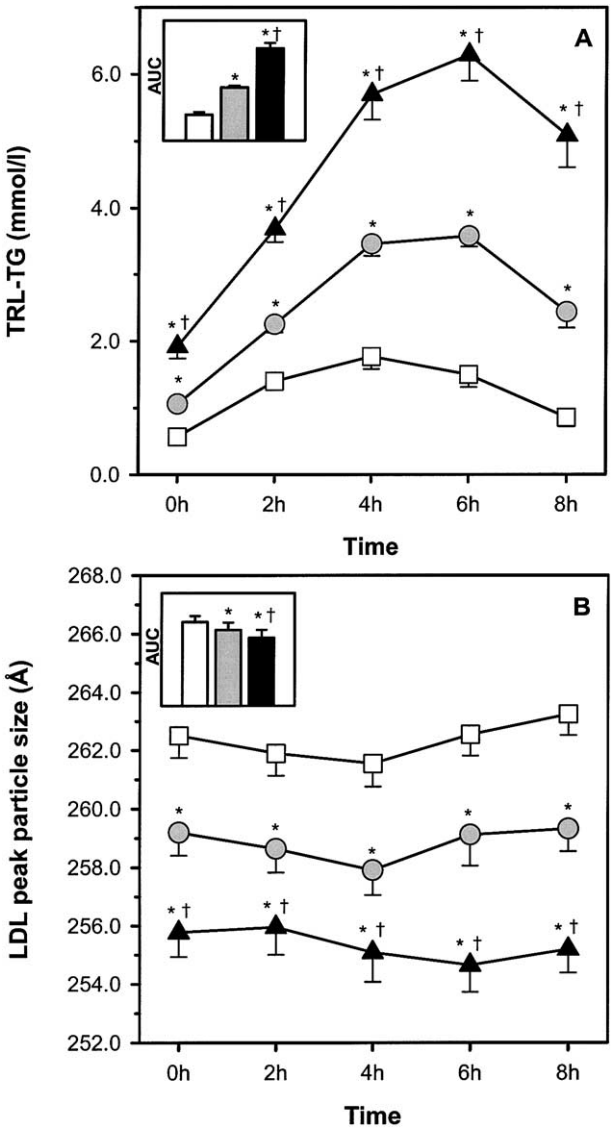

Fig 5. (A) Postprandial TRL-TG and (B) LDL peak particle size among subjects in tertile 1 (□), characterized by low AUC TRL-TG, in tertile 2 (○) characterized by intermediate AUC TRL-TG, and in tertile 3 (▲) characterized by high AUC TRL-TG. Bars represent AUC for each subgroup. Data are means ± SEM. *$P < .02$ different from men in tertile 1 and †$P < .03$ different from men in tertile 2.

To control for the well-known effect of TG on LDL size, 12 men were individually matched for similar fasting TRL-TG levels (within a variation of ± 0.1 mmol/L), but with different AUC TRL-TG (Table 2 and Fig 6). No difference was found in the fasting lipoprotein-lipid profile including, of course, fasting TG concentrations ($P = .12$, NS) (Table 2). However, subjects characterized by a high AUC TRL-TG showed greater fasting glucose concentrations ($P < .02$), as well as elevated visceral AT accumulation ($P < .05$) compared with fasting TRL-TG matched subjects with low AUC TRL-TG (Table 2). Finally, men with a high AUC TRL-TG were characterized by a lower LDL peak particle size, 6 ($P < .01$) and 8 ($P < .02$) hours after the fat load as opposed to men with a low AUC TRL-TG (Fig 6).

DISCUSSION

The increased CHD risk associated with the presence of small, dense LDL particles is more and more recognized.[15,27] For instance, although not a unanimous finding,[28] some studies have reported that the presence of the small, dense LDL phenotype increased by about 3-fold the risk of developing CHD when subjects with this phenotype were compared with individuals with large, buoyant LDL particles.[15,27] In this regard, it has been shown that the best predictor of LDL particle size was

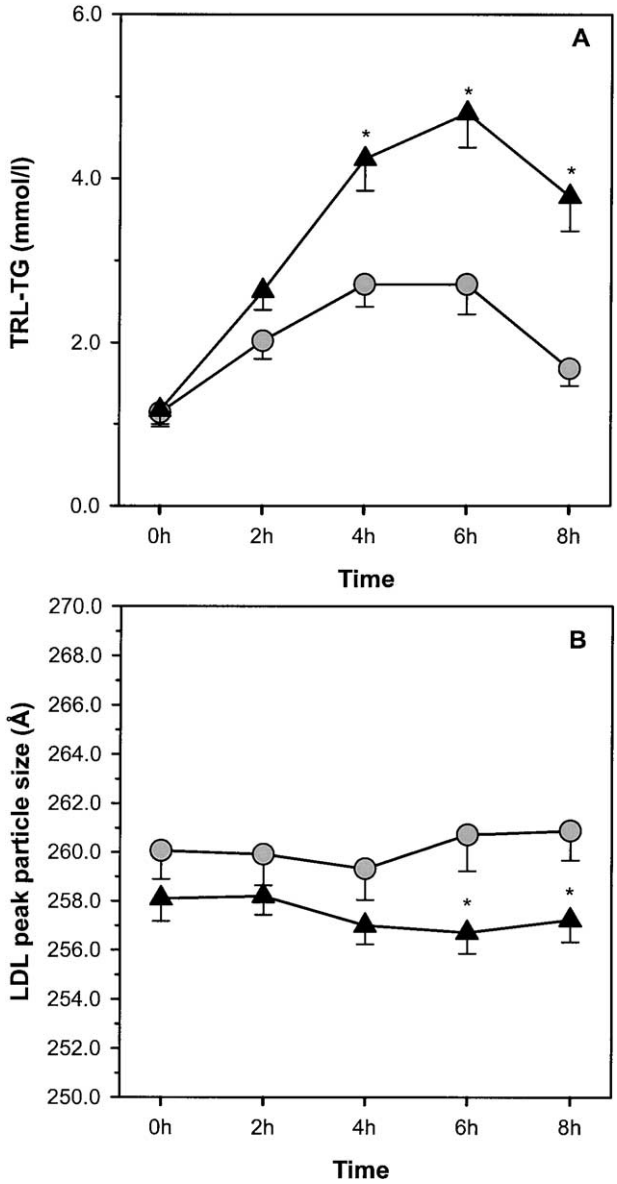

Fig 6. (A) Postprandial TRL-TG and (B) LDL peak particle size in the 2 groups of men (n = 12) matched for fasting TRL-TG, but with a low (○) or high (▲) AUC TRL-TG. Data are means ± SEM. *$P < .02$ different from men with low AUC TRL-TG.

Table 2. Physical Characteristics and Fasting Metabolic Profile of Men Matched for Similar Fasting TRL-TG Levels But With Either a Low or a High Total AUC TRL-TG

	Low AUC TRL-TG (n = 12)	High AUC TRL-TG (n = 12)
Age (yr)	49.1 ± 8.4	48.6 ± 9.0
Body mass index (kg/m^2)	27.7 ± 3.2	29.7 ± 4.9
Fat mass (kg)	24.3 ± 6.7	26.0 ± 10.8
Waist circumference (cm)	93.5 ± 6.7	101.8 ± 12.4
Abdominal adipose tissue areas (cm^2)		
Total	406.8 ± 114.9	465.7 ± 158.9
Visceral	129.1 ± 31.6	176.7 ± 66.0*
Subcutaneous	277.7 ± 109.4	289.0 ± 108.0
LDL peak particle size (Å)	260.1 ± 4.0	258.1 ± 3.2
Cholesterol (mmol/L)	5.27 ± 0.74	5.50 ± 0.72
Triglycerides (mmol/L)	1.62 ± 0.51	2.05 ± 0.77
LDL cholesterol (mmol/L)	3.74 ± 0.64	3.76 ± 0.74
HDL cholesterol (mmol/L)	0.94 ± 0.17	0.98 ± 0.12
Apolipoprotein B (g/L)	1.11 ± 0.16	1.14 ± 0.17
Cholesterol/HDL cholesterol	5.72 ± 1.10	5.73 ± 1.11
Postheparin plasma lipase activities		
LPL (nmol · min^{-1} · mL^{-1})	43.9 ± 20.4	48.7 ± 23.3
HTGL (nmol · min^{-1} · mL^{-1})	212.7 ± 79.8	181.7 ± 89.9
HTGL/LPL	6.74 ± 5.40	5.52 ± 5.55
Fasting insulin (pmol/L)	60.8 ± 22.7	97.5 ± 60.5
Fasting glucose (mmol/L)	5.23 ± 0.30	5.73 ± 0.61*

NOTE. Data are means ± SD.

Abbreviations: LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase.

*Different from men with low AUC TRL-TG ($P < .05$).

fasting TG concentration,[16] which emphasizes the importance for the clinician to pay attention to hypertriglyceridemia as a crude marker for the presence of small, dense LDL particles. In accordance with this notion, we found that fasting TG and TRL-TG levels were strongly correlated with fasting LDL particle size. A similar correlation was observed 4 hours after the ingestion of the high-fat meal, which induced a marked postprandial hyperTG state and a significant reduction in LDL particle size.

From a metabolic standpoint, postprandial lipemia can be considered as a transient or exacerbated hyperTG state. In this regard, Zilversmit[2] was the first to suggest that atherogenesis could be a postprandial phenomenon. Although it has been shown that the presence of small, dense LDL phenotype may be an additional fasting marker of postprandial hyperlipidemia,[4] postprandial changes in LDL particle size during a hyperTG state has not been investigated so far in asymptomatic healthy men. In the present study, the reduction in LDL particle size during the postprandial state was significant, but transient and of lower magnitude than what would have been expected from the postprandial TG levels achieved.

Only few studies have documented the transient reduction in LDL particle size or composition during an oral fat load.[5-9] Lupattelli et al[6] found a slight decrease 6 hours after the fat load in patients with peripheral arterial disease compared with control subjects. Another study reported a significant decrease in LDL particle size at the 4- and 6-hour time points in postmenopausal women with mixed hyperlipidemia compared with hypercholesterolemic and normolipemic women.[5] As previously reported in these studies, the magnitude of postprandial lipemia could affect LDL particle size. During the postprandial phase, lipid transfer proteins found in plasma allow the exchange of lipids between different lipoprotein fractions. One of these transfer proteins, cholesteryl ester transfer protein (CETP), favors the exchange of the TG found in TRL for esterified cholesterol.[7] Such reciprocal exchange leads to the formation of LDL particles enriched in TG. These TG-enriched particles are good substrates for HTGL, leading to a decrease in LDL particle size.[29] In the present study, there was a significant decrease in LDL particle size 4 hours after the oral fat load. However, changes in LDL particle size were not correlated with changes in TRL-TG concentrations. These results suggest that the duration of the hyperTG state was not sufficient to allow a substantial TG enrichment and lipolysis of LDL particles, which would have produced substantial changes in LDL size. Along these lines, there was a progressive enrichment of LDL with TG during the 8-hour postprandial period, suggesting that the TG-enriched LDL may become a good substrate for the enzyme HTGL had we monitored LDL size for a longer postprandial period. Further studies are required to validate this hypothesis.

We also examined the relationship between postprandial TRL-TG concentrations and variations in postprandial LDL peak particle size. For that purpose, we compared men divided according to tertiles of AUC TRL-TG. Comparison of postprandial AUC TRL-TG in these tertiles revealed that men characterized by the highest AUC TRL-TG had also the lowest AUC LDL peak particle size. However, areas under the response curve of LDL particle size (a cumulative index of postprandial change in LDL size) were similar among the 3 subgroups. These results suggest that LDL particle size was largely influenced by fasting TG levels. Indeed, it has been

shown that small, dense LDL phenotype may represent an additional fasting marker of an impaired clearance of TRL.[4]

To further examine the importance of fasting TRL-TG levels as a potential modulator of LDL particle size, we compared 2 subgroups of men matched for their fasting TRL-TG levels, but with either a low or a high AUC TRL-TG. Comparison of postprandial LDL peak particle size in these 2 groups revealed that men characterized by a high AUC TRL-TG presented a lower LDL peak particle size compared with those showing a low AUC TRL-TG. Moreover, these men with the higher AUC TRL-TG and with the lower fasting LDL peak particle size were also characterized by a higher accumulation of visceral AT. This observation is in accordance with previously published results that have underlined the importance of visceral AT accumulation in delayed postprandial TRL clearance and the presence of small, dense LDL phenotype.[3,16,30,31] It has been suggested that visceral AT accumulation is a major modulator of postprandial metabolic accumulation of TRL via the associated overproduction of very–low-density lipoproteins.[3] Competition for the catalytic action of LPL between TRL fractions during the postprandial period could be responsible, at least in part, for the delayed clearance of TRL due to the saturation of LPL.[32] Moreover, the reduced catabolic rate of TRL in viscerally obese patients could also be due to the fact that LPL activity is decreased and the postprandial AT LPL response is impaired in viscerally obese insulin-resistant patients.[33,34] Such notion is supported by the negative correlation that we found between LPL activity and AUC of TRL-TG ($r = -.38$, $P < .01$) in men of the present study. The prolonged accumulation of TRL after the oral fat load provides favorable conditions for CETP activity, allowing the exchange of TG from TRL to LDL, with the reciprocal transfer of cholesteryl esters to TRL. This process contributes to generate TG-rich LDL particles, which are good substrates for HTGL leading to the formation of small, dense LDL particles.[29] However, results of the present study indicate that even the induction of hypertriglyceridemia for up to 8 hours was not sufficient to substantially reduce LDL size, which appears to be affected to a greater extend by a chronic hyperTG state.

In our study, subjects were not allowed to eat during 8 hours. However, we have to keep in mind that, in a normal situation, individuals eat approximately 3 to 4 times per day and are seldom in the fasting state for a long time. Moreover, our subjects' usual daily fat intake was not as elevated as in the present fat load study. In the present study, we found that after 8 hours, TRL-TG levels had not returned to fasting values. Thus, we hypothesize that TRL-TG concentrations could even reach higher levels over 3 to 4 meals during the daytime period and, thus, the impact on LDL particle size could be even more important than what was observed in the present study.

In summary, this study demonstrates that postprandial hypertriglyceridemia induced by a high fat meal was only associated with a transient reduction in LDL particle size. Moreover, despite similar TG levels at baseline, men characterized by the highest postprandial lipemia were characterized by an excess of visceral AT and smaller LDL particles at the end of the fat load compared with men with a lower AUC TRL-TG. However, to the best of our knowledge, no prospective study has established the independent contribution of postprandial hyperlipidemia to the prediction for CHD risk. Prospective studies will be needed to examine this issue.

ACKNOWLEDGMENT

We thank the staff of the Physical Activity Sciences Laboratory for the data collection and the staff of the Lipid Research Center for their excellent and dedicated work.

REFERENCES

1. Després JP, Lemieux I, Prud'homme D: Treatment of obesity: Need to focus on high risk abdominally obese patients. BMJ 322:716-720, 2001

2. Zilversmit DB: Atherogenesis: A postprandial phenomenon. Circulation 60:473-485, 1979

3. Couillard C, Bergeron N, Prud'homme D, et al: Postprandial triglyceride response in visceral obesity in men. Diabetes 47:953-960, 1998

4. Lemieux I, Couillard C, Pascot A, et al: The small, dense LDL phenotype as a correlate of postprandial lipemia in men. Atherosclerosis 153:423-432, 2000

5. Pirro M, Lupattelli G, Siepi D, et al: Postprandial lipemia and associated metabolic disturbances in healthy and hyperlipemic postmenopausal women. Metabolism 50:330-334, 2001

6. Lupattelli G, Pasqualini L, Siepi D, et al: Increased postprandial lipemia in patients with normolipemic peripheral arterial disease. Am Heart J 143:733-738, 2002

7. Karpe F, Tornvall P, Olivecrona T, et al: Composition of human low density lipoprotein: effects of postprandial triglyceride-rich lipoproteins, lipoprotein lipase, hepatic lipase and cholesteryl ester transfer protein. Atherosclerosis 98:33-49, 1993

8. Attia N, Durlach V, Paul JL, et al: Modulation of low density lipoprotein subclasses by alimentary lipemia in control and normotriglyceridemic non-insulin-dependent diabetic subjects. Atherosclerosis 113:197-209, 1995

9. Dubois C, Beaumier G, Juhel C, et al: Effects of graded amounts (0-50 g) of dietary fat on postprandial lipemia and lipoproteins in normolipidemic adults. Am J Clin Nutr 67:31-38, 1998

10. Lohman T, Roche A, Martorel R: The Airlie (VA) consensus conference standardization of anthropometric measurements. Standardization of anthopometric measurements. Champaign, IL, 1988, pp 39-80

11. van der Kooy K, Seidell JC: Techniques for the measurement of visceral fat: A practical guide. Int J Obes Relat Metab Disord 17:187-196, 1993

12. Behnke AR, Wilmore JH: Evaluation and Regulation of Body Build and Composition. Englewood Cliffs, NJ, Prentice-Hall 1974, pp 20-37

13. Siri WE: The gross composition of the body. Adv Biol Med Phys 4:239-280, 1956

14. Ferland M, Després JP, Tremblay A, et al: Assessment of adipose tissue distribution by computed axial tomography in obese women: Association with body density and anthropometric measurements. Br J Nutr 61:139-148, 1989

15. Lamarche B, Tchernof A, Moorjani S, et al: Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. Circulation 95:69-75, 1997

16. Tchernof A, Lamarche B, Prud'homme D, et al: The dense LDL phenotype. Association with plasma lipoprotein levels, visceral obesity, and hyperinsulinemia in men. Diabetes Care 19:629-637, 1996

17. St-Pierre AC, Ruel IL, Cantin B, et al: Comparison of various

electrophoretic characteristics of LDL particles and their relationship to the risk of ischemic heart disease. Circulation 104:2295-2299, 2001

18. Moorjani S, Dupont A, Labrie F, et al: Increase in plasma high-density lipoprotein concentration following complete androgen blockage in men with prostatic carcinoma. Metabolism 36:244-250, 1987

19. Laurell CB: Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. Anal Biochem 15:45-52, 1966

20. Nilsson-Ehle P, Ekman R: Specific assays for lipoprotein lipase and hepatic lipase activities of post heparin plasma, in Peeters H (ed): Protides and Biological Fluids, vol 25. Oxford, UK, Pergamon, 1978, pp 243-246

21. St-Amand J, Moorjani S, Lupien PJ, et al: The relation of plasma triglyceride, apolipoprotein B, and high-density lipoprotein cholesterol to postheparin lipoprotein lipase activity is dependent on apolipoprotien E polymorphism. Metabolism 45:261-267, 1996

22. Burnham KP, Anderson DR: Model Selection and Inference: A Pratical Information-Theoretic Approach. New York, NY, Springer, 1998

23. Mardia KV: Applications of some measures of multivariate skewness and kurtosis in testing normality and robustness studies. Sankhya B 36:115-128, 1974

24. WHO Consultation on Obesity: Preventing and managing the global epidemic. Geneva, World Health Organisation 1997, pp 1-276

25. Després JP, Lamarche B: Effects of diet and physical activity on adiposity and body fat distribution: Implications for the prevention of cardiovascular disease. Nutr Res Rev 6:137-159, 1993

26. Connelly PW, Poapst M, Davignon J, et al: Reference values of plasma apolipoproteins A-I and B, and association with nonlipid risk factors in the populations of two Canadian provinces: Quebec and Saskatchewan. Canadian Heart Health Surveys Research Group. Can J Cardiol 15:409-418, 1999

27. Gardner CD, Fortmann SP, Krauss RM: Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. JAMA 276:875-881, 1996

28. Campos H, Genest JJ Jr, Blijlevens E, et al: Low density lipoprotein particle size and coronary artery disease. Arterioscler Thromb Vasc Biol 12:187-195, 1992

29. Després JP: Obesity and lipid metabolism: Relevance of body fat distribution. Curr Opin Lipidol 2:5-15, 1991

30. Pouliot MC, Després JP, Nadeau A, et al: Visceral obesity in men: Associations with glucose tolerance, plasma insulin, and lipoprotein levels. Diabetes 41:826-834, 1992

31. Després JP, Moorjani S, Ferland M, et al: Adipose tissue distribution and plasma lipoprotein levels in obese women. Importance of intra-abdominal fat. Arteriosclerosis 9:203-210, 1989

32. Brunzell JD, Hazzard WR, Porte D Jr, et al: Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. J Clin Invest 52:1578-1585, 1973

33. Patsch JR, Prasad S, Gotto AM Jr, et al: High density lipoprotein$_2$. Relationship of the plasma levels of this lipoprotein species to its composition, to the magnitude of postprandial lipemia, and to the activities of lipoprotein lipase and hepatic lipase. J Clin Invest 80:341-347, 1987

34. Jeppesen J, Hollenbeck CB, Zhou MY, et al: Relation between insulin resistance, hyperinsulinemia, postheparin plasma lipoprotein lipase activity, and postprandial lipemia. Arterioscler Thromb Vasc Biol 15:320-324, 1995