Differences in Postprandial Concentrations of Very–Low-Density Lipoprotein and Chylomicron Remnants Between Normotriglyceridemic and Hypertriglyceridemic Men With and Without Coronary Heart Disease

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It has been suggested that the postprandial elevation of plasma triglycerides is more closely linked to coronary heart disease (CHD) than the fasting triglyceride level. However, the postprandial situation is complex, as hepatogenous triglyceride-rich lipoprotein (TRL) particles (apolipoprotein [apo]B-100 and very–low-density lipoprotein [VLDL]) are mixed in the blood with apoB-48–containing lipoproteins secreted from the intestine. To analyze the relative proportion of liver-derived and intestinal apoB-containing TRL in subjects with and without CHD, we performed standardized oral fat-loading tests in young survivors of myocardial infarction, a large proportion of whom are hypertriglyceridemic (HTG), as well as sex- and population-matched healthy control subjects. A special effort was made to recruit healthy HTG subjects as controls for the HTG patients. Fasting plasma triglycerides (3.74 ± 1.35 *v* 3.01 ± 0.83, NS), low-density lipoprotein (LDL) cholesterol, and VLDL lipids, and apoB-100 and apoB-48 content at Svedberg flotation rate (Sf) 60-400, Sf 20-60, and Sf 12-20 did not differ between HTG patients (n = 10) and HTG controls (n = 14). Normotriglyceridemic (NTG) patients (n = 15) had higher fasting plasma triglycerides (1.44 ± 0.39 *v* 0.98 ± 0.33 mmol/L, $P < .05$) and LDL cholesterol (4.07 ± 0.71 *v* 3.43 ± 0.64, $P < .05$) than NTG controls (n = 34). The triglyceride elevation was accounted for by a higher level of small VLDL (apoB-100 in the Sf 20-60 fraction, 52 ± 17 *v* 29 ± 20 mg/L, $P < .05$). HTG patients responded with clearly elevated plasma triglycerides in the late postprandial phase, ie, 7, 8, and 9 hours after fat intake. Essentially, this was explained by a retention of large VLDL particles, since HTG patients exhibited no major differences in apoB-48 concentrations in the Sf > 400, Sf 60-400, and Sf 20-60 fractions but showed marked differences in the level of apoB-100 at Sf 60-400 (large VLDL) 9 hours after fat intake when compared with HTG controls (101 ± 13 *v* 57 ± 5 mg/L, $P < .01$). NTG patients were characterized by a more rapid increase of large VLDL in the early postprandial state, ie, 3 hours after fat intake, with a mean increase from baseline to 3 hours of 24.1 ± 6.7 mg/L for NTG patients and 11.8 ± 2.0 mg/L for controls ($P < .05$). ApoB-48 levels were also slightly higher, but all TRL parameters returned to baseline within 9 hours after fat intake. In conclusion, elevated triglyceride levels in the postprandial state in CHD patients are explained to a large extent by the accumulation of endogenous TRL. This suggests that the postprandial dyslipidemia encountered in CHD is more dependent on a failure of regulation of endogenous TRL versus the exogenous TRL species.

ALTHOUGH HYPERTRIGLYCERIDEMIA is a common feature of patients with coronary heart disease (CHD), it is generally not independently associated with CHD in a statistical sense.[1] However, triglycerides are carried in cholesterol-containing triglyceride-rich lipoproteins (TRLs), which are candidate atherogenic lipoproteins. TRLs are also implicated in impaired fibrinolysis and endothelial dysfunction.[2] The high degree of variability in plasma triglycerides, both within an individual and between individuals, is a likely explanation for the lack of statistical association between hypertriglyceridemia and future CHD in prospective epidemiological studies.

It has been suggested that the postprandial elevation of plasma triglycerides is more closely linked to CHD than the fasting level. Patsch and et al[3] found that plasma triglycerides measured 6 to 8 hours after a large high-fat meal were highly discriminative for CHD among normotriglyceridemic (NTG) individual. This finding was later confirmed by others.[4] Furthermore, we recently found that the plasma triglyceride concentration measured 6 hours after a mixed meal was associated with signs of early atherosclerosis in healthy men examined by carotid artery B-mode.[5] This association was independent of plasma low-density lipoprotein (LDL) cholesterol and fasting plasma triglycerides.

The postprandial situation displays heterogeneity with respect to the metabolism of TRL. TRLs containing apolipoprotein (apo)B-100 are secreted from the liver (very–low-density lipoprotein [VLDL]), whereas apoB-48 is secreted from the intestine in chylomicrons after absorption of dietary lipids. Chylomicrons and VLDL compete for the same lipolytic pathway, which results in postprandial accumulation of VLDL,[6-8] as chylomicrons seem to be the favored substrate for lipoprotein lipase.[9,10]

The patterns of elevation of apoB-100 and apoB-48 in subfractions of TRL after fat intake in hypertriglyceridemic (HTG) men with and without CHD have not been described. Therefore, we performed standardized oral fat-loading tests in young survivors of myocardial infarction, a large proportion of whom are HTG, as well as sex- and population-matched healthy control subjects. A special effort was made to recruit healthy HTG subjects as controls for the HTG patients.

SUBJECTS AND METHODS

Subjects

Three groups of men were recruited: NTG and HTG healthy men and patients who had survived a myocardial infarction before the age of 45 years. A total of 33 healthy normolipidemic men were recruited from the general population according to principles previously described.[11]

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Homozygosity for the apoE3 allele was an inclusion criterion. In addition, 15 healthy, mildly to moderately HTG men were recruited as lipid-matched controls for the HTG patients. The HTG controls were recruited from a register of patients at the Sollentuna health care center north of Stockholm. This center conducts a cardiovascular prevention program including routine measurements of fasting serum lipids on all subjects visiting the center.[12] From this database, male subjects meeting the following criteria were identified: two of three fasting plasma triglyceride determinations within the past 2 years above 3.0 mmol/L, absence of any known cardiovascular disease or diabetes mellitus, and age between 35 and 55 years. Twenty subjects were identified, of whom 15 fulfilled the additional criterion of fasting triglycerides above 2.2 mmol/L on the day of investigation. Most of the HTG controls had consulted a dietician providing similar advice as summarized later herein for the patients. None had a history of cardiovascular disease, and all denied any kind of chest pain during physical exercise.

A total of 24 consecutive male postinfarction patients aged less than 45 years were enrolled from four hospitals during 1 year. One patient with suspected familial hypercholesterolemia was excluded. Subjects with manifest diabetes mellitus (repeated fasting blood glucose ≥7.0 mmol/L or medication with oral antidiabetics or insulin) or alcohol abusers also were not included. Patients were investigated 3 to 6 months after the acute event, except for two subjects who underwent coronary artery bypass grafting within 3 months after the acute event, who were investigated 3 to 6 months after surgery. Patients were considered HTG if fasting plasma triglycerides were greater than 2.2 mmol/L.

At the time of the myocardial infarction, all patients were instructed to follow a diet low in fat and high in complex carbohydrates, with limited intake of alcohol. The energy percentage (E%) of the recommended diet was less than 30E% fat, 10 to 15E% protein, and the remaining energy from carbohydrates. The ratio of saturated to monounsaturated and polyunsaturated fat was 1:1:1. Dietary recall was not used.

There was no clinical or laboratory evidence of thyroid dysfunction or other conditions leading to secondary hyperlipoproteinemias in any of the patients or controls studied. All subjects provided informed consent, and the study was approved by the local ethics committee at Karolinska Hospital.

Oral Fat Load

Participants were admitted early in the morning to the Clinical Research Unit for a mixed-meal oral fat tolerance test. They were fasted for 12 hours, and were asked to refrain from smoking during the fasting period and from alcohol intake during the preceding 3 days. The protocol for the fat tolerance test was as previously described.[7] An emulsion consisting of soybean oil (Karlshamns Oils & Fats, Karlshamn, Sweden; 50 g/m^2 body surface area), glucose (50 g/m^2), egg white protein (Sigma 0500, 25 g/m^2; Sigma, St Louis, MO), dried egg yolk (Sigma 0625, 6.3 g/m^2), and 200 mL water prepared with lemon flavoring (60.2E% fat, 13.3E% protein, and 26.5E% carbohydrate) was ingested within 10 minutes between 7:00 and 7:30 AM. The test meal was well tolerated by all subjects. Blood samples were obtained through an indwelling catheter. A fasting blood sample was obtained before intake of the test meal. Subsequent blood samples were drawn hourly, and the last sample was taken 9 hours after ingestion of the emulsion. Participants were allowed to ambulate throughout the test.

Analytical Methods

Venous plasma anticoagulated with EDTA was recovered within 30 minutes of venipuncture by low-speed centrifugation (1,750 × *g* for 20 minutes at +1°C). Sodium azide (1.0 mol/L), phenylmethylsulfonyl flouride (10 mmol/L, dissolved in isopropanol), and aprotinin (10,000 Kallikrein inhibitory unit [KIU]/mL, Trasylol; Bayer, Leverkusen, Germany) were immediately added to the isolated plasma before fractionation of TRL to final concentrations of 1.0 mmol/L, 10 μmol/L, and 50 KIU/mL, respectively. Fasting and postprandial plasma triglycerides and fasting plasma concentrations of major lipoprotein fractions were determined as previously described.[7] Fractionation of TRL was achieved by cumulative density gradient ultracentrifugation, and the TRL content of apoB-48 and apoB-100 was determined by analytical sodium dodecyl sulfate–polyacrylamide gel electrophoresis.[13]

Plasma insulin levels were measured in heparinized plasma using a DAKO enzyme-linked immunosorbent assay kit (6219; DAKO, Cambridgeshire, UK). Samples were analyzed in triplicate. The assay is without cross-reactivity for either proinsulin or the split products 32-33 split proinsulin and des 31-32 split proinsulin.

Statistics

Conventional methods were used for calculation of the mean ± SD. Coefficients of skewness and kurtosis were calculated to test deviations from normal distribution. Logarithmic transformation was performed on the individual values for skewed variables, and a normal distribution of transformed values was confirmed before statistical computations and significance testing. Wilcoxon's signed rank test was used for group comparisons not reaching normal distribution after logarithmic transformation. Statistical comparisons were made between NTG patients and controls and HTG patients and controls, respectively. Group comparisons were performed with Student's unpaired *t* test or analysis of covariance using the body mass index (BMI) as a covariate.

To estimate the overall response of plasma triglycerides during the entire 9-hour postprandial period, the area under the postprandial triglyceride curve (AUC) was calculated using the trapezoidal rule.

RESULTS

Basic Clinical Characteristics and Fasting Plasma Lipids and Lipoproteins

NTG patients had higher fasting plasma triglycerides and VLDL lipids than population-based NTG control subjects (Table 1). The increase in VLDL lipids was explained by a higher concentration of small VLDL particles (Sf 20-60 apoB-100, 52.1 ± 17.0 *v* 29.3 ± 19.7 mg/L in patients *v* controls, $P < .05$). In addition, the LDL cholesterol level was slightly increased (4.07 ± 0.71 *v* 3.43 ± 0.64 mmol/L, $P < .05$). As a consequence of their recent myocardial infarction, 11 of 14 NTG patients were on β-blocker medication.

Plasma triglycerides were similar in the two HTG groups (Table 1). HTG control subjects were slightly older than HTG patients (46.9 ± 3.2 *v* 40.2 ± 3.3 years, $P < .01$), whereas the patients had a higher BMI (29.2 ± 1.4 *v* 26.1 ± 2.6 kg/m^2, $P < .05$).

Plasma insulin levels were clearly elevated in the two HTG groups (controls, 64.0 ± 34.4 pmol/L; patients, 93.6 ± 72.4 pmol/L, $P = .22$) versus the corresponding NTG groups (controls, 44.5 ± 38.7 pmol/L; patients, 41.9 ± 18.2 pmol/L, NS; case-control differences, $P < .01$ for controls and $P < .001$ for patients).

A majority of HTG patients were on β-blocker medication, in contrast to HTG controls.

Table 1. Age, BMI, Fasting Plasma Lipids, Lipoprotein Lipids, and TRL ApoB, Plasma Insulin, and ApoE Genotype in the Study Groups

	NTG		HTG	
Parameter	Controls (n = 33)	Patients (n = 14)	Controls (n = 15)	Patients (n = 10)
Age (yr)	42.7 ± 2.5	43.3 ± 1.6	46.9 ± 3.2	40.2 ± 3.3†
BMI (kg/m²)	24.0 ± 2.6	25.0 ± 3.7	26.1 ± 2.6	29.2 ± 1.4*
Cholesterol (mmol/L)				
Total	4.90 ± 0.76	5.68 ± 0.93*	6.05 ± 0.93	6.23 ± 1.27
VLDL	0.27 ± 0.13	0.41 ± 0.12*	1.04 ± 0.40	1.47 ± 0.73
LDL	3.43 ± 0.64	4.07 ± 0.71*	3.86 ± 0.67	3.88 ± 0.78
HDL	1.24 ± 0.31	1.09 ± 0.38	0.94 ± 0.18	0.75 ± 0.18
Triglycerides (mmol/L)				
Total	0.98 ± 0.33	1.44 ± 0.39†	3.01 ± 0.83	3.75 ± 1.35
VLDL	0.69 ± 0.33	1.04 ± 0.34*	2.52 ± 0.96	3.24 ± 1.34
LDL	0.27 ± 0.07	0.33 ± 0.09	0.39 ± 0.10	0.40 ± 0.15
HDL	0.11 ± 0.03	0.12 ± 0.03	0.15 ± 0.03	0.15 ± 0.04
ApoB-100 (mg/L)				
Sf60-400	13.2 ± 9.9	19.3 ± 9.8	59.5 ± 25.7	76.0 ± 27.3
Sf20-60	29.3 ± 19.7	52.1 ± 17.0*	85.4 ± 36.5	117.8 ± 48.7
Sf12-20	38.2 ± 24.5	42.4 ± 19.3	74.7 ± 31.4	81.5 ± 50.4
Plasma insulin (pmol/L)‡	44.5 ± 38.7	41.9 ± 18.2	64.0 ± 34.4	93.6 ± 72.4
ApoE genotype (n)				
3/3	33	10	9	6
3/4	—	3	3	3
2/3	—	1	2	1
β-Blocker medication (n)	—	11	1	9
Thiazide diuretics (n)	—	—	1	1

NOTE. Values are the mean ± SD.

†Statistical differences calculated with Student's *t* test between NTG and HTG subgroups: $*P < .01$ and $†P < .001$.

‡Plasma insulin was a highly skewed variable, and logarithmic transformation did not result in normalization; thus, group differences were studied by Mann-Whitney *U* test. Comparing HTG patients and controls and NTG patients and controls did not reveal any statistically significant differences, whereas the comparison of controls (NTG *v* HTG) did ($P < .01$). The corresponding comparison for patients was $P < .001$.

Postprandial Triglyceride

Plasma triglycerides were higher in NTG patients versus NTG controls at all time points, but the statistically significant difference in the fasting level was lost between 4 and 6 hours after intake of the fat load (Fig 1). Both groups returned to baseline values by 9 hours. Peak values were attained between the third and fifth hour in both groups. However, the incremental AUC for triglycerides did not differ between the groups (controls, 6.6 ± 4.4 mmol/L · h; patients, 7.7 ± 4.8 mmol/L · h, NS), nor the relative increase in plasma triglycerides calculated from baseline at any time point.

HTG patients and controls had a much more prominent increase of plasma triglycerides than NTG subjects. In the later part of the postprandial period, HTG patients exhibited persisting high levels of plasma triglycerides compared with HTG controls. In contrast to HTG controls, fasting plasma triglyceride levels were not attained by 9 hours in HTG patients. The rate of triglyceride clearance in the later part (from 5 hours and onward for HTG controls and from 6 hours and onward for HTG patients) of the fat tolerance test was analyzed by regression analysis. The rationale for this analysis was the assumption that most lipid absorption had already taken place and that conditions close to saturation kinetics existed due to the high plasma triglyceride level. The clearance of plasma triglycerides was 27% slower for patients versus controls (0.66 *v* 0.91 mmol/L/h; individual slopes, 0.71 ± 0.35 *v* 0.97 ± 0.48 mmol/L/h, $P < .05$ by Wilcoxon's signed rank test) (Fig 2).

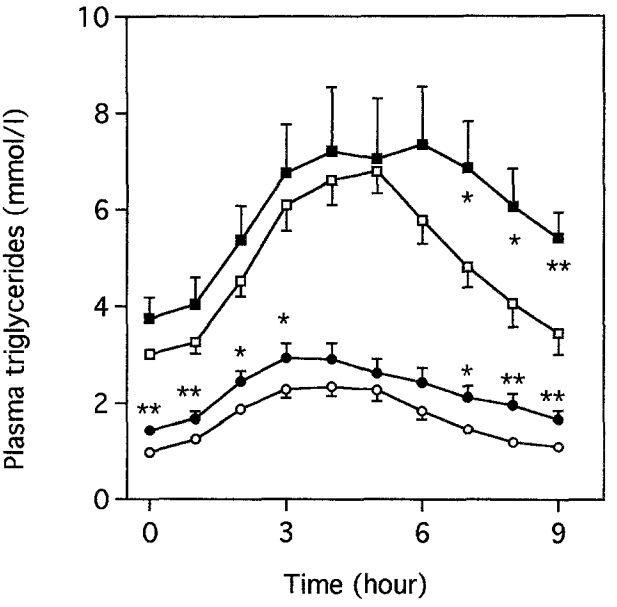

Fig 1. Plasma triglycerides after ingestion of the oral fat load. Values are the mean ± SEM, with the SEM indicated by bars. Group differences were calculated between HTG patients (■) and controls (□) and between NTG patients (●) and controls (○), respectively: $**P < .01$ and $*P < .05$. Group differences were calculated by Student's *t* test.

The incremental AUC for triglycerides did not differ significantly between HTG groups (controls, 17.4 ± 7.9 mmol/L · h; patients, 21.4 ± 14.8 mmol/L · h, NS). The fasting triglyceride level is known to mirror the postprandial triglyceride level, and it was therefore not surprising to observe a good correlation between the fasting plasma triglyceride level and the triglyceride AUC in all groups. However, it was noted that the slope for the regression line between fasting and AUC triglycerides was less steep in the HTG control group compared with the other groups. Accordingly, there was a lesser triglyceridemic effect than could be anticipated from the fasting triglyceride value. This finding may also indicate a patent removal system for triglycerides in healthy HTG subjects compared with HTG patients (Fig 3).

Postprandial Levels of ApoB-48 and ApoB-100 in TRL Subfractions of NTG Subjects

The response of apoB-48 and apoB-100 to the fat load in subfractions of TRL is shown in Fig 4. Essentially, apoB-48 was

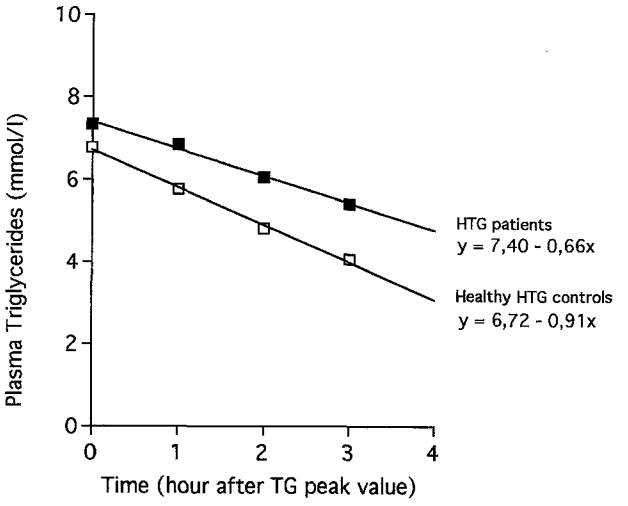

Fig 2. Rate of triglyceride clearance at the end of the postprandial phase in HTG patients and HTG controls.

not present in the Sf >400 fraction of fasting plasma in NTG subjects, and both NTG patients and controls showed a return to very low levels by 9 hours. However, NTG patients did exhibit a slightly higher peak value at 3 hours (0.34 ± 0.06 *v* 0.16 ± 0.06 mg/L, $P < .05$).

About half of the NTG subjects had a fasting level higher than the detection limit (>0.02 mg/L) for apoB-48 in the Sf 60-400 fraction. The Sf 60-400 fraction also exhibited the largest postprandial increase of apoB-48 of all TRL fractions among NTG subjects. The level was twofold higher in patients versus controls (3 hours, 2.00 ± 0.36 *v* 1.07 ± 0.11 mg/L, $P < .01$; 6 hours, 1.24 ± 0.21 *v* 0.64 ± 0.10 mg/L, $P < .01$).

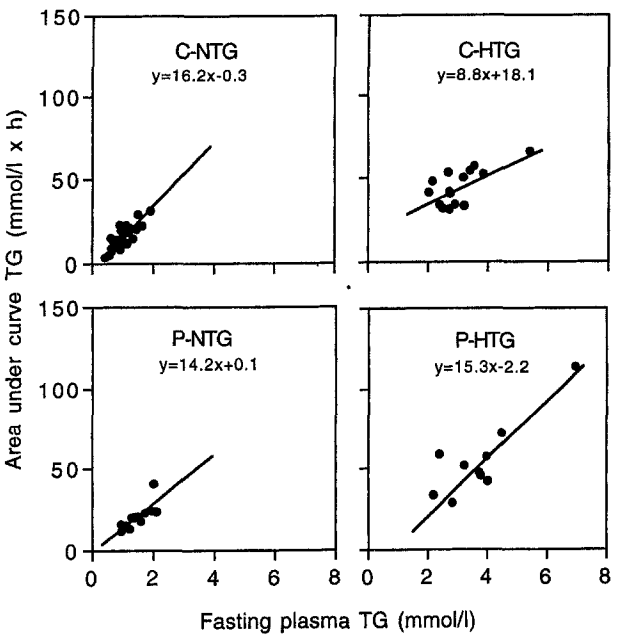

Fig 3. Relationships between fasting plasma triglycerides and the AUC for plasma triglycerides after fat intake in NTG control (C-NTG) and patients (P-NTG) and HTG control (C-HTG) and patients (P-HTG).

Both groups returned to values close to baseline by 9 hours. The apoB-100 content in the Sf 60-400 fraction almost doubled in NTG controls and more than doubled in NTG patients between 0 and 3 hours. In absolute terms, the mean increase was 24.1 ± 6.7 mg/L for patients and 11.8 ± 2.0 mg/L for controls ($P < .05$). Both groups returned to baseline by 9 hours.

Almost all NTG subjects had an apoB-48 level well above the detection limit in the Sf 20-60 fraction isolated from fasting plasma. The fasting plasma concentration was higher in patients versus controls (0.83 ± 0.15 *v* 0.32 ± 0.05 mg/L, $P < .001$). Both groups exhibited a doubling of the apoB-48 content in the Sf 20-60 fraction between 0 and 3 hours and returned to baseline by 9 hours. In contrast, the apoB-100 concentration was essentially unchanged after fat intake in the Sf 20-60 fraction.

The concentration of apoB-100 in the Sf 12-20 fraction (intermediate-density lipoprotein [IDL] fraction) was 42.2 ± 5.1 mg/L in NTG patients and 38.2 ± 4.4 mg/L in NTG controls (NS). Neither the apoB-100 content nor the minute apoB-48 content in the IDL fraction changed significantly in response to fat intake in either NTG groups (data not shown).

The general impression from the comparison of apoB-48 and apoB-100 levels in the TRL fraction was that the ratio between the two apoB species seemed fairly constant, which is exemplified in Fig 5 by the correlation between apoB-48 and apoB-100 in the Sf 60-400 fraction 6 hours after fat ingestion in all subjects grouped together. All groups seem to have the same regression line ($r = .87, P < .001$).

Postprandial Levels of ApoB-48 and ApoB-100 in TRL Subfractions of HTG Subjects

HTG patients and controls exhibited much higher postprandial levels of apoB-48 in the Sf >400 fraction than NTG subjects. HTG patients, in contrast to HTG controls, failed to clear most of the apoB-48 in the Sf >400 fraction by 9 hours after intake of the test meal (0.65 ± 0.13 *v* 0.29 ± 0.08 mg/L, $P < .05$). A similar pattern was observed for the Sf 60-400 fraction, ie, much higher plasma levels of apoB-48 were found in HTG subjects who failed to clear apoB-48 by 9 hours after fat intake. Likewise, the postprandial level of apoB-100 in the Sf 60-400 fraction showed a clearly abnormal pattern in HTG patients compared with HTG controls. The curves departed from a similar level to a peak between 3 and 6 hours, and then deviated between 6 and 9 hours. HTG patients had a clearly elevated level of apoB-100 in the Sf 60-400 fraction at 9 hours compared both with baseline (100.7 ± 13.0 *v* 76.0 ± 8.6 mg/L, $P < .01$) and with HTG controls (100.7 ± 13.0 *v* 57.1 ± 5.0 mg/L, $P < .01$).

It is concluded that the accumulation of Sf 60-400 apoB-100 particles in the later postprandial phase is likely to contribute significantly to the persisting plasma triglyceride elevation in HTG patients. Neither apoB-48 nor apoB-100 content increased in response to fat intake in the Sf 20-60 fraction in either HTG group. The concentration of apoB-100 in the IDL fraction did not differ between the two HTG groups.

Influence of BMI and Plasma Insulin on Postprandial Triglyceride and TRL ApoB Response to Fat Intake

There was a significant difference in the BMI for the two HTG groups, and the BMI was therefore used as a covariate in

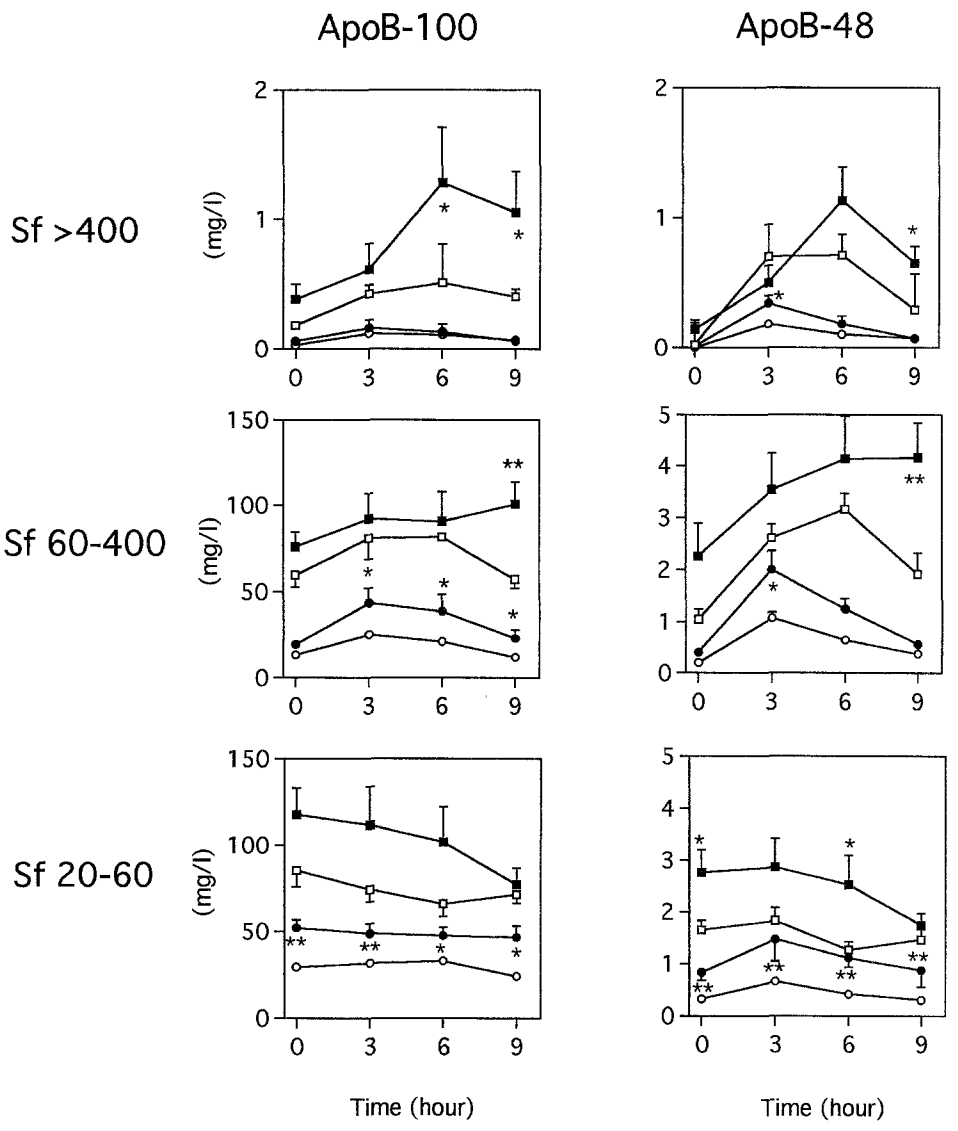

Fig 4. Line plots for apoB-48 and apoB-100 concentrations in Sf >400, Sf 60-400, and Sf 20-60 fractions after ingestion of the oral fat load. Values are the mean ± SEM, with the SEM indicated by bars. Group differences were calculated between HTG patients (■) and controls (□) and between NTG patients (●) and controls (○), respectively: **$P < .01$ and *$P < .05$. Group differences were calculated by Student's t test.

the analysis of group differences for postprandial triglycerides and TRL apoB levels. The group differences at 7 and 8 hours were not significantly different when either the BMI or insulin level were used as a covariate in comparing HTG patients and controls. However, the difference at 9 hours did remain significantly ($P = .03$). The marked difference between HTG controls and patients in Sf 60-400 VLDL apoB-100 at 9 hours was not affected by using the BMI or plasma insulin as a covariate ($P < .01$). Using the BMI or plasma insulin as a covariate for lipids and lipoproteins in the comparison of NTG patients and controls did not alter the significant baseline differences in LDL cholesterol or small VLDL apoB-100 concentrations. Nor were the significant postprandial differences in apoB-100 content in the Sf 60-400 or Sf 20-60 fractions altered after correction for the BMI or plasma insulin.

Plasma insulin was closely correlated with the triglyceridemic response after meal intake, as was the incremental AUC for triglycerides ($r = .58$, $P < .001$ in NTG controls and $r = .56$, $P < .001$ in all subjects grouped together).

DISCUSSION

The present study demonstrates differences in the contribution of liver-derived and intestinally derived apoB-containing TRL particles after fat intake in NTG and HTG men with and without CHD. Collectively, the patients seem to have a disturbance in the handling of liver-derived TRL; for NTG patients, it is observed as a rapidly increasing level of large VLDL particles after fat intake, and for HTG patients, a sustained elevation of large VLDL in the late postprandial phase. Differences between the patient and control groups in the postprandial handling of intestinally derived TRL particles (chylomicrons and chylomicron remnants containing apoB-48) were less pronounced.

Our group and others have previously concluded that the number of TRL particles derived from the liver exceeds by far the number of TRL particles originating from the intestine in NTG subjects.[7,14] From the present study, we find that this also holds true for HTG subjects, as there is not a disproportionate increase of apoB-48–containing particles in HTG patients

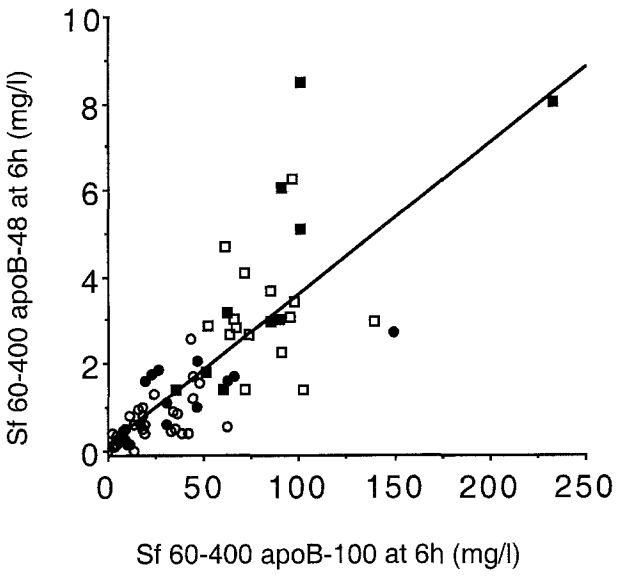

Fig 5. Relationship between apoB-48 and apoB-100 content in the Sf 60-400 fraction 6 hours after fat intake in all subjects grouped together ($r = .87$, $P < .001$). (○) NTG control, (●) NTG patients, (□) HTG control, (■) HTG patients.

compared with HTG controls. This argues against a specific role of intestinal TRL remnants in the development of CHD. Rather, it seems that the pathologic stigmata of the metabolism of postprandial TRL particles in HTG patients are accounted for by liver-derived TRL particles. The persisting postprandial plasma triglyceride elevation in HTG patients was mostly explained by the grossly elevated plasma level of large VLDL particles.

It seems that different mechanisms operate in determining the lipoprotein response to an oral fat load in NTG and HTG patients and controls. Essentially, both NTG patients and controls returned to baseline triglyceride levels by 9 hours after fat intake. However, the postprandial excursions of the various TRL populations differed. Patients exhibited a more rapid initial increase of large VLDL. We have previously shown that the postprandial increase of large VLDL depends on competition with chylomicrons for the same lipolytic pathway.[10] This was shown in a kinetic model using apoB labeling with stable isotopes and intravenous infusion of a chylomicron-like triglyceride emulsion to mimic postprandial triglyceridemia. The increase in large VLDL was found to correspond well with the basal synthetic rate of VLDL. Accordingly, the initial rapid increase of the large liver-derived TRL in NTG patients in this study would reflect overproduction of VLDL, which is unmasked in the postprandial state. However, the removal pathways seem to be patent, as total plasma triglycerides returned to the baseline level within 9 hours.

HTG patients exhibited clear difficulties in controlling plasma triglyceride levels after fat intake. Since the total plasma level was high (between 3 and 6 mmol/L) at all time points studied, it could be anticipated that conditions close to saturation of triglyceride removal existed in both HTG groups, as well as in the later postprandial period. The decline of plasma triglycerides in the later part of the postprandial phase was slower in HTG patients versus HTG controls, which argues for the proposition that the postprandial dyslipoproteinemia of HTG patients is explained to some extent by removal defects. Accumulation of large VLDL, which showed an initial increase after fat intake and then increased further between 6 and 9 hours, is an important explanation for the sustained plasma triglyceride elevation in HTG patients. Interestingly, apoB-48 in the Sf >400 fraction decreased between these time points. Chylomicrons and chylomicron remnants are the main candidates to compete with VLDL for lipolysis.[10] An alternative and perhaps additional explanation for the highly abnormal TRL pattern in HTG patients is the presence of obesity (a significantly elevated BMI). A high BMI is associated with insulin resistance. It has recently been shown that subjects with insulin resistance fail to respond with insulin-mediated suppression of the hepatic secretion of large VLDL.[15] The late postprandial elevation of large VLDL in HTG patients may therefore reflect a lack of meal-stimulated suppression of VLDL secretion.

A major difference between a majority of patients and controls in the present study is the use of β-blockers. We have recently conducted a double-blind, placebo-controlled study of the metoprolol effects on postprandial lipoprotein metabolism.[16] As expected, metoprolol induced a small but significant elevation of fasting plasma triglycerides, which was accounted for by a slight elevation of large VLDL, whereas the concentration of small VLDL was unchanged. The effect of metoprolol on triglycerides and TRL metabolism seemed consistent between subjects. Furthermore, none of the subtle metoprolol-specific effects on postprandial lipoprotein metabolism observed in that study could be found among the differences observed in the comparison of NTG patients and controls or HTG patients and controls. This argues against the proposition that case-control differences observed in this study were biased by β-blocker medication.

Hughes et al[17] have also compared HTG subjects with and without CHD. They focused on changes in the lipid composition of major lipoproteins in the postprandial state. Although analysis of the fasting plasma VLDL composition showed an increased lipid content in HTG patients, postprandial differences in VLDL composition between cases and controls were not recorded. The lipid-enriched VLDL likely reflects an abundance of large VLDL and is thus in line with our results. Furthermore, they found less phospholipid accumulation in HDL in patients, which was interpreted as a hampered lipolysis of chylomicrons in the patients.

The present study confirms previous observations that plasma triglycerides measured late in the postprandial state (well beyond the peak level) are discriminative for CHD, in contrast to fasting plasma triglycerides,[3,4] and adds to the mechanistic framework of this finding. The late postprandial elevation of plasma triglycerides is explained largely by the pathologic metabolism of liver-derived TRL and not, as one may anticipate, by accumulation of intestinal TRL remnants.

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