Alimentary Lipemia, Postprandial Triglyceride-Rich Lipoproteins, and Common Carotid Intima-Media Thickness in Healthy, Middle-Aged Men

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Background—Alimentary lipemia has been associated with coronary heart disease and common carotid artery intima-media thickness (IMT). This study was designed to investigate the relations of subclasses of postprandial triglyceride-rich lipoproteins (TRLs) with IMT.

Methods and Results—Ninety-six healthy 50-year-old men with an apolipoprotein (apo) E3/E3 genotype underwent an oral fat tolerance test and B-mode carotid ultrasound examination. The apo B-48 and apo B-100 contents of each fraction of TRLs were determined as a measure of chylomicron remnant and VLDL particle concentrations. In the fasting state, LDL cholesterol ($P<0.05$) and basal proinsulin ($P<0.05$) were significantly related to IMT, whereas HDL cholesterol, plasma triglycerides, and insulin were not. In the postprandial state, plasma triglycerides at 1 to 4 hours ($P<0.01$ at 2 hours), total triglyceride area under the curve (AUC) ($P<0.05$), incremental triglyceride AUC ($P<0.01$), and the large VLDL (Sf 60 to 400 apo B-100) concentration at 3 hours ($P<0.05$) were significantly related to IMT. Multivariate analyses showed that plasma triglycerides at 2 hours, LDL cholesterol, and basal proinsulin were consistently and independently related to IMT when cumulative tobacco consumption, alcohol intake, waist-to-hip circumference ratio, and systolic blood pressure were included as confounders.

Conclusions—These results provide further evidence for postprandial triglyceridemia as an independent risk factor for early atherosclerosis and also suggest that the postprandial triglyceridemia is a better predictor of IMT than particle concentrations of individual TRLs. (Circulation. 1999;100:723-728.)

Key Words: lipids lipoproteins ultrasonics arteries

Triglyceride-rich lipoproteins (TRLs) of different origins, particle sizes, and metabolic fates have been implicated in atherogenesis and coronary heart disease (CHD). Nevertheless, the status of plasma triglycerides and of individual TRLs as risk factors for CHD has been much debated as a consequence of the diverging results of prospective epidemiological studies.1,2 Some clinical data also indicate a role of postprandial lipoproteins in CHD. Peak and late postprandial triglyceridemia as well as postprandial retinyl palmitate concentrations, the latter being a marker of intestinally derived TRLs, are associated with CHD in case-control studies.3-8 Furthermore, postprandial plasma levels of small chylomicron remnants are related to the rate of progression of coronary atherosclerosis in young male postinfarction patients.9 Both the intestinal chylomicrons and chylomicron remnants containing apolipoprotein [apo] B-48) and the liver-derived TRLs (VLDL and VLDL remnants containing apo B-100) contribute to the triglyceridemia seen after fat intake.10,11 The postprandial increase in TRL particle number is accounted for primarily by VLDL,12,13 particularly the large VLDL species.12 In contrast, ≈80% of the postprandial triglyceridemia is accounted for by chylomicrons and their remnants,11 whereas ≈90% of the cholesterol accumulation in the TRL fraction during alimentary lipemia is confined to VLDL.11,13

To evaluate the atherogenic propensity of different subclasses of postprandial TRLs, we related the plasma levels of chylomicron remnants and VLDL attained during alimentary lipemia to carotid intima-media thickness (IMT) in a group of healthy 50-year-old men. TRLs were fractionated by cumulative density gradient ultracentrifugation, and the apo B-48 and B-100 contents of each fraction were determined as a measure of chylomicron remnant and VLDL particle concentrations.

Methods

Subjects
A total of 96 healthy 50-year-old white men living in the northern parts of the county of Stockholm participated in the study. They were...
randomly selected from a registry comprising all permanent residents. Inclusion criteria, in addition to male sex and age of 50 years, were northern European or North American descent, the presence of an apo E3/E3 genotype, and acquisition of technically satisfactory carotid ultrasound images. Exclusion criteria were chronic disease of any kind, a history of CHD or arterial thromboembolic disease, familial hypercholesterolemia, body mass index >32 kg/m², alcohol abuse, or psychiatric disorders that would interfere with compliance, and participation in other ongoing studies. Of 412 men originally invited to a screening visit, 324 (79%) accepted. Of these, 80 were excluded in telephone interviews before the screening visit. A total of 110 men (45% of the 244 screenees) were subsequently found not to possess the apo E3/E3 genotype. A further 31 individuals were excluded according to ≥1 of the exclusion criteria after the screening visit, and acceptable carotid ultrasound images could not be obtained in 7 screenees. The study was approved by the Ethics Committee of the Karolinska Hospital, and all subjects gave their informed consent to participate.

Blood Sampling
Venous blood samples for lipoprotein determinations were drawn into precooled sterile tubes (Vacutainer, Becton Dickinson) containing Na₂EDTA (final concentration 4 mmol/L), which were instantly put into ice water. Plasma was then recovered within 30 minutes by low-speed centrifugation (1,750g, 20 minutes, +1°C) and was kept at this temperature throughout the preparation procedures. Phenylmethylsulfonyl fluoride (10 mmol/L, dissolved in isopropanol) and aprotinin (1400 μg/mL) (Trasyol, Bayer) were immediately added to the isolated plasma before fractionation of TRLs to final concentrations of 10 μmol/L, and 28 μg/mL, respectively.

Oral Fat Load
The test meal consisted of pasta, boiled drawn chicken breast meat, green peas, and mayonnaise. The mayonnaise was prepared from soybean oil (Karlshamns Oils & Fats AB). The total energy content of the meal was 1000 kcal, with 60% of energy (E%) from fat, 13 E% from protein, and 27 E% from carbohydrate. This corresponds to a fat load of ~65 g. A fasting blood sample was taken before the test meal. Blood samples were then drawn every hour for determination of plasma triglycerides and after 3 and 6 hours for determination of apo B-48 and apo B-100 in Svedberg flotation units (Sf).

Fasting plasma concentrations of cholesterol and triglycerides in VLDL, LDL, and HDL were determined by a combination of preparative ultracentrifugation, precipitation of apo B–containing lipoproteins, and lipid analyses. Apo E genotype was determined by a polymerase chain reaction technique.

Subfractions of TRL
TRLs were subfractionated by cumulative density gradient ultracentrifugation. Consecutive runs calculated to float Sf >400, Sf 60 to 400, and Sf 20 to 60 particles were made, and the Sf 12 to 20 fraction was recovered after the last ultracentrifugal run by slicing the tube 29 mm from the top after the Sf 20 to 60 lipoproteins had been aspirated. The apo B-48 and apo B-100 concentrations in all fractions were then determined by SDS-PAGE. Apo B-100 derived from LDL was used as a reference protein and for standard curve dilutions. Gels were stained by Coomassie G-250 (Serva) and then scanned with a laser scanner (Ultroscan XL, Pharmacia-LKB). By the present methodology, the limit for detection of apo B-48 and apo B-100 is 0.02 mg/L plasma concentration.

Determination of Glucose, Insulin, and Proinsulin
Blood was collected into vacuum tubes containing heparin (143 USP units) for determination of glucose and insulin. Blood glucose was measured by a glucose oxidase method (Kodak Ektachem). Insulin and intact proinsulin were measured by ELISA based on 2 monoclonal antibodies (DAKO Insulin and DAKO Intact Proinsulin, DAKO Diagnostics Ltd). The monoclonal antibodies used in the insulin assay have very low cross-reactivity with proinsulin.

Carotid Artery Ultrasound Examinations
Measurement of carotid artery IMT was done according to the European Lacidipine Study on Atherosclerosis ultrasound protocol. The ultrasound device used was a 2000 Li sa (Biosound, Inc) with an 8-MHz high-resolution annular array scanner. The scanners were recorded on S-VHS videotapes and sent to the Center for Medical Ultrasound, Division of Vascular Ultrasound Research, Wake Forest University, Winston-Salem, NC, for reading. In the present report, only the common carotid artery far-wall IMT (mean of right and left artery registrations) is used as a measure of early atherosclerosis, and IMT henceforth refers to this segment of the carotid artery. The intrasonographer coefficients of variation were 3.8% and 5.1%, respectively, for the 2 sonographers. The intersonographer coefficient of variation was 4.7%.

Statistical Analyses
The individual values of skewed variables were log-normalized before statistical tests. To estimate the overall response of plasma triglycerides during the entire 6-hour postprandial period, the total area under the curve (AUC) or the incremental AUC with respect to the fasting plasma triglyceride level was calculated. The associations between clinical and metabolic variables and IMT were first assessed by calculation of univariate Pearson correlation coefficients. The influence of cumulative tobacco consumption, alcohol intake, waist-to-hip circumference ratio (WHR), and systolic blood pressure was then controlled by calculation of partial correlation coefficients. Three multivariate models were subsequently generated by multiple stepwise linear regression analysis to identify variables independently correlating with IMT. Variables that showed a significant univariate association with the IMT variable were included in the multivariate analysis. In all 3 models, cumulative tobacco consumption, alcohol intake, WHR, and systolic blood pressure were first entered as forced variables. A forward approach was used for the multivariate analysis, with significance levels set to <0.25 to enter and >0.10 to leave the model. All statistical tests were 2-sided, and probability values of <0.05 were considered significant.

Results
The basic characteristics of the 96 participants are shown in Table 1. Two thirds were current or previous smokers. The vast majority of the participants were nonobese, normotensive, and without a family history of CHD. The ultrasound examination revealed that, taken as a group, the 50-year-old men enrolled in the study had a fairly normal IMT. Systolic blood pressure, cumulative tobacco consumption, alcohol intake, WHR, and body mass index did not correlate significantly with IMT.

Fasting Plasma Lipid and Lipoprotein Concentrations and Glucose-Insulin Homeostasis
Fasting cholesterol and triglyceride concentrations in plasma and the major lipoprotein fractions along with the Pearson correlation coefficients of these variables with IMT are shown in Table 2. Plasma and LDL cholesterol concentrations showed significant positive correlations with IMT (r=0.23, P<0.05 and r=0.23, P<0.05). In contrast, neither the IDL fraction (Sf 12 to 20 apo B-100) nor the VLDL or HDL cholesterol and triglyceride levels correlated significantly with IMT. Fasting proinsulin was associated with IMT (r=0.26, P<0.05), whereas fasting plasma glucose and insulin were not.
Postprandial Triglyceride and TRL Responses

The plasma triglyceride level doubled and reached its peak 3 hours after intake of the test meal (Figure), as expected in this population of healthy individuals. The apo B-48 and apo B-100 concentrations in the Sf > 400, Sf 60–400, and Sf 20–60 fractions were increased at 3 hours, the exception being Sf 20–60 apo B-100 (reflecting small VLDL particles), which tended to be lower at this time point (Table 3).

Baseline values were attained at 6 hours for all subfractions except the larger chylomicron remnant species reflected by Sf 60–400 apo B-48.

### TABLE 1. General Characteristics of the Study Group

| No. of subjects | 96 |
| Positive family history of CHD, % | 12 |
| Smokers, % | |
| Current | 33 |
| Former | 29 |
| Cumulative tobacco consumption, cigarette-years | 71 (0–360) |
| Alcohol intake, g/d | 18 (10–34) |
| BMI, kg/m² | 25.2 (23.7–27.0) |
| WHR | 0.94 (0.90–0.97) |
| Blood pressure, mm Hg | |
| Systolic | 122 (115–130) |
| Diastolic | 80 (75–85) |
| Common carotid artery IMT, mm | |
| Far wall | 0.85 (0.75–0.95) |
| Near wall | 0.86 (0.79–0.95) |

BMI indicates body mass index. Values are median (interquartile range). A positive family history of CHD was considered to be present when CHD had been diagnosed in 1 first-degree relative <60 years old.

### Relationships of Postprandial Triglycerides and TRLs to Common Carotid IMT

The total triglyceride AUC correlated significantly with IMT ($r = 0.25$, $P < 0.05$), as did the incremental triglyceride AUC ($r = 0.28$, $P < 0.01$). Significant relations with IMT were also seen for the plasma triglyceride concentrations measured in the early postprandial phase, at 1 to 4 hours after intake of the test meal, with the strongest correlations attained at 2 hours. In contrast, the late postprandial triglyceride determinations were not related to IMT. Of the TRL particle measurements, only the large VLDL (Sf 60–400 apo B-100) concentration

### TABLE 2. Fasting Glucose, Insulin, Cholesterol, and Triglyceride Concentrations in Plasma and Major Lipoprotein Fractions, and Relationships to Common Carotid Artery IMT

| Glucose, mmol/L | 4.7 (4.4–5.1) | 0.08 |
| Insulin, pmol/L | 32 (25–49) | 0.18 |
| Proinsulin, pmol/L | 2.8 (2.2–3.8) | 0.26* |
| Cholesterol, mmol/L | 5.38 (4.63–5.96) | 0.23* |
| Plasma apo B-100 | 0.08 (0.01–0.29) | 0.01 (0–0.10) |
| Apo B-48 | 0.18 (0.05–0.40) | 0.03 (0–0.10) |
| Sf 60–400 apo B-100 | 15.3 (5.6–27.0) | 25.7 (14.2–41.9) |
| Apo B-48 | 0.16 (0–0.50) | 0.48 (0.18–1.05) |
| Sf 20–60 apo B-100 | 28.0 (18.1–40.5) | 23.5 (17.4–31.4) |
| Apo B-48 | 0.43 (0.21–0.82) | 0.70 (0.47–0.98) |
| Triglycerides, mmol/L | 1.08 (0.80–1.68) | 0.17 |
| Plasma | 1.08 (0.80–1.68) | 0.17 |
| VLDL | 0.71 (0.46–1.29) | 0.17 |
| LDL | 0.27 (0.23–0.31) | 0.18 |
| HDL | 0.11 (0.08–0.31) | 0.03 |
| IDL, mg/L | 45.3 (31.1–62.5) | 0.13 |
| Apo B-100 | 0.05 (0.01–0.25) | 0.04 |

Values are median (interquartile range) or Pearson correlation coefficient ($r$). $^*P < 0.05$.

### TABLE 3. Apo B-100 and B-48 Responses to the Mixed Meal in Sf > 400, Sf 60–400, Sf 20–60, and Sf 12–20 Subfractions of TRLs

<table>
<thead>
<tr>
<th>Time, h</th>
<th>0</th>
<th>3</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo B-100</td>
<td>0.08 (0.01–0.29)</td>
<td>0.01 (0–0.10)</td>
<td>r = 0.14</td>
</tr>
<tr>
<td>Apo B-48</td>
<td>0.18 (0.05–0.40)</td>
<td>0.03 (0–0.10)</td>
<td>r = 0.17</td>
</tr>
<tr>
<td>Sf 60–400, mg/L</td>
<td>15.3 (5.6–27.0)</td>
<td>25.7 (14.2–41.9)</td>
<td>15.9 (5.7–32.8)</td>
</tr>
<tr>
<td>Apo B-100</td>
<td>0.16 (0–0.50)</td>
<td>1.27 (0.63–2.02)</td>
<td>0.48 (0.18–1.05)</td>
</tr>
<tr>
<td>Apo B-48</td>
<td>0.03</td>
<td>0.21*</td>
<td>0.12</td>
</tr>
<tr>
<td>Sf 20–60, mg/L</td>
<td>28.0 (18.1–40.5)</td>
<td>23.5 (17.4–31.4)</td>
<td>27.4 (18.9–37.5)</td>
</tr>
<tr>
<td>Apo B-100</td>
<td>0.43 (0.21–0.82)</td>
<td>0.70 (0.47–0.98)</td>
<td>0.41 (0.22–0.77)</td>
</tr>
<tr>
<td>Apo B-48</td>
<td>0.14</td>
<td>0.06</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Values are median (interquartile range). $r$ values indicate Pearson correlation coefficients with IMT for the respective fraction and time point. $^*P < 0.05$. $^{**}P < 0.01$. 

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Line plot of plasma triglyceride concentrations during a mixed-meal type of oral fat tolerance test in 96 healthy 50-year-old men. Values are median and 75th percentile, the latter indicated by bars. $r$ values indicate Pearson correlation coefficients for associations with common carotid intima-media thickness at respective time points. $^*P < 0.05$; $^{**}P < 0.01$.
at 3 hours was found to correlate significantly with IMT ($r=0.21$, $P<0.05$, Table 3). The smaller VLDL particles and the chylomicron remnants (apo B-48 concentrations in TRL fractions) were unrelated to IMT.

### Multivariate Analyses of Lipid and Lipoprotein Relationships to Common Carotid IMT

In the multivariate analyses (Table 4), cumulative tobacco consumption, alcohol intake, WHR, and systolic blood pressure were first forced into the model. In the first model, in which only fasting variables were considered, LDL cholesterol was the strongest determinant of IMT, accounting for 7% of the variation (a 1-mmol/L difference in LDL cholesterol was associated with a 0.05-mm difference in IMT), whereas proinsulin contributed another 4% (a 2-pmol/L difference in proinsulin was associated with a 0.04-mm difference in IMT). In the second model, plasma triglycerides at 2 hours and Sf 60–400 apo B-100 at 3 hours after intake of the test meal were added as independent variables to the variables considered for inclusion in the first model. In this model, fasting plasma triglycerides were also added as a forced variable. The early postprandial triglyceride response turned out to be the strongest predictor of IMT, accounting for 8% of its variation (a 2-mmol/L difference in plasma triglycerides at 2 hours after intake of the test meal was associated with a 0.12-mm difference in IMT). The second model explained a total of 21% of the variation in IMT. When the variables considered in model 2 were evaluated in current and previous smokers only, postprandial triglycerides at 2 hours (increase in multiple $R^2=0.11$) and proinsulin (increase in multiple $R^2=0.04$) were found to relate independently to IMT, whereas LDL cholesterol did not. Furthermore, among the forced variables, cumulative tobacco consumption (increase in multiple $R^2=0.07$), systolic blood pressure (increase in multiple $R^2=0.04$), and WHR (increase in multiple $R^2=0.01$) were associated with IMT (multiple $R^2=0.29$).

### Discussion

The aim of the present study was to investigate the influence of postprandial lipoproteins on early stages of atherosclerosis, as reflected by B-mode ultrasound measurements of the common carotid artery IMT, in a group of healthy middle-aged men with an apo E3/E3 genotype. The main finding was that the triglyceride response after an oral fat load related to IMT independently of clinical risk factors and plasma LDL and HDL cholesterol levels and accounted for a substantial proportion of the between-individual variation in IMT. In addition to postprandial triglyceridemia, basal proinsulin and LDL cholesterol concentrations were independent predictors of IMT. Although the postprandial large VLDL particle number (Sf 60 to 400 apo B-100 at 3 hours after intake of the test meal) correlated significantly with IMT in univariate analyses, it did not prove to be an independent predictor of IMT in the multivariate analysis. Furthermore, there was no association between postprandial chylomicron remnant particle number and IMT.

B-mode ultrasound measurement of the IMT of the common carotid artery was used to assess early stages of atherosclerosis. Several basic observations justify the use of this surrogate measurement. Comparison between IMT measured by B-mode ultrasound and by light microscopy demonstrates a good correspondence. IMT also correlates with many established risk factors for atherosclerotic disease, such as smoking, hypertension, hypercholesterolemia, and increasing age. Furthermore, carotid IMT reflects the severity of atherosclerotic disease in coronary arteries and predicts future cardiac events. Because age, sex, and apo E genotype are strong determinants of common carotid IMT, we included only 50-year-old men with an apo E3/E3 genotype to avoid these confounders.

In agreement with the majority of previous studies, we found a positive association between the LDL cholesterol concentration and IMT. However, in a lipid-lowering trial, Hidse et al found that the IDL mass concentration was associated with progression of carotid IMT, whereas VLDL and LDL were not. We did not find a significant relation between IDL and IMT, which might reflect differences in the groups studied, their coronary artery disease patients as opposed to our group of healthy individuals. Of note, LDL cholesterol, which included IDL in our study, lost some of its correlation with IMT when postprandial lipids and lipoproteins were taken into account in multivariate analysis. HDL

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**Table 4. Multiple Stepwise Regression Analysis of the Relations of Proinsulin, Fasting and Postprandial Lipids and Lipoproteins to Common Carotid IMT**

<table>
<thead>
<tr>
<th></th>
<th>Partial Correlation Coefficient*</th>
<th>P</th>
<th>Regression Coefficient</th>
<th>Increase in Multiple $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma TG</td>
<td>0.13</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal proinsulin</td>
<td>0.23†</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.27†</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG at 2 h</td>
<td>0.29‡</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sf 60–400 apo B-100 at 3 h</td>
<td>0.21</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Within each model, the variables were forced into the model first. *Controlling for cumulative tobacco consumption, alcohol intake, WHR, and systolic blood pressure. Cumulative variables included only 50-year-old men with an apo E3/E3 genotype. $P<0.05$, ‡$P<0.01$.
cholesterol, on the other hand, is not consistently found to be related with IMT. This might reflect the heterogeneity of the cohorts studied. In this group of healthy middle-aged men with normal HDL cholesterol levels, HDL cholesterol did not correlate significantly with IMT.

Only a few studies have examined the relations between postprandial lipids and lipoproteins and carotid IMT. Postprandial triglycerides, peak postprandial triglycerideremia, and late postprandial triglyceride levels have been found to be associated with early carotid atherosclerosis in healthy normolipidemic and mildly to moderately hyperlipidemic individuals independently of established risk factors. Furthermore, Gronholdt et al. in a group of 85 patients with symptomatic carotid atherosclerosis, found that fasting plasma and VLDL triglycerides, along with postprandial chylomicron remnants/VLDL triglycerides and the postprandial triglyceride AUC were independent predictors of the presence of echoluent plaques in the carotid arteries.

Using analytical SDS-PAGE, the present study focused on elucidating the relationships of specific measurements of the mass concentrations of postprandial VLDL and chylomicron remnants of different particle size to early atherosclerosis in healthy middle-aged men. Interestingly, the early postprandial triglycerideremia response was more strongly related to carotid IMT than either clinical risk factors, the fasting concentrations of plasma lipids and major lipoproteins, or the postprandial plasma concentrations of VLDL and chylomicron remnants.

The physical characteristics and particle composition of all major plasma lipoproteins are influenced by postprandial lipemia. These effects are mediated by the cholesteryl ester transfer protein (CETP), which catalyzes the transfer of cholesteryl esters from HDL and LDL to chylomicrons, VLDL, and IDL and the reciprocal transfer of triglycerides. The magnitude and duration of postprandial lipemia determines how much cholesterol is diverted from LDL and HDL into TRLs, as well as the extent to which triglyceriderich LDL and HDL particles are converted into smaller and denser particle species by hepatic lipase (reviewed in Reference 31). The strong relationship between degree of postprandial lipemia and IMT observed in the present study may thus reflect a general proatherogenic effect of alimentary lipemia on the entire lipoprotein system. Why early rather than late postprandial triglyceride levels were most strongly related to IMT is unknown but might be explained by the inclusion of apo E3 homozygotes only, because postprandial lipoprotein metabolism is impaired in individuals carrying the E4 allele. Basal plasma proinsulin, but not insulin, related significantly to IMT independently of clinical risk factors as well as fasting and postprandial lipoprotein concentrations. This is in agreement with the findings of Haffner et al., who found a significant relation between plasma proinsulin concentration and carotid IMT in a group of 985 nondiabetic individuals, and this relation was stronger than that between insulin and IMT. Furthermore, Båvenholm et al. found that basal proinsulin correlated significantly with severity of global coronary atherosclerosis determined by angiography in a group of young postinfarction patients, also when plasma insulin and major lipoproteins were taken into account in multivariate analysis. The corollary is that plasma proinsulin, a marker of β-cell dysfunction, may be implicated in early atherosclerosis independently of established clinical risk factors, glucose tolerance, insulin sensitivity, and TRLs. The biological mechanism remains unknown.

In conclusion, the present study shows that postprandial triglycerideremia is a fairly strong determinant of early atherosclerosis in healthy middle-aged men independently of conventional clinical risk factors and LDL cholesterol. The role of proinsulin in early atherosclerosis should be the subject of future studies.

Acknowledgments

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References


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