Postprandial dyslipidemia in men with visceral obesity: an effect of reduced LDL receptor expression?

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Postprandial dyslipidemia in men with visceral obesity: an effect of reduced LDL receptor expression? Am J Physiol Endocrinol Metab 281: E626–E632, 2001.—Postprandial lipemia after an oral fat challenge was studied in middle-aged men with visceral obesity. The two groups had similar plasma cholesterol levels, but obese subjects had higher levels of plasma triglyceride and reduced amounts of high-density cholesterol. Fasting plasma insulin was fourfold greater in obese subjects because of concomitant insulin resistance, with a calculated HOMA score of 3.1 ± 0.6 vs. 0.8 ± 0.2, respectively. Plasma apolipoprotein B48 (apoB48) and retinyl palmitate (RP) after an oral fat challenge were used to monitor chylomicron metabolism. Compared with lean subjects, the fasting concentration of apoB48 was more than twofold greater in obese individuals, suggestive of an accumulation of posthydrolyzed particles. After the oral lipid load, the incremental areas under the apoB48 and RP curves (IAUC) were both significantly greater in obese subjects (apoB48: 97 ± 17 vs. 44 ± 12 μg·ml⁻¹·h; RP: 3,120 ± 511 vs. 1,308 ± 177 U·ml⁻¹·h, respectively). A delay in the conversion of chylomicrons to remnants probably contributed to postprandial dyslipidemia in viscerally obese subjects. The triglyceride IAUC was 68% greater in obese subjects (4.7 ± 0.6 vs. 2.8 ± 0.8 mM·h, P < 0.06). Moreover, peak postprandial triglyceride was delayed by ~2 h in obese subjects. The reduction in triglyceride lipolysis in vivo did not appear to reflect changes in hydrolytic enzyme activities. Postheparin plasma lipase rates were found to be similar for lean and obese subjects. In this study, low-density lipoprotein (LDL) receptor expression on mononuclear cells was used as a surrogate marker of hepatic activity. We found that, in obese subjects, the binding of LDL was reduced by one-half compared with lean controls (70.9 ± 15.07 vs. 38.9 ± 4.6 ng LDL bound/μg cell protein, P = 0.02). Because the LDL receptor is involved in the removal of proatherogenic chylomicron remnants, we suggest that the hepatic clearance of these particles might be compromised in insulin-resistant obese subjects. Premature and accelerated atherogenesis in viscerally obese, insulin-resistant subjects may in part reflect delayed clearance of postprandial lipoprotein remnants.

postprandial lipemia; insulin resistance

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Visceral obesity is typically seen in overweight men and is clinically important because it is often the precursor of non-insulin-dependent diabetes mellitus, atherosclerosis, and cardiovascular disease (1–2). Increased atherosclerotic risk in obesity is attributed to several metabolic abnormalities, including insulin resistance, hypertension, and dyslipidemia. Lipid abnormalities in obesity differ from nonobese subjects in that the plasma concentration of cholesterol is not normally elevated. Rather, there is typically an accumulation of triglyceride-rich lipoproteins (2, 9, 33).

After secretion, triglyceride-rich lipoproteins from the intestine (chylomicrons) and from the liver (very low density lipoproteins (VLDL)) are hydrolyzed by enzymes located on the endothelium of capillary-rich tissue before being cleared from blood by high-affinity receptor pathways (11). It is unclear whether, in obesity, a defect in secretion, hydrolysis, and/or particle uptake is responsible for concomitant hypertriglyceridemia and which lipoprotein type contributes most significantly. Presently, there is paradoxical evidence suggesting that the defect is primarily central, that is, a consequence of VLDL oversecretion in response to increased substrate supply (8, 14). On the other hand, postprandial dyslipidemia is said to be a contributing factor of hypertriglyceridemia in obesity, and several laboratories have reported an elevated triglyceride response in obese subjects after an oral fat load (7, 22).

There is an accumulating body of evidence to suggest that postprandial dyslipidemia is an independent risk factor for atherosclerosis and cardiovascular disease (12). However, it is important to distinguish between the accumulation of poorly hydrolyzed chylomicrons and remnant lipoproteins that have undergone significant lipolysis. It is the latter that are thought to confer increased atherosclerotic risk because of greater arterial uptake and retention (16). On the basis that insulin stimulates lipoprotein lipase activity in some tissues (20), a number of laboratories have suggested that, in obesity, postprandial dyslipidemia occurs primarily because of reduced lipolysis by endothelial
lipases (25). A reduced hydrolytic capacity would predictably result in an accumulation of large triglyceride-rich lipoproteins. On the other hand, insulin is a potent stimulator of LDL receptor expression (34), which is the primary mechanism by which chylomicron remnants are cleared in vivo (3, 11). In contrast to a defect in lipolysis, decreased LDL receptor expression would lead to the accumulation of smaller, denser remnant lipoproteins. Although a number of studies have provided evidence for a positive association between central obesity, insulin resistance, and glucose metabolism, it is less clear whether and by what mechanism insulin per se regulates the metabolism chylomicrons in vivo. In studies of subjects with insulin resistance, some laboratories have reported an inverse correlation of insulin sensitivity with fasting and postprandial triglyceride (8, 31), yet others have found no such association (10, 26).

Delineation of the aberrant mechanisms responsible for postprandial dyslipidemia in subjects with visceral obesity may be important both with respect to expected clinical outcomes and in considering intervention strategies. Austin et al. (1) identified that coronary heart disease risk was three- to sixfold higher in otherwise healthy dyslipidemic male subjects without diabetes or significant obesity. Clearly, identification of a specific defect in receptor-mediated clearance would emphasize the importance of considering interventions that promote receptor expression as a means of reducing cardiovascular disease risk.

To explore further the putative regulatory role of insulin in postprandial lipemia, we chose to investigate chylomicron kinetics in healthy lean men and in viscerally obese subjects without concomitant hypercholesterolemia. The hypothesis that formed the basis of this study was that the metabolism of chylomicron remnants would be disturbed in viscerally obese non-diabetic subjects, and that this disturbance would be inversely related to the level of insulin sensitivity. We predicted that the primary defect in remnant metabolism was one of delayed clearance via high-affinity processes and less likely to be a consequence of slower conversion to the remnant form, that is, reduced lipoysis.

**METHODS**

**Subjects**

Thirty-five male subjects (14 lean, 21 obese) <60 yr of age were recruited from the general community. All subjects underwent a medical examination. Exclusion criteria included smoking within 2 yr, liver or endocrine dysfunction, malabsorption syndrome, anemia, hypothyroidism, apolipoprotein E2/E2 genotype, and the use of lipid-lowering or hypertensive agents. Diabetes was excluded on the basis of fasting plasma glucose being <7 mM and a normal response to an oral glucose challenge. Subjects with total plasma cholesterol >6 mmol/dL or LDL cholesterol >4 mmol/dL were excluded to avoid the potential confounder of genetic hyperlipidemia. Informed consent was obtained for all subjects. All procedures were approved by the ethics committee, Royal Perth Hospital, and conformed to the Helsinki Declaration.

**Anthropometric Measurements**

Body weight, height, and waist and hip circumferences were measured following standardized procedures and using a single trained observer. Waist-to-hip ratio (WHR) was calculated and used as a measure of visceral obesity, which was defined as having a WHR >1.0.

**Postprandial Lipoprotein Assessment**

**Oral fat load.** Subjects fasted for 14 h and then consumed a fat load consisting of 100 ml of cream (fat content 47% wt/wt) and retinyl palmitate (RP; 900 mg/kg body weight) flavored with 1 g of chocolate powder. On the day preceding the study, subjects abstained from alcohol, and the evening meal was low in fat (<20 g fat). Venous blood samples were collected into tubes containing EDTA just before the meal and at 2-h intervals up to 10 h, via a Teflon catheter inserted into the antecubital vein. After the 10-h blood sample, subjects were given an intravenous injection of 50 U/kg heparin, and blood was drawn 15 min later for determination of lipase activities. Subjects remained in a semirecumbent position during the study, were allowed bathroom access, and were provided with water at all times.

Blood samples were centrifuged at ~2,000 g for 10 min. Plasma was collected for determination of apolipoprotein B_{48} (apoB_{48}), RP, lipids, insulin, and lipase activities. Aliquots of plasma awaiting analysis were stored at −80°C.

**ApoB_{48} determination.** ApoB_{48} was quantitated using a Western blotting/enhanced chemiluminescence procedure as previously described (32). Complete recovery of chylomicrons and hydrolyzed remnants requires isolation by ultracentrifugation encompassing a density of <1.063 g/ml (5,760,000 g/h, Beckman SW41 rotor). Apolipoproteins from lipoprotein isolates were separated on a 5–20% SDS polyacrylamide gel and transferred to polyvinylidene fluoride membranes (IPVH-000–10, Millipore). The membranes were incubated with an antibody to apoB (no. Q497, Dako, Glostrup, Denmark), and protein was visualized using anti-rabbit IgG (HRP conjugated; no. NA934, Amersham) and an enhanced chemiluminescence reagent (RPN 2106, Amersham). Membranes were exposed to blue-light film (RPN 3103, Amersham) and developed in an AGFA-Gevaert Rapidoprint X-Ray Developer. ApoB_{48} bands were identified and quantified by densitometry against purified apoB_{48} protein of known mass. The mean intra- and interassay coefficients of variance for apoB_{48} were each <4%.

**Quantitation of RP.** RP was extracted immediately after sample isolation, with appropriate precautions for exposure to light. It was quantitated by HPLC (model 1050, Hewlett-Packard) on a reverse-phase C_{18} column (LiChrospher 100 RP-18, Hewlett-Packard) with methanol as the mobile phase (17). Quantitation was based on the retention time and area response of purified RP, and retinyl acetate was used as an internal standard. The coefficient of variance for RP determination by HPLC was 2.4%.

**Postprandial assessment.** Postprandial metabolism was quantified by calculating the area under the curve (AUC) and the incremental AUC (IAUC) for plasma triglycerides, apoB_{48}, and RP. Concentrations obtained over the 10-h period after the ingestion of the fat meal were used for this calculation. The IAUC was estimated as the difference between the area defined below the baseline concentration and the area under the plasma curve between 0 and 10 h. In those patients in whom the 10-h concentration was lower than that at baseline, the AUC represented that area below a line connecting the baseline and 10-h concentration levels. The IAUC represents the increase in area after the response of
the fat load above fasting concentrations. The SAAM-II program (SAAM Institute, Seattle, WA) was used to perform the calculations by use of linear interpolation between sequential data points.

Measurement of LDL receptor activity in human monocytes. Measurement of LDL receptor activity in human monocytes was done according to the method of Roach et al. (30). Briefly, on the day of the postprandial challenge, monocytes were isolated from whole blood using a Ficoll separation method and frozen at −80°C in a background solution of 20% (vol/vol) sucrose. LDL gold was bound to the monocytes, and total and nonspecific binding was determined by measuring the absorbance of the bound gold when fixed with a silver stain enhancer (Amersham IntenseSE BL) by use of the Cobas Mira Autoanalyzer (Roche, Nutley, NJ).

Lipoprotein and hepatic lipase activity assay. Measurement of lipoprotein lipase (LPL) and hepatic lipase (HL) from postheparin plasma was done by monitoring the release of unesterified fatty acids from a triolein emulsion (15). Briefly, a gum arabic emulsion containing 10 μmol of [14C]triolen per milliliter and [9,10-3H(N)]oleic acid as internal standard were prepared by sonication. To measure total lipase activity, heat-inactivated human serum was added as an additional source of apolipoprotein C-II (LPL activator) to postheparin plasma. To begin the reaction, substrate was added and the tube was incubated in a shaking water bath at 37°C. The assay was stopped by addition of propan-2-ol-hexane-0.5 M H2SO4 (40:10:1, vol/vol). Fatty acids were extracted into solvent after a further addition of hexane and then 0.05 M H2SO4. The tube contents were shaken, and phase separation was achieved by low-speed centrifugation. Aliquots of the upper phase were transferred into tubes containing 0.1 M NaOH in ethylene glycol and were mixed thoroughly. The upper hexane layer was removed, and aliquots of the lower phase were transferred into liquid scintillation vials. Radioactivity is determined by counting in dual label mode with a stain enhancer (Amersham IntenseSE BL) by use of the Cobra Mira Autoanalyzer (Roche, Nutley, NJ). The activity was calculated as the difference between total hydrolytic rates and HL activities.

Lipids and insulin assays. Plasma triglyceride (TG-HR II, Waco Pure Chemical, Osaka, Japan) and cholesterol (TR13315 Trace Scientific, Melbourne, Australia) were determined by enzymatic colorimetric kits. Plasma insulin was measured using an ELISA kit (K6219, Dako Diagnostics).

Measurement of insulin resistance state. Estimation of the subjects’ state of insulin resistance was by calculation of a homeostatic model assessment (HOMA) score, defined as the product of fasting insulin concentration (mU/l) and fasting glucose concentration (mM) divided by 22.5.

Statistical Analysis

Statistical analysis was by parametric methods with SPSS for Windows (SPSS, Chicago, IL). The LDL receptor data were not normally distributed and were therefore log-transformed. Two-sample comparisons were by Student’s t-tests. Associations between variables were assessed using linear regression. Two-tailed levels of significance were used.

RESULTS

Descriptive statistics for variables obtained at screening are presented in Table 1. None of the control or obese subjects had a history of hypertension or myocardial infarction. Obese subjects were significantly heavier and had significantly greater waist, WHR, and BMI than age-matched controls. The fasting plasma concentration of cholesterol was not significantly different in overweight men compared with lean controls. LDL cholesterol was modestly greater vs. controls. Fasting plasma triglycerides were increased twofold in overweight men compared with the control group and were accompanied by a significant reduction in the plasma concentration of high-density lipoprotein cholesterol. Obese subjects had significantly elevated fasting insulin and were considered insulin resistant on the basis of the HOMA score (19).

Chylomicron kinetics were studied in lean and viscerally obese men using apoB48 and retinyl ester incorporated into chylomicrons. The IAUC values (corrected for fasting levels) for apoB48 and RP are shown in Fig. 1, A and B, respectively. The AUCs for each marker of chylomicron kinetics were found to be significantly greater in obese subjects compared with lean controls (Table 2). Moreover, we found a significantly higher concentration of plasma apoB48 in obese subjects before the lipid meal (31.5 ± 7.5 vs. 12.69 ± 1.65 μg/ml, P < 0.005).

LPL and HL activities were determined in postheparin plasma collected at the conclusion of the oral fat challenge. We found no difference in the activities of either LPL or HP (Fig. 2) in obese vs. lean subjects. However, the triglyceride kinetic data in vivo suggested that there may have been some delay in net lipolytic rates. In obese subjects, plasma triglyceride concentration was at its highest 6 h after the lipid meal, whereas in lean subjects this occurred at 4 h. Moreover, the triglyceride IAUC was 68% greater in obese subjects after normalization for the fasting levels (4.7 ± 0.6 vs. 2.8 ± 0.8 mM·h; P < 0.06; Fig. 3C and Table 2).

LDL receptor activity was assessed by measuring the binding of gold-labeled LDL to mononuclear cells collected on the morning of the postprandial assessment. Figure 3 shows that binding of gold-labeled LDL to mononuclear cells of obese subjects was only 55% that of controls (70.9 ± 15.07 vs. 38.9 ± 4.6, P = 0.021).

<table>
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<th>Table 1. Subject characteristics obtained at screening</th>
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Values are means ± SE; n, no. of male subjects in group. Wt, weight; Ht, height; WHR, waist-to-hip ratio. Determined from fasting blood: TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; homeostatic model assessment (HOMA) score: product of fasting insulin concentration (mU/l) and fasting glucose concentration (mM) divided by 22.5.
Correlation analysis was used to explore potential regulatory factors of postprandial dyslipidemia in viscerally obese and lean subjects. Predictably, BMI and waist circumference correlated strongly with fat mass ($r = 0.79, P = 0.003$ and $r = 0.83, P = 0.001$, respectively). There was also a strong positive relationship between obesity (assessed from BMI) and fasting plasma insulin or the insulin receptor as assessed by use of the HOMA score ($r = 0.70, P = 0.0001$). There was a weak but significant correlation of BMI with fasting apoB48 ($r = 0.35, P = 0.021$) and postprandial lipemia ($r = 0.51, P = 0.002$). In contrast, we found no association between fasting insulin or insulin resistance and $RP_{AUC}$, $apoB_{48-IAUC}$, or fasting $apoB_{48}$.

**DISCUSSION**

The major findings of this study are that men with visceral obesity have postprandial dyslipidemia, possibly as a consequence of decreased clearance via high-affinity pathways. Viscerally obese men were found to have significantly reduced LDL-receptor binding of lipoproteins on circulating mononuclear cells compared with lean healthy controls. In vivo, the LDL receptor is considered to be a primary route of remnant clearance and, when compromised, is known to lead to remnant accumulation in other nonobese dyslipidemic phenotypes (16, 28). Mononuclear cell receptor expression closely parallels hepatic activity (27), suggesting that reduced clearance of chylomicron remnants in insulin-resistant subjects may have contributed to postprandial dyslipidemia and been responsible for the accumulation of proatherogenic remnants in the fasted state. A reduction in LDL-receptor expression would also predictably lead to raised plasma LDL cholesterol, yet hypercholesterolemia is not a concomitant feature of the insulin-resistant state. What appear to be paradoxical findings may be explained in the relative affinity of the LDL receptor for lipoproteins that utilize apoE as the ligand vs. those that utilize $apoB_{100}$. Remnant lipoproteins bind to the LDL receptor via apoE and require approximately four receptors for internalization, whereas LDL requires one receptor for uptake, because binding occurs via $apoB_{100}$. Hence, in subjects with visceral obesity, a modest reduction in LDL-receptor expression would influence clearance of apoE-containing lipoproteins to a greater extent than those lipoproteins that bind via $apoB_{100}$. In other words, an accumulation of remnant lipoproteins might occur before that of LDL. Indeed remnant competition for receptor-mediated clearance might be responsible for LDL accumulation. It was interesting to note that, in this study, obese subjects had significantly greater LDL cholesterol than lean subjects. However, at a mean concentration of just 3.3 mM, this would not necessarily be considered to be of clinical significance.

If, as we have suggested, insulin insensitivity leads to a reduction in LDL-receptor expression and consequently remnant dyslipidemia, one might have ex-
expected to identify an association between the two variables, but we found no such relationship. However, this approach makes the assumption that insulin concentration is controlled to optimize LDL-receptor expression, an argument that in our view has little physiological basis. Rather, insulin concentrations would be critically controlled by glucose homeostasis, in which case decreased LDL-receptor activity would then be a secondary phenomenon associated with the insulin-resistant state. Clearly, there are limitations in seeking associations between measures of insulin sensitivity (particularly those derived from glucose challenges) and lipid homeostasis. However, a lack of association does not exclude insulin regulation of the processes surrounding lipid metabolism. Hyperinsulinemia is thought to be a compensatory mechanism designed to correct for metabolic abnormalities in response to a state of hormone resistance. Our observations of postprandial dyslipidemia in hyperinsulinemic obese subjects suggest that compensatory oversecretion of insulin was insufficient to overcome abnormal kinetics of insulin action on postprandial lipemia. Interestingly, similar conclusions have been drawn with respect to the impact of hyperinsulinemia on glucose homeostasis (28).

Reduced rates of triglyceride lipolysis by endothelial lipases are widely thought to contribute to hypertriglyceridemia in insulin-resistant and diabetic subjects (37) on the basis of known stimulatory effects of insulin on adipose tissue LPL. In vivo, clearance of triglyceride is primarily a reflection of the hydrolytic cascade and to a lesser extent is a consequence of lipoprotein internalization by high-affinity pathways. In this study, hydrolytic capacity did not appear to be diminished in obese subjects on the basis of postheparin lipase activities determined ex vivo. Nonetheless, a significant delay in the peak triglyceride response and greater triglyceride IAUC suggested that conversion of triglyceride-rich lipoproteins to remnants may have been aberrant in viscerally obese subjects. Whereas our observations are consistent with the views of some laboratories (37), others have found no evidence of defective lipolysis in viscerally obese subjects. In fact, Minihane et al. (23) recently reported a more favorable postprandial triglyceride response with greater fat accumulation around the waist. These and other paradoxical observations might be explained by the intriguing findings of Potts et al. (25), who indirectly compared VLDL- and chylomicron-triglyceride lipolysis by monitoring, in vivo, triglyceride extraction through a perfused adipose tissue bed. In their study of subjects with diabetes mellitus, VLDL-triglyceride hydrolysis was reduced, whereas chylomicron triglyceride extraction was surprisingly increased. This is the first discriminatory evidence of substrate specificity of endothelial lipases for triglyceride-rich lipoproteins. If these observations are to be extrapolated to our study and to that of some others (4, 8), they would suggest that hypertriglyceridemia in insulin-resistant viscerally obese men might predominantly reflect an accumulation of poorly hydrolyzed VLDL, as well as of properly hydrolyzed chylomicron remnants. Consistent with this possibility were the recent results of Mekki et al. (22), who found that postprandial dyslipidemia in viscerally obese individuals was accompanied by an accumulation of chylomicrons that were smaller in size. Their observations could be explained as an accumulation of postlipolyzed remnant particles.

Postprandial dyslipidemia may not necessarily be confined to an accumulation of lipoproteins of intestinal origin. Competition for endothelial lipases and high-affinity uptake pathways may lead to a concomitant increase in lipoproteins of hepatic origin. Moreover, increased substrate delivery to the liver after an oral fat challenge may also encourage greater rates of VLDL secretion. However, the latter is unlikely to be of significance given the acute experimental design employed. Lewis et al. (14) attempted to distinguish between triglyceride-rich lipoprotein particles derived from the intestine and liver. On the basis of cumulative increment in total plasma triglycerides vs. retinyl esters, they concluded that postprandial lipemia was primarily due to endogenous hepatic lipoproteins. However, we think that this approach may be flawed because of the known differences in incorporation and secretion between chylomicron triglycerides and vitamin A (6). Most studies suggest an ~2-h lag time between the two markers, with triglycerides appearing before the esterified vitamin.

In our study, we utilized two markers of chylomicrons, including apoB_{48}, to monitor chylomycin kinetics, the latter being an equivocal marker of intestinally derived lipoproteins. The apoB_{48} and RP IAUCs after the oral lipid challenge were both substantially greater in obese subjects compared with the lean control group, demonstrating a metabolic defect. We are unable to delineate whether chylomicron dyslipidemia in obese subjects is due to overproduction, a delay in hydrolysis, and/or defects in clearance pathways. However, given that the apoB_{48} concentration was significantly greater in fasted obese subjects (where production is presumably reduced) and that LDL-receptor activity was halved, we would suggest that a delay in clearance is quite likely. Whichever marker of chylomicrons was
used, neither correlated with the level of insulin sensitivity, possibly for the reasons already eluded to. Byrne et al. (4) investigated the triglyceride response to a fat meal in hyperinsulinenic men and also concluded that, although insulin resistance was associated with fasting triglyceride concentrations, there was no evidence of a relationship with postprandial lipemia. However, in contrast, others have found associations between markers of chylomicron metabolism and insulin sensitivity. In a complementary study, Mekki et al. (22) reported that most postprandial triglyceriderich lipoprotein abnormalities did indeed correlate with plasma levels of insulin in subjects with android obesity. It is possible that the different findings between laboratories might have reflected the type of lipid challenge provided. Mekki et al. used a mixed meal containing carbohydrates, which induced an acute insulin response. It may be that the hyperinsulinenic response after the mixed meal provided acute regulation of chylomicron metabolism. In contrast, in our study and in the study of Byrne et al., a carbohydrate-free lipid challenge was given. We found that this type of meal did not induce a postprandial insulin response (unpublished observations).

In animals and in cultured cells, the apoC-III gene is transcriptionally downregulated by insulin through an insulin-responsive element-like sequence in the promoter region. Loss of insulin regulation of the apoC-III gene was demonstrated in diabetic mice (5) and may occur in insulin-resistant states such as visceral obesity. In vitro, apoC-III inhibits LPL activity and the uptake of remnant lipoproteins (35). Moreover, apoC-III levels correlate with plasma triglyceride levels (36). Although not measured in this study, raised apoC-III may have been a contributing factor to hypertriglyceridemia and remnant dyslipidemia in viscerally obese subjects.

Collectively, we have shown for the first time that subjects with visceral obesity have an accumulation in plasma of lipoproteins of intestinal origin. Subtle and perhaps chronic changes in the clearance of posthydrolyzed chylomicrons might contribute to the elevation of these proatherogenic lipoproteins. Insulin may be central to the metabolic defect of chylomicron dyslipidemia, and therefore one would predict that interventions aimed at restoring insulin sensitivity might attenuate the raised concentration of these proatherogenic lipoproteins.

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