Atherogenic Nature of Triglycerides, Postprandial Lipidemia, and Triglyceride-Rich Remnant Lipoproteins

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In addition to low-density lipoproteins, plasma chylomicrons and very-low-density lipoproteins (VLDL) contribute to atherogenesis. When triglyceride-rich particles bind to arterial endothelium and to deendothelialized areas, locally present lipoprotein lipase initiates triglyceride hydrolysis and decreases the size of the adhering particles. Additional changes in composition are brought about by the exchange of lipids between chylomicron/VLDL remnants and the cholesteryl ester-rich low- and high-density lipoproteins. These exchanges are mediated by lipid transfer proteins in plasma. Animal studies with doubly labeled lipoproteins show that the size of lipoprotein particles determines their rate of entering the artery and contributes to the formation of lesions. This model supports epidemiologic studies that have identified plasma triglycerides as a risk factor for atherogenesis. The model for a causal role of pre- and postprandial triglyceride-rich lipoproteins in atherogenesis suggests that measuring them may improve the assessment of cardiovascular risk factors.

**Indexing Terms:** chylomicrons/hypertriglyceridemia/lipoprotein lipase/lipid transfer protein/metabolism

A previous review (1) posed the question: Do plasma triglyceride-rich lipoproteins contribute to atherogenesis in addition to the much better established causative role of low-density lipoproteins? A subsequent article addressed more specifically the role of the postprandial lipid particles in plasma (2). In both instances I proposed that triglyceride-rich and cholesteryl-containing particles were bound to arterial endothelium or to deendothelialized areas, where lipoprotein lipase would then initiate triglyceride hydrolysis and decrease the size of the adhering particles so that they could enter the deeper structures of the arterial wall. Here I will review the current evidence for a causal role of endogenous and postprandial triglyceride-rich particles in atherogenesis. Havel, in a recent review of studies on lipoproteins contributing to postprandial hyperlipidemia, concluded that chylomicron and very-low-density lipoprotein (VLDL) remnants are atherogenic (3).

**Lipoprotein Metabolism**

Triglyceride-rich lipoproteins in plasma originate either in the liver (VLDL) or intestine (chylomicron). Both also contain cholesterol, cholesteryl ester, and phospholipid, as well as several proteins. A large lipoprotein, apoprotein B (apoB), is present in both types of particles, but, in humans, the intestinal polypeptide contains only 48% of the liver protein, hence the names apoB-48 and apoB-100. These proteins are envisioned as a coat for particles that are packed with lipids: Triglyceride and esterified cholesterol are present primarily in the particle core, whereas the unesterified cholesterol and phospholipid, with apoB and a variety of proteins, are located on the surface.

During their presence in plasma, both surface and core lipids are subject to mutual exchange of lipid molecules with other lipoproteins. These transfers are mediated by lipid-transfer proteins (4–8). One consequence of this bidirectional lipid "hetero-exchange" is that, in the presence of increased serum triglyceride concentrations, a net transfer of triglyceride from VLDL and chylomicrons to low- and high-density lipoproteins (LDL and HDL, respectively) takes place with a simultaneous back-transfer of cholesteryl ester from LDL and HDL to the lower-density particles. Consequently, these particles, while shedding some of their triglycerides, acquire larger amounts of cholesteryl ester. This hetero-exchange (7, 9) accounts for the lower ratio of total cholesterol/apoB in LDL, both in humans and in experimental animals, at high concentrations of serum triglycerides (10). The lipid exchange activity is markedly increased during hyperlipidemic states in animals (11) and in humans (12). It seems likely that the remnant particles, while they circulate and acquire additional cholesteryl ester as the result of the lipid exchange with HDL, will become more atherogenic because of the increased cholesterol content of the remnant particles (11).

The hydrolysis of triglycerides by lipoprotein lipase produces some further changes in the chylomicrons and VLDL. Distributed over the vascular surfaces, lipoprotein lipase seems to bind to the lipid particles during the process of lipolysis (13). A much smaller particle that results from this lipolytic process, the chylomicron or VLDL remnant, may undergo further changes in composition due to exchanges of lipids and smaller proteins on the particle surface. One of the surface proteins, apoE, is acquired from HDL and is responsible for much of the binding of chylomicron remnants by hepatocytes. This binding is probably mediated by heparan sulfate proteoglycans and/or lipoprotein lipase as well as lipo-

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1 Nonstandard abbreviations: HDL, IDL, LDL, VLDL, high-, intermediate-, low-, and very-low-density lipoproteins; apo, apoprotein; CHD, coronary heart disease; and CAD, coronary artery disease.

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protein receptors such as the LDL receptor, the LDL receptor-related protein, and the apoE receptor (14–17). An additional chylomicron remnant receptor has been described and has been named the lipolysis-stimulated receptor. This receptor appears to be activated by the presence of free fatty acids in the lipid particles (18).

The extent to which VLDL in normal individuals is converted to LDL was thought to be near 100%, but has more recently been estimated as <50% (19–21). In endogenous hypertriglyceridemia, remnants are circulating for longer periods; they have been shown to bind and become internalized at different stages of lipolysis by the LDL receptor (22) and probably also by the hepatic chylomicron receptors (21). Hypertriglyceridemia, after ingestion of a high-fat meal, can frequently be represented by a biphasic curve. The early part is due to the influx of chylomicrons, whereas at later times the triglycerides are a mixture of those originating in intestine and liver (23).

The relative plasma triglyceride mass originating in the intestine can be estimated by determining the ratio of plasma retinyl esters to triglyceride after feeding a high-fat meal enriched with retinol (24–27). By this procedure, a moderate increase in postprandial chylomicron concentrations was observed in type III and a larger increase in type IV patients (28). Similarly, after feeding a meal containing fat plus retinol, a delayed clearance of chylomicron remnants in patients with type III hyperlipoproteinemia (29) or with familial combined hyperlipidemia (30) could be demonstrated.

Postprandial hyperlipoproteinemia can also be analyzed into two components by measuring the relative increases in apoB-48 and apoB-100 in plasma (26, 27). Because each particle contains a single apoB molecule, the increments of these apoB's are a measure of the number of particles derived from intestine and liver. In humans fed a fat meal that also contains retinol, some of the retinyl esters are associated with apoB-100, particularly at the later time intervals (26, 27).

In subjects with mild triglyceridemia and hypoalphalipoproteinemia, a close association with coronary artery disease (CAD) is observed; they also show an impaired chylomicron clearance (31). During alimentary lipidemia there appears to be a competition between the clearance of VLDL and chylomicrons. For example, in a study of the metabolism of triglyceride-rich lipoproteins in normo- and hypertriglyceridemic persons, the latter showed delayed clearance of chylomicrons (32) and a pronounced increase in the larger chylomicron remnants after an oral fat load (33). This increase could have resulted from a competition of lipid particles for available lipoprotein lipase (34).

The above findings suggest that chylomicron remnant clearance might be a saturable process. This is confirmed by a direct experiment in which retinyl ester-labeled plasma chylomicrons were injected into healthy subjects (35). An important determinant of the clearance of chylomicron remnants is the phenotype of apoE associated with these particles (36). Grundy and Vega (34), who have discussed different connections between heart disease and hypertriglyceridemia, stress that knowing these connections is important in devising therapies.

Arterial Flux of Lipoproteins

An in vivo approach to the role of different lipoproteins in atherogenesis was pursued in rabbits with isotopically labeled lipoprotein fractions (37, 38). The results were expressed as intimal clearance of a lipoprotein by the aorta, in analogy with the renal clearance of solutes. The arterial clearance was defined as the influx of lipoprotein cholesterol mass (picomoles per square centimeter of arterial surface per hour) divided by its concentration in plasma. This clearance is a measure of arterial permeability to different lipoprotein fractions, whereas cholesterol mass influx depends on both arterial permeability and plasma lipoprotein concentrations. The intimal clearance of VLDL-cholesterol or apoB-100 was less than that for LDL, HDL, or plasma albumin, with the arterial clearance being inversely related to the logarithm of their molecular diameters (33). Arterial clearances of LDL and VDL/intermediate-density lipoprotein (IDL)-cholesterol not only was related to the size of the lipoprotein particles, but also increased greatly with lesion progression. The arterial clearance of plasma cholesterol ester in arteries with maximal lesions was 50-fold that for those with minimal lesions (39). It is not known whether this increase signifies greater permeability or increased arterial cellular activity.

Determining the influx of VLDL or chylomicron remnants in arteries of human subjects, of course, is much more difficult. When the simultaneous influx of labeled IDL and VLDL in carotid arteries was measured, intimal clearance of the VLDL particles was not detectable, but intimal clearance of LDL and of IDL remnants was appreciable and about equal in magnitude (40).

From the foregoing results one would expect that the arterial clearance of the larger chylomicrons would be significantly less than that of their remnants. In a study in which cholesteryl ester-labeled rabbit thoracic duct lymph chylomicrons and plasma chylomicron remnants were injected simultaneously into hypercholesterolemic rabbits (41), the direct uptake of chylomicron cholesteryl ester was <1–5% of the cholesteryl ester influx from other plasma lipoproteins. Similar findings were observed in severely hypertriglyceridemic and hypercholesterolemic alloxan-diabetic rabbits (42–44), rabbits known to develop few, if any, arterial lesions (45). In the rabbits' plasma, more than half of the cholesterol was present in triglyceride-rich particles >75 nm in diameter, and the arterial influx of these particles was extremely slow (42). This slow influx is probably mediated, in part, by the lower concentrations of heparin-releasable lipoprotein lipase present (43), which, at normal values, would convert the large lipoprotein particles to smaller remnants.

Apparently, therefore, the direct atherogenic impact of the chylomicrons themselves is negligible. However, the conversion of chylomicrons to remnants with significant amounts of cholesteryl ester derived from ab-
sorbed cholesterol and from hetero-exchange with other lipoproteins may account for significant atherogenesis when these remnants interact with the arterial wall.

Triglyceride as Risk Factor for Cardiovascular Disease

**Fasting triglyceridemia.** The hypothesis that triglyceride-rich lipoproteins make an independent contribution to atherosclerosis has received support from animal studies (see above) and is gaining support for humans as well (34, 46–63). A comprehensive review of the relationship of plasma triglycerides and coronary heart disease (CHD) in men and women was published by Austin in 1991 (58). She reviewed case-control, cross-sectional, and prospective studies as well as several angiographic investigations. Most of the studies reported a positive univariate relation between plasma triglycerides and CHD in men and women, but when these relationships were progressively adjusted for plasma total cholesterol, LDL-cholesterol, and HDL-cholesterol, the relationship in many of the studies was weakened or disappeared altogether.

When individuals exhibit increased plasma triglycerides plus another lipid-related risk factor, the relationship with CHD may be strengthened. Increased serum triglycerides plus a low HDL-cholesterol have been postulated as lipid-related risk factors for CHD in addition to total or LDL-cholesterol (see 31). On the basis of the Framingham data, Castelli (64) concluded that a hypo-HDL/hypertriglyceridemia syndrome is common in our society, accounting for twice as many cases of CHD than the highest lipid risk factor. In a summary of the PROCAM study after 6 years of follow-up, Assmann and Schulte (59) reported that, upon multivariate analysis of the data, hypertriglyceridemia was a powerful risk factor in the presence of a high LDL/HDL-cholesterol ratio. Although this subgroup represented only 4.3% of all participants, it contained 25% of the incidence of atherosclerotic CAD. Similar analyses of data from the Helsinki Heart Study (65) strongly supported these results, but the study from Rome by Menotti et al. (66) found no evidence for triglycerides as an independent risk factor. An angiographic study relating plasma lipoproteins to lesion progression and clinical events demonstrated that increased concentrations of remnants, as well as low concentrations of HDL-cholesterol, were indicators of progressing coronary artery stenosis, whereas LDL-cholesterol was not (67).

Part of the difficulty in the interpretation of epidemiologic and case-control studies results from the frequently observed inverse correlation between fasting concentrations of plasma HDL-cholesterol and VLDL-triglyceride. Subsequent analysis of the data by multiple regression often fails to identify plasma triglyceride as an independent risk factor for CHD. When, therefore, a correlation between plasma VLDL and CHD is observed, the usual interpretation is that the CHD is "caused" by low HDL concentrations rather than the increased triglyceride (68). The causal inference from statistical analysis is weak unless the results are also supported by a biomedical model. Moreover, the multivariate analysis has been criticized (61) because of the metabolic linkage between HDL-cholesterol and triglyceride metabolism and the relatively large variance for plasma triglyceride compared with that for HDL-cholesterol (58, 61).

**Postprandial triglyceridemia.** In a case control study of 82 subjects with CAD (62), Simons et al. measured a variety of plasma lipids and lipoproteins as well as other risk factors in both fasting subjects and the same subjects 4 h after a triglyceride/cholesterol-rich meal. The presence of CAD was significantly related to postprandial plasma concentrations of cholesterol and triglycerides, the total cholesterol/HDL-cholesterol ratio, and the apo B-48/apo B-100 ratio in the Sf >60 fraction. Chylomicrons and their remnants were independent predictors of atherosclerosis and CAD in a dose-response fashion. Groot et al. (57) also concluded that delayed clearance of chylomicron particles may account for increased CHD risk.

In a case-control study of about 100 individuals, Patsch et al. (69) evaluated the role of plasma triglycerides in CAD. Multivariate analysis showed that the magnitude of postprandial hypertriglyceridemia was an independent predictor of the presence or absence of stenoses. In a review of hyperlipidemia by Miesenböck and Patsch (23), they present a "triglyceride intolerance hypothesis," in which CAD is linked to an impaired triglyceride transport. Because, according to these authors, the triglyceride metabolic capacity determines the concentration of HDL-cholesterol, they postulate that the generally accepted relation between low HDL and CAD may be a marker for a causal relation between plasma triglyceride and CAD. Furthermore, in persons with prolonged increases of plasma triglycerides, either fasting or postprandial, the process of hetero-exchange (7, 9, 11), as explained earlier, would enrich the triglyceride-rich particles in cholesteryl ester and thereby make these particles more atherogenic (11, 23).

In an angiographic study on survivors of a myocardial infarction before age 45, Karpe et al. were unable to relate HDL-cholesterol to the progression of coronary atherosclerosis; however, the number of small chylomicron remnants during the postprandial phase appeared to explain the observed disease progression (70, 71). Ryu et al. observed that, in middle-aged subjects with moderate hypercholesterolemia, the peak postprandial triglyceride response after a fatty meal was correlated with carotid artery wall thickness (72). They concluded, on the basis of multivariate analysis, that prolonged exposure to postprandial lipid particles promotes atherogenesis.

Chung et al. (73) isolated liposome-like particles from postmortem human aortas. These particles, present in the extracellular spaces of the arterial wall, resembled both chemically and morphologically the surface material released from triglyceride-rich lipoproteins during lipolysis. These findings support the conclusion from epidemiological studies that triglyceride-containing lipoproteins are causally related to atherogenesis. However, as we discussed above, the size of the lipoprotein...
particles is one of the determinants of their arterial uptake. The smaller particles may be strongly atherogenic, whereas the larger ones may contribute to atherogenesis only if the body is capable of degrading them to smaller ones.

In a recent reevaluation of the remnant hypothesis, Slyper (74) states that there is no good in vivo evidence that HDL-cholesterol reflects the extent of reverse cholesterol transport and concludes, "The atherogenic remnant hypothesis provides a more satisfactory explanation for many of the facts than does the LDL–HDL model."

**Dietary Fats**

The effect of dietary fats on serum cholesterol concentration has been widely investigated by epidemiological, clinical, and experimental animal studies for the past 50 years or so (75–79). Much less has been learned about the effects of dietary fats on serum triglyceride concentrations. In one study on young normolipidemic volunteers, the substitution of polyunsaturated fat for saturated fat in their diet resulted in a 45% decrease of postprandial lipoprotein particles as measured by apoB-48. This decrease apparently resulted from an increased chylomicron and remnant clearance on the polyunsaturated fat diet (80).

A metaanalysis of 27 trials on the effect of dietary fatty acids on serum lipids and lipoproteins (81) compared the effects of dietary fats and carbohydrate on serum triglyceride concentration. Regardless of the degree of saturation/unsaturation, the replacement of dietary carbohydrate by fat lowered the fasting serum concentration of triglycerides. The only category of dietary fats that showed a more pronounced triglyceride-lowering effect than the others was the fish oils (81–85).

Eight normolipidemic men, ages 19–37, were given diets or single meals of saturated vs n-6 or n-3 polyunsaturated fats; their chylomicron concentrations were significantly greater after the consumption of saturated fat (86). Compared with other oils, the ingestion of fish oils markedly lowered the concentrations of endogenous and postprandial triglycerides (83, 85, 86). The effect of chronic fish oil consumption was not associated with increases in post-heparin lipase activity, and the hypertriglyceridemic effect was probably not due to accelerated chylomicron clearance (82), a supposition confirmed by intravenous fat-clearance tests (85).

A dietary fat load in elderly individuals, with or without fasting hypertriglyceridemia, produced a delayed peak concentration of plasma triglyceride (87). With use of retinyl ester as a marker for chylomicrons, a comparison of younger and older individuals clearly showed a higher retinyl ester response for the older individuals, which could be traced to slower clearance of chylomicron retinyl esters (88). Healthy octogenarians with no CHD may present an exception to this rule, demonstrating decreases in neither chylomicron clearance nor lipoprotein lipase activity (89). Of course, this "exception" may simply explain the favorable health status of these octogenarians.

**Thrombosis**

Some 46 publications on HDL, triglycerides, and the coagulation system between 1986 and the beginning of 1992 have been noted in Current Bibliographies in Medicine (90); I shall touch on only a few of these.

An increase in the number of circulating triglyceride particles is known to lead to unfavorable changes in the pro-atherogenic thrombotic system such as increased factor VII, factor X, and fibrinogen. Earlier studies are included in a review of hypertriglyceridemia by Grundy and Vega (34). The increased thrombogenicity of high-fat diets has been ascribed to the postprandial activation of factor VII (91). Salomaa et al. (92) found no significant differences between the procoagulatory effects of saturated and n-6 polyunsaturated dietary fats (as cream and sunflower oil, respectively). Yet, a study by Mitroupoulos et al. (93) found a strong association between plasma stearic acid concentration and increases of factor VIIc after a diet high in saturated fat.

**Summary**

This review updates the evidence for a model whereby triglyceride-rich lipoproteins contribute to atherogenesis and (or) thrombotic events that precede myocardial infarction or stroke. The binding of VLDL or chylomicrons to arterial surfaces containing lipoprotein lipase is followed by triglyceride lipolysis and hetero-exchange, whereby the particles decrease in size and become enriched in cholesteryl esters. The simultaneous release of fatty acids may cause endothelial injury and initiate thrombotic events. In individuals with high concentrations of VLDL or chylomycin remnants as well as in those with increased LDL, arterial uptake of free and esterified cholesterol is greater than that in individuals with lower concentrations of lipoproteins. Because lipoprotein influx proceeds in the postprandial state as well as fasting, a person with relatively high consumption of fats and cholesterol may be at higher risk for CHD than is indicated by the lipid or lipoprotein profile measured in the fasting subject.

**References**


CLINICAL CHEMISTRY, Vol. 41, No. 1, 1995 157


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