Postprandial Lipemia and Cardiovascular Disease

Dianne Hyson, PhD, John C. Rutledge, MD, and Lars Berglund, MD, PhD

Address
Department of Medicine, University of California, Davis, 4150 V Street, Suite G400, Sacramento, CA 95817, USA.
E-mail: lberglund@ucdavis.edu

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Postprandial lipemia, characterized by a rise in triglyceride-rich lipoproteins after eating, is a dynamic, nonsteady-state condition in which humans spend the majority of time. There are several lines of evidence suggesting that postprandial lipemia increases risk of atherogenesis. Clinical data show a correlation between postprandial lipoproteins and the presence/progression of coronary artery disease and carotid intimal thickness. Mechanistic studies demonstrate that triglyceride-rich lipoprotein remnants may have adverse effects on endothelium and can penetrate into the subendothelial space. Exchange of core lipids between postprandial lipoproteins and low-density lipoprotein (LDL)/high-density lipoprotein (HDL) is increased during prolonged lipemia, resulting in small, dense LDL particles and reduced HDL cholesterol levels. Hemostatic variables, including clotting factors, platelet reactivity, and monocyte cytokine expression, may be increased during postprandial lipemia. Collectively, these data suggest that assessment and treatment of atherosclerosis should include parameters related to postprandial lipemia.

Introduction

Much of our knowledge about the relationship between lipid and lipoprotein metabolism and development of atherosclerosis and cardiovascular disease is based on measurements in the fasting state. Although such measurements remain the foundation of clinical assessment and an important basis for decisions regarding hypolipidemic interventions, it should be acknowledged that we spend a considerable amount of time in a nonfasting, postprandial state. Based on typical American eating patterns, most people consume three or more meals a day, with each containing 20 to 70 g of fat [1]. Each of these meals is most likely consumed before plasma triglycerides have returned to baseline levels from the lipemic conditions resulting from the previous intake. Thus, humans spend the majority of their day in a postprandial (fed) state, with a continual fluctuation in the degree of lipemia throughout the day. The postprandial state is a dynamic, nonsteady-state condition, with rapid remodeling of lipoproteins compared with the relatively stable fasting condition. Determination of the postprandial response is complex, and it is, therefore, more challenging to assess the cardiovascular risk associated with postprandial lipemia than during fasting conditions. In spite of this, it is becoming increasingly evident that future efforts to study and treat lipids related to atherogenesis should include postprandial parameters.

Metabolism of Postprandial Triglyceride-rich Lipoproteins

Chylomicron production and secretion

Upon digestion and absorption of dietary fat, short- and medium-chain fatty acids are albumin-bound and transported directly to the liver. Long-chain fatty acids are re-esterified into triglycerides (TG) and "packaged" into large chylomicron (CM) particles in the Golgi complex of intestinal cells. Assembly and secretion of CM is dependent upon the presence of apolipoprotein (apo) B-48, which in humans is synthesized only in the intestine [1]. The fasting level of apoB-48 is very low or barely detectable in most individuals [2,3].

Upon entering the circulation, CMs interact with lipoprotein lipase (LPL) to hydrolyze TG to monoglycerides and fatty acids on the surface of endothelial cells, primarily in adipose and muscle tissue [4]. These hydrolytic products are either bound to albumin or rapidly taken up by muscle for oxidation or by adipose tissue for storage [4].

After approximately 90% of the hydrolysis is complete, the CMs, now designated as CM remnants (CMR), are released back into the circulation [2]. ApoE is the predominant protein remaining with the CMR and is important in mediating the hepatic uptake of these particles [5]. Upon binding to the receptors, CMR are rapidly internalized via coated pits on the cell and the particles are subsequently degraded in the lysosomes [4].

Very low-density lipoprotein metabolism

At least two apparent populations of very low-density lipoprotein (VLDL) particles, ranging in size from 50 to 70 nm, are secreted by the liver [6]. Secretion of the larger population, the postprandial VLDL particles, appears to be

regulated by insulin-sensitive mechanisms in the fed state [5]. The regulation of the second, TG-poorer population of VLDL is less well characterized. In the postprandial state, insulin stimulates endothelial LPL to hydrolyze CM, generating a source of long-chain fatty acids to be shunted to the liver [7]. De novo synthesis of fatty acids as a source of hepatic TG for VLDL is not likely a significant source of fatty acids in humans under normal conditions [3,8••]. Newly synthesized VLDL contains apoB-100, as well as some apoE and apoC [4,5]. It has been suggested that apoE plays a role in the synthesis and secretion pathways for VLDL [9–11]. Upon release into the circulation, VLDL acquires additional apoE and apoC from circulating HDL [4,5]. The subsequent metabolism of VLDL follows a path similar to that of CM, where VLDL competes with CM and CMR for LPL. However, because VLDL is smaller than CM, each particle presumably interacts with fewer LPL molecules and is hydrolyzed more slowly. The on-going TG depletion and concurrent loss of apoE and apoC result in progressively smaller VLDL (referred to as VLDL remnants) or intermediate-density lipoproteins (IDL), and ultimately LDL particles. ApoB-100 remains with the particle until the final degradation occurs in the hepatocytes.

The competition between intestinal and hepatic triglyceride-rich lipoproteins (TGRL) for the same lipolytic and receptor-mediated uptake pathways accounts, in part, for the accumulation of these particles during the postprandial period [12]. Primarily, endogenous or hepatic TGRL accumulate in the plasma after fat intake, presumably due to less efficient hydrolysis of VLDL by LPL [4,13,14]. At the peak of postprandial lipemia, the increase in apoB-100–containing particles is much greater than that of apoB-48–containing particles, accounting for up to 80% of the increase in particle number [14]. However, due to the large size of CM and CMR, approximately 80% of the postprandial rise in TG is accounted for by apoB-48–containing particles (*ie*, large quantities of TG are transported in relatively few large CM particles). However, the half-life of CM particles and remnants is variable, and for smaller size particles may be as long as circulating VLDL of corresponding size [15].

During the postprandial period there is an active exchange of lipids between circulating lipoproteins [16]. The outcome of the lipid exchange is cholesteryl ester (CE) enrichment of TGRL at the expense of CE in LDL and high-density lipoprotein (HDL). The lipid exchange between lipoproteins during prolonged postprandial lipemia is of interest because of the relationship between lipoprotein size, composition, and potential atherogenicity [6,17].

Factors Affecting the Postprandial Response

A variety of factors affect the duration and extent of elevated TG in the postprandial period. In particular, fasting levels of plasma TG tend to be correlated with the magnitude of postprandial lipemic response [1]. Thus, hypertriglyceridemic individuals have a fourfold increase in the half-life of circulating TGRL, particularly those of intestinal origin, possibly due to a reduction in LPL activity.

Several conditions characterized by elevated TG and insulin resistance are associated with exaggerated postprandial lipemia, such as the dyslipidemia that accompanies diabetes [18,19]. In a recent study, the degree of insulin sensitivity was a determinant of postprandial lipemia among healthy middle-aged men [20]. The mechanisms are not entirely understood but are likely due to aberrant insulin-mediated suppression of hepatic VLDL production and fatty-acid release from adipose tissue [5]. The resulting increase in VLDL secretion is associated with prolonged residence time in the circulation due to increased competition with intestinal CM for the common removal pathways, as described earlier.

Obesity is associated with several metabolic abnormalities, including hypertriglyceridemia and hyperinsulinemia, that would predict an exaggerated postprandial lipid response. However, even in the absence of these associated conditions, obese individuals may have up to three times higher postprandial TG levels than non-obese control patients [21]. In a postprandial study of non-obese and obese subjects, Goldberg *et al*. [22•] reported a significant correlation between LPL activity and the postprandial TG response only among the non-obese subjects. These findings suggest a different relationship between LPL activity and lipoproteins in obesity.

Protocols for assessing postprandial lipemic response usually involve administering a fat challenge or test meal to an individual following an overnight fast and then obtaining blood samples at hourly or bi-hourly intervals for 6 to 24 hours afterward. Postprandial lipemia is influenced by the amount and type of dietary fat present in the test meal, as well as other dietary components including fiber, glucose, starch, and alcohol [23–25]. Intake of long-chain omega (n)-3 polyunsaturated fatty acids (predominantly fish oil), results in lower TG levels and attenuates postprandial lipemia [26]. The habitual diet of an individual may also influence the postprandial response [25].

Apart from the habitual diet, the postprandial response is affected by other lifestyle factors. Exercise has been shown to blunt the TG response during and after the activity [27]. In general, participation in regular exercise lowers fasting TG. The postprandial response to an oral fat load is lower and clearance rates of TGRL are higher in endurance-trained individuals compared with untrained control subjects, although this may not be applicable to moderate exercise [28].

In general, tolerance to oral fat intake decreases with age [1]. Information on postprandial lipemia in children is sparse, although in a recent study fasting triacylglycerol and HDL cholesterol, but not LDL cholesterol levels, predicted the postprandial response. Interestingly, there was a significant difference in postprandial response between children and their mothers in spite of similar baseline triglyceride levels [29•].

Gender also plays a role in postprandial lipemia. Premenopausal women tend to have lower fasting and postprandial TG levels compared to men [1]. However, menopause is associated with altered lipid parameters including increases in fasting TG levels and exaggerated postprandial lipemia [30]. Hormone replacement therapy is associated with an increase in triglycerides in parallel with a decrease in remnant cholesterol levels [31]. These results suggest that estrogen might induce a shift in the distribution pattern of triglyceride-rich lipoproteins, with a decrease of the more atherogenic fractions.

Genetic factors also play a role in the postprandial response. ApoE isoforms are important determinants of postprandial lipemia. It has been demonstrated that apoE2 homozygous subjects have the lowest affinity for TGRL-remnant receptor(s), and this genotype is associated with delayed postprandial clearance. Compared with apoE3 homozygous patients, apoE4 carriers tend to have enhanced clearance of remnants [32,33]. Beyond apoE, other genetic variants have also been shown to influence postprandial clearance, including apolipoproteins AI and AIV [34–36].

Several clinical studies have provided evidence that subjects with diagnosed coronary artery disease (CAD) have a prolonged postprandial response, as well as higher TG levels for several hours post-consumption compared with disease-free control subjects [5,37,38]. The increased TGRL production in the postprandial period may be independent of fasting TG plasma levels in subjects with CAD.

Experimental Evidence Linking Postprandial Lipemia with Atherosclerosis

The suggestion of a relationship between specific lipoprotein classes (including VLDL and IDL) and CAD was proposed over 50 years ago by Gofman *et al.* [39]. The extent to which fasting TG (*ie*, hepatic VLDL) contributes to the risk of CAD has been debated and is still unresolved. The potential atherogenicity of postprandial TG levels and TGRL did not gain widespread attention until the idea was put forth in a widely quoted paper by Zilversmit in 1979 [40], who proposed that hydrolysis of CM by LPL resulted in the subsequent internalization of CE-enriched CMR by arterial smooth muscle cells. A confirmation of this hypothesis has been complicated by the multiple factors impacting the postprandial response, the lack of standardized methodology, and the considerable heterogeneity among postprandial TRGL species. Evidence supporting an association between postprandial lipemia and atherosclerosis has been provided by clinical trials and mechanistic studies of both direct and indirect effects of TGRL using animal models and cell culture.

Clinical trials

Several clinical studies have shown that delayed elimination of postprandial TGRL is associated with atherosclerosis. There are also reports of an association between postprandial lipemic response and subsequent progression of atherosclerosis in patients with pre-existing CAD.

In men, the presence of CAD is associated with higher postprandial TG concentrations in plasma compared with healthy controls, even after correction for higher levels of fasting TG in the CAD group [16,38,41,42]. Subjects with CAD had higher plasma TG values from 4 to 8 hours compared with control subjects [38], and incremental TG levels in men with CAD were significantly elevated at 6 and 8 hours postprandially compared with healthy men. The data are less clear for women. One smaller study reported elevated postprandial TG and apoB-48 concentrations in women with coronary artery stenosis [42]. However, a larger study showed no significant relationship between prolonged postprandial lipemia and CAD in middle-aged women [43]. In a number of studies, carotid intimal-medial thickness (IMT) is used as a surrogate marker for atherosclerosis [44–46]. Boquist *et al.* [44] showed that several postprandial measurements, including total TG area under the curve and plasma TG levels between 1 and 4 hours, correlated with IMT. Other consistent IMT predictors included LDL cholesterol level and basal proinsulin levels [44]. Of note, this is one of the few studies to implicate an early postprandial TG level as a predictive factor for atherosclerosis. Other studies have confirmed a positive association between carotid IMT and postprandial lipemia [45,46]. Collectively, studies of IMT are suggestive of a link between postprandial metabolism and early manifestations of atherosclerosis. However, these data do not address the issue of whether prolonged postprandial lipemia predicts risk of developing CAD or whether the presence of CAD results in subsequent impairment of postprandial TGRL.

In order to address this question, one cross-sectional study examined postprandial TG levels after consumption of a high-fat liquid drink in healthy sons of men with angiographic evidence of severe CAD compared with sons of control subjects without CAD [47]. In spite of comparable fasting lipids between groups, sons of patients with CAD had significantly higher plasma TG after 8, 10, and 12 hours postprandially, indicative of delayed clearance of TG. These data were some of the first to suggest that altered postprandial lipid metabolism might be associated with familial risk for CAD. In another study in offspring of patients with CAD, young males with (case subjects) or without (control subjects) a paternal history of CAD underwent a postprandial study. Although no difference in postprandial TG was found in the groups as whole, subgroup analysis revealed an increased postprandial response among cases with a moderate elevation of fasting triglyceride levels [48].

There is evidence that higher levels of TGRL or their remnants predict progression of disease in subjects with established CAD. In The Montreal Heart Study, undertaken in 335 men and women with moderate to extensive CAD, the concentration of hepatic TGRL remnants predicted

progression of atherosclerosis [4]. Plasma levels of VLDL, IDL, and remnant cholesterol were positively correlated with angiographically determined progression of lesions in univariate analysis. IDL concentration was also a significant correlate in multivariate analysis. After a 4- to 6-year follow-up period, CAD-related clinical events were positively correlated to remnant cholesterol concentrations. Interestingly, LDL cholesterol concentrations were not related to either lesion progression or clinical events [4]. However, as the authors pointed out, because estimation of remnant cholesterol concentration is cumbersome and may be imprecise, few studies have examined the independent effect of TGRL remnants on CAD risk.

In a recent summary of clinical studies of postprandial lipemia and atherosclerosis, Karpe [5] suggested that elevated plasma TG measured at late postprandial time points after fat intake "might reveal a state of fat intolerance linked to an elevated risk of CAD that is under genetic control and cannot be detected by simple measurement of fasting plasma triglycerides." However, additional studies are needed to determine the effect of specific TGRL fractions and underlying mechanisms for a link between postprandial lipemia and atherosclerosis.

Mechanistic evidence

The pathogenesis of the relationship between postprandial TGRL and CAD remains unclear, but experimental evidence has provided several plausible mechanisms. Atherogenic effects may be mediated directly by TGRL particles or components of the particles. In addition, indirect mechanisms of TGRL atherogenicity may be due to metabolic changes associated with the presence of postprandial TGRL.

Direct effects of triglyceride-rich lipoproteins

Studies designed to assess the direct atherogenicity of postprandial TGRL have focused on characterizing their interaction with the arterial endothelium, determining the ability of postprandial TGRLR to penetrate the endothelial layer to the subintimal space, and assessing TGRL interaction with monocyte-macrophages and other components of the developing atherosclerotic lesion.

A variety of in vitro and clinical studies suggest that postprandial CM and VLDL are associated with adverse effects on arterial endothelium. In cell culture studies, TGRL, particularly postprandial remnants, is directly cytotoxic to endothelial cells [49]. Notably, HDL protected against the injury mediated by these particles. Further, TGRL lipolysis products, including free fatty acids (FFA), may impair endothelial function. Cell culture studies in a porcine pulmonary artery model showed that presence of FFA enhanced LDL uptake, suggestive of increased permeability [50]. Increased permeability was also seen during perfusion of murine arteries with triglyceride-rich emulsions in the presence of LPL [51]. Lipoprotein lipase is present in normal arterial endothelium as well as in atheroma [52]. Thus, arterial endothelial cells may be exposed to high levels of TGRL products, particularly FFA, in the postprandial state, although in vivo the cytotoxicity of FFA may be attenuated by circulating albumin [53]. However, in cultured endothelial cells, a high FFA to albumin ratio correlated with an augmented VLDL toxicity, suggesting that a high FFA concentration may reduce the protective effect of albumin [53]. Collectively, these in vitro studies suggest that TGRL and products of TGRL hydrolysis have the potential to promote endothelial dysfunction, which is thought to be important in the initiation of atherosclerosis.

Clinical evidence also demonstrates that postprandial TGRL adversely affects the endothelium by mediating changes in vascular tone. After consumption of a high-fat meal, a reduction in flow-induced dilation of the brachial artery correlated with postprandial plasma TG concentration in healthy subjects [54]. A similar response was seen after infusion of a lipid emulsion in seven healthy male subjects [55]. Further, TGRL remnant concentration in healthy subjects correlated with an impaired epicardial coronary vasomotor response, and was inversely related to coronary blood flow under fasting conditions [56]. It has been proposed that TGRL's effects on endothelial tone is mediated in part by reduced nitric oxide production, either because of the TGRL particles themselves or due to oxidized LDL associated with the postprandial period [5,56]. Consumption of L-arginine attenuates endothelial impairment at 4 and 6 hours postprandially, presumably due to increased availability of nitric oxide [57].

In view of the presence of endothelial dysfunction as an early event in atherosclerosis [58], evidence from clinical and basic science studies suggests that TGRL may play a role in the initiation of atherosclerosis. However, in order to perpetuate the progression of the disease, TGRL or its contents need to penetrate into and remain in the intimal space of the arterial wall. Lipoprotein flux into the endothelium increases in direct proportion to TGRL's concentration in plasma and decreases as particle sizes become larger [59]. The exact details of this transport are not completely delineated, and although several possible routes of lipoprotein transport across the arterial endothelium have been suggested, the primary pathway is thought to be transcytosis [60,61]. This process involves formation of vesicles on the luminal surface of arterial endothelial cells, which migrate to the basolateral surface of arterial endothelial cells, where their contents are expelled by exocytosis into the subendothelial space [60]. These transcytotic vesicles have been shown to accommodate lipoproteins up to 70 nm in diameter, which excludes the possibility of transporting unhydrolyzed TGRL, such as chylomicrons (75 to 1200 nm), by this route. However, smaller CM and VLDL remnants (40 to 70 nm) might enter the arterial wall by this mechanism. In addition, activation of endothelial cells and paracellular pathways may allow entrance of larger-sized particles.

Animal studies provide evidence for influx and selective retention of CMR and VLDL. Endogenously radioiodinated CMR [62] or fluorescently labeled CMR (rhodamine-succinimidyl ester) [63] were perfused

through in situ rabbit coronary arteries. CMR associated with the arterial tissue within 5 minutes of exposure, possibly due to transcytosis. Further, arterial efflux of CMR was incomplete, with focal accumulation of these lipoproteins in the subintimal space.

Several lines of evidence suggest that TGRL particles smaller than CM such as VLDL and VLDL remnants can access the arterial intima. A dual isotope method was used to demonstrate influx of radiolabeled VLDL, IDL, and LDL into healthy and lesioned arterial intima of hypercholesterolemic rabbits [64]. There was an inverse relationship between lipoprotein diameter and fractional loss from the arterial intima (*ie*, a combination of efflux back into the arterial lumen, degradation of the particles, or irreversible attachment of lipoproteins to arterial wall components) [64]. VLDL, VLDL remnants, IDL, and also LDL were more likely to be "trapped" in the arterial intimal and inner medial areas than smaller particles such as HDL.

It is intriguing that the presence of VLDL- and IDL-sized particles has been reported in human intima as well as in atherosclerotic plaque. Rapp *et al*. [65] used selective affinity immunosorption to directly examine human aortic plaque for the presence of apoB-100–containing TGRL [65]. The plaque samples were found to contain VLDL and IDL with a lipid composition similar to the corresponding plasma lipoproteins, suggesting that TGRL can enter and be retained in atherosclerotic plaque.

The assessment of a direct effect of postprandial TGRL on atherogenic mechanisms also relates to the nature of their interaction with components in the intimal space. Incubation of macrophages with CM and large VLDL from hypertriglyceridemic subjects resulted in conversion into cells resembling foam cells in atherosclerotic lesions [66]. Furthermore, significant increases in macrophage TG and CE content have been observed after 4-hour incubation with TGRL. In addition, surface remnants of TGRL hydrolysis were shown to be cytotoxic to macrophages, although this effect could be inhibited by the addition of HDL to the media [37].

Indirect effects of triglyceride-rich lipoproteins

In addition to the possibility of direct effects of postprandial TGRL, there is mounting evidence that metabolic changes occurring during prolonged or elevated postprandial lipemia may be proatherogenic. Of particular interest is TGRL-mediated modification in LDL composition and size.

Lipoprotein modification

In the postprandial period, there is an enhanced exchange of core lipids between circulating lipoproteins. VLDL is the predominant TGRL species to become enriched with CE during this period, possibly due to a prolonged residence time and opportunity for lipid exchange [14]. In the postprandial state, similar to that of hypertriglyceridemic subjects, it is postulated that the extent of exchange may be determined by particle residence time in the circulation [67]. This implies an enhanced exchange in patients with prolonged postprandial lipemia. The resultant TG-enriched LDL and HDL particles are subject to lipolysis by hepatic lipase, thus forming small, dense particles.

Karpe *et al*. [16] showed that postprandial TGRL levels and lipoprotein lipase activity accounted for about 50% of the variability in LDL particle size. The size of circulating LDL is not acutely affected by the ingestion of a fat-rich meal [37], but there is a consistent relationship between increased fasting TG levels, increased postprandial TG, and the presence of atherogenic small, dense LDL [17]. A detailed analysis of the correlation between fasting plasma TG levels and LDL subclasses suggests that above a fasting TG level of 132 mg/dL (1.5 mmol/L), small dense LDL is more common [6]. The relationship between small, dense LDL and plasma TG has been defined mainly in the fasting state, although metabolic processes in the postprandial state are important in the generation of small dense LDL [6].

Small, dense LDL particles appear to be highly atherogenic by several related mechanisms [6,68]. Prospective studies confirm that small, dense LDL is highly predictive of CAD and is present in 40% to 50% of all patients with CAD in spite of normal fasting-LDL cholesterol levels [6]. In a group of young post-infarction men, apoB-48 levels correlated with plasma levels of small dense LDL [16]. Another study in diabetic subjects found a higher oxidative susceptibility of postprandial LDL particles [69]. Postprandial LDL promoted a significantly higher degree of CE accumulation and was more susceptible to copper-induced oxidation [69].

High-density lipoprotein effects

The composition and cholesterol concentration of HDL is inversely related to the magnitude of postprandial lipemia and the plasma concentration of TG. Lipolysis of TGRL affects the rate of formation of HDL particles [37]. Another mechanism for this association may be a postprandial increase of CETP-mediated CE transfer from HDL to TGRL [16], proposed to be one of the atherogenic changes mediated by prolonged postprandial lipemia [38].

Hemostatic changes

Postprandial lipemia has been shown to be associated with changes in hemostatic variables known to promote risk for thrombotic events [70]. Epidemiologic data have shown that the coagulation activity of factor VII (FVIIc) predicts coronary heart disease [71]. Following intake of a fat-rich meal, FVIIc is transiently increased due to an increase in plasma concentration of activated FVII, increasing the possibility of initiating a thrombotic response that may increase the likelihood of a clinically significant thrombosis [70].

Apart from the effect on thrombogenic factors, circulating postprandial lipoproteins may also impact platelet reactivity [72]. Although a variety of platelet activation markers have been studied to determine if platelets are indeed affected by postprandial lipemia, results are con-

flicting [73,74]. Recent advances in flow cytometry have provided the opportunity to more accurately assess platelet activation by the expression of surface and intracellular proteins. Using this technology, postprandial lipemia was associated with a mild increase in platelet reactivity that increased the expression of cell-surface markers in healthy men [75,76••]. Furthermore, platelet-monocyte aggregation and monocyte intracellular cytokine expression were elevated during the postprandial period and remained elevated after plasma TG levels returned to baseline [76••].

Conclusions

There is growing evidence that postprandial lipemia is associated with proatherogenic conditions, and clinical studies provide evidence that exposure to postprandial lipoproteins is associated with cardiovascular diseases. The degree of postprandial lipemia is variable between individuals, and influenced by both genetic and environmental factors. Recent studies indicate that atherogenicity of postprandial lipemia is associated with properties of triglyceride-rich lipoproteins such as their size, composition, and metabolism, as well as with their secondary effects on cholesterol-rich lipoproteins, such as LDL and HDL. Further, postprandial lipemia may mediate a prothrombotic state and induce inflammatory changes in the vessel wall, as well as in circulating leukocytes and platelets. Although clinical and in vitro data provide convincing evidence that postprandial lipemia contributes to the risk of cardiovascular disease, the nature of the association and underlying mechanisms remain to be established.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Cohn J: **Postprandial plasma lipoprotein changes in human subjects of different ages.** *J Lipid Res* 1988, **29:**469–479.
2. Havel R: **Chylomicron remnants: hepatic receptors and metabolism.** *Curr Opin Lipidol* 1995, **6:**312–316.
3. Parks E, Krauss R, Christiansen M, *et al.*: **Effects of a low-fat, high carbohydrate diet on VLDL-triglyceride assembly, production, and clearance.** *J Clin Invest* 1999, **104:**1087–1096.
4. Havel R: **Triglyceride-rich lipoproteins and atherosclerosis—new perspectives.** *Am J Clin Nutr* 1994, **59:**795–799.
5. Karpe F: **Postprandial lipoprotein metabolism and atherosclerosis.** *J Int Med* 1999, **246:**341–355.
6. Griffin B: **Lipoprotein atherogenicity: an overview of current mechanisms.** *Proc Nutr Soc* 1999, **58:**163–169.
7. Frayn KN, Shadid S, Hamlani R, *et al.*: **Regulation of fatty acid movement in human adipose tissue in the postabsorptive-to-postprandial transition.** *Am J Physiol* 1994, **266:**E308–E317.
8. •• Parks E, Hellerstein M: **Carbohydrate-induced hypertriacylglycerolemia: historical perspective and review of biological mechanisms.** *Am J Clin Nutr* 2000, **71:**1–21.
Comprehensive review of the inter-relationship between carbohydrate and lipid metabolism.
9. Mensenkamp AR, Jong MC, van Goor H, *et al.*: **Apolipoprotein E participates in the regulation of very low density lipoprotein–triglyceride secretion by the liver.** *J Biol Chem* 1999, **274:**35711–35718.
10. Huang Y, Ji ZS, Brecht WJ, *et al.*: **Overexpression of apolipoprotein E3 in transgenic rabbits causes combined hyperlipidemia by stimulating hepatic VLDL production and impairing VLDL lipolysis.** *Arterioscler Thromb Vasc Biol* 1999, **19:**2952–2959.
11. Maugeais C, Tietge UJ, Tsukamoto K, *et al.*: **Hepatic apolipoprotein E expression promotes very low density lipoprotein-apolipoprotein B production in vivo in mice.** *J Lipid Res* 2000, **41:**1673–1679.
12. Bjorkegren J, Packard CJ, Hamsten A, *et al.*: **Accumulation of large very low density lipoprotein in plasma during intravenous infusion of a chylomicron-like triglyceride emulsion reflects competition for a common lipolytic pathway.** *J Lipid Res* 1996, **37:**76–86.
13. Cohn J, Johnson E, Millar J, *et al.*: **Contribution of apoB-48 and apoB-100 triglyceride-rich lipoproteins (TRL) to postprandial increases in the plasma concentration of TRL triglycerides and retinyl esters.** *J Lipid Res* 1993, **34:**2033–2040.
14. Schneeman BO, Kotite L, Todd KM, *et al.*: **Relationships between the responses of triglyceride-rich lipoproteins in blood plasma containing apolipoproteins B-48 and B-100 to a fat-containing meal in normolipidemic humans.** *Proc Natl Acad Sci U S A* 1993, **90:**2069–2073.
15. Lichtenstein AH, Hachey DL, Millar JS, *et al.*: **Measurement of human apolipoprotein B-48 and B-100 kinetics in triglyceride-rich lipoproteins using [5,5,5–2H3]leucine.** *J Lipid Res* 1992, **33:**907–914.
16. Karpe F, Tornvall P, Olivecrona T, *et al.*: **Composition of human low density lipoprotein: effects of postprandial triglyceride-rich lipoproteins, lipoprotein lipase, hepatic lipase and cholesteryl ester transfer protein.** *Atherosclerosis* 1993, **98:**33–49.
17. Krauss R: **Heterogeneity of plasma low-density lipoproteins and atherosclerosis risk.** *Curr Opin Lipidol* 1991, **5:**339–349.
18. Lewis GF, O'Meara NM, Soltys PA, *et al.*: **Fasting hypertriglyceridemia in noninsulin-dependent diabetes mellitus is an important predictor of postprandial lipid and lipoprotein abnormalities.** *J Clin Endocrinol Metab* 1991, **72:**934–944.
19. Ida-Chen Y, Swami S, Skowronski R, *et al.*: **Differences in postprandial lipemia between patients with normal glucose tolerance and non-insulin dependent diabetes mellitus.** *J Clin Endocrin* 1996, **76:**172–177.
20. Boquist S, Hamsten A, Karpe F, *et al.*: **Insulin and non-esterified fatty acid relations to alimentary lipaemia and plasma concentrations of postprandial triglyceride-rich lipoproteins in healthy middle-aged men.** *Diabetologia* 2000, **43:**185–193.
21. Lewis G, O'Meara N, Soltys P, *et al.*: **Postprandial lipoprotein metabolism in normal and obese subjects: comparison after vitamin A fat-loading test.** *J Clin Endocrin Metab* 1990, **71:**1041–1050.

22.• Goldberg, IJ, Vanni-Reyes T, Ramakrishnan R, *et al.*: **Circulating lipoprotein profiles are modulated differently by lipoprotein lipase in obese humans.** *J Cardiovasc Risk* 2000, **7:**41–47.
Results suggest that obesity modulates the relationship between lipoprotein lipase activity and postprandial response.
23. Cohen J, Berger G: **Effect of glucose ingestion on postprandial lipemia and triglyceride clearance in humans.** *J Lipid Res* 1990, **31:**597–602.
24. van Tol A, van der Gaag M, Scheek L, *et al.*: **Changes in postprandial lipoproteins of low and high density caused by moderate alcohol consumption with dinner.** *Atherosclerosis* 1998, **141(suppl 1):**S101–S103.
25. Williams C: **Dietary interventions affecting chylomicron and chylomicron remnant clearance.** *Atherosclerosis* 1998, **141(suppl 1):**S87–S92.
26. Tinker L, Parks E, Behr S, *et al.*: **(n–3) fatty acid supplementation in moderately hypertriglyceridemic adults changes postprandial lipid and apolipoprotein B responses to a standardized test meal.** *J Nutr* 1999, **129:**1126–1134.
27. Hardman AE: **The influence of exercise on postprandial triacylglycerol metabolism.** *Atherosclerosis* 1998, **141(suppl 1):**S93–S100.
28. Gill J, Mees G, Frayn K, *et al.*: **Moderate exercise, postprandial lipaemia and triacylglycerol clearance.** *Eur J Clin Invest* 2001, **31:**201–207.
29.• Couch SC, Isasi CR, Karmally W, *et al.*: **Predictors of postprandial triacylglycerol response in children: the Columbia University Biomarkers Study.** *Am J Clin Nutr* 2000, **72:**1119–1127.
A study in children showing that postprandial lipemia is predicted by fasting TG and HDL cholesterol levels, and that children's postprandial response is different to maternal patterns in spite of similar baseline TG.
30. van Beek A, de Ruitjer-Heijstek F, Erkelens D, *et al.*: **Menopause is associated with reduced protection from postprandial lipemia.** *Arterioscler Thromb Vasc Biol* 1998, **19:**2737–2741.
31. Ossewaarde ME, Dallinga-Thie GM, Bots ML, *et al.*: **Treatment with hormone replacement therapy lowers remnant lipoprotein particles in healthy postmenopausal women: results from a randomized trial.** *Eur J Clin Invest* 2003, **33:**376–382.
32. Weintraub MS, Eisenberg S, Breslow JL: **Dietary fat clearance in normal subjects is regulated by genetic variation in apolipoprotein E.** *J Clin Invest* 1987, **80:**1571–1577.
33. Dallongeville J, Tiret L, Visvikis S, *et al.*: **Effect of apo E phenotype on plasma postprandial triglyceride levels in young male adults with and without a familial history of myocardial infarction: the EARS II study. European Atherosclerosis Research Study.** *Atherosclerosis* 1999, **145:**381–388.
34. Ostos MA, Lopez-Miranda J, Ordovas JM, *et al.*: **Dietary fat clearance is modulated by genetic variation in apolipoprotein A–IV gene locus.** *J Lipid Res* 1998, **39:**2493–2500.
35. Lopez–Miranda J, Ordovas JM, Ostos MA, *et al.*: **Dietary fat clearance in normal subjects is modulated by genetic variation at the apolipoprotein B gene locus.** *Arterioscler Thromb Vasc Biol* 1997, **17:**1765–1773.
36. Marin C, Lopez-Miranda J, Gomez P, *et al.*: **Effects of the human apolipoprotein A–I promoter G–A mutation on postprandial lipoprotein metabolism.** *Am J Clin Nutr* 2002, **76:**319–325.
37. Cohn J: **Postprandial lipemia: emerging evidence for atherogenicity of remnant lipoproteins.** *Can J Cardiol* 1998, **14:**18B–27B.
38. Patsch J, Miesenbock G, Hopferwieser T, *et al.*: **Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state.** *Arterioscler Thromb* 1992, **12:**1336–1345.
39. Gofman J, Lindgren F, Elliot H, *et al.*: **The role of lipids and lipoproteins in atherosclerosis.** *Science* 1950, **111:**166–171.
40. Zilversmit D: **Atherogenesis: a postprandial phenomenon.** *Circulation* 1979, **60:**473–485.
41. Groot PH, van Stiphout WA, Krauss XH, *et al.*: **Postprandial lipoprotein metabolism in normolipidemic men with and without coronary artery disease.** *Arterioscler Thromb* 1991, **11:**653–662.
42. Meyer E, Westerveld HT, de Ruyter-Meijstek FC, *et al.*: **Abnormal postprandial apolipoprotein B-48 and triglyceride responses in normolipidemic women with greater than 70% stenotic coronary artery disease: a case-control study.** *Atherosclerosis* 1996, **124:**221–235.
43. Ginsberg HN, Jones J, Blaner WS, *et al.*: **Association of postprandial triglyceride and retinyl palmitate responses with newly diagnosed exercise-induced myocardial ischemia in middle-aged men and women.** *Arterioscler Thromb Vasc Biol* 1995, **15:**1829–1838.
44. Boquist S, Ruotolo G, Tang R, *et al.*: **Alimentary lipemia, postprandial triglyceride-rich lipoproteins, and common carotid intima-media thickness in healthy, middle-aged men.** *Circulation* 1999, **100:**723–728.
45. Karpe F, de Faire U, Mercuri M, *et al.*: **Magnitude of alimentary lipemia is related to intima-media thickness of the common carotid artery in middle-aged men.** *Atherosclerosis* 1998, **141:**307–314.
46. Ryu J, Howard G, Craven T, *et al.*: **Postprandial lipemia and carotid atherosclerosis.** *Stroke* 1992, **23:**823–828.
47. Uiterwaal C, Grobbee D, Witteman J, *et al.*: **Postprandial triglyceride response in young adult men and familial risk of coronary atherosclerosis.** *Ann Intern Med* 1994, **121:**576–583.
48. Tiret L, Gerdes C, Murphy MJ, *et al.*: **Postprandial response to a fat tolerance test in young adults with a paternal history of premature coronary heart disease—the EARS II study (European Atherosclerosis Research Study).** *Eur J Clin Invest* 2000, **30:**578–585.
49. Spiedel M, Booyse F, Abrams A, *et al.*: **Lipolysed hypertriglyceridemic serum and trigylceride–rich lipoprotein cause lipid accumulation in and are cytotoxic to cultured human endothelial cells.** *Thromb Res* 1990, **48:**251–264.
50. Hennig B, Shasby D, Spector A: **Exposure to fatty acid increases human low density lipoprotein transfer across cultured endothelial monolayers.** *Circ Res* 1985, **57:**776–780.
51. Rutledge JC, Woo MM, Rezai AA, *et al.*: **Lipoprotein lipase increases lipoprotein binding to the artery wall and increases endothelial layer permeability by formation of lipolysis products.** *Circ Res* 1997, **80:**819–828.
52. Yla-Herttuala S, Lipton BA, Rosenfeld ME, *et al.*: **Macrophages and smooth muscle cells express lipoprotein lipase in human and rabbit atherosclerotic lesions.** *Proc Natl Acad Sci U S A* 1991, **88:**10143–10147.
53. Arbogast B: **Purification and identification of very low density lipoprotein toxicity preventing activity.** *Atherosclerosis* 1988, **73:**259–267.
54. Vogel RA, Corretti MC, Plotnick GD: **Effect of a single high-fat meal on endothelial function in healthy subjects.** *Am J Cardiol* 1997, **79:**350–354.
55. Lundman P, Eriksson M, Schenck-Gustafsson K, *et al.*: **Transient triglyceridemia decreases vascular reactivity in young, healthy men without risk factors for coronary heart disease.** *Circulation* 1997, **96:**3266–3268.
56. Kugiyama K, Doi H, Motoyama T, *et al.*: **Association of remnant lipoprotein levels with impairment of endothelium-dependent vasomotor function in human coronary arteries.** *Circulation* 1998, **97:**2519–2526.
57. Marchesi S, Lupattelli G, Siepi D, *et al.*: **Oral L-arginine administration attenuates postprandial endothelial dysfunction in young healthy males.** *J Clin Pharm Ther* 2001, **26:**343–349.
58. Ross R: **Atherosclerosis—an inflammatory disease.** *N Engl J Med* 1999, **340:**115–126.
59. Nordestgaard B, Wootton R, Lewis B: **Selective retention of VLDL, IDL, and LDL in the arterial intima of genetically hyperlipidemic rabbits in vivo: molecular size as a determinant of fractional loss from the intima-inner media.** *Arterioscler Thromb* 1995, **15:**534–542.

60. Simionescu M, Simionescu N: **Endothelial transport of macromolecules: transcytosis and endocytosis: a look from cell biology.** *Cell Biol Rev* 1991, **25:**5–78.
61. Simionescu M, Simionescu N: **Proatherosclerotic events—pathobiochemical changes occurring in arterial wall before monocyte migration.** *FASEB J* 1993, **7:**1359–1366.
62. Mamo J, Wheeler J: **Chylomicrons or their remnants penetrate rabbit thoracic aorta as efficiently as do smaller macromolecules, including low-density lipoprotein, high density lipoprotein and albumin.** *Coronary Artery Dis* 1994, **5:**695–705.
63. Proctor S, Mamo J: **Retention of fluorescent-labeled chylomicron remnants within the intima of the arterial wall—evidence that plaque cholesterol may be derived from postprandial lipoproteins.** *Eur J Clin Invest* 1998, **28:**497–503.
64. Shaikh M, Wootton R, Nordestgaard B, *et al.*: **Quantitative studies of transfer in vivo of low density, Sf 12-60 and Sf 60-400 lipoproteins between plasma and arterial intima in humans.** *Arterioscler Thromb* 1991, **11:**569–577.
65. Rapp J, Lespine A, Hamilton R, *et al.*: **Triglyceride-rich lipoproteins isolated by selected-affinity anti-apoprotein B immunosorption from human atherosclerotic plaque.** *Arterioscler Thromb* 1994, **14:**1767–1774.
66. Gianturco S, Bradley W: **Pathophysiology of triglyceride-rich lipoproteins in atherothrombosis: cellular aspects.** *Clin Cardiol* 1999, **22:**II-7–II-14.
67. Mann CJ, Yen FT, Grant AM, *et al.*: **Mechanism of plasma cholesteryl ester transfer in hypertriglyceridemia.** *J Clin Invest* 1991, **88:**2059–2066.
68. Austin M, King M, Vranizan K, *et al.*: **Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary artery disease.** *Arterioscler Thromb* 1990, **82:**495–506.
69. Diwadkar V, Anderson J, Bridges S, *et al.*: **Postprandial low-density lipoproteins in type 2 diabetes are oxidized more extensively than fasting diabetes and control samples.** *PSEBM* 1999, **222:**178–184.
70. Miller GJ: **Postprandial lipaemia and haemostatic factors.** *Atherosclerosis* 1998, **141(suppl 1):**S47–S51.
71. Meade T, Mellows S, Brozovic M, *et al.*: **Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study.** *Lancet* 1986, **6:**533–537.
72. Nordoy A, Strom E, Gjesdal K: **The effect of alimentary hyperlipidaemia and primary hypertriglyceridaemia on platelets in man.** *Scan J Haematol* 1974, **12:**329–340.
73. Jakubowski J, Ardlie N, Chesterman C, *et al.*: **Acute postprandial lipaemia does not influence the in vivo activity of human platelets.** *Thromb Res* 1985, **39:**725–732.
74. Fuhrman B, Brook J, Aviram M: **Increased platelet aggregation during alimentary hyperlipemia in normal and hypertriglyceridemic subjects.** *Ann Nutr Metab* 1986, **30:**250–260.
75. Broijersen A, Karpe F, Hamsten A, *et al.*: **Alimentary lipemia enhances the membrane expression of platelet P–selectin without affecting other markers of platelet activation.** *Atherosclerosis* 1998, **137:**107–113.
76.•• Hyson DA, Paglieroni TG, Wun T, *et al.*: **Postprandial lipemia is associated with platelet and monocyte activation and increased monocyte cytokine expression in normolipemic men.** *Clin Applied Thromb Hemost* 2002, **8:**147–155.
This study demonstrated that modest postprandial lipemia in healthy young men was associated with activation of platelets, elevated platelet-monocyte aggregation, and increased expression of intracellular cytokines by monocytes. The activated state persisted after postprandial TG levels returned to fasting concentrations.