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Chylomicrons: A Key Biomarker and Risk Factor for Cardiovascular Disease and for the Understanding of Obesity

Boudewijn Klop · Manuel Castro Cabezas

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Abstract Cardiovascular disease can be considered a condition of chronic low-grade inflammation. Postprandial hyperlipidemia and obesity can both exacerbate inflammatory processes. Postprandial lipemia stimulates the activation of leukocytes, the production of chemokines, and activation of the complement system. Obesity is also associated with postprandial hyperlipidemia by hepatic overproduction of very low-density lipoprotein (VLDL) and consequently delayed clearance of intestinally derived chylomicrons due to competition for the same metabolic pathways. Insulin resistance is one of the key elements leading to hepatic VLDL overproduction and is also a key factor in the generation of inflammation. These metabolic derangements cause accumulation of atherogenic remnant lipoproteins, which is also a proatherogenic mechanism. Change in lifestyle is the most important therapeutic strategy to stop this vicious circle of postprandial hyperlipidemia, obesity, inflammation, insulin resistance, and cardiovascular disease.

Keywords Triglyceride · Apolipoprotein B48 · Adiposity · Atherosclerosis · Inflammation

Introduction

The study of lipoprotein metabolism has been a major focus of interest during the past few decades. Special attention has been directed toward the metabolism of low-density lipoproteins (LDL) in relation to cardiovascular disease (CVD). This knowledge has led to major breakthroughs in the field of atherosclerosis [1]. Less information has been obtained on the metabolism of triglyceride-rich lipoproteins (TRLs). Although many studies were directed toward the investigation of fasting triglycerides (TG), the factors involved in the regulation of postprandial lipemia are less well known. This is surprising, as humans are in a postprandial state most of the day [2, 3].

Increasing evidence has linked several changes during the postprandial phase, such as chylomicron remnant accumulation, release of fatty acids during lipolysis of TRLs, cytokine production, leukocyte activation, atherosclerosis, obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) [4–8]. Despite the fact that postprandial lipemia, and therefore chylomicron metabolism, is crucial and may be the link between all these conditions and metabolic aspects, there has been no large intervention trial directed to modulate postprandial lipemia to decrease cardiovascular risk. Neither are there specific drugs available for the modulation of postprandial chylomicron metabolism. This article gives an overview on the current knowledge concerning chylomicron remnant metabolism in relation to atherosclerosis and obesity.

Metabolism of Chylomicrons

Since the study and semi-quantification of chylomicrons by light microscopy more than half a century ago [9], our knowledge about chylomicrons has greatly expanded. Chylomicrons are the largest TRLs, ranging from 75 nm to 450 nm, containing about 4% proteins, 80% TG, 12% cholesterol, and 4% phospholipids with apolipoprotein (apo)

B. Klop · M. Castro Cabezas (✉)
St Franciscus Gasthuis Rotterdam, Department of Internal Medicine, Centre for Diabetes and Vascular Medicine, PO Box 10900, 3004 BA Rotterdam, The Netherlands
e-mail: m.castrocabezas@sfg.nl

B. Klop
e-mail: b.klop@sfg.nl

B48 as the most important structural protein [10]. Chylomicrons transport dietary lipids and fat-soluble vitamins to the blood and in humans are solely synthesized in the intestine, especially in the postprandial period following fat absorption [11]. Recent work has clarified some of the molecular mechanisms involved in the intracellular assembly of chylomicrons. The synthesis of chylomicrons starts with the ingestion of food containing phospholipids, sterols, fat-soluble vitamins, and TG, which are a major energy source for the body. Ingested TG are digested by pancreatic lipase resulting in free fatty acids (FFA) and 2-monoacylglycerols (MAG). Both FFA and MAG are absorbed from the intestinal lumen by passive diffusion and protein-dependent mechanisms. Inside the enterocyte, FFA and MAG are carried from the cytoplasm to the endoplasmatic reticulum where they are synthesized again to TG by several enzymes [12•]. Within the endoplasmatic reticulum, TG together with cholesteryl esters and phospholipids are assembled into prechylomicrons, which are merged from two different primordial chylomicrons. One primordial chylomicron contains a dense lipid core with phospholipids and cholesterol together with one apoB48 molecule chaperoned by the microsomal transfer protein (MTP) complex [13], whereas the other primordial chylomicron consists of a large particle with cholesteryl esters and TG together with one apoA-IV molecule [14•]. These two primordial chylomicrons merge together into one large prechylomicron with a core of neutral lipids and a surrounding monolayer with phospholipids and both apoB48 and apoA-IV. Subsequently, prechylomicrons are transported to the Golgi by prechylomicron transport vesicles in which multiple proteins, such as CD36, apoB48, and many others, are involved [14•]. Within the Golgi, another apolipoprotein, apoA-I, attaches to prechylomicrons to form mature chylomicrons, which will finally be secreted into the lymphatics [15, 16].

Once in the lymphatics, chylomicrons enter the circulation by the thoracic duct where apoA-IV gets displaced for apoC-II and apoE, two other essential apolipoproteins [17]. ApoC-II serves as a cofactor of lipoprotein lipase (LPL) for the lipolysis of TG from chylomicrons, whereas apoE is involved in the recognition of specific receptors on the endothelium [18]. Deficiency of apoC-II or of LPL causes chylomicronemia. Recently, another necessary cofactor for the lipolysis of TG has been identified [19••]. Deficiency of glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), which binds LPL and functions as a platform for lipolysis on endothelial cells, causes chylomicronemia as well [19••]. In GPIHBP1-deficient mice, it was shown that GPIHBP1 is necessary for the processing of apoB48 and apoB100-containing lipoproteins [20••]. The lipolytic processing of TG from chylomicrons occurs on the luminal surface of capillaries, mainly in the heart, skeletal muscle, and adipose tissue that require fatty acids for storage or energy. The TG from chylomicrons are hydrolyzed by LPL into FFA, which are internalized by the endothelium via cell surface receptors like CD36 and via other processes such as non-specific carriers (eg, albumin) [21, 22]. Once internalized, FFA diffuse to the plasma membrane of adipocytes or myocytes [21]. Subsequently, chylomicrons shrink in diameter and become denser in cholesterol, resulting in chylomicron remnants that are removed from circulation by the liver to form hepatic apoB-carrying TRLs, the very low-density lipoproteins (VLDL). Finally, adequate lipolysis of chylomicrons (and VLDL) is necessary for the intravascular formation of nascent atheroprotective high-density lipoprotein (HDL) particles [23].

Postprandial Lipemia and Atherosclerosis

One of the first reports linking hypertriglyceridemia to cardiovascular disease is the description by Nicolaes Tulp (1593–1674), who was immortalized in the "Anatomical lesson" by Rembrandt, describing a patient with severe hypertriglyceridemia who probably died from a seizure [24]. Since the mid-twentieth century, several publications appeared showing that patients with coronary heart disease (CHD) have increased postprandial lipemia [2, 25, 26]. Convincing evidence establishing the role of postprandial hyperlipidemia and chylomicron remnants in atherosclerosis was provided by research coming from some outstanding groups in the past three decades [27–30].

Atherosclerosis is a chronic disease that takes years to develop, but endothelial function already becomes transiently impaired after one single high-fat meal and is associated with abnormal postprandial TG responses [31–33]. Most of the postprandial studies were performed using experimental situations where participants underwent standardized oral fat loading tests. However, these tests are not suitable to screen large populations or to use as a diagnostic tool for clinical practice. They are laborious, require a metabolic ward, and are inconvenient for subjects, as they need to fast for a long period and to be hospitalized during the test. Work from our laboratory described the technique of self-measured capillary TG to establish postprandial hyperlipidemia in individual subjects without the need for laborious and time-consuming oral fat loading tests. It was demonstrated that daytime triglyceridemia measured in this way is also increased in patients with premature CHD compared to healthy controls [34–38].

Recently, large, prospective epidemiologic studies have shown that a single measurement of non-fasting TG is associated with an increased risk of CVD independent from classical risk factors [5, 39]. For every 1-mmol/l increase in non-fasting TG, a significant increase in death was found, with multifactorially adjusted hazard ratios of 1.2 to 1.8 for

men and 1.3 to 3.3 for women. Similar significant trends were found for myocardial infarction and ischemic heart disease in both men and women [5]. Therefore, it was suggested that non-fasting TG are stronger predictors of CVD than fasting TG [5, 39]. In contrast, TG were not predictive for CHD in 302,430 subjects without initial vascular disease after adjustment for HDL cholesterol and non-HDL cholesterol [40]. Abnormalities in TG reflect metabolic derangements and may be used as biomarkers for cardiovascular risk because of their strong relation with atherogenic remnant lipoproteins (chylomicron remnants and hepatic-derived VLDL remnants) [41].

Mechanisms of Atherogenesis of Chylomicron Remnants

In the circulation, chylomicron remnants exchange TG for cholesteryl esters with HDL and LDL particles. This exchange increases in hyperlipidemic states and it seems likely that chylomicron remnants become more atherogenic when the amount of cholesteryl esters within chylomicron remnants increases [42]. By the early 1980s, it was shown by Stender and Zilversmit [43] that chylomicrons transfer cholesteryl esters to the intima media layer of the arterial wall. More recent studies by Proctor and Mamo [44] provided evidence that whole chylomicron remnants migrate into the subendothelial space in vivo. The depleted chylomicron remnants decrease sufficiently in size to permit arterial passage and subsequently deposition of lipids, which is most probably a misbalanced equilibrium where delivery of lipoproteins exceeds the efflux. Most likely, uptake occurs via cellular gap junctions and via transcytosis [44]. Besides indirect evidence for the atherogenicity of chylomicron remnants, a direct relationship between chylomicronemia and atherosclerosis was shown recently in mice deficient for GPIHBP1 [20••]. This mouse model is of special interest to further investigate multiple factors potentially altering the atherogenicity of chylomicron remnants.

Others have clearly shown that the postprandial situation has a direct negative effect on endothelial function [32, 33]. Atherosclerosis is considered to be partially an inflammatory disease and postprandial neutrophil count increases with upregulated proinflammatory cytokines and oxidative stress, contributing to endothelial dysfunction [4, 45]. In vitro monocytes showed a fivefold increased expression of the endothelial adhesion molecule CD11b, whereas granulocytes showed an increased expression of both CD11b and CD66b after incubation with TRLs [4]. In vivo expression of CD11b and CD11c on monocytes increased postprandially [45, 46••]. TRLs become internalized by monocytes through the low-density lipoprotein receptor–related protein-1 (LRP-1), which stimulates expression of CD11c. Monocytes with internalized TRLs showed increased expression of vascular cell adhesion molecules, enhancing their potential to home in on vascular lesions [46••]. Leukocytes of fasting patients with CHD have an increased lipid content when compared to controls, and it was suggested that this was due to the uptake of chylomicrons in the bloodstream [47]. Furthermore, uptake of chylomicron remnants by human monocytes has been demonstrated in experiments in vitro [48]. Leukocytes are also able to take up retinyl esters, which have been used as markers of intestinally derived TRLs [49]. Recently, we have shown that apoB containing lipoproteins are detectable on neutrophils and monocytes and that postprandial leukocytes transport dietary fatty acids [4]. This opens the possibility that direct activation of leukocytes may occur in the circulation by interaction with chylomicrons and their remnants. Activated leukocytes are able to destabilize atherosclerotic plaques by production of reactive oxygen species. Once monocytes reside within the arterial wall, they differentiate into macrophages with subsequent risk of turning into highly atherogenic foam cells [50]. Importantly, chylomicron remnants can induce foam cell formation without the need to become modified, in contrast to native LDL [51, 52]. In this respect, chylomicron remnants may be the most atherogenic lipoproteins in human physiology and, therefore, chylomicron remnant accumulation should be considered a relevant factor contributing to cardiovascular risk.

Besides activation of leukocytes, the innate immune system also becomes activated postprandially. Postprandially, C3 levels were increased and correlated to postprandial triglyceridemia [53]. In addition, in vitro experiments demonstrated that chylomicrons directly stimulate adipose tissue to produce C3 [54]. Therefore, triglyceridemia may modulate C3 levels directly. Patients with a deficiency in mannose binding lectin (MBL), one of the key molecules of one of the three complement activation pathways, showed a significantly increased postprandial accumulation of chylomicron remnants despite reduced concentrations of chylomicrons [55]. More studies are needed to investigate the exact molecular basis of complement activation in relation to chylomicron metabolism.

Crosslink Between Obesity, Chylomicrons, and Atherosclerosis

Obesity has been associated with increased mortality, largely due to increased incidence of CVD [56]. This elevated cardiovascular risk can be attributed to an increment in risk factors such as fasting hypertriglyceridemia, high LDL cholesterol, decreased HDL cholesterol, elevated blood glucose and insulin levels, and high blood pressure. However, obesity also has a direct impact on CVD after correction for these risk factors, suggesting that obesity is an independent risk factor for CVD [57].

Postprandial lipemia is already increased in mildly obese subjects despite having similar fasting TG concentrations. In subjects with visceral adiposity and in other conditions of insulin resistance, there is an increased FFA flux from the abdominal fat to the liver, resulting in increased hepatic VLDL production [58]. Competition for clearance between chylomicrons and VLDL will occur, because they both share the same metabolic pathway, leading to increased postprandial lipemia (Fig. 1) [59, 60]. Another mechanism is the production of apoE-deficient chylomicrons in insulin resistance hampering the clearance of these aberrant chylomicrons [61]. This is also reflected by higher apoB48 concentrations in obese subjects compared to healthy subjects in both the fasted and the fed state, which can be measured easily with a novel enzyme-linked immunosorbent assay (ELISA) [62]. After an oral fat challenge, postprandial lipemia increased even more in subjects with both obesity and T2DM, especially when macrovascular disease was apparent [63]. When the metabolism of adipose tissue was improved by rosiglitazone, a peroxisome proliferator–activated receptor γ agonist, the postprandial clearance of chylomicrons was significantly improved in subjects with T2DM [64]. Interestingly, in patients with HIV lipodystrophy (a condition characterized by a loss of subcutaneous fat), rosiglitazone caused a harmful increase in accumulation of postprandial remnant particles, despite evidence for improved FFA metabolism [65•]. Thus, modulation of adipose tissue metabolism by glitazones may have different consequences in different patients.

Besides delayed clearance of TRLs in obese subjects, emerging evidence also shows intestinal overproduction of chylomicrons as a major contributor of postprandial lipemia in insulin resistance [61]. In an animal model, proteins involved in the assembly of prechylomicron transport vesicles, which is the rate-limiting step in transportation of TG through the enterocyte, were increased in the insulin-resistant gut [61]. Moreover, in insulin-resistant states and T2DM, FFA plasma concentrations are increased and it was shown in vivo that a continuous intravenous infusion of FFA stimulates both intestinal and hepatic TRL production [66]. Postprandial storage of FFA from TG is reduced in abdominally obese subjects together with an inability to induce FFA storage with each sequential meal. This could be the pathophysiologic explanation for ectopic fat deposition contributing to further increase in insulin resistance [67•].

As explained earlier, postprandial lipemia induces an atherogenic inflammatory response, which may be one of the key mechanisms linking obesity, insulin resistance, and increased postprandial lipemia. Ex vivo endothelial inflammation after incubation with postprandially derived TRLs correlated positively with waist circumference [68]. Excessive adipose tissue is associated with increased proinflammatory factors, such as tumor necrosis factor-α, interleukin-6, and interleukin-8, and accumulation of adipose tissue macrophages. In a recent study, significantly increased mRNA expressions of different chemokine ligands and receptors were found in monocytes as well as in adipose tissue from obese subjects with and without T2DM [69]. This results in a vicious circle of postprandial lipemia, obesity, inflammation, insulin resistance, and weight gain, subsequently leading to a higher risk of CVD (Fig. 2).

Therapeutic Strategies to Reduce Postprandial Lipemia

The type of diet and amount of food intake influences postprandial lipemia. It is known that polyunsaturated fatty

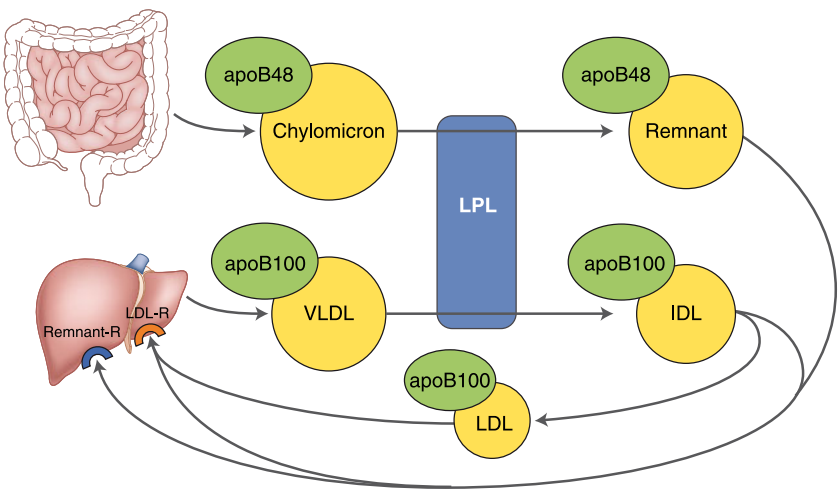

Fig. 1 Schematic representation of the common metabolic pathway for the lipolysis of triglyceride-rich lipoproteins (chylomicrons, chylomicron remnants, and very low-density lipoprotein [VLDL] particles) by lipoprotein lipase (LPL). Competition will occur for the clearance of VLDL and chylomicron remnants in the presence of postprandial hyperlipidemia due to limited LPL availability in the postprandial state. apoB48—apolipoprotein B48; IDL—intermediate-density lipoprotein; LDL—low-density lipoprotein; R—receptor

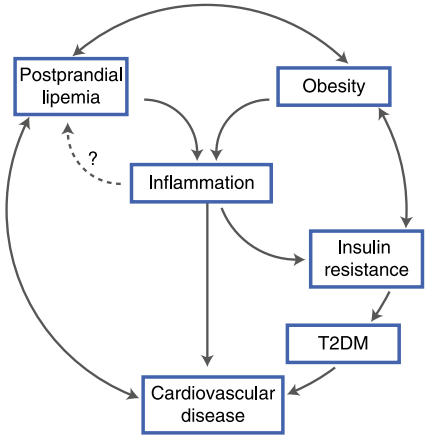

Fig. 2 Schematic representation of the vicious circle of postprandial lipemia, obesity, inflammation, insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular disease

acids (PUFAs) and monounsaturated fatty acids (MUFAs) reduce the risk for atherosclerosis compared to saturated fatty acids (SFAs). Several studies have shown that the type of dietary fat correlates with the composition of chylomicrons and influences the rate of hepatic removal of chylomicron remnants. Chylomicron remnants enriched with PUFAs were taken up more rapidly compared to those chylomicron remnants rich with MUFAs or SFAs [52, 70]. This could be an explanation for the favorable cardiovascular effects of PUFAs by reducing the chance of interaction between chylomicron remnants and macrophage foam cell formation. Recently, it was shown that obese subjects benefit from the consumption of a meal with olive oil (22% SFA, 38% MUFAs, 4% PUFAs) compared to a meal with butter (35% SFAs, 22% MUFAs, 4% PUFAs) or walnuts (20% SFAs, 24% MUFAs, 16% PUFAs, 4% α-linolenic acid) with reduced chylomicron remnant concentrations. However, the type of ingested fat did not influence the postprandial response in lean subjects [71]. Moreover, the amount of ingested fat remains the most important dietary factor influencing postprandial lipemia, not the qualitative aspects of the dietary fat [70]. After 2 weeks of a very low caloric diet in obese subjects with type 2 diabetes mellitus, postprandial lipemia was significantly improved and proinflammatory factors in subcutaneous adipose tissue and peripheral monocytes were reduced [69].

In obese subjects, moderate weight loss induced by a diet low in carbohydrates and SFAs combined with a slight increase in physical activity resulted in 27% to 46% reduction in postprandial lipemia, which was similar to lean subjects [72]. Physical activity has also shown to reduce postprandial lipemia in multiple studies. Acute bouts of exercise reduce postprandial lipemia by 24% to 35% and increase LPL activity. Furthermore, physical activity the day before a high-fat meal improves significantly the clearance of TRLs postprandially [70], but its positive effect attenuates after 2 to 3 days [73]. This shows that exercise that is frequently performed is usually an efficient and cost-effective method to decrease TG concentrations [73]. Besides to high-fat meals and physical inactivity, postprandial lipemia is increased by smoking, another well-known cardiovascular risk factor. Smokers have a 50% greater postprandial lipemia despite similar fasting TG concentrations compared to non-smokers. Smoking increases primarily chylomicrons and their remnants, shown by increased apoB48 concentrations but not apoB100 [70]. However, the direct effect on postprandial lipemia by cessation of smoking has not been studied yet.

Despite aggressive LDL cholesterol lowering by statin therapy, approximately two thirds of all cardiovascular events still occur. Statins are highly effective in reducing LDL cholesterol but they do not affect TG sufficiently to be of clinical relevance in hypertriglyceridemic conditions. However, rosuvastatin is able to reduce the postprandial proinflammatory and procoagulant changes in subjects with CHD [74]. This independent effect from rosuvastatin may protect against CHD when hyperlipidemia is present. In contrast to statins, pharmacotherapy with fibrates is effective in lowering TG concentrations. Despite hypertriglyceridemia being common in the Western population, fibrates are used in only 3.6% of hypertriglyceridemic subjects [75]. Controversy remains regarding the effectiveness of fibrates on cardiovascular morbidity and mortality. Recently, a large meta-analysis of fibrates in 45,058 participants was performed [76•]. This study showed a modest but significant relative risk reduction of 10% for major cardiovascular events and 13% reduction in coronary events, but mortality remained unaltered. At this stage, there are no data available on comparative studies regarding lifestyle modification versus lipid-lowering therapy on the modulation of postprandial lipemia.

Besides lifestyle interventions and pharmacotherapy with fibrates, bariatric surgery may be indicated for subjects with morbid adiposity, which facilitates a substantial weight loss and decreases cardiovascular mortality. It has been shown that bariatric surgery reduces TG concentrations by 25% and cholesteryl ester transfer protein by 15% ultimately increasing HDL cholesterol after surgery [77•]. So far, no large-scale studies have been carried out to investigate the effects of weight loss by bariatric surgery on postprandial lipoprotein metabolism.

Conclusions

Much research on the understanding of chylomicron synthesis and secretion has already been done, and continuation of this research is needed to develop specific interventions interfering with postprandial lipemia. However,

not all hypertriglyceridemic conditions are identical and it would be helpful to develop a more specific classification of hypertriglyceridemias. This would help to design studies with targeted interventions in more specific conditions. It remains unknown what the precise role of inflammatory factors is for normal postprandial handling of chylomicrons and if there is a nutritional or pharmacologic method to modulate the postprandial inflammatory response. Lifestyle changes still remain the most important strategy in stopping the vicious circle of postprandial lipemia, obesity, inflammation, insulin resistance, and cardiovascular disease. Fibrates may be indicated in hypertriglyceridemic subjects with low HDL cholesterol and with a high risk for cardiovascular disease.

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- • Of importance
- •• Of major importance

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