

## Regulation of postprandial lipemia: an update on current trends

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**Abstract:** People spend a large percentage of their waking hours in the postprandial state. Postprandial lipemia is associated with disruptions in lipoprotein metabolism and inflammatory factors, cardiovascular disease, MetS, and diabetes. Commonly, the dietary sources of fat exceed the actual needs and the tissues are faced with the excess, with accumulation of chylomicrons and remnant particles. This review will summarize recent findings in postprandial lipemia research with a focus on human studies. The effects of dietary factors and other meal components on postprandial lipemia leads to the following question: do we need a standardized oral lipid tolerance test (OLTT)? An overview of recent findings on FABP2, MTP, LPL, apoAV, and ASP and the effects of body habitus (sex influence and body size), as well as exercise and weight loss, on postprandial lipemia will be summarized.

**Key words:** triglyceride rich lipoprotein, cardiovascular disease, acylation stimulating protein, lipoprotein lipase, insulin resistance, dietary fat, exercise.

**Résumé :** Les gens passent la plupart de leur temps éveillé en état post-prandial. La lipémie post-prandiale est associée à des perturbations du métabolisme des lipoprotéines et des facteurs inflammatoires, à la maladie cardiovasculaire, au syndrome métabolique ainsi qu'au diabète. Les sources alimentaires de gras dépassent généralement les besoins réels et les tissus doivent composer avec un surplus de gras, une accumulation de chylomicrons et des particules en trop. Cet article-synthèse présente le bilan des dernières études sur la lipémie post-prandiale et donne une grande place aux études sur les humains. Les effets des facteurs alimentaires et d'autres constituants des repas sur la lipémie post-prandiale soulèvent la question suivante : devons-nous élaborer un test oral de tolérance aux lipides (OLTT) ? Nous présentons un aperçu des études sur les protéines de liaison des acides gras (FABP2), les protéines microsomiques de transfert des triglycérides (MTP), la lipoprotéine lipase (LPL), les apolipoprotéines A-5 (apoAV), les protéines stimulatrices de l'acylation (ASP). Nous exposons aussi les effets de l'habitus corporel (influence du sexe et de la corpulence), de l'activité physique et de la perte de poids sur la lipémie post-prandiale.

**Mots clés :** lipoprotéine riche en triglycérides, maladie cardiovasculaire, protéine stimulant l'acylation, lipoprotéine lipase, insulino-résistance, gras alimentaire, activité physique.

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### Clinical implications of exaggerated postprandial lipemia

It is well recognized that alterations in plasma lipid and lipoprotein concentrations increase the risk of cardiovascular

disease and are associated with obesity, MetS, and diabetes (Kolovou et al. 2005a; Graham 2004). These criteria are primarily based on blood sampling conducted in the fasting state, especially for disease evaluation. Although it is true that elevated fasting TG can often be indicative of delayed

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**Abbreviations:** ABC, ATP binding cassette; Apo, apolipoprotein; ASP, acylation stimulating protein; AUC, area under the curve; CAD, cardiovascular disease; CHYLO, chylomicron; CR, chylomicron remnant; FABP, fatty acid binding protein; GLP, glucagon-like protein; hFH, heterozygous familial hypercholesterolemia; HL, hepatic lipase; IGT, impaired glucose tolerance; Lp(a), lipoprotein (a); LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein; MUFA, monounsaturated fatty acid; NEFA, non-esterified fatty acid; NGT, normal glucose tolerance; OLTT, oral lipid tolerance test; PUFAs, polyunsaturated fatty acid; SFA, saturated fatty acid; T2D, type 2 diabetes; TG, triglyceride; TRL, triglyceride rich lipoprotein; VAT, visceral adipose tissue; VLDLR, VLDL receptor.

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postprandial TG clearance (Cianflone et al. 2004), this is not always the case. There are a number of examples (as described later) where, in spite of a normal fasting plasma TG, subjects manifest delayed postprandial TG clearance. Thus, analysis of postprandial TG clearance can provide additional information on overall physiological processes as well.

### **Dietary fat composition effects on postprandial lipemia**

Numerous studies have demonstrated a beneficial effect of PUFAs on cardiovascular disease risk factors, as well as morbidity and mortality (Kris-Etherton et al. 2004). Of the individual fatty acid classes, PUFAs (specifically *n*-6 PUFAs) have the most potent cholesterol-lowering effects of the individual fatty-acid classes (Kris-Etherton et al. 2004). Further, PUFAs have favorable effects on postprandial lipemia (Kris-Etherton et al. 2004). In fact, part of the beneficial effects of PUFAs on hepatic lipoproteins may be mediated within the postprandial phase. Chung et al. have demonstrated that dietary fats, while serving as precursors of TRL, also influence circulating LDL and HDL levels (Chung et al. 2004). In vivo postprandial clearance of LDL and HDL cholesterol was greater after a PUFA-enriched diet than an SFA diet, owing to increased cholesterol ester transfer protein-mediated transfer of LDL and HDL cholesterol ester towards the TRL (followed by hepatic removal) (Chung et al. 2004). MUFA, SFA and PUFA diets can alter other lipoproteins as well, such as Lp(a) (Tholstrup and Samman 2004). Downstream, alterations in dietary fatty acid composition can translate into reduction of other factors associated with endothelial dysfunction, such as reduction in antibodies to modified LDL (Gradek et al. 2004) and decreased activation of monocyte NF- $\kappa$ B (Bellido et al. 2004).

The dietary components responsible for such changes are not always as evident. For example, dairy butter fat (high in SFA) modified to reduce the saturated to unsaturated fatty acid ratio (replacement of 16% of SFAs by MUFAs and PUFAs) increased postprandial lipemia, which is not a beneficial change for CAD risk (Poppitt et al. 2004). Characteristics such as solidity and melting point of the fat may have effects that are relevant. Thus, although SFAs are typically considered the most deleterious, when stearic acid (18:0) is compared with other SFAs such as palmitic (16:0), myristic, or lauric acids, or with diets high in *trans* and oleic acid (MUFAs), stearic acid results in smaller postprandial increases in factor VII, and does not support the hypothesis that stearic acid is more thrombotic (Tholstrup 2005). Stearic acid presented as cocoa butter results in similar postprandial lipemia and factor VII activation as high MUFA sunflower oil, but when stearate is presented as shea butter, this results in decreased postprandial lipemia and activation of factor VII (Sanders and Berry 2005). Diets rich in palm oil, lard, or puff-pastry margarine (which differ in SFA and *trans* MUFA content but are all "solid" fats) had similar effects on postprandial response in obese and non-obese subjects (Jensen et al. 1999). However, administration of modified milk fats of varying melting profiles to guinea pigs did influence postprandial lipemia (Asselin et al. 2004). It has been suggested that differences in positional

composition of the fatty acids in triglycerides may affect the physical properties of the fats (Berry and Sanders 2005). Thus, the differences in responses may relate to varying melting points and solid fat contents of the diets under physiological temperatures. These differences in fat texture (and in fat taste) also elicit an array of orosensory stimulation and cephalic phase responses including release of digestive enzymes, which lead to alterations in ingestion, digestion, and absorption of fat independent of the effect of the diet components. These combined processes affect postprandial lipemia (review Mattes 2005).

Related to the issue of fat composition, a novel fat primarily containing diacylglycerol has been investigated for its effects on lipid metabolism (review Tada and Yoshida 2003). Consumption of this oil demonstrates decreases in fasting TG, as well as postprandial lipemia in healthy subjects, insulin-resistant subjects, and diabetic subjects (Takase et al. 2005). These changes may be mediated through increased oxidation and decreased storage of this type of fat.

### **Effect of carbohydrate and protein on postprandial lipemia**

Within any isocaloric dietary modification that alters the fat composition, there are corresponding changes in the carbohydrate and protein content that can impact postprandial lipemia and confound interpretations. Very low carbohydrate diets have become increasingly popular, but little is known of their effects on lipids and other cardiovascular risk factors. In healthy women, a very low carbohydrate diet (compared with a low fat diet) increased total, LDL, and HDL cholesterol, but decreased fasting TG and postprandial lipemia (Volek et al. 2003). In contrast to fat absorption (which is extremely efficient), cholesterol absorption is much less efficient and this can impact on postprandial lipemia. Individuals with a high cholesterol absorption ratio (based on serum cholestanol-cholesterol ratios) demonstrate increased CHYLO cholesterol linked to increased fasting LDL cholesterol (Agren et al. 2006).

A high carbohydrate diet vs. a high protein diet with the same fat content produced an increase in postprandial lipoprotein apoB48 profile, which is indicative of increased CHYLO and CR (Mamo et al. 2005). As with fats, an additional factor is the carbohydrate composition: slowly digestible carbohydrate reduces postprandial lipemia (both of intestinal and hepatic origin) in obese insulin-resistant subjects (Harbis et al. 2004) as does acarbose, an alpha-glucosidase inhibitor that delays the digestion of carbohydrate (Ogawa et al. 2004). Addition of different types of protein (whole milk vs. fermented milk, addition of casein or soy protein) has been suggested to modify postprandial lipemia via effects on gastric emptying and insulinotropic activity, effects that can even neutralize the postprandial lipemia-induced endothelial dysfunction (based on assessment of flow-mediated vasodilatation) (Westphal et al. 2006).

### **Do we need a standardized OLTT?**

There are countless studies evaluating postprandial lipid metabolism, only a small proportion of which are discussed in the present review. Almost every author presents data on standardized meals, with appropriate comparison to control

groups. However, between studies, these “standardized” meals vary widely. As summarized in a recent review by Kolovou et al. (2005a), fat loads vary widely in almost every parameter possible. Fat load tests vary in the total caloric content, ranging from 250 to 2500 kcal total, from 50% to 100% fat, 0% to 50% carbohydrate, and 0% to 20% protein. Further, the meals may be entirely liquid, solid, or a mixture with varying caloric density, which is an important consideration in subjects that have, for example, undergone gastric bypass.

Differences in fat distribution between SFAs, MUFAs, and PUFAs as well as positional distribution within the TG molecule can be problematic when comparing postprandial lipemia effects. Diets high in safflower oil are primarily polyunsaturated, diets high in olive oil are primarily monounsaturated, and diets enriched in butter contain mainly saturated fats (Dworatzek et al. 2004). In many cases, the fatty-acid diet composition is not calculated nor are sufficient details provided. Finally, the addition of other components, such as the type of carbohydrate (complex vs. sugar), protein source, or other components (as described above), can influence postprandial lipemia.

Further, the times when blood samples are drawn, the length of the studies, and the sample analysis are not necessarily uniform. For example, the evaluation of TRLs can be based on TG, apoB48 or other components of the TRL, and the separation of the particles by ultracentrifugation into large TRLs vs. small TRLs varies widely. In the past few years, additional methods for evaluation have included retinyl palmitate tracers (Cohn et al. 1993), immunochemical methods for isolation of RLP (Cohn et al. 1999), and a remnant-like emulsion breath test (Redgrave et al. 2001).

In addition to all of the acute components listed above, changes in dietary patterns and exercise prior to the fatload test may influence both fasting lipoproteins and postprandial responses. The CHYLO response to a fat challenge can vary by as much as 50% according to the fat, carbohydrate, and protein content of daily food intake (Slivkoff-Clark et al. 2004). Chronic consumption of reduced-caloric high-carbohydrate diets can exaggerate plasma TG levels. It has been demonstrated that in non-obese, normolipidemic subjects, standardizing food intake for 3 d reduced the intra-individual variability associated with postprandial chylomicronemia (assessed as apoB48 concentration), but a more prolonged time may be required to achieve the same effect on postprandial TG lipemia (Slivkoff-Clark et al. 2004).

### Gatekeeper proteins regulating postprandial lipemia

Various dietary factors affect postprandial metabolism (absorption, lipolysis, and hepatic remnant clearance), yet the precise mechanisms have not necessarily been pinpointed. However, there are a number of transporters, enzymes, and hormones that directly influence and act as “gatekeepers” of these processes. Each protein appears to have a specific and individual role in the overall process; the following section reviews recent developments in these areas.

### Proteins affecting intestinal absorption

Intestinal absorption of fat is efficient. Following uptake of fatty acids into enterocytes and re-esterification to TG, CHYLOs are assembled and released through the lymphatic system. Intestinal FABP2 and MTP play important roles in these processes. FABP2 is involved in the intracellular transport of long-chain fatty acids via a collisional mechanism, whereas MTP regulates the assembly of CHYLOs in the intestine (described below).

A common alanine for threonine substitution (A54→T) in FABP2 has been associated with hypertriglyceridemia, increased BMI, hyperinsulinemia, and insulin resistance (Hegele et al. 1996). In humans, the T54 allele is associated with increased postprandial lipemia in obese and diabetic subjects (Georgopoulos et al. 2000). However, not all studies have supported the associations with postprandial lipemia. When matched for both visceral adipose tissue and fasting plasma TG levels, no difference was found in postprandial TG clearance following a 64% fat mixed meal (Dworatzek et al. 2004). When diet–gene interactions of FABP2 A54T were tested using 3 different diets (butter, safflower oil, and olive oil), the T54 group had increased CHYLO cholesterol after olive oil only (enriched in oleic acid) (Dworatzek et al. 2004). This is relevant, as the T54 variant is associated with increased transport and secretion of triacylglycerol in *in vitro* enterocyte and tissue models (Baier et al. 1996). Further, this mutation affects the entry of long-chain fatty acids into the FABP2 protein (Zhang et al. 2003) with a two-fold greater binding affinity to the long-chain fatty acids oleate and arachidonate as compared with the A54 isoform (Baier et al. 1996), which may explain the diet–gene interaction, as well as some of the discrepancies in the literature.

MTP is a heterodimeric lipid-transfer protein responsible for the assembly of intestinal CHYLO, as well as hepatic VLDL. Absence of MTP results in an inability to form CHYLO as demonstrated in abetalipoproteinemia (Wetterau et al. 1992). The promoter region contains both negative insulin response elements and positive cholesterol response elements, and intestinal mRNA and protein are increased in animal models of insulin resistance and diabetes (Lewis et al. 2005). Two recent studies have examined directly the relationship between intestinal MTP gene expression and postprandial lipoprotein composition in diabetic and non-diabetic subjects. (Phillips et al. 2005; Lally et al. 2006). Both studies demonstrated increased intestinal MTP mRNA in diabetic subjects, with a decrease in statin-treated patients. Further, there was a positive correlation between the MTP mRNA and postprandial CHYLO cholesterol – B48 ratio, suggesting that the level of MTP directly impacts postprandial lipoproteins. A number of polymorphisms in the promoter region of MTP have been identified, although associations with fasting lipids were negative, it has been hypothesized that the presence of other conditions (such as diabetes) may amplify the effects of MTP polymorphisms and reveal themselves in postprandial lipemia changes (Phillips et al. 2004). Accordingly, the effect of 3 polymorphisms in a diabetic population revealed that the common –493G→T polymorphism is associated with increased postprandial apoB48, but significantly lower LDL cholesterol, suggest-

ing that this polymorphism may decrease risk of atherosclerosis (Phillips et al. 2004).

Cholesterol absorption can also influence postprandial lipemia (as mentioned above), (Agren et al. 2006). The relationship between CHYLO composition and expression of Niemann–Pick C1-like 1 (NPC1L1), which regulates cholesterol absorption and ABC transporters G5 and G8 (ABCG5 and ABCG8), which regulate cholesterol homeostasis were examined (Lally et al. 2006). Diabetic subjects expressed increased intestinal NPC1L1 but decreased ABCG5 and ABCG8. Statin therapy increased expression of the ABC transporters. Interestingly, postprandial CHYLO correlated not only with MTP, but also with NPC1L1 expression.

In addition to functional proteins that directly influence CHYLO formation and postprandial lipemia, a number of gastrointestinal hormones are implicated in postprandial lipemia. Administration of the gastrointestinal-derived GLP1 in healthy male volunteers abolishes the postprandial increase in TG and decreases NEFA, presumably as a result of delayed gastric emptying, although effects mediated through insulin-mediated inhibition of adipose lipolysis may also contribute (Meier et al. 2006a). By contrast, administration of GLP2 in healthy male volunteers led to significantly higher postprandial plasma TG and NEFA, and increased circulating glucagon. Changes in postprandial lipid excursion seem to reflect enhanced intestinal nutrient absorption but not gastric emptying although changes in adipose lipolysis (secondary to the changes in circulating glucagons) cannot be ruled out (Meier et al. 2006b).

Overall, these studies demonstrate that numerous intestinal factors such as FATP2, MTP, and gastrointestinal hormones regulate postprandial lipemia, and are in turn modified through diet–gene–disease–pharmacological interactions.

### Effect of peripheral adipose clearance on postprandial lipemia

Lipoprotein lipase (LPL) is a glycoprotein enzyme produced primarily by adipose and muscle. Anchored on the luminal surface of capillary endothelial cells, LPL hydrolyzes the TG in CHYLO and VLDL, releasing NEFAs that are stored (adipose) or oxidized (muscle). LPL is key to this process, and in the absence of LPL (such as in genetic mutations) there is complete absence of CHYLO hydrolysis. The enzyme LPL and consequently the overall TG storage process are primarily regulated through both the amounts and the activity of the protein, which is in turn modulated via various protein helpers, as well as through hormonal regulation (review (Faraj et al. 2004a)).

Genetic mutations in LPL can produce partial LPL defects and are associated with changes in lipid profile (Mailly et al. 1995). However, other genetic variations, which are common in the population, may also influence lipoprotein metabolism. The LPL variant S447→X, present in 18%–22% of individuals, results in alteration of the penultimate amino acid from Ser to a stop codon. This mutation is associated with increased LPL mass (Zhang et al. 1996; Kastelein et al. 2000). Evaluation of postprandial lipid clearance in men has demonstrated that this LPL variant is associated with attenuation of apoB48 and triglyceride postprandial increases

and increased preheparin LPL mass (Nierman et al. 2005), consistent with a lower risk for CAD. Conversely, the *HindIII* polymorphisms (also indicated as H1/H2), located in the intron between exon 8 and 9 on the LPL gene, are associated with delayed TG clearance and may contribute to familial combined hyperlipidemia (Lopez-Miranda et al. 2004).

A substantial body of evidence has accumulated showing that apoE polymorphisms play a crucial role in the clearance of TRL and apoCII is well recognized as a co-factor activator of LPL (Dart et al. 1997). Variations in plasma apoCIII are strong correlates of fasting and postprandial lipemia responses to high MUFA and high carbohydrate diets, with increased levels of apoCIII associated with delayed postprandial TG clearance (Archer et al. 2005).

Several studies have examined the impact of various apoAV polymorphisms on postprandial lipemia. Moreno and colleagues, as well as Jang and colleagues, both demonstrate that carriers of the –1131T→C allele had significantly increased postprandial lipemia (Moreno et al. 2006; Jang et al. 2004). On the other hand, previous studies do not support this (Masana et al. 2003; Martin et al. 2003). Factors such as caloric content and fat composition likely contribute to these differences. There are several mechanisms proposed to explain why this polymorphism may be responsible for the differences in postprandial lipemia in humans (Moreno et al. 2006; Jang et al. 2004): (i) the C allele is associated with lower plasma apoAV, (ii) higher levels of apoAV are associated with enhanced LPL activity, (iii) VLDL lacking apoAV have reduced receptor binding, suggesting reduced CHYLO remnant clearance, and (iv) apoAV influences assembly of VLDL (which can influence CHYLO clearance). All these points are consistent with decreased TRL production and increased TRL catabolism demonstrated in mice and can influence postprandial lipemia (Fruchart-Najib et al. 2004).

### Regulation of lipoprotein lipase

One additional participant in this lipolytic process is the VLDLR, a member of the LDL receptor family with distinctive ligand-binding properties and tissue distribution (Sakai et al. 1994). VLDLR is uniquely expressed at sites involved in peripheral TG clearance, including adipose, heart, and muscle tissue (Sakai et al. 1994). VLDLR appears to be involved in the transcytosis of active LPL across endothelial cells, and may facilitate the binding of TRLs in the capillary bed in concert with LPL (Goudriaan et al. 2004). The role of VLDLR in CHYLO clearance was evaluated in VLDLR knockout mice. In spite of unchanged fasting lipid levels, postprandial TG levels were increased 9 fold in knockout mice following a fat load. There was no observable effect on adipose tissue uptake of NEFA, suggesting that VLDLR facilitates postprandial LPL-mediated TG hydrolysis and absence of VLDLR is associated with reduced activity of LPL (Goudriaan et al. 2004).

A number of hormones contribute to modulation of overall LPL activity. These include insulin, TNF $\alpha$ , acylation-stimulating protein (ASP), and possibly adiponectin. In the postprandial state, adipose tissue LPL is increased relative to fasting levels, whereas muscle LPL tends to be reduced (Boivin et al. 1994). In adipocytes, insulin acutely increases LPL activity and secretion, mostly through changes at the

post-translational level. This raises the question: are the postprandial increases in LPL solely mediated by the postprandial increases in insulin? Based on studies by Picard and colleagues in rodents, the simple answer would appear to be “yes” (Picard et al. 1999). Changes in adipose tissue LPL activity were proportional to the changes in insulin, even in the absence of nutrient absorption. Conversely, the usual postprandial changes in adipose and muscle LPL did not occur in the absence of an increase in insulinemia.

Although insulin clearly plays a major role in influencing LPL activity, insulin is not the only component that influences postprandial lipemia clearance.  $\text{TNF}\alpha$  is a cytokine with a wide range of activities. It is produced primarily by monocytes and macrophages, although significant amounts are secreted by other cell types including adipocytes. Increased production has been implicated in the pathogenesis of insulin resistance and type 2 diabetes (review Robinson and Graham 2004). Several variants have been identified, such as the polymorphism at position -308, which involves a substitution of G to A and leads to a higher rate of gene transcription. It has been suggested that this may lead to increased predisposition of several chronic inflammatory related diseases (Cuenca et al. 2001). In Polish Caucasians from obese families, male “A” allele carriers were characterized by significantly increased levels of TG and NEFA during OLTTS. Thus, in addition to the known association of  $\text{TNF}\alpha$  with insulin resistance,  $\text{TNF}\alpha$  can potentially suppress lipid genes including LPL and glycerol phosphate dehydrogenase (review Faraj and Cianflone 2004).

TG clearance occurs as a two-step process: first, lipoproteins are hydrolyzed by LPL-releasing NEFA; second, NEFA is taken up into the cell and re-esterified to a storage TG molecule. Numerous studies in vitro and in vivo have demonstrated that excess generation and local accumulation of NEFA will inhibit LPL (Saxena et al. 1989). Therefore, processes that amplify the ability of the adipocyte to rapidly take up and store NEFA as TG will indirectly increase the hydrolytic efficiency of LPL. ASP is one such hormone. Also known as C3adesArg, ASP is an adipokine produced through the cleavage of complement C3 by adipsin (see Maslowska et al. 2005 for review). ASP interacts with C5L2, a G protein coupled receptor, activating an intracellular pathway that leads to increased glucose transport and TG storage (Kalant et al. 2005; Maslowska et al. 2006). Studies in ASP-deficient C3 knockout mice demonstrate a delayed TG clearance (in spite of normal insulin levels), which is normalized with injection of ASP (Maslowska et al. 2005). This effect is maintained in mice treated with a high fat diet or in genetically obese *ob/ob* mice deficient in ASP. This delay in TG clearance leads to a leaner mouse with reduced adipose tissue, resistant to diet-induced obesity. In vitro studies demonstrated that although ASP has no direct effect on LPL activity (in contrast to insulin), the clearance of TRLs is enhanced by ASP through increasing TG storage and relieving NEFA inhibition of LPL (Faraj et al. 2004a). The effectiveness of adipose tissue trapping of LPL-derived NEFA determines overall LPL activity, which in turn determines the efficiency of postprandial TG clearance (Faraj et al. 2004a). In contrast to the effects of ASP on adipose tissue, ASP decreased in situ muscle LPL activity, similar to the effects of insulin (Faraj et al. 2004b).

In human studies, fasting ASP is influenced by diet, body size (obesity), exercise, and metabolic status (cardiovascular disease and diabetes) (Matthan et al. 2001; Schrauwen et al. 2005; Maslowska et al. 1999; Cianflone et al. 2003). In normal healthy men and women, stratification of fasting ASP by tertiles demonstrated a delayed postprandial TG and NEFA clearance in the subjects with the highest fasting ASP, a correlation that remained even after correction for differences in fasting TG. Interestingly, the precursor to ASP, complement C3, also demonstrates similar associations with postprandial TG lipemia, as well as correlations with MetS indices (van Oostrom et al. 2006). The association between increased fasting ASP and postprandial lipemia likely reflects ASP resistance, as proposed and described elsewhere (Cianflone et al. 2004; Havel 2004), similar to the insulin resistance paradigm. Fasting plasma ASP and C3 may be useful markers to identify subjects with postprandial delayed TG clearance or MetS.

In contrast to the adipokine ASP, which is associated with increased TG storage and efficiency of postprandial lipemia, adiponectin has been shown to have the opposite effect. Adiponectin is known to enhance TG lipoprotein catabolism and fatty acid oxidation, and has been linked to fasting TG and HDL independently of insulin sensitivity and visceral obesity (Baratta et al. 2004). In mice administration of adiponectin reduced postprandial NEFA and altered VLDL apoB catabolism (Yamauchi et al. 2002). In patients with nonalcoholic steatohepatitis, the magnitude of postprandial lipemia was substantially higher than in controls, and was inversely related to fasting adiponectin levels (Musso et al. 2005). Conversely, both the amount and type of dietary fat can regulate adiponectin secretion (Seo et al. 2004).

At the level of peripheral clearance, especially in adipose tissue, the central component is LPL. But LPL does not act alone: it is supported by numerous stimulatory and inhibitory co-factors (apoCII, apoCIII, apoE, apoAV, and LRP) and influenced at both the gene and activity level by insulin,  $\text{TNF}\alpha$ , and ASP. Not only do all these factors contribute to postprandial clearance, many of these factors in turn are influenced by dietary factors, creating a complex web of interdependence.

### Regulation of hepatic CHYLO and remnant clearance

As with peripheral lipid clearance, hepatic uptake of CR is controlled by a battery of apoproteins and receptors. One of the first factors recognized to play a critical role was apoE. ApoE acts as a specific ligand for the LDL receptor, LRP and the VLDLR (review St Clair and Beisiegel 1997). Human apoE occurs as 3 main isoforms: apoE3, apoE2, and apoE4, the latter two resulting from a single amino acid change. Consequently apoE2 has a lower in vitro receptor binding activity compared to apoE3, and apoE4 has also been associated with delayed postprandial TG clearance (St Clair and Beisiegel 1997). In addition to the qualitative modification of the apoE structure owing to the amino acid sequence, polymorphisms in the proximal promoter region have been described at positions -491A→T, -427T→C, and -219G→T (Lambert et al. 2000). In young normolipidemic apoE3/E3 men, subjects with the -219T genotype

have lower serum apoE levels, and a higher postprandial response than carriers of the G allele in spite of similar fasting TG levels (Moreno et al. 2003).

Although apoE is clearly the major ligand of CR and interacts with multiple receptors, numerous experiments in cells and animal models show that LPL bound to apoB lipoproteins (including CR) also enhances their uptake via receptor mediated pathways (Beisiegel et al. 1991). A low concentration of circulating LPL has been detected in vivo, and high levels of NEFA not only interfere with LPL activity (as discussed above) but also enhance disassociation of LPL from the endothelial cell surface, increasing circulating levels (Saxena et al. 1989). Interestingly, the lipolytic function of LPL is not required for mediation of lipoprotein particle uptake based on studies with LPL inhibitors and catalytically inactive LPL (Nykjaer et al. 1994). Whether this is a normal physiological function of LPL still remains to be answered. A recent study by Zheng and colleagues examined this aspect in normolipidemic human subjects (Zheng et al. 2006). Following an oral fat load, LPL containing apoB lipoproteins were isolated by immunoaffinity chromatography and analyzed. Their results suggested that apoB lipoproteins containing LPL had significantly enhanced rates of clearance, and neither size nor apoE content could explain the increased clearance rates. This was especially true for apoB48 intestinal lipoproteins (CHYLO and CR).

Within the hepatic space, a number of receptors have been linked in various ways to CR clearance. These include LDL receptor, LRP, SR-B1, ABCA1, and HL (van Eck et al. 2005). HL is a lipolytic enzyme that is synthesized in parenchymal liver cells, secreted, and bound extracellularly to the liver (Nilsson-Ehle et al. 1980). HL hydrolyzes phospholipids and triglycerides, participating in the metabolism of IDL, LDL, and HDL. Although this is the major role of HL, a possible role has emerged in the uptake of remnant particles. Inhibition of HL leads to impairment of CR clearance, and various HL gene promoter polymorphisms appear to influence HL activity (Guerra et al. 1997). Functional genetic variants of HL with high population frequencies include  $-250G \rightarrow A$ ,  $-514C \rightarrow T$ ,  $-710T \rightarrow C$ , and  $-763A \rightarrow G$ . The  $-514C \rightarrow T$  polymorphism mediates changes in the level of HL. The effect on postprandial lipemia was tested in normolipidemic apoE3 participants (Gomez et al. 2004). Carriers of the T allele had significantly lower postprandial apoB, which contrasts with the results obtained in a separate study (Jansen et al. 1999). This also contrasts with the existing knowledge that the T allele is associated with lower HL activity, and the proposed effects of HL on TRL metabolism (Deeb and Peng 2000).

Although the LDL receptor and LRP are well established as clearance mechanisms for remnants (CR and VLDL remnants) (review Willnow 1997), the role of other receptors is now also emerging. SR-B1 is a cell-surface glycoprotein comprising 2 transmembrane and 2 cytoplasmic domains, as well as a large extracellular loop containing several glycosylation sites (review van Eck et al. 2005). This highly conserved protein is expressed in liver and other tissues important to cholesterol metabolism, with distinctive binding sites for phospholipids, advanced glycation end products,

apoptotic cells, and native and modified lipoproteins. SR-B1 has been well characterized with respect to HDL metabolism, but less so in the clearance of apoB-containing lipoproteins. In vitro, SR-B1 recognizes both apoE as well as apoB, and studies in SR-B1 knockout mice further support a role in postprandial lipid metabolism. Consistent with this, the association of CHYLO-type particles to freshly isolated hepatocytes is reduced in SR-B1 knockout mice. In humans, several studies on common polymorphisms of CLA-1 (the human homologue of SR-B1) demonstrate that some variants are associated with altered lipid metabolism, including apoB lipoproteins; effects that vary according to age and gender (review van Eck et al. 2005). Further, carriers of the 2 alleles in exon 1 of the SR-B1 gene demonstrate reduced fasting LDL and TG, and were more responsive to changes in dietary saturated fat intake (Perez-Martinez et al. 2003). It has also been suggested that SR-B1 may be involved in intestinal absorption of TG. Perez-Martinez and colleagues have demonstrated that a common polymorphism (1/2) is associated with accelerated clearance of postprandial TG, in particular small TRL, in normolipidemic apoE3 subjects (Perez-Martinez et al. 2004).

ABCA1 belongs to a large family of conserved transmembrane proteins that use ATP as energy to drive the transport of a wide variety of molecules across the plasma membrane (review van Eck et al. 2005). ABC transporters typically consist of two 6-helix transmembrane domains with two nucleotide-binding domains. ABCA1 has been shown to interact with apoA1, lipidating and forming nascent HDL (van Eck et al. 2005). In addition to apoA1, other apolipoproteins with amphipathic helical motifs such as apoAII, apoCI, apoCII, apoCIII, and apoE also efficiently induce lipid efflux by the same mechanism. Tangier disease results in extremely low plasma HDL as a result of ABCA1 dysfunction. Cardiovascular disease patients with low HDL frequently have increased fasting TG and delayed postprandial TG clearance. Consistent with that, Tangier disease patients display delayed TG clearance postprandially (Kolovou et al. 2003). These effects on postprandial lipemia may be a simple consequence of the interaction between HDL and apoB metabolism. We have previously demonstrated that an increase in the efflux of cholesterol from hepatocytes to apoA1 results in a decrease in secretion of apoB-containing lipoproteins (Sniderman et al. 2003). Sahoo et al. (2004) demonstrated that this effect is nullified in hepatocytes lacking ABCA1.

Contrasting data have been obtained in other studies. A decrease in plasma TG levels was observed in ABCA1 knockout mice with a complete absence of postprandial CHYLO (Orso et al. 2000). Patients with Tangier disease evidence a 40% decrease in total plasma apoB levels (Schaefer et al. 2001). Correspondingly, overexpression of ABCA1 in mice resulted in increased apoB and TG levels (Wellington et al. 2003). A recent study examined targeted disruption in hepatic ABCA1 using plasmid-based small interference RNA (siRNA) methodology to generate a recombinant adenovirus to selectively downregulate hepatic ABCA1 in mice (Ragozin et al. 2005). Following a fat load, the postprandial increase in CHYLO and CHYLO-associated apoB and apoE were significantly reduced as compared to controls. Although the mechanism for this ef-

fect remains unknown, it could not be explained by either reduced intestinal fat absorption or decreased hepatic VLDL secretion, but appeared to be associated with increased CHYLO clearance. Clearly, either positively or negatively, ABCA1 appears to influence postprandial lipid metabolism.

In humans, the influence of any of these receptors on postprandial lipemia is difficult to determine due to the limited methods available to evaluate individual receptor activity and function in humans, and the absence of epidemiological studies. The combination of indirect methodology in physiological studies coupled to direct testing in biological cell and animal models will provide the best insights in the future.

### **Effect of sex-related fat distribution on postprandial lipemia**

Men and women have different fat distribution; men typically store excess fat in visceral adipose tissue depots, whereas women tend to preferentially store fat in the subcutaneous adipose tissue depots of the buttocks and thighs. This difference in fat distribution may be associated with the relative atherogenic risk. Women have lower postprandial TG response and more rapid clearance of dietary CHYLO TG than men (Knuth and Horowitz 2006; review Graham 2004).

Unfortunately, this postprandial lipemic protection is lost after menopause. Postmenopausal women have decreased CHYLO clearance capacity and endogenous estrogen deficiency is associated with a more adverse lipid profile, which increases the risk for CAD. The Framingham Study reported postmenopausal women had a 2–3 times greater risk of developing CAD compared to premenopausal women of the same age (Kannel 1987). Even artificially induced menopause (oophorectomy) increases the risk of myocardial infarct (Kannel 1987), whereas estrogen-replacement therapy reduces this risk (van Beek et al. 1999). When pre and postmenopausal women were matched for age and fasting TG, the postmenopausal women nonetheless displayed higher postprandial lipemia, specifically a delayed CHYLO response (van Beek et al. 1999).

Abdominal obesity is associated with accumulation of visceral adipose tissue (VAT) and insulin resistance and is a contributing factor for exaggerated postprandial lipemia. In a study conducted by Blackburn et al. (2003), who examined impaired glucose tolerant (IGT) men to normal glucose tolerant (NGT) men, IGT men displayed increased BMI, body mass, VAT, waist circumference, fasting TG, insulin, and glucose (by study design). The IGT subjects also had higher postprandial lipemia after a fat load. Interestingly, when IGT and NGT men were matched for VAT, there was no longer any difference between the groups in postprandial lipid response. Moreover, after adjusting for fasting glucose and OGTT, subjects with increased VAT displayed higher postprandial TG levels compared to men with less VAT. The authors also confirmed a positive correlation between postprandial lipemia and VAT accumulation. These results suggest that VAT had a greater effect on postprandial lipemia than glucose intolerance (Blackburn et al. 2003).

MetS is defined as having at least 3 of the 5 following

symptoms: increased fasting TG, decreased HDL-C, increased glucose, abdominal obesity, and hypertension (review Robinson and Graham 2004). Men with MetS displayed delayed postprandial lipid clearance after a fat load compared to men with hypertension or controls (Kolovou et al. 2005b). Sub-group analysis of MetS subjects with hypertension showed delayed clearance compared to hypertensive patients alone. However, these groups had different BMI and fasting TG levels. TG AUC was greater in MetS with hyperTG compared to MetS patients with normal TG. A linear regression analysis found only fasting TG to correlate with postprandial TG response in these subjects. However, both MetS and hypertensive men with normal fasting TG displayed exaggerated postprandial lipemic response compared to controls (Kolovou et al. 2005b). This was also seen in postmenopausal women with MetS and normal TG levels (Kolovou et al. 2006a). Therefore, independent of fasting lipid levels, severe postprandial lipemia may be considered as an additional component of the associated risk of developing chronic disease.

### **Diabetes and postprandial lipemia**

Peripheral insulin resistance is the hallmark of type 2 diabetes (T2D) and those with severe T2D often have impaired insulin secretion as well. T2D subjects have increased incidence of cardiovascular morbidity and mortality. A common feature of diabetic dyslipidemia is fasting hyperTG and lipid abnormalities in the postprandial state. Several studies have reported correlations between fasting TG levels and postprandial response after a fat meal and this could contribute to the observed elevated health risks of T2D (Hauner 2002; Annuzzi et al. 2004).

Nonetheless, study participants with well-controlled diabetes (normal TG and glucose levels) also displayed increased TG response after a fat meal. Specifically, there was an increase in VLDL and CHYLO remnants as measured by delayed clearance of TG, cholesterol, apoB48 and apoB100 in large VLDL fractions, which increases the CAD risk in these patients, despite normal fasting TG (Rivellese et al. 2004). In a similar set of patients, Annuzzi et al. (2004) conducted hyperinsulinemic glycemic clamp studies in addition to evaluating postprandial response. After controlling for insulin and glucose levels in mild diabetics, they reported that hyperinsulinemia and hyperglycemia do not have an effect on postprandial lipemia per se, whereas insulin sensitivity does (Annuzzi et al. 2004). Moreover, both studies showed diabetics have increased CR production and attributed this to a lack of insulin-induced inhibition of hepatic VLDL synthesis (Rivellese et al. 2004; Annuzzi et al. 2004).

### **Postprandial lipemia and cardiovascular disease**

In addition to diabetes, numerous disease states are also associated with postprandial lipemia. Patsch et al. (1992) was the first to demonstrate that postprandial TG levels were highly discriminatory between healthy individuals and those with cardiovascular disease (CAD), and this has since been confirmed by many studies (review Kolovou et al. 2005a). However, it is not always clear whether postprandial

lipemia is an independent risk factor (especially independent of fasting TG). Many CAD patients continue to have cardiovascular events despite effective lowering of their LDL cholesterol. However, LDL cholesterol alone may not reflect total CAD risk and other dyslipidemic states, such as impaired postprandial lipemia, may contribute as well (review Nicholls and Lundman 2004). Increased postprandial lipid intolerance is seen in smokers, even with normal fasting TG levels, which may contribute to their increased CAD risk (Eliasson et al. 1997). Heterozygous familial hypercholesterolemia (hFH) is a genetic disease causing reduced activity of LDL receptors, which in turn leads to increased total cholesterol, LDL cholesterol and the development of xanthomas and atherosclerosis. Kolovou et al. showed that postmenopausal women with hFH exhibit increased postprandial TG clearance compared to premenopausal hFH women. The authors attributed this to estrogen-deficiency with increased fasting TG values, resulting in postprandial lipemia (Kolovou et al. 2004). However, when hFH postmenopausal women with normal fasting TG were compared with controls, the presence of hFH was still associated with an exaggerated postprandial response (Kolovou et al. 2006b). This is also true for men with hFH (Kolovou et al. 2005c), since, as outlined above, LDL receptor is important for CHYLO and VLDL remnant clearance. Therefore, despite normal fasting TG levels, high-risk patients would benefit from treatment to reduce postprandial lipemic response which contributes to increased incidence of cardiovascular events.

### Endothelial dysfunction and postprandial lipemia

Postprandial lipoproteins have direct effects on the endothelium by infiltrating the arterial wall and contributing to accumulation of atheromatous plaques (Zilvermit 1979). A pro-oxidative state accompanies meal ingestion, which results in increases in biomarkers of inflammation and adhesion (cytokines and soluble adhesion molecules) and endothelial dysfunction, all of which are factors in the development of CAD (review Bowen and Borthakur 2004). A large body of *in vitro* and *in vivo* studies support the direct atherogenicity of TRL and their remnants (reviews Cohn 1998; Karpe 1999) and it has recently become recognized that endothelial dysfunction is evident during the hours following fat ingestion (Vogel et al. 1997; Evans et al. 2000). In plasma, alterations in C-reactive protein, IL-6, and TNF $\alpha$  have been noted following a meal (Lanes et al. 2004). The source of these pro-inflammatory cytokines is unknown, but adipose tissue is one likely candidate, especially derived from resident macrophage populations (Wellen and Hotamisligil 2003). The greater magnitude of these plasma hormones in obese or diabetic subjects, and their decrease induced by weight loss, support that adipose tissue is a source (Giugliano et al. 2004).

These resultant changes in endothelial function, after a single fat meal, have been documented through decreases in flow-mediated dilatation of the brachial artery (van Oostrom et al. 2003) and through increases in circulating levels of endothelial cell microparticles (a sensitive indicator of endothelial disturbance) (Ferreira et al. 2004). Changes in lipids following a meal can result in an increase in blood coagula-

bility, with elevations in plasma factor VII coagulant activity (Miller et al. 1991; Silveira et al. 1994), which initiates the thrombotic response following plaque rupture. Furthermore, activation of neutrophils, leukocytes, platelets, and monocytes has been documented (van Oostrom et al. 2003; Hyson et al. 2002), although not all reports agree (Jakubowski et al. 1985). These effects appear to be especially marked after a fat meal (van Oostrom et al. 2003). Interestingly, it may not be only the CHYLO and CR that induce these responses, since LDL isolated from postprandial blood appeared to be able to substantially increase the expression of endothelial ICAM-1 (intracellular adhesion molecule-1) while LDL isolated from fasting plasma had no effect (Marchang et al. 2006).

Many of these changes are transient in nature. However, in the context of daily living, multiple meal consumption over the day, which takes many hours to process, results in an almost continuous state of metabolic disturbance. Repeated exposure of the blood vessel wall to the activities of pro-inflammatory cytokines and pro-oxidants may eventually damage the endothelium and promote atherogenesis. Realistically, in fact, the dynamic postprandial state prevails during most of our waking hours, and constitutes the "normal" physiological state.

### Effects of exercise and weight loss on postprandial lipemia

Daily physical activity is highly recommended, as exercise has been shown to ameliorate CAD risk. Exercise before a fat meal will increase postprandial TG clearance and the degree of reduction is associated with the energy expended (reviews Kolovou et al. 2005a; Graham 2004; Pettit and Cureton 2003). Interestingly, it is only exercise-induced energy deficiency that ameliorates TG response, as a comparable dietary-induced energy deficiency does not improve postprandial clearance (Gill and Hardman 2000). Moreover, detraining in athletes rapidly increases postprandial TG response to the level of untrained subjects (review Gill and Hardman 2003). Thus, energy expenditure and enhanced insulin sensitivity associated with exercise are fundamental for reductions in postprandial lipemia. Here we will briefly summarize recent articles focusing on the exercise intensity, type (aerobic or resistance training), and duration (time, continuous, or intermittent activities) and their effect on postprandial lipemia (Table 1).

Low-intensity exercise (25%  $VO_{2max}$ ) performed 1 h before a fat meal resulted in increased total fat oxidation; however, there were no improvements in TG clearance over no-exercise control, thus the total amount of fat oxidation does not seem to contribute to better postprandial clearance. Interestingly, moderate-intensity exercise (65%  $VO_{2max}$ ) performed to expend the same amount of energy as the low-intensity protocol successfully reduced TG AUC by 39% compared with control and by 34% compared with low-intensity exercise (Katsanos et al. 2004). Moreover, the rate of fat oxidation ( $\text{cal}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) in the moderate-intensity group was higher, leading the authors to speculate that there is increased intramuscular fat oxidation, followed by a depletion of intramuscular TG (~6–8 h after exercise) and increased LPL activity to restore muscle TG. This was

**Table 1.** Summary of studies on the influence of exercise on postprandial lipemia.

Reference	Subjects	Exercise	Duration	Energy expended	Oxygen consumption	Time before fat load	Fat load content	Additional meal consumed	Postprandial response
(Katsanos et al. 2004)	Healthy 12 M	Treadmill (AE)	237 min	4.6 MJ	VO <sub>2max</sub> 25%	1 h	Liquid meal 84% fat	Pre-exercise snack (-)	No $\Delta$
(Pfeiffer et al. 2005)	Healthy 16 M	Treadmill (AE)	90 min 30 min	0.88 MJ	VO <sub>2max</sub> 65% VO <sub>2max</sub> 50%	3 h	Mixed meal 0.5 g fat (53 kJ) /kg BM	Post-exer mixed meal 0.5 g fat (+)	$\downarrow$ TG AUC No $\Delta$
(Herd et al. 2001)	Healthy 8 M	Cycling (AE)	60 min 90 min 90 min	1.8 MJ 2.63 MJ 4.5 MJ	VO <sub>2max</sub> 60%	16 h	Mixed meal 1.4 g fat (73kJ) /kg BM		No $\Delta$ No $\Delta$ $\downarrow$ TG AUC
(Gill and Hardman 2000)	Post-menopausal 11 W	Treadmill (AE)	90 min	1.73 MJ	VO <sub>2max</sub> 60%	Day before	Mixed meal 1.7 g (99kJ) /kg FFBM		$\downarrow$ TG AUC
(Petitt et al. 2003)	Trained 10 M / 4 W	Dietary restriction Walking (AE) 10 reps/10 exer (RE)	90 min	1.7 MJ, 1.7 MJ	VO <sub>2max</sub> 12%	16 h	Mixed meal 66% fat, 5.1 MJ		No $\Delta$
(Shannon et al. 2005)	Trained 4 M /6 W	10 reps/8 exer (RE), 1 set	90 min 20 min	0.57 MJ	VO <sub>2max</sub> 12% N/A	13 h	Liquid meal 66.8% fat (95 kJ) /kg FFBM	Post-exer meal 30% fat (-)	$\downarrow$ TG AUC No $\Delta$
(Burns et al. 2005)	Healthy 11 M	10 reps/8 exer (RE), 3 sets 10 reps/8 exer (RE), 5 sets 10 reps/11 exer (RE), 4 sets	48 min 90 min 88 min	1.72 MJ 2.58 MJ 2.3 MJ	1.22 L/min	16 h	Mixed meal 1.2 g fat/kg BM 68 kJ/kg BM	Post-exer meal (-)	No $\Delta$ No $\Delta$ No $\Delta$
(Miyashita et al. 2006)	Healthy 10 M	Treadmill (AE) CON INT	30 min	1.96 MJ	VO <sub>2max</sub> 70%	17 h	Mixed meal 56% fat, 3.7 MJ	Post-exer mixed meal 56% fat (+)	$\downarrow$ TG AUC
(Altena et al. 2004)	Inactive 7 M /11 F	Treadmill (AE) CON Treadmill (AE) INT	10 $\times$ 3 min 30 min 3 $\times$ 10 min	N/A 2.01 MJ	VO <sub>2max</sub> 60%	12 h	Liquid meal 88% fat		No $\Delta$ $\downarrow$ TG AUC

**Note:** AE, aerobic exercise; BM, body mass; CON, continuous; FFBM, fat free body mass; INT, intermittent; M, men; N/A, not available; RE, resistance exercise; W, women; No  $\Delta$ , no difference;  $\downarrow$  TG AUC, significant reduction in TG area under the curve (AUC); - or +, the additional meal was provided before or after administration of the fat load, respectively.

demonstrated in another study by muscle biopsy analysis in young healthy men who engaged in moderate exercise (60%  $\text{VO}_{2\text{max}}$ ) for 90 min, then were examined 16 h later. The effect of prior exercise attenuated postprandial lipemic response and increased muscle LPL activity (Herd et al. 2001). LPL activity was reported to be increased with endurance training and decreased in detrained athletes. Moreover, after one exercise session muscle LPL mRNA levels were upregulated at 4 h, returning to baseline only 24 h later (Gill and Hardman 2003). Of note, some studies (Katsanos et al. 2004; Gill and Hardman 2000), but not all (Herd et al. 2001) showed that moderate intensity exercise reduced postprandial insulinemia. Therefore, the effects may be mediated through insulin inhibition of LPL activity in muscle (as discussed above).

At a given energy deficit, exercise intensity impacts the lipemic response, but does the type of activity also play a role? A single session of resistance exercise was compared to aerobic exercise matched for the same duration and energy expenditure (12%  $\text{VO}_{2\text{max}}$ , 1.7 MJ) in healthy weight-trained individuals. Resistance exercise attenuated the postprandial lipemic response by 14% compared to no exercise and 18% compared to aerobic exercise (Petitt et al. 2003). By contrast, another study reported that increasing amounts of acute resistance exercise did not significantly alter postprandial TG clearance 13 h after a fat meal (Shannon et al. 2005). However, a eucaloric meal was administered following the exercise session to maintain energy balance, and this may have masked the expected reduction in postprandial lipemia. Similarly, there was no amelioration in postprandial response after resistance exercise compared to no-exercise control in untrained healthy males expending 2.3 MJ energy (Burns et al. 2005). It was suggested that skeletal muscle damage might have reduced LPL activity. Thus, it is unclear whether there are always benefits, with regards to postprandial lipemia, of resistance exercise before the consumption of a fat meal.

Exercise duration and exercise pattern (continuous or intermittent) can also regulate postprandial clearance. Modest changes (not significant) in postprandial response were reported when young healthy men performed moderate walking (50%  $\text{VO}_{2\text{max}}$ ) for 60 or 90 min, but not for 30 min (Pfeiffer et al. 2005). Continuous (30 min of treadmill running) and intermittent (accumulation of ten 3 min bouts throughout the day) high-intensity aerobic exercise (70%  $\text{VO}_{2\text{max}}$ ) was examined in young healthy males (Miyashita et al. 2006). The following day, postprandial TG AUC was reduced to a similar extent, -24% and -22%, for continuous and intermittent exercise, respectively (Miyashita et al. 2006). Yet when three 10 min intermittent exercise bouts were compared with 30 min of continuous exercise, only the intermittent workout significantly reduced the postprandial lipemic response by 27% versus 16% by continuous exercise (not significant) (Altena et al. 2004). The investigators suggest there is excess post-oxygen consumption between intermittent exercise sessions, which increases the rate of oxygen intake after strenuous activities, altering overall energy expenditure. However, it still remains unclear whether continuous or intermittent exercises have different effects on postprandial lipemia.

## Effects of weight loss on postprandial lipemia

Weight loss has been shown to increase insulin sensitivity and reduce atherosclerotic risk. Overweight men involved in a 16 week diet intervention lost an average of 10 kg and successfully improved insulin and HOMA scores; moreover, there was a 27.5% increase in LDL receptor binding in mononuclear cells (James et al. 2003). Previously obesity, insulin resistance and dyslipidemia have been shown to reduce LDL receptor binding compared to controls (James et al. 2003). Although improved LDL receptor function was reported, there was no change in postprandial TG response before and after intervention, yet CHYLO metabolism was significantly improved after weight loss as evaluated by retinyl palmitate AUC. Interestingly, even modest weight loss (2–3 kg) from dieting improves postprandial TG clearance in overweight women (Volek et al. 2004); however, this may be gender specific as discussed before.

In summary, daily exercise and a healthy lifestyle can significantly reduce postprandial lipemia and ultimately CAD risk. However, based on our interpretation of the studies reviewed, as well as a meta-analysis study (Petitt and Cureton 2003), there is no clear consensus on which type of exercise is better. The variability in study design makes comparisons difficult (see Table 1). Discrepancies exist between exercise period, administration of fat meal, fat meal content, and number of meals given. Also subjects vary from trained athletes to healthy subjects to inactive groups and sample sizes are relative low due to complex study designs.

## Conclusions

Throughout the day, people are primarily in a postprandial state; thus fasting lipid values may not always reflect the relative risk of diabetes, MetS, or CAD. Many factors influence postprandial lipemia, including endogenous expression of intestinal, adipose, and hepatic proteins such as FABP2, MTP, LPL, apoAV, ASP, SR-B1, and ABCA1. Additional factors include dietary composition, body fat distribution, clinical status, exercise, and weight loss. Oral lipid tolerance testing (OLTT) would supply clinicians with pertinent information regarding the health status of their patients. However, at this point, there are no standardized tests and the evaluation is complex and time consuming. Therefore, it is useful to examine other potential markers of delayed lipid clearance such as apoAV, C3, ASP, and others. Analysis of these candidate markers may be easier and cheaper to implement and still provide valuable information.

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## References

- Agren, J.J., Hallikainen, M., Vidgren, H., Miettinen, T.A., and Gylling, H. 2006. Postprandial lipemic response and lipoprotein composition in subjects with low or high cholesterol absorption efficiency. *Clin. Chim. Acta*, **366**: 309–315. doi:10.1016/j.cca.2005.11.006. PMID:16364276.

- Altena, T.S., Michaelson, J.L., Ball, S.D., and Thomas, T.R. 2004. Single sessions of intermittent and continuous exercise and postprandial lipemia. *Med. Sci. Sports Exerc.* **36**: 1364–1371. doi:10.1249/01.MSS.0000135793.43808.6C. PMID:15292745.
- Annucci, G., De Natale, C., Iovine, C., Patti, L., Di Marino, L., Coppola, S., et al. 2004. Insulin resistance is independently associated with postprandial alterations of triglyceride-rich lipoproteins in type 2 diabetes mellitus. *Arterioscler. Thromb. Vasc. Biol.* **24**: 2397–2402. PMID:15458975.
- Archer, W.R., Desroches, S., Lamarche, B., Deriaz, O., Landry, N., Fontaine-Bisson, B., et al. 2005. Variations in plasma apolipoprotein C-III levels are strong correlates of the triglyceride response to a high-monounsaturated fatty acid diet and a high-carbohydrate diet. *Metabolism*, **54**: 1390–1397. doi:10.1016/j.metabol.2005.05.004. PMID:16154441.
- Asselin, G., Lavigne, C., Bergeron, N., Angers, P., Belkacemi, K., Arul, J., and Jacques, H. 2004. Fasting and postprandial lipid response to the consumption of modified milk fats by guinea pigs. *Lipids*, **39**: 985–992. doi:10.1007/s11745-004-1320-5. PMID:15691020.
- Baier, L.J., Bogardus, C., and Sacchettini, J.C. 1996. A polymorphism in the human intestinal fatty acid binding protein alters fatty acid transport across Caco-2 cells. *J. Biol. Chem.* **271**: 10892–10896. PMID:8631905.
- Baratta, R., Amato, S., Degano, C., Farina, M.G., Patane, G., Vigneri, R., et al. 2004. Adiponectin relationship with lipid metabolism is independent of body fat mass: evidence from both cross-sectional and intervention studies. *J. Clin. Endocrinol. Metab.* **89**: 2665–2671. doi:10.1210/jc.2003-031777. PMID:15181039.
- Beisiegel, U., Weber, W., and Bengtsson-Olivecrona, G. 1991. Lipoprotein lipase enhances the binding of chylomicrons to low density lipoprotein receptor-related protein. *Proc. Natl. Acad. Sci. U.S.A.* **88**: 8342–8346. doi:10.1073/pnas.88.19.8342. PMID:1656440.
- Bellido, C., Lopez-Miranda, J., Blanco-Colio, L.M., Perez-Martinez, P., Muriana, F.J., Martin-Ventura, J.L., et al. 2004. Butter and walnuts, but not olive oil, elicit postprandial activation of nuclear transcription factor kappaB in peripheral blood mononuclear cells from healthy men. *Am. J. Clin. Nutr.* **80**: 1487–1491. PMID:15585759.
- Berry, S.E., and Sanders, T.A. 2005. Influence of triacylglycerol structure of stearic acid-rich fats on postprandial lipaemia. *Proc. Nutr. Soc.* **64**: 205–212. doi:10.1079/PNS2005422. PMID:15960865.
- Blackburn, P., Lamarche, B., Couillard, C., Pascot, A., Tremblay, A., Bergeron, J., et al. 2003. Contribution of visceral adiposity to the exaggerated postprandial lipemia of men with impaired glucose tolerance. *Diabetes Care*, **26**: 3303–3309. PMID:14633818.
- Boivin, A., Montplaisir, I., and Deshaies, Y. 1994. Postprandial modulation of lipoprotein lipase in rats with insulin resistance. *Am. J. Physiol.* **267**: E620–E627. PMID:7943313.
- Bowen, P.E., and Borthakur, G. 2004. Postprandial lipid oxidation and cardiovascular disease risk. *Curr. Atheroscler. Rep.* **6**: 477–484. PMID:15485594.
- Burns, S.F., Corrie, H., Holder, E., Nightingale, T., and Stensel, D.J. 2005. A single session of resistance exercise does not reduce postprandial lipaemia. *J. Sports Sci.* **23**: 251–260. doi:10.1080/02640410410001730142. PMID:15966343.
- Chung, B.H., Cho, B.H., Liang, P., Doran, S., Osterlund, L., Oster, R.A., et al. 2004. Contribution of postprandial lipemia to the dietary fat-mediated changes in endogenous lipoprotein-cholesterol concentrations in humans. *Am. J. Clin. Nutr.* **80**: 1145–1158. PMID:15531660.
- Cianflone, K., Xia, Z., and Chen, L.Y. 2003. Critical review of acylation-stimulating protein physiology in humans and rodents. *Biochim. Biophys. Acta*, **1609**: 127–143. PMID:12543373.
- Cianflone, K., Zakarian, R., Couillard, C., Delplanque, B., Despres, J.P., and Sniderman, A. 2004. Fasting acylation-stimulating protein is predictive of postprandial triglyceride clearance. *J. Lipid Res.* **45**: 124–131. PMID:14563826.
- Cohn, J.S. 1998. Postprandial lipemia: emerging evidence for atherogenicity of remnant lipoproteins. *Can. J. Cardiol.* **14**: Suppl B, 18B–27B. PMID:9627538.
- Cohn, J.S., Johnson, E.J., Millar, J.S., Cohn, S.D., Milne, R.W., Marcel, Y.L., et al. 1993. 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.* **34**: 2033–2040. PMID:8301224.
- Cohn, J.S., Marcoux, C., and Davignon, J. 1999. Detection, quantification, and characterization of potentially atherogenic triglyceride-rich remnant lipoproteins. *Arterioscler. Thromb. Vasc. Biol.* **19**: 2474–2486. PMID:10521378.
- Cuenca, J., Perez, C.A., Aguirre, A.J., Schiattino, I., and Aguillon, J.C. 2001. Genetic polymorphism at position-308 in the promoter region of the tumor necrosis factor (TNF): implications of its allelic distribution on susceptibility or resistance to diseases in the Chilean population. *Biol. Res.* **34**: 237–241. PMID:11715861.
- Dart, A., Sherrard, B., and Simpson, H. 1997. Influence of apo E phenotype on postprandial triglyceride and glucose responses in subjects with and without coronary heart disease. *Atherosclerosis*, **130**: 161–170. doi:10.1016/S0021-9150(96)06062-5. PMID:9126660.
- Deeb, S.S., and Peng, R. 2000. The C-514T polymorphism in the human hepatic lipase gene promoter diminishes its activity. *J. Lipid Res.* **41**: 155–158. PMID:10627514.
- Dworatzek, P.D., Hegele, R.A., and Wolever, T.M. 2004. Postprandial lipemia in subjects with the threonine 54 variant of the fatty acid-binding protein 2 gene is dependent on the type of fat ingested. *Am. J. Clin. Nutr.* **79**: 1110–1117. PMID:15159243.
- Eliasson, B., Mero, N., Taskinen, M.R., and Smith, U. 1997. The insulin resistance syndrome and postprandial lipid intolerance in smokers. *Atherosclerosis*, **129**: 79–88. doi:10.1016/S0021-9150(96)06028-5. PMID:9069521.
- Evans, M., Anderson, R.A., Graham, J., Ellis, G.R., Morris, K., Davies, S., et al. 2000. Ciprofibrate therapy improves endothelial function and reduces postprandial lipemia and oxidative stress in type 2 diabetes mellitus. *Circulation*, **101**: 1773–1779. PMID:10769276.
- Faraj, M., and Cianflone, K. 2004. Differential regulation of fatty acid trapping in mouse adipose tissue and muscle by ASP. *Am. J. Physiol. Endocrinol. Metab.* **287**: E150–E159. doi:10.1152/ajpendo.00398.2003. PMID:15191884.
- Faraj, M., Lu, H.L., and Cianflone, K. 2004a. Diabetes, lipids, and adipocyte secretagogues. *Biochem. Cell Biol.* **82**: 170–190. doi:10.1139/o03-078. PMID:15052336.
- Faraj, M., Sniderman, A.D., and Cianflone, K. 2004b. ASP enhances in situ lipoprotein lipase activity by increasing fatty acid trapping in adipocytes. *J. Lipid Res.* **45**: 657–666. PMID:14703506.
- Ferreira, A.C., Peter, A.A., Mendez, A.J., Jimenez, J.J., Mauro, L.M., Chirinos, J.A., et al. 2004. Postprandial hypertriglyceridemia increases circulating levels of endothelial cell microparticles. *Circulation*, **110**: 3599–3603. doi:10.1161/01.CIR.0000148820.55611.6B. PMID:15569844.
- Fruchart-Najib, J., Bauge, E., Niculescu, L.S., Pham, T., Thomas,

- B., Rommens, C., et al. 2004. Mechanism of triglyceride lowering in mice expressing human apolipoprotein A5. *Biochem. Biophys. Res. Commun.* **319**: 397–404. PMID:15178420.
- Georgopoulos, A., Aras, O., and Tsai, M.Y. 2000. Codon-54 polymorphism of the fatty acid-binding protein 2 gene is associated with elevation of fasting and postprandial triglyceride in type 2 diabetes. *J. Clin. Endocrinol. Metab.* **85**: 3155–3160. doi:10.1210/jc.85.9.3155. PMID:10999802.
- Gill, J.M., and Hardman, A.E. 2000. Postprandial lipemia: effects of exercise and restriction of energy intake compared. *Am. J. Clin. Nutr.* **71**: 465–471. PMID:10648259.
- Gill, J.M., and Hardman, A.E. 2003. Exercise and postprandial lipid metabolism: an update on potential mechanisms and interactions with high-carbohydrate diets (review). *J. Nutr. Biochem.* **14**: 122–132. PMID:12742539.
- Giugliano, G., Nicoletti, G., Grella, E., Giugliano, F., Esposito, K., Scuderi, N., et al. 2004. Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women. *Br. J. Plast. Surg.* **57**: 190–194. doi:10.1016/j.bjps.2003.12.010. PMID:15006519.
- Gomez, P., Miranda, J.L., Marin, C., Bellido, C., Moreno, J.A., Moreno, R., et al. 2004. Influence of the -514C/T polymorphism in the promoter of the hepatic lipase gene on postprandial lipoprotein metabolism. *Atherosclerosis*, **174**: 73–79. doi:10.1016/j.atherosclerosis.2003.12.038. PMID:15135253.
- Goudriaan, J.R., Espirito Santo, S.M., Voshol, P.J., Teusink, B., van Dijk, K.W., van Vlijmen, B.J., et al. 2004. The VLDL receptor plays a major role in chylomicron metabolism by enhancing LPL-mediated triglyceride hydrolysis. *J. Lipid Res.* **45**: 1475–1481. PMID:15145981.
- Gradek, W.Q., Harris, M.T., Yahia, N., Davis, W.W., Le, N.A., and Brown, W.V. 2004. Polyunsaturated fatty acids acutely suppress antibodies to malondialdehyde-modified lipoproteins in patients with vascular disease. *Am. J. Cardiol.* **93**: 881–885. doi:10.1016/j.amjcard.2003.12.028. PMID:15050493.
- Graham, T.E. 2004. Exercise, postprandial triacylglyceridemia, and cardiovascular disease risk. *Can. J. Appl. Physiol.* **29**: 781–799. PMID:15630150.
- Guerra, R., Wang, J., Grundy, S.M., and Cohen, J.C. 1997. A hepatic lipase (LIPC) allele associated with high plasma concentrations of high density lipoprotein cholesterol. *Proc. Natl. Acad. Sci. U.S.A.* **94**: 4532–4537. doi:10.1073/pnas.94.9.4532. PMID:9114024.
- Harbis, A., Perdreau, S., Vincent-Baudry, S., Charbonnier, M., Bernard, M.C., Raccach, D., et al. 2004. Glycemic and insulinemic meal responses modulate postprandial hepatic and intestinal lipoprotein accumulation in obese, insulin-resistant subjects. *Am. J. Clin. Nutr.* **80**: 896–902. PMID:15447896.
- Hauner, H. 2002. The mode of action of thiazolidinediones. *Diabetes Metab. Res. Rev.* **18**: Suppl 2, S10–S15. doi:10.1002/dmrr.249. PMID:11921433.
- Havel, P.J. 2004. Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. *Diabetes*, **53**: Suppl 1, S143–S151. PMID:14749280.
- Hegele, R.A., Harris, S.B., Hanley, A.J., Sadikian, S., Connelly, P.W., and Zinman, B. 1996. Genetic variation of intestinal fatty acid-binding protein associated with variation in body mass in aboriginal Canadians. *J. Clin. Endocrinol. Metab.* **81**: 4334–4337. doi:10.1210/jc.81.12.4334. PMID:8954037.
- Herd, S.L., Kiens, B., Boobis, L.H., and Hardman, A.E. 2001. Moderate exercise, postprandial lipemia, and skeletal muscle lipoprotein lipase activity. *Metabolism*, **50**: 756–762. doi:10.1053/meta.2001.24199. PMID:11436177.
- Hyson, D.A., Paglieroni, T.G., Wun, T., and Rutledge, J.C. 2002. Postprandial lipemia is associated with platelet and monocyte activation and increased monocyte cytokine expression in normolipemic men. *Clin. Appl. Thromb. Hemost.* **8**: 147–55. PMID:12121056.
- Jakubowski, J.A., Ardlie, N.G., Chesterman, C.N., McGready, J.F., and Morgan, F.J. 1985. Acute postprandial lipaemia does not influence the in vivo activity of human platelets. *Thromb. Res.* **39**: 725–732. doi:10.1016/0049-3848(85)90256-7. PMID:2934861.
- James, A.P., Watts, G.F., Barrett, P.H., Smith, D., Pal, S., Chan, D.C., et al. 2003. Effect of weight loss on postprandial lipemia and low-density lipoprotein receptor binding in overweight men. *Metabolism*, **52**: 136–141. doi:10.1053/meta.2003.50032. PMID:12601621.
- Jang, Y., Kim, J.Y., Kim, O.Y., Lee, J.E., Cho, H., Ordovas, J.M., et al. 2004. The -1131T→C polymorphism in the apolipoprotein A5 gene is associated with postprandial hypertriacylglycerolemia; elevated small, dense LDL concentrations; and oxidative stress in nonobese Korean men. *Am. J. Clin. Nutr.* **80**: 832–840. PMID:15447887.
- Jansen, H., Chu, G., Ehnholm, C., Dallongeville, J., Nicaud, V., and Talmud, P.J. 1999. The T allele of the hepatic lipase promoter variant C-480T is associated with increased fasting lipids and HDL and increased preprandial and postprandial LpCIII:B: European Atherosclerosis Research Study (EARS) II. *Arterioscler. Thromb. Vasc. Biol.* **19**: 303–308. PMID:9974411.
- Jensen, J., Bysted, A., Dawids, S., Hermansen, K., and Holmer, G. 1999. The effect of palm oil, lard, and puff-pastry margarine on postprandial lipid and hormone responses in normal-weight and obese young women. *Br. J. Nutr.* **82**: 469–479. PMID:10690162.
- Kalant, D., MacLaren, R., Cui, W., Samanta, R., Monk, P.N., Laporte, S.A., et al. 2005. C5L2 is a functional receptor for acylation-stimulating protein. *J. Biol. Chem.* **280**: 23936–23944. doi:10.1074/jbc.M406921200. PMID:15833747.
- Kannel, W.B. 1987. Metabolic risk factors for coronary heart disease in women: perspective from the Framingham Study. *Am. Heart J.* **114**: 413–419. doi:10.1016/0002-8703(87)90511-4. PMID:3604900.
- Karpe, F. 1999. Postprandial lipoprotein metabolism and atherosclerosis. *J. Intern. Med.* **246**: 341–355. doi:10.1046/j.1365-2796.1999.00548.x. PMID:10583705.
- Kastelein, J.J., Jukema, J.W., Zwinderman, A.H., Clee, S., van Boven, A.J., Jansen, H., et al. 2000. Lipoprotein lipase activity is associated with severity of angina pectoris. REGRESS Study Group. *Circulation*, **102**: 1629–1633. PMID:11015339.
- Katsanos, C.S., Grandjean, P.W., and Moffatt, R.J. 2004. Effects of low and moderate exercise intensity on postprandial lipemia and postheparin plasma lipase activity in physically active men. *J. Appl. Physiol.* **96**: 181–188. PMID:12949025.
- Knuth, N.D., and Horowitz, J.F. 2006. The elevation of ingested lipids within plasma chylomicrons is prolonged in men compared with women. *J. Nutr.* **136**: 1498–1503. PMID:16702311.
- Kolovou, G., Daskalova, D., Anagnostopoulou, K., Hoursalas, I., Voudris, V., Mikhailidis, D.P., et al. 2003. Postprandial hypertriglyceridaemia in patients with Tangier disease. *J. Clin. Pathol.* **56**: 937–941. doi:10.1136/jcp.56.12.937. PMID:14645354.
- Kolovou, G.D., Anagnostopoulou, K.K., Pilatis, N.D., Giannopoulou, M., Hoursalas, I.S., Pavlidis, A.N., et al. 2004. The influence of natural menopause on postprandial lipemia in heterozygotes for familial hypercholesterolemia. *J. Womens Health (Larchmt)*, **13**: 1119–1126. PMID:15650345.
- Kolovou, G.D., Anagnostopoulou, K.K., Daskalopoulou, S.S., Mikhailidis, D.P., and Cokkinos, D.V. 2005a. Clinical relevance of postprandial lipaemia. *Curr. Med. Chem.* **12**: 1931–1945. doi:10.2174/0929867054546609. PMID:16101498.

- Kolovou, G.D., Anagnostopoulou, K.K., Pavlidis, A.N., Salpea, K.D., Iraklianos, S.A., Tsarpalis, K., et al. 2005b. Postprandial lipemia in men with metabolic syndrome, hypertensives and healthy subjects. *Lipids Health Dis.* **4**: 21. doi:10.1186/1476-511X-4-21. PMID:16197542.
- Kolovou, G.D., Anagnostopoulou, K.K., Pilatis, N.D., Iraklianos, S., Hoursalas, I.S., Liberi, S., et al. 2005c. Heterozygote men with familial hypercholesterolaemia may have an abnormal triglyceride response post-prandially. Evidence for another predictor of vascular risk in familial hypercholesterolaemia. *Int. J. Clin. Pract.* **59**: 311–317. doi:10.1111/j.1742-1241.2004.00223.x. PMID:15857328.
- Kolovou, G.D., Anagnostopoulou, K.K., Pavlidis, A.N., Salpea, K.D., Hoursalas, I.S., Manolis, A., et al. 2006a. Postprandial lipaemia in menopausal women with metabolic syndrome. *Maturitas*, **55**: 19–26. doi:10.1016/j.maturitas.2006.01.002. PMID:16443339.
- Kolovou, G.D., Anagnostopoulou, K.K., Salpea, K.D., Pilatis, N.D., Iraklianos, S., Grapsa, G., et al. 2006b. Postprandial lipemia in postmenopausal women with high fasting high density lipoprotein cholesterol. *Am. J. Med. Sci.* **331**: 10–16. doi:10.1097/0000441-200601000-00005. PMID:16415657.
- Kris-Etherton, P.M., Hecker, K.D., and Binkoski, A.E. 2004. Polyunsaturated fatty acids and cardiovascular health. *Nutr. Rev.* **62**: 414–426. doi:10.1301/nr.2004.nov.414-426. PMID:15622714.
- Lally, S., Tan, C.Y., Owens, D., and Tomkin, G.H. 2006. Messenger RNA levels of genes involved in dysregulation of postprandial lipoproteins in type 2 diabetes: the role of Niemann-Pick C1-like 1, ATP-binding cassette, transporters G5 and G8, and of microsomal triglyceride transfer protein. *Diabetologia*, **49**: 1008–1016. doi:10.1007/s00125-006-0177-8. PMID:16518588.
- Lambert, J.C., Brousseau, T., Defosse, V., Evans, A., Arveiler, D., Ruidavets, J.B., et al. 2000. Independent association of an APOE gene promoter polymorphism with increased risk of myocardial infarction and decreased APOE plasma concentrations—the ECTIM study. *Hum. Mol. Genet.* **9**: 57–61. doi:10.1093/hmg/9.1.57. PMID:10587578.
- Lanes, R., Paoli, M., Carrillo, E., Villaroel, O., and Palacios, A. 2004. Peripheral inflammatory and fibrinolytic markers in adolescents with growth hormone deficiency: relation to postprandial dyslipidemia. *J. Pediatr.* **145**: 657–661. PMID:15520769.
- Lewis, G.F., Uffelman, K., Naples, M., Szeto, L., Haidari, M., and Adeli, K. 2005. Intestinal lipoprotein overproduction, a newly recognized component of insulin resistance, is ameliorated by the insulin sensitizer rosiglitazone: studies in the fructose-fed Syrian golden hamster. *Endocrinology*, **146**: 247–255. PMID:15486228.
- Lopez-Miranda, J., Cruz, G., Gomez, P., Marin, C., Paz, E., Perez-Martinez, P., et al. 2004. The influence of lipoprotein lipase gene variation on postprandial lipoprotein metabolism. *J. Clin. Endocrinol. Metab.* **89**: 4721–4728. doi:10.1210/jc.2003-031642. PMID:15356086.
- Maily, F., Tugrul, Y., Reymer, P.W., Bruin, T., Seed, M., Groenemeyer, B.F., et al. 1995. A common variant in the gene for lipoprotein lipase (Asp9→Asn). Functional implications and prevalence in normal and hyperlipidemic subjects. *Arterioscler. Thromb. Vasc. Biol.* **15**: 468–478. PMID:7749858.
- Mamo, J.C., James, A.P., Soares, M.J., Griffiths, D.G., Purcell, K., and Schwenke, J.L. 2005. A low-protein diet exacerbates postprandial chylomicron concentration in moderately dyslipidaemic subjects in comparison to a lean red meat protein-enriched diet. *Eur. J. Clin. Nutr.* **59**: 1142–1148. doi:10.1038/sj.ejcn.1602224. PMID:16015257.
- Marschang, P., Gotsch, C., Kirchmair, R., Kaser, S., Kahler, C.M., and Patsch, J.R. 2006. Postprandial, but not postabsorptive low-density lipoproteins increase the expression of intercellular adhesion molecule-1 in human aortic endothelial cells. *Atherosclerosis*, **186**: 101–106. doi:10.1016/j.atherosclerosis.2005.07.014. PMID:16122754.
- Martin, S., Nicaud, V., Humphries, S.E., and Talmud, P.J. 2003. Contribution of APOA5 gene variants to plasma triglyceride determination and to the response to both fat and glucose tolerance challenges. *Biochim. Biophys. Acta*, **1637**: 217–225. PMID:12697303.
- Masana, L., Ribalta, J., Salazar, J., Fernandez-Ballart, J., Joven, J., and Cabezas, M.C. 2003. The apolipoprotein AV gene and diurnal triglyceridaemia in normolipidaemic subjects. *Clin. Chem. Lab. Med.* **41**: 517–521. doi:10.1515/CCLM.2003.078. PMID:12747596.
- Masłowska, M., Vu, H., Phelis, S., Sniderman, A.D., Rhode, B.M., Blank, D., et al. 1999. Plasma acylation stimulating protein, adipin and lipids in non-obese and obese populations. *Eur. J. Clin. Invest.* **29**: 679–686. doi:10.1046/j.1365-2362.1999.00514.x. PMID:10457151.
- Masłowska, M., Wang, H.W., and Cianflone, K. 2005. Novel roles for acylation stimulating protein/C3adesArg: a review of recent in vitro and in vivo evidence. *Vitam. Horm.* **70**: 309–332. PMID:15727809.
- Masłowska, M., Legakis, H., Assadi, F., and Cianflone, K. 2006. Targeting the signaling pathway of acylation stimulating protein. *J. Lipid Res.* **47**: 643–652. PMID:16333141.
- Mattes, R.D. 2005. Fat taste and lipid metabolism in humans. *Physiol. Behav.* **86**: 691–697. doi:10.1016/j.physbeh.2005.08.058. PMID:16249011.
- Matthan, N.R., Cianflone, K., Lichtenstein, A.H., Ausman, L.M., Jauhiainen, M., and Jones, P.J. 2001. Hydrogenated fat consumption affects acylation-stimulating protein levels and cholesterol esterification rates in moderately hypercholesterolemic women. *J. Lipid Res.* **42**: 1841–1848. PMID:11714853.
- Meier, J.J., Gethmann, A., Gotze, O., Gallwitz, B., Holst, J.J., Schmidt, W.E., et al. 2006a. Glucagon-like peptide 1 abolishes the postprandial rise in triglyceride concentrations and lowers levels of non-esterified fatty acids in humans. *Diabetologia*, **49**: 452–458. doi:10.1007/s00125-005-0126-y. PMID:16447057.
- Meier, J.J., Nauck, M.A., Pott, A., Heinze, K., Goetze, O., Bulut, K., et al. 2006b. Glucagon-like peptide 2 stimulates glucagon secretion, enhances lipid absorption, and inhibits gastric acid secretion in humans. *Gastroenterology*, **130**: 44–54. doi:10.1053/j.gastro.2005.10.004. PMID:16401467.
- Miller, G.J., Martin, J.C., Mitropoulos, K.A., Reeves, B.E., Thompson, R.L., Meade, T.W., et al. 1991. Plasma factor VII is activated by postprandial triglyceridaemia, irrespective of dietary fat composition. *Atherosclerosis*, **86**: 163–171. doi:10.1016/0021-9150(91)90212-L. PMID:1872911.
- Miyashita, M., Burns, S.F., and Stenel, D.J. 2006. Exercise and postprandial lipemia: effect of continuous compared with intermittent activity patterns. *Am. J. Clin. Nutr.* **83**: 24–29. PMID:16400045.
- Moreno, J.A., Lopez-Miranda, J., Marin, C., Gomez, P., Perez-Martinez, P., Fuentes, F., et al. 2003. The influence of the apolipoprotein E gene promoter (–219G/ T) polymorphism on postprandial lipoprotein metabolism in young normolipemic males. *J. Lipid Res.* **44**: 2059–2064. PMID:12923233.
- Moreno, R., Perez-Jimenez, F., Marin, C., Moreno, J.A., Gomez, P., Bellido, C., et al. 2006. A single nucleotide polymorphism of the apolipoprotein A-V gene –1131T > C modulates postprandial lipoprotein metabolism. *Atherosclerosis*, [online]. doi:10.1016/j.atherosclerosis.2005.11.029. PMID:16386743.

- Musso, G., Gambino, R., Durazzo, M., Biroli, G., Carello, M., Faga, E., et al. 2005. Adipokines in NASH: postprandial lipid metabolism as a link between adiponectin and liver disease. *Hepatology*, **42**: 1175–1183. doi:10.1002/hep.20896. PMID:16231364.
- Nicholls, S., and Lundman, P. 2004. The emerging role of lipoproteins in atherogenesis: beyond LDL cholesterol. *Semin. Vasc. Med.* **4**: 187–195. doi:10.1055/s-2004-835377. PMID:15478040.
- Nierman, M.C., Rip, J., Kuivenhoven, J.A., van Raalte, D.H., Hutten, B.A., Sakai, N., et al. 2005. Carriers of the frequent lipoprotein lipase S447X variant exhibit enhanced postprandial apoprotein B-48 clearance. *Metabolism*, **54**: 1499–1503. doi:10.1016/j.metabol.2005.05.016. PMID:16253639.
- Nilsson-Ehle, P., Garfinkel, A.S., and Schotz, M.C. 1980. Lipolytic enzymes and plasma lipoprotein metabolism. *Annu. Rev. Biochem.* **49**: 667–693. doi:10.1146/annurev.bi.49.070180.003315. PMID:6996570.
- Nykjaer, A., Nielsen, M., Lookene, A., Meyer, N., Roigaard, H., Etzerodt, M., et al. 1994. A carboxyl-terminal fragment of lipoprotein lipase binds to the low density lipoprotein receptor related protein and inhibits lipase-mediated uptake of lipoprotein in cells. *J. Biol. Chem.* **269**: 31747–31755. PMID:7989348.
- Ogawa, S., Takeuchi, K., and Ito, S. 2004. Acarbose lowers serum triglyceride and postprandial chylomicron levels in type 2 diabetes. *Diabetes Obes. Metab.* **6**: 384–390. doi:10.1111/j.1462-8902.2004.00362.x. PMID:15287932.
- Orso, E., Broccardo, C., Kaminski, W.E., Bottcher, A., Liebisch, G., Drobnik, W., et al. 2000. Transport of lipids from golgi to plasma membrane is defective in tangier disease patients and Abc1-deficient mice. *Nat. Genet.* **24**: 192–196. PMID:10655069.
- Patsch, J.R., Miesenbock, G., Hopferwieser, T., Muhlberger, V., Knapp, E., Dunn, J.K., et al. 1992. Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state. *Arterioscler. Thromb.* **12**: 1336–1345. PMID:1420093.
- Perez-Martinez, P., Ordovas, J.M., Lopez-Miranda, J., Gomez, P., Marin, C., Moreno, J., et al. 2003. Polymorphism exon 1 variant at the locus of the scavenger receptor class B type I gene: influence on plasma LDL cholesterol in healthy subjects during the consumption of diets with different fat contents. *Am. J. Clin. Nutr.* **77**: 809–813. PMID:12663276.
- Perez-Martinez, P., Lopez-Miranda, J., Ordovas, J.M., Bellido, C., Marin, C., Gomez, P., et al. 2004. Postprandial lipemia is modified by the presence of the polymorphism present in the exon 1 variant at the SR-BI gene locus. *J. Mol. Endocrinol.* **32**: 237–245. doi:10.1677/jme.0.0320237. PMID:14766005.
- Petitt, D.S., and Cureton, K.J. 2003. Effects of prior exercise on postprandial lipemia: a quantitative review. *Metabolism*, **52**: 418–424. doi:10.1053/meta.2003.50071. PMID:12701052.
- Petitt, D.S., Arngrimsson, S.A., and Cureton, K.J. 2003. Effect of resistance exercise on postprandial lipemia. *J. Appl. Physiol.* **94**: 694–700. PMID:12391139.
- Pfeiffer, M., Ludwig, T., Wenk, C., and Colombani, P.C. 2005. The influence of walking performed immediately before meals with moderate fat content on postprandial lipemia. *Lipids Health Dis.* **4**: 24. doi:10.1186/1476-511X-4-24. PMID:16209707.
- Phillips, C., Mullan, K., Owens, D., and Tomkin, G.H. 2004. Microsomal triglyceride transfer protein polymorphisms and lipoprotein levels in type 2 diabetes. *QJM*, **97**: 211–218. doi:10.1093/qjmed/hch040. PMID:15028851.
- Phillips, C., Mullan, K., Owens, D., and Tomkin, G.H. 2005. Intestinal microsomal triglyceride transfer protein in type 2 diabetic and non-diabetic subjects: The relationship to triglyceride-rich postprandial lipoprotein composition. *Atherosclerosis*, **187**: 57–64. PMID:16183064.
- Picard, F., Naimi, N., Richard, D., and Deshaies, Y. 1999. Response of adipose tissue lipoprotein lipase to the cephalic phase of insulin secretion. *Diabetes*, **48**: 452–459. PMID:10078543.
- Poppitt, S.D., Keogh, G.F., Mulvey, T.B., Phillips, A., McArdle, B.H., MacGibbon, A.K., et al. 2004. Effect of moderate changes in dietary fatty acid profile on postprandial lipaemia, haemostatic and related CVD risk factors in healthy men. *Eur. J. Clin. Nutr.* **58**: 819–827. doi:10.1038/sj.ejcn.1601882. PMID:15116086.
- Ragozin, S., Niemeier, A., Laatsch, A., Loeffler, B., Merkel, M., Beisiegel, U., et al. 2005. Knockdown of hepatic ABCA1 by RNA interference decreases plasma HDL cholesterol levels and influences postprandial lipemia in mice. *Arterioscler. Thromb. Vasc. Biol.* **25**: 1433–1438. PMID:15845910.
- Redgrave, T.G., Watts, G.F., Martins, I.J., Barrett, P.H., Mamo, J.C., Dimmitt, S.B., et al. 2001. Chylomicron remnant metabolism in familial dyslipidemias studied with a remnant-like emulsion breath test. *J. Lipid Res.* **42**: 710–715. PMID:11352977.
- Rivellese, A.A., De Natale, C., Di Marino, L., Patti, L., Iovine, C., Coppola, S., et al. 2004. Exogenous and endogenous postprandial lipid abnormalities in type 2 diabetic patients with optimal blood glucose control and optimal fasting triglyceride levels. *J. Clin. Endocrinol. Metab.* **89**: 2153–2159. doi:10.1210/jc.2003-031764. PMID:15126535.
- Robinson, L.E., and Graham, T.E. 2004. Metabolic syndrome, a cardiovascular disease risk factor: role of adipocytokines and impact of diet and physical activity. *Can. J. Appl. Physiol.* **29**: 808–829. PMID:15630152.
- Sahoo, D., Trischuk, T.C., Chan, T., Drover, V.A., Ho, S., Chimini, G., et al. 2004. ABCA1-dependent lipid efflux to apolipoprotein A-I mediates HDL particle formation and decreases VLDL secretion from murine hepatocytes. *J. Lipid Res.* **45**: 1122–1131. PMID:14993246.
- Sakai, J., Hoshino, A., Takahashi, S., Miura, Y., Ishii, H., Suzuki, H., et al. 1994. Structure, chromosome location, and expression of the human very low density lipoprotein receptor gene. *J. Biol. Chem.* **269**: 2173–2182. PMID:8294473.
- Sanders, T.A., and Berry, S.E. 2005. Influence of stearic acid on postprandial lipemia and hemostatic function. *Lipids*, **40**: 1221–1227. doi:10.1007/s11745-005-1489-7. PMID:16477806.
- Saxena, U., Witte, L.D., and Goldberg, I.J. 1989. Release of endothelial cell lipoprotein lipase by plasma lipoproteins and free fatty acids. *J. Biol. Chem.* **264**: 4349–4355. PMID:2925647.
- Schaefer, E.J., Brousseau, M.E., Diffenderfer, M.R., Cohn, J.S., Welty, F.K., O'Connor, J., Jr., et al. 2001. Cholesterol and apolipoprotein B metabolism in Tangier disease. *Atherosclerosis*, **159**: 231–236. doi:10.1016/S0021-9150(01)00688-8. PMID:11689226.
- Schrauwen, P., Hesselink, M.K., Jain, M., and Cianflone, K. 2005. Acylation-stimulating protein: effect of acute exercise and endurance training. *Int. J. Obes. (Lond)*. **29**: 632–638. doi:10.1038/sj.ijo.0802949. PMID:15809665.
- Seo, J.B., Moon, H.M., Noh, M.J., Lee, Y.S., Jeong, H.W., Yoo, E.J., et al. 2004. Adipocyte determination- and differentiation-dependent factor 1/sterol regulatory element-binding protein 1c regulates mouse adiponectin expression. *J. Biol. Chem.* **279**: 22108–22117. doi:10.1074/jbc.M400238200. PMID:15037635.
- Shannon, K.A., Shannon, R.M., Clore, J.N., Gennings, C., Warren, B.J., and Potteiger, J.A. 2005. Resistance exercise and postprandial lipemia: The dose effect of differing volumes of acute resistance exercise bouts. *Metabolism*, **54**: 756–763. doi:10.1016/j.metabol.2005.01.017. PMID:15931610.
- Silveira, A., Green, F., Karpe, F., Blomback, M., Humphries, S., and Hamsten, A. 1994. Elevated levels of factor VII activity in

- the postprandial state: effect of the factor VII Arg-Gln polymorphism. *Thromb. Haemost.* **72**: 734–739. PMID:7900081.
- Slivkoff-Clark, K., James, A.P., Kerr, D., Soares, M.J., and Mamo, J.C. 2004. The effect of diet standardization on postprandial chylomicron response. *Asia Pac. J. Clin. Nutr.* **13**: Suppl, S69. PMID:15294560.
- Sniderman, A.D., Zhang, Z., Genest, J., and Cianflone, K. 2003. Effects on apoB-100 secretion and bile acid synthesis by redirecting cholesterol efflux from HepG2 cells. *J. Lipid Res.* **44**: 527–532. PMID:12562860.
- St Clair, R.W., and Beisiegel, U. 1997. What do all the apolipoprotein E receptors do? *Curr. Opin. Lipidol.* **8**: 243–245. PMID:9335946.
- Tada, N., and Yoshida, H. 2003. Diacylglycerol on lipid metabolism. *Curr. Opin. Lipidol.* **14**: 29–33. doi:10.1097/00041433-200302000-00006. PMID:12544658.
- Takase, H., Shoji, K., Hase, T., and Tokimitsu, I. 2005. Effect of diacylglycerol on postprandial lipid metabolism in non-diabetic subjects with and without insulin resistance. *Atherosclerosis*, **180**: 197–204. doi:10.1016/j.atherosclerosis.2004.11.020. PMID:15823293.
- Tholstrup, T. 2005. Influence of stearic acid on hemostatic risk factors in humans. *Lipids*, **40**: 1229–1235. doi:10.1007/s11745-005-1490-1. PMID:16477807.
- Tholstrup, T., and Samman, S. 2004. Postprandial lipoprotein(a) is affected differently by specific individual dietary fatty acids in healthy young men. *J. Nutr.* **134**: 2550–2555. PMID:15465746.
- van Beek, A.P., de Ruijter-Heijstek, F.C., Erkelens, D.W., and de Bruin, T.W. 1999. Menopause is associated with reduced protection from postprandial lipemia. *Arterioscler. Thromb. Vasc. Biol.* **19**: 2737–2741. PMID:10559019.
- van Eck, M., Pennings, M., Hoekstra, M., Out, R., and Van Berkel, T.J. 2005. Scavenger receptor BI and ATP-binding cassette transporter A1 in reverse cholesterol transport and atherosclerosis. *Curr. Opin. Lipidol.* **16**: 307–315. PMID:15891392.
- van Oostrom, A.J., Sijmonsma, T.P., Verseyden, C., Jansen, E.H., de Koning, E.J., Rabelink, T.J., et al. 2003. Postprandial recruitment of neutrophils may contribute to endothelial dysfunction. *J. Lipid Res.* **44**: 576–583. PMID:12562833.
- van Oostrom, A.J., Alipour, A., Plokker, T.W., Sniderman, A.D., and Cabezas, M.C. 2006. The metabolic syndrome in relation to complement component 3 and postprandial lipemia in patients from an outpatient lipid clinic and healthy volunteers. *Atherosclerosis*, [online]. doi:10.1016/j.atherosclerosis.2006.01.009.
- Vogel, R.A., Corretti, M.C., and Plotnick, G.D. 1997. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am. J. Cardiol.* **79**: 350–354. doi:10.1016/S0002-9149(96)00760-6. PMID:9036757.
- Volek, J.S., Sharman, M.J., Gomez, A.L., Scheett, T.P., and Kraemer, W.J. 2003. An isoenergetic very low carbohydrate diet improves serum HDL cholesterol and triacylglycerol concentrations, the total cholesterol to HDL cholesterol ratio and postprandial lipemic responses compared with a low fat diet in normal weight, normolipidemic women. *J. Nutr.* **133**: 2756–2761. PMID:12949361.
- Volek, J.S., Sharman, M.J., Gomez, A.L., DiPasquale, C., Roti, M., Pumerantz, A., et al. 2004. Comparison of a very low-carbohydrate and low-fat diet on fasting lipids, LDL subclasses, insulin resistance, and postprandial lipemic responses in overweight women. *J. Am. Coll. Nutr.* **23**: 177–184. PMID:15047685.
- Wellen, K.E., and Hotamisligil, G.S. 2003. Obesity-induced inflammatory changes in adipose tissue. *J. Clin. Invest.* **112**: 1785–1788. doi:10.1172/JCI200320514. PMID:14679172.
- Wellington, C.L., Brunham, L.R., Zhou, S., Singaraja, R.R., Visscher, H., Gelfer, A., et al. 2003. Alterations of plasma lipids in mice via adenoviral-mediated hepatic overexpression of human ABCA1. *J. Lipid Res.* **44**: 1470–1480. PMID:12730295.
- Westphal, S., Taneva, E., Kastner, S., Martens-Lobenhoffer, J., Bode-Boger, S., Kropf, S., et al. 2006. Endothelial dysfunction induced by postprandial lipemia is neutralized by addition of proteins to the fatty meal. *Atherosclerosis*, **185**: 313–319. doi:10.1016/j.atherosclerosis.2005.06.004. PMID:16029877.
- Wetterau, J.R., Aggerbeck, L.P., Bouma, M.E., Eisenberg, C., Munck, A., Hermier, M., et al. 1992. Absence of microsomal triglyceride transfer protein in individuals with abetalipoproteinemia. *Science*, **258**: 999–1001. doi:10.1126/science.1439810. PMID:1439810.
- Willnow, T.E. 1997. Mechanisms of hepatic chylomicron remnant clearance. *Diabet. Med.* **14**: Suppl 3, S75–S80. doi:10.1002/(SICI)1096-9136(199708)14:3+<S75::AID-DIA449>3.3.CO;2-0. PMID:9272618.
- Yamauchi, T., Kamon, J., Minokoshi, Y., Ito, Y., Waki, H., Uchida, S., et al. 2002. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat. Med.* **8**: 1288–1295. doi:10.1038/nm788. PMID:12368907.
- Zhang, H., Henderson, H., Gagne, S.E., Clee, S.M., Miao, L., Liu, G., et al. 1996. Common sequence variants of lipoprotein lipase: standardized studies of in vitro expression and catalytic function. *Biochim. Biophys. Acta*, **1302**: 159–166. PMID:8695666.
- Zhang, F., Lucke, C., Baier, L.J., Sacchetti, J.C., and Hamilton, J.A. 2003. Solution structure of human intestinal fatty acid binding protein with a naturally-occurring single amino acid substitution (A54T) that is associated with altered lipid metabolism. *Biochemistry*, **42**: 7339–7347. doi:10.1021/bi0273617. PMID:12809489.
- Zheng, C., Murdoch, S.J., Brunzell, J.D., and Sacks, F.M. 2006. Lipoprotein lipase bound to apolipoprotein B lipoproteins accelerates clearance of postprandial lipoproteins in humans. *Arterioscler. Thromb. Vasc. Biol.* **26**: 891–896. PMID:16410459.
- Zilversmit, D.B. 1979. Atherogenesis: a postprandial phenomenon. *Circulation*, **60**: 473–485. PMID:222498.