GENETIC DISORDERS OF TRIGLYCERIDE METABOLISM

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Received 12 June 2015

ABSTRACT

Hypertriglyceridemia (HTG) can result from a variety of causes. Mild to moderate HTG occurs commonly as part of the metabolic syndrome, can be the result of several genetic mutations, and can be secondary to several diseases and drugs. Very severe HTG can result from rare mutations in the lipoprotein lipase complex, where it is termed the familial chylomicronemia syndrome. Multifactorial chylomicronemia syndrome develops as a result of the co-existence of genetic and secondary forms of HTG. Some but not all causes of mild to moderate HTG are associated with an increased risk of premature cardiovascular disease, while very severe HTG can lead to pancreatitis and other features of the chylomicronemia syndrome. Appropriate management of the patient with HTG requires knowledge of the likely cause of the HTG, which can lead to prevention of its complications.

PHYSIOLOGY

A detailed overview of lipoprotein physiology is provided in the chapter on Lipoprotein Metabolism. Here we will briefly review some aspects the metabolism of the triglyceride (TG)-rich lipoproteins of particular relevance to this chapter.

Secretion of TG-rich Lipoproteins Into Plasma

TGs are transported through plasma as very low density lipoproteins (VLDL), which transport TGs primarily made in the liver, and as chylomicrons, which transport dietary (exogenous) fat. VLDL secretion by the liver is regulated in several ways. Each VLDL particle has one apoB100 molecule, making apoB100 availability a key determinant of

the number of VLDL particles, and hence, TG secretion by the liver. In addition to one molecule of apoB-100, each VLDL particle contains multiple copies of other apolipoproteins, together with varied amounts of TGs, cholesteryl esters and phospholipids. The extent of TG synthesis by the liver is in part determined by the flux of free fatty acids (FFA) to the liver. The addition of TG to the developing VLDL particle in the endoplasmic reticulum is mediated by the enzyme microsomal triglyceride transfer protein (MTP). The pool of apoB100 in the liver is not typically regulated by its level of synthesis, which is relatively constant, but by its level of degradation, which can occur in several proteolytic pathways [1]. Insulin also plays a role in the regulation of VLDL secretion - it decreases hepatic VLDL production by limiting fatty acid influx into the liver, decreases the stability of, and promotes the posttranslational degradation of apoB100 [2]. Recent studies have shown that apoC-III, an apolipoprotein previously thought to primarily play a role in inhibiting TG removal (see below), also is involved in the assembly and secretion of VLDL [3]. VLDL also is produced by enterocytes in the gut during fasting.

The consumption of dietary fat results in the formation of chylomicrons by enterocytes. Fatty acids and monoacylglycerols that result from digestion of dietary TGs by acid and pancreatic lipases are transported into enterocytes by mechanisms that are not completely understood. In the enterocyte, monoacylglycerol and fatty acids are resynthesized into TGs by the action of the enzymes acyl-coenzyme A: monoacylglycerol acyltransferase (MGAT) and acyl-coenzyme A: diacylglycerol acyltransferase (DGAT) 1 and 2. The resulting TGs are packaged with apoB48 to form chylomicrons, a process also mediated by MTP [4]. Chylomicrons then pass into the thoracic duct from where they enter plasma and acquire additional apolipoproteins. Of particular relevance to their clearance from plasma is the acquisition of apoC-II and apoC-III.

Catabolism of TG-rich Lipoproteins

TGs in both VLDL and chylomicrons are hydrolyzed by the lipoprotein lipase (LPL) complex. LPL is synthesized by several tissues, including adipose tissue, skeletal muscle and cardiac myocytes. After secretion by adipocytes, the enzyme is transported by glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1 (GPIHBP1) to the luminal side of the capillary endothelium, where it becomes tethered to glycosaminoglycans (GAGs). This pool of LPL is referred to as “functional LPL”, since it is available to hydrolyze TGs in both VLDL and chylomicrons. LPL can be liberated from these GAG binding sites by heparin injection. Several other proteins, reviewed in [5], regulate LPL activity. These include apoC-II, which activates LPL, and apoC-III, which inhibits LPL in addition to its effect on VLDL secretion alluded to earlier. Both are produced by the liver and are present on TG-rich lipoproteins. ApoE also is present on the TG-rich lipoproteins and plays an important role in the uptake and clearance of the remnants of the TG-rich lipoproteins that result from hydrolysis of TGs in these lipoproteins. Other activators of LPL include apoA-IV [6], apoA-V [7-9] and lipase maturation

factor 1 (LMF1) [10, 11]. In addition, several members of the angiopoeitin-like (ANGPTL) protein family play a role in regulating LPL activity. ANGPTL3 is produced by the liver and is an endocrine regulator by inhibiting LPL in peripheral tissues [5, 12, 13]. ANGPTL4 is produced in several tissues [5], where it inhibits LPL in a paracrine fashion [5, 14]. Both ANPGTL3 and ANGPTL4 retard the clearance of the TG-rich lipoproteins [5].

The core TGs in VLDL and chylomicrons are hydrolyzed by apoC-II activated LPL; free fatty acids thus formed are taken up by adipocytes and reincorporated into TGs for storage, or in the skeletal muscle, utilized for energy. Hydrolysis of chylomicron-TG results in TG-poor, cholesteryl ester and apoE-enriched particles called chylomicron remnants, which under physiological conditions are removed by the liver by binding to LDL receptors, LDL receptor related protein and cell surface proteoglycans [9, 15]. Hepatic TG lipase and apoA-V also are involved in the remnant clearance process [7-9, 16, 17].

Normal range for plasma triglycerides and definition of hypertriglyceridemia

Statistical Determination of a Normal Range

Normal ranges often are defined by statistical upper limit (e.g., >95th percentile or >2SD from the mean) for a normal local population. However, it is important to appreciate that TGs increase with age [18], differ between males and females [19], and that their distribution within populations is heavily skewed to the right [20, 21]. Because of this skewed distribution, logarithmic transformation is required to establish statistical normal ranges. A more rational approach might be to define normal as a level below which complications do not occur.

Normal Range Based on Risk of Complication of HTG

Use of such an approach to the establishment of a normal range for plasma TG concentrations requires a detailed knowledge of the morbidities associated with elevated TG levels. The major complications of hypertriglyceridemia (HTG) are (1) increased risk of cardiovascular disease (CVD); (2) acute pancreatitis; and (3) fatty liver (steatosis) and non-alcoholic steatohepatitis (NASH). The consequences of HTG are discussed in detail later. As will be evident later, different complications occur at different levels of TGs. For example, the risk of pancreatitis occurs at much higher TG levels than does the risk of premature CVD. Moreover, the *cause* of the HTG can be an important determinant of risk. Equivalent TG levels may not confer equal risk of CVD in different familial forms of HTG. Rather, the specific form of the HTG, associated lipid and lipoprotein abnormalities, and other CVD risk factors may be more important

determinants of CVD risk than the TG level per se. Thus establishing a normal range is far more complicated than simply applying statistical approaches.

Normal Range According to Guidelines

Despite these concerns regarding establishment of an upper limit of normal for TGs, most guidelines define values for HTG, often without a strong biological rationale. Definitions for the diagnosis of HTG provided in several guidelines are shown in Table 1.

Cutpoints for HTG were first defined by the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP). The term moderate HTG has been used more recently by the Endocrine Society [22] for TG levels between 200 to 999 mg/dl, severe HTG for 1000 to 1999 mg/dl and very severe HTG for values >2000 mg/dL. Hegele et al have recently proposed a simplified classification of hypertriglyceridemia [23]. On the basis of genetic data, they divide HTG into two states: severe (TG concentration >10 mmol/L or 885 mg/dl), which is more likely to have a monogenic component; and mild-to-moderate (TG concentration 2-10 mmol/L, or 175-885 mg/dL). Mild-to-moderate HTG is typically multigenic and results from the cumulative burden of common and rare variants in more than 30 genes, as quantified by genetic risk scores. Rare autosomal recessive monogenic HTG usually results from large-effect mutations in six different genes. Both can be exacerbated by non-genetic factors.

Table 1. Definition of hypertriglyceridemia according to various clinical guidelines

Guideline	Classification	Levels
NCEP/ ATP III [24] American Heart Association [25] National Lipid Association [26]	Normal Borderline-high TGs High TGs Very high TGs	<150 mg/dL (< 1.7 mmol/L) 150-199 mg/dL (1.7-2.3 mmol/L) 200-499 mg/dL (2.3-5.6 mmol/L) ≥500 mg/dL (≥5.6 mmol/L)
The Endocrine Society [27]	Normal Mild HTG Moderate HTG Severe HTG	<150 mg/dL (< 1.7 mmol/L) 150-199 mg/dL (1.7-2.3 mmol/L) 200-999 mg/dL (2.3-11.2 mmol/L) 1000-1999 mg/dL (11.2-22.4

	Very severe HTG	mmol/L) ≥2000 mg/dL (≥22.4 mmol/L)
European Society of Cardiology/European Atherosclerosis Society [28]	Normal HTG Severe HTG	<1.7 mmol/L (<150mg/dL) 1.7-9.9 mmol/L (150-884 mg/dL) ≥ 10 mmol/L (885mg/dL)
Hegele [23]	Normal Mild to moderate Severe	<2.0 mmol/L (<175 mg/dL) 2.0-10 mmol/L (175- 885 mg/dL) >10 mmol/dL (>885 mg/dL)

Thus, establishing a precise definition of what constitutes abnormal TG values is fraught with problems, and evaluation of plasma TG values in the individual patient should be interpreted in the light of these considerations. For example, an acceptable level for the prevention of pancreatitis is likely to be quite different from that at which CVD risk might be increased. The impact of HTG on CVD risk needs to be evaluated in the context of the genetic cause of the HTG, a family history of premature CVD, associated abnormalities of lipids and lipoproteins, and other CVD risk factors, particularly those associated with the metabolic syndrome (see later).

Causes of hypertriglyceridemia

In general, HTG has been classified as primary, when a genetic or familial basis is suspected, or secondary, where other conditions that can raise TG levels can be identified. In many situations HTG is polygenic or multifactorial with environmental influences. One classification of genetic forms of HTG identifies two major forms of HTG, namely familial combined hyperlipidemia (FCHL) and familial HTG (FHTG). FCHL is believed to predispose an individual to premature CVD whereas FHTG does not raise the CVD risk to the same extent [29].

Genetic Disorders Leading to Mild to Moderate Hypertriglyceridemia

Familial Combined Hyperlipidemia (FCHL)

FCHL was first described in 1973 in families of survivors of myocardial infarction who presented with variable lipid abnormalities [30, 31]. This phenotype also been observed in other cohorts [32]. Affected family members can present with hypercholesterolemia alone, HTG alone, or with elevations in both. FCHL is estimated to have a population prevalence of 1-2% [29] making it the most common inherited form of dyslipidemia. The association of FCHL with premature CVD is well established [33-35]. Thus, identifying this disorder is of particular importance for management of cardiometabolic health on a global scale [36].

Pathogenesis

FCHL is believed to be a consequence of several metabolic defects that differ among families. The characteristic abnormalities in FCHL is an increase in apoB levels and increased number of small dense LDL particles, a phenotype similar to the metabolic syndrome and type 2 diabetes [37]. These primary defects occur due to 1) hepatic overproduction of VLDL particles due to increased apoB synthesis in the setting of disordered adipose metabolism [38, 39], insulin resistance [40-43] and liver fat accumulation, and, 2) impaired clearance of apoB containing particles [44, 45]. Increased VLDL secretion results in an elevated plasma apoB and HTG [40]. Long residence time of VLDL particles favors the formation of small dense LDL [44]. An abundance of small dense LDL particles traditionally is associated with the presence of HTG; however in FCHL individuals, these LDL characteristics remain even after correction of the HTG by treatment with fibrates [46, 47].

In FCHL, visceral adiposity appears to be an important determinant of insulin resistance, which occurs commonly in these subjects [48-51]. Other abnormalities that have been reported in FCHL include impaired lipolysis due to decreased cyclic AMP dependent signaling [38, 51], abnormal adipocyte TG turnover [52], fatty liver [53], increased arterial stiffness [54] and increased carotid intimal-medial thickness [55].

Genetics

Although originally described as a monogenic form of HTG [30, 31], FCHL more likely is a complex genetic disorder in which the interaction of multiple susceptibility genes with environmental components contributes to the phenotype of mixed dyslipidemia. Genome wide association studies (GWAS) and linkage approaches have been utilized to screen the genome in FCHL families from different populations to identify loci linked to the phenotype. At least 35 genes have been implicated in the development of FCHL, most frequently those associated with plasma lipid metabolism. One chromosomal locus that has been consistently linked to FCHL is 1q21–23 [56]. Linkage to several FCHL traits

has been observed, including apoB, plasma TG and cholesterol levels [57]. The apolipoprotein A1/C3/A4/A5 gene cluster, which associates with TG levels and LDL particle size, is an important modifier gene present at the 1q21–23 locus that has been linked with FCHL and its related traits in several (but not all) studies [58]. The exact gene at this locus influencing the FCHL phenotype is not yet known due to their close positional relationship and the presence of linkage disequilibrium [56]. Another commonly linked gene in FCHL is the ubiquitous transcription factor upstream stimulatory factor 1 (USF1), which has numerous target genes, including several related to lipid and glucose metabolism [59]. Determining how genetic variance in USF1 contributes to the cause and phenotype of FCHL has thus far remained elusive.

Some of the currently known gene associations in FCHL are listed in Table 2 and a detailed review of gene associations in FCHL is available [56]. In general, implicated genes are primarily those involved in VLDL production, catabolism and adipose tissue function. Implicated genes include hormone sensitive lipase (LIPC), which enables lipolysis of TG-rich lipoproteins, although its association with FCHL has been inconsistent [60-62], dysfunctional variants of LPL [63-68], adipose TG lipase (PNPLA2) [69] and the Pro446Leu variant of the glucokinase regulator gene (GCKR) that results in increased hepatic gluconeogenesis and reduced beta-oxidation [70].

In summary, the entity that is classified as FCHL on clinical grounds is likely quite heterogeneous in nature and in most instances not likely to be a monogenic disorder, with each pedigree composed of variable subsets of genetic risk factors with some degree of overlap among families.

Table 2. Selected genes with roles in FCHL

Locus	Gene	Gene name	Protein function
Genes linked to VLDL overproduction			
2p23	GCKR	Glucokinase (hexokinase 4) regulator	Inhibitor of glucokinase in liver
1q22-q23	USF1	Upstream transcription factor 1	Transcription factor that regulates many genes involved in lipid metabolism
Genes with involvement in TG metabolism and clearance			
11q23-24	APOA-I, APOC-III, APOA-IV, APOA-V	Apo A-I, apoC-III, apoA-IV, apoA-V	ApoA-1-cholesterol efflux; ApoC-III- inhibitor of LPL and HL; apoA-V-lipoprotein catabolism?

8p22	LPL	Lipoprotein lipase	TG hydrolysis in heart, muscle, adipose
15q21-23	HL	Hepatic lipase	TG hydrolysis in liver
Genes involved in adipose dysfunction			
1q22-q23	USF1	Upstream transcription factor 1	Transcription factor that regulates many genes involved in lipid metabolism
19q13	LIPE	Hormone sensitive lipase	In WAT, hydrolyzes TG to FFA

Adapted from reference [56].

Diagnosis

It remains difficult to distinguish FCHL from other forms of HTG, including the HTG associated with the metabolic syndrome. Although it is now evident that FCHL likely encompasses a heterogeneous group of disorders, there is clinical utility in making the diagnosis, since it identifies individuals **and families** who are at a high risk of developing premature CVD and who might benefit from lipid-lowering therapy. FCHL indeed is the commonest clinical form of familial atherogenic dyslipidemia. Affected individuals can present with elevations in cholesterol or TG levels or both. However, the presence of multiple forms of hyperlipidemias within a family is no longer a required diagnostic criterion. Elevated levels of apoB (> 90 percentile) and small dense LDL particles always are seen and are now considered diagnostic criteria for FCHL [71], although assessment of LDL particle size and/or density if not routinely done in clinical practice. The presence of elevated TG and apoB levels in at least 2 family members is considered necessary for a definitive diagnosis of FCHL [72]. A nomogram to calculate the probability of FCHL in an individual can be of value [73]. Patients with FCHL also frequently have other cardiovascular risks such as visceral adiposity, insulin resistance, impaired glucose tolerance and hypertension. An increased understanding of the relationship between genetic variants and FCHL phenotypes may eventually lead to a redefinition of this disorder.

Familial Hypertriglyceridemia (FHTG)

FHTG is also an inherited clinical entity, believed by some to be an autosomal dominant disorder, and may affect up to 1% of the population [33, 34, 74].

Pathophysiology

This disorder is characterized by increased TG synthesis, where normal numbers of very large triglyceride-enriched VLDL particles are secreted [42]. FHTG, but not FCHL, frequently is associated with a defective regulation of bile acid synthesis, resulting in abnormally high production rate of bile acids, which associates with the subsequent development of HTG [75]. Affected people have elevated VLDL levels, but normal levels of LDL and HDL cholesterol, and are generally asymptomatic unless very severe HTG develops. Although FHTG did not appear to be associated with an increased risk of premature CVD in an early study [33], baseline TG levels predicted subsequent CVD mortality after 20 years of follow up among relatives in FHTG families [34], adding to the evidence for the importance of HTG as a risk factor for CVD [76]. In the population-based Family Heart Study, individuals with FCHL and FHTG were very similar with respect to metabolic profile, associated risk factors such as abdominal obesity and insulin resistance, and premature CAD risk [77]. These observations suggest that identification of the metabolic syndrome may be more beneficial in risk stratifying patients with isolated HTG than trying to identify the specific form of HTG. . However, very severe HTG can occur in FHTG, when secondary causes of HTG such as untreated diabetes or use of triglyceride-raising drugs are present concurrently, in which case they are at risk of developing the Multifactorial Chylomicronemia Syndrome (MFCS), described below, and pancreatitis [78].

Genetics

The genetics of FHTG is poorly understood. The HTG often is not expressed until adulthood and likely is influenced by dietary, environmental and other factors. Accumulation of common and rare genetic variants that increase an individual's susceptibility may result in FHTG [79]. Those individuals are at risk for developing severe HTG, have been postulated to carry more DNA variants and have stronger secondary or metabolic stressors [80].

Diagnosis

The diagnosis of FHTG is made by obtaining a detailed family history and examination of fasting lipoprotein profiles of the patient and relatives. TG levels range from about 250-1000 mg/dl in approximately one half of first-degree relatives without elevated LDL cholesterol levels. Determining whether an individual with modest HTG has FHTG is indeed challenging; however a strong family history of premature CVD usually is lacking. In patients with elevated TGs in the absence of a personal or family history of clinical CAD, the presence of normal apoB levels may help distinguish FHTG from FCHL, where apoB levels are higher [73, 81].

Remnant Removal Disease (Dysbetalipoproteinemia)

Remnant removal disease, dysbetalipoproteinemia or type III hyperlipoproteinemia, is a rare autosomal recessive disorder that can present with elevated TG levels. This disorder is characterized by the accumulation of remnant lipoproteins and predisposes to premature cardiovascular disease [82, 83]. Affected individuals also are at increased risk for peripheral vascular disease [84].

Pathogenesis and genetics

Remnant removal disease requires homozygosity for the apoE2 genotype or a dominant negative mutation in the apoE gene, which results in impaired hepatic uptake of apoE-containing lipoproteins. Three common isoforms of apoE occur in humans, apoE2, apoE3, and apoE4 [85]. Each differs in isoelectric point by one charge unit, apoE4 being the most basic isoform and apoE2 the most acidic. ApoE3 (Cys112→Arg158) is the most frequently occurring isoform. ApoE2 (Arg158→Cys) and apoE4 (Cys112→Arg) differ from apoE3 by single amino acid substitutions at positions 158 and 112, respectively [86]. The prevalence of apoE2 homozygosity in Caucasian populations is estimated to be about 1% [87].

In the absence of additional genetic, hormonal, or environmental factors, remnants do not accumulate to a degree sufficient to cause hyperlipidemia on apoE2 homozygotes; in fact, hypolipidemia is commonly seen in this situation. Remnant accumulation results when the E2/2 genotype is accompanied by a second genetic or acquired defect that causes either overproduction of VLDL [88 89] (such as FCHL) or a reduction in LDL receptor activity (such as occurs in heterozygous FH [90] or hypothyroidism [91]). Thus, full phenotypic expression requires the presence of other environmental or genetic factors [92]. In these circumstances, the reduced uptake of remnant lipoproteins by the liver results in reduced conversion of VLDL and IDL to LDL, with subsequent accumulation of remnant lipoproteins [93, 94], hence the term remnant removal disease. While the apoE2 genotype is inherited in a recessive manner, rarer apoE variants such as apoE3-Leiden [95] and apoE2 (Lys1463Gln) that also can cause remnant accumulation are dominantly inherited [96].

Diagnosis

Patients with remnant removal disease have roughly equal elevations in plasma cholesterol and TGs. The disease rarely manifests before adulthood. It is more commonly seen in men than in women, where expression seldom occurs before menopause since estrogen has a protective effect in women who are apoE2 homozygotes [87]. Palmar xanthomas (Figure 1), orange lipid deposits in the palmar or plantar creases, are pathognomonic of remnant removal disease but are not always present. Tuberoeruptive xanthomas often are found at pressure sites on the elbows, knees and buttocks. The presence of remnant removal disease should be suspected when total cholesterol and triglyceride levels that range from 300 to 1000 mg/dl and are

roughly equal in magnitude. VLDL particles are cholesterol- enriched, which can be determined by isolation of VLDL by ultracentrifugation and by the demonstration of beta migrating VLDL on electrophoresis. A VLDL-cholesterol/plasma TG ratio of <0.30 is usually observed [97]. The diagnosis of remnant removal disease should be confirmed by demonstrating the presence of the E2/E2 genotype.

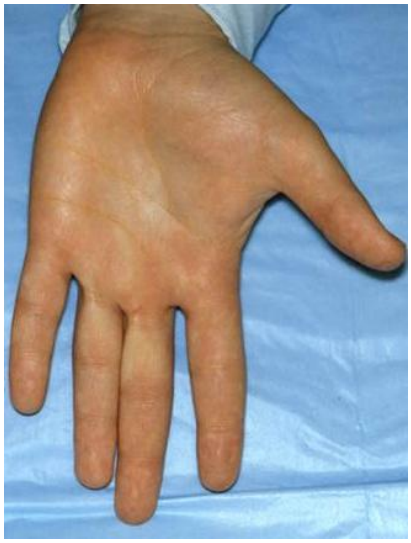

Figure 1. ***Palmar Xanthomas:*** ***Note the orange-yellow discoloration confined to the palmar creases.***

Hypertriglyceridemia in Lipodystrophy Syndromes

The lipodystrophies are a group of heterogeneous inherited or acquired disorders that are characterized by selective loss of body fat [98]. Loss of fat can be either *localized* to small discrete areas, in some cases *partial* with loss from extremities or *generalized*, with fat loss from nearly the entire body. Inherited lipodystrophies, while rare, can be autosomal dominant or recessive. Some forms manifest at birth, while others become evident later in life.

Partial or generalized lipodystrophic disorders frequently are associated with significant metabolic derangements associated with severe insulin resistance that often accompanies these conditions. The extent of fat loss sometimes determines the severity of metabolic complications [99]. HTG is a common accompaniment of many lipodystrophies, often in conjunction with low HDL-C levels. Potential mechanisms for the development of HTG relate to decreased storage capacity of fat in adipose tissue, with increased hepatic VLDL synthesis and delayed clearance [99]. Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disorder in which near total absence of subcutaneous adipose tissue is evident from birth. HTG and hepatic steatosis are evident at a young age and are often difficult to control. Severe HTG, often associated with eruptive xanthoma and recurrent pancreatitis, can occur in patients with CGL. The prevalence of HTG in case series of CGL patients is over 70% [99, 100]. Plasma TGs are normal or slightly increased during early childhood, with severe HTG

manifesting at puberty along with onset of diabetes mellitus. The Dunnigan variety of familial partial lipodystrophy (FPL) is a rare autosomal dominant disorder in which fat loss mostly involves the extremities and the trunk and is due to LMNA mutations [98]. HTG occurs at a later age than in CGL patients. FPL patients also can present with eruptive xanthomas and pancreatitis. Plasma TG levels in women with FPL are 2–3 times higher than in males [101]. Patients with the Kobberling variety of partial lipodystrophy lose subcutaneous fat on their limbs, but not on their abdomen. They too can have severe HTG, marked insulin resistance and are prone to develop pancreatitis and premature CVD [102]. Some lipodystrophies, where fat loss appears to be proportionate to loss of total and lean body mass, do not result in dyslipidemia. Elevated TG levels have been reported in patients with atypical progeroid syndrome due to LMNA mutations [103, 104]. Of the acquired lipodystrophies, the HIV-associated form usually is characterized by more moderate HTG. HIV-associated lipodystrophy occurs in patients receiving protease inhibitor containing highly active anti-retroviral therapy regimens [105]. Fat loss occurs in the face, buttocks and extremities.

Hypertriglyceridemia as a Component of the Metabolic Syndrome

The metabolic syndrome is a cluster of risk factors that is associated with an increased risk of developing premature CVD [106, 107]. Various definitions exist for the diagnosis of the metabolic syndrome. One of the most widely used is that from the NCEP ATP-III panel, which requires the presence of 3 of more of the following [24]:

- Central or abdominal obesity (measured by waist circumference):
  - Men - 40 inches or above
  - Women - 35 inches or above
- TGs greater than or equal to 150 mg/dL
- HDL cholesterol:
  - Men - Less than 40 mg/dL
  - Women - Less than 50 mg/dL
- Blood pressure greater than or equal to 130/85 mmHg
- Fasting glucose greater than or equal to 100 mg/dL

There are several other features of the metabolic syndrome that are not included in this definition, including insulin resistance, hypercoagulability, and the presence of inflammatory markers such as elevated levels of C-reactive protein [108]. It is estimated that up to one quarter to one third of the US population could have the metabolic syndrome [109], which constitutes a major risk for CVD in this country. Després and colleagues have coined the term “hypertriglyceridemic waist” to describe patients with HTG and central obesity who are at increased risk of developing CVD [110]. There is likely to be considerable overlap between these individuals and those classified as having the metabolic syndrome, although HTG is a requirement for being classified as having a “hypertriglyceridemic waist”.

The mechanism by which plasma TG levels are increased as part of the metabolic syndrome may relate to insulin resistance, since the presence of hepatic insulin resistance is believed to prevent the physiological effect of insulin in lowering VLDL secretion[111-113] described earlier. Overproduction of TG by the insulin resistant liver also is likely to be playing a major role in the pathogenesis of the HTG associated with type 2 diabetes [112]. However, diabetes also leads to a defect in adipose tissue LPL that may take as long as 3 months to correct [114]. The relationship between obesity and HTG also is complex. Obesity can generally be divided into two major categories - metabolically unhealthy and metabolically healthy (or less unhealthy) obesity [115, 116]. The former category occurs as part of the metabolic syndrome, the latter not so [117] . An important feature of the HTG that occurs as part of the metabolic syndrome, including that seen in diabetes, is that it is accompanied by the accumulation of a preponderance of small dense low density lipoprotein (LDL) particles, LDL-cholesterol levels that are usually high normal or normal, and abnormalities in high density lipoprotein (HDL)-cholesterol content and HDL composition. The latter is characterized by low levels of HDL_2 and a reduction in the ratio of apolipoprotein A-I/A-II [81]. This constellation of lipid and lipoprotein abnormalities has been termed diabetic dyslipidemia [118], but a similar lipoprotein pattern is characteristic of the metabolic syndrome [119].

Secondary Causes of Hypertriglyceridemia

These are described in greater detail in the chapter on Secondary Disorders of Lipid and Lipoprotein Metabolism. However, in the section where we describe MFCS we will briefly touch on some aspects of secondary forms of HTG, since they assume importance in the pathogenesis of the very severe HTG seen in the MFCS, where they often co-exist in individuals with genetic forms of HTG. In our experience, the commonest secondary forms of HTG that interact with familial forms of HTG are type 2 diabetes (usually as part of the metabolic syndrome), alcohol, the use of TG-raising drugs and chronic kidney disease (CKD)[78, 120, 121].

Very Severe Hypertriglyceridemia

In the late 1960s Fredrickson, Levy and Lees [122] classified hypertriglyceridemia into types dependent on the pattern of lipoproteins on paper electrophoresis and the presence or absence of chylomicrons in fasting plasma. They recognized that acute pancreatitis and eruptive xanthomata occurred in the presence of chylomicronemia that accumulate in what they termed Type I and Type V hyperlipoproteinemia. Chylomicrons are present in the post-prandial state, and usually are present in fasting plasma when TG levels exceed 1000 mg/dl, but are absent in fasting plasma below that value [123]. The term chylomicronemia syndrome was first used to describe a constellation of clinical findings that occurred in association with very high TG levels [124]. Causes of the chylomicronemia syndrome can be divided into familial chylomicronemia syndrome (FCS) due to mutations in the LPL complex, and multifactorial chylomicronemia

syndrome (MFCS), which includes patients with very severe HTG who do not have classical FCS. Genetic and secondary forms of HTG nearly always co-exist in individuals with MFCS.

Familial Chylomicronemia Syndrome (FCS)

FCS that results from a monogenic disorder occurs very rarely, with an estimated prevalence of about 1 in 1,000,000 [125]. It usually is due to mutations in one or more genes of the LPL complex that affect chylomicron catabolism. The most common gene affected in FCS is LPL itself, in which patients are homozygous or compound heterozygous for two defective LPL alleles. Over 100 mutations that result in LPL deficiency have been described [126, 127]. Loss of function mutations account for over 90% of cases [125]. Many are missense mutations, some in catalytically important sites and some in regions that predispose to instability of the homodimeric structure of LPL required for enzyme activity [128]. However, many common LPL gene variants have been described that have no clinical phenotype [129]. Mutations in the APOC2 gene, which encodes apoC-II, an activator of LPL, is the second most commonly reported cause of FCS. Mutations have been described in about 20 families.

Much less commonly FCS can be due to homozygous mutations in other components of the LPL complex such as GPIHBP1, apoA-V and LMF1 (Table 3), each of which plays an important role in determining LPL function [130]. The lipoprotein phenotype in these mimics that seen that in classical LPL deficiency. ApoA-V plays a role in stabilizing the lipoprotein–enzyme complex thereby enhancing lipolysis; thus, defective or absent apoA-V can result in reduced efficiency of LPL-mediated lipolysis [7]. A small number of individuals with homozygous mutations in Apo A-V have been described [131]. GPIHBP1 directs transendothelial LPL transport and helps anchor chylomicrons to the endothelial surface near LPL, thereby providing a platform for lipolysis. Loss of function mutations in this gene has been described in several families [125]. LMF1 is an endoplasmic reticulum chaperone protein required for post-translational activation of LPL; mutations in this protein have been identified in 2 patients [132].

These disorders usually present in childhood with very high TG levels and chylomicronemia syndrome. Other physical findings include eruptive xanthomas, lipemia retinalis and hepatosplenomegaly (see below). The main risk in these individuals is the predisposition to acute pancreatitis, a serious condition that can result in the systemic inflammatory response syndrome, multi-organ failure and death.

Table 3. **Rare genetic disorders affecting the LPL complex**

Disorder	Inheritance	Incidence	Lipid phenotype	Underlying defect	Clinical features
LPL deficiency	Autosomal recessive	1 in 1,000,000	Marked HTG/chylomicronemia in infancy or childhood	Very low or absence of LPL activity; ?circulating inhibitor of LPL	Hepatosplenomegaly; severe chylomincronemia in infancy
Apo C-II deficiency	Autosomal recessive	Rare	Marked HTG/chylomicronemia in infancy or childhood	Absent apo C-II	Hepatosplenomegaly; severe chylomicronemia in adolescence and adulthood
Apo A-V mutation	Unknown	Rare	Marked HTG/chylomicronemia later in adulthood	Defective or absent apo A-V	Chylomicronemia in late adulthood
GHIHBP1 mutation	Unknown	Rare	Marked HTG/chylomicronemia in adulthood	Defective or absent GHIHBP1	Chylomicronemia in late adulthood
LMF1 mutation	Unknown	Rare	Marked HTG/chylomicronemia in adulthood	Defective or absent LMF1	Chylomicronemia in late adulthood

Adapted from Ref [125]

Multifactorial Chylomicronemia Syndrome (MFCS)

The prevalence of MFCS is much greater than FCS [126]. Most, if not all, patients with MFCS have a familial form of moderate HTG co-existing with one or more secondary forms of HTG [133, 134]. The most common secondary cause of HTG in the past was undiagnosed or untreated diabetes [78], although earlier detection of diabetes may be making the association of marked hyperglycemia of untreated diabetes with very severe HTG less common. More recently, MFCS commonly results from the addition of specific drugs in patients with an underlying familial form of HTG [22]. These include the use of beta-adrenergic blocking agents (selective and non-selective) and/or diuretics (thiazides and loop-diuretics such as furosemide) for hypertension, retinoid therapy for acne, oral estrogen therapy for menopause or birth control, selective estrogen receptor modulators (particularly raloxifene) for osteoporosis or breast cancer therapy, protease inhibitors for HIV/AIDS, atypical anti-psychotic drugs, alcohol and possibly sertraline [126]. Rarer causes of very severe HTG include autoimmune disease (sometimes with LPL- specific antibodies), asparaginase therapy for acute lymphoblastic leukemia [135, 136] and bexarotene, a RXR agonist used in the treatment of cutaneous T cell lymphoma [137]. In addition, weight regain following successful weight loss has been associated with increasing TG levels [22, 126]. Very severe HTG also can be seen in lipodystrophic syndromes (see earlier) where plasma TGs can be very elevated and control of both HTG and diabetes can be difficult [102, 138].

Table 4. Secondary causes that can contribute to severe HTG

Conditions
Hypothyroidism
Uncontrolled diabetes
Pregnancy
Nephrotic syndrome
Acute hepatitis
Weight regain after weight loss
Sepsis
Autoimmune chylomicronemia • Systemic lupus erythematosis • Anti-LPL antibodies
Rare genetic conditions
Glycogen storage disorders
Lipodystrophies • Congenital- generalized or partial • Acquired- HIV, autoimmune
Drugs
Alcohol
Beta blockers
Diuretics
Oral estrogens
Selective estrogen reuptake modulators - tamoxifen, raloxifene
Androgens
Glucocorticoids
Atypical anti-psychotics
Sertraline (?)
Bile acid resins
Sirolimus, tacrolimus
Cyclosporine
RXR agonists -bexarotene, isotretinoin
HIV Protease inhibitors
L- asparaginase
Alpha-interferon

Following correction of treatable secondary forms of HTG in the MFCS, TG levels usually decrease to the moderately elevated levels seen in their affected relatives [133, 134]. Recently Johansen and Hegele have reported several single nucleotide polymorphisms that account for about 20% of the TG elevation in individuals with very severe HTG. How the many common genetic variants that have small effects in patients with severe HTG [139] (see earlier) relates to the coexistence of familial and secondary forms of HTG, which in our experience is the usual cause of MFCS, is unknown. Perhaps an additional single nucleotide variant is required in addition to the familial and secondary forms of HTG in order to develop TG levels above 2000 mg/dl [140].

Consequences of Hypertriglyceridemia

Increased Risk of Cardiovascular Disease

Epidemiology

HTG has long been known to be a risk factor for CVD [25, 141-144], which has been reconfirmed in meta-analyses [76]. However, HTG also is frequently associated with low levels of HDL-cholesterol and an accumulation of remnants of the TG-rich lipoproteins, both known risk factors for CVD. When adjusted for both HDL-cholesterol and non-HDL cholesterol, which contains both remnants of the TG-rich lipoproteins and LDL, the association of TGs with CVD risk remained significant, although somewhat attenuated [19]. Postprandial TGs are elevated throughout the day in subjects with HTG, and postprandial TG-rich lipoproteins and their remnants also have been hypothesized to be important in the pathogenesis of atherosclerosis [144]. It is therefore of interest that non-fasting TGs also has been associated with CVD risk [144-146], despite non-fasting TGs being quite variable. However, unlike the situation with elevated LDL levels, the magnitude of the TG elevation does not appear to correlate with the extent of CVD risk. In particular, very severe HTG per se does not appear to confer increased CVD risk, possibly because the chylomicrons that accumulate are too large to enter the arterial intima [147, 148].

TGs in the pathogenesis of CVD

Although chylomicrons may be too large to enter the arterial intima, apoE-and cholesterol-enriched remnants of the TG-rich lipoproteins can enter with ease [146] and can bind vascular proteoglycans, similar to LDL [149, 150]. Modification of these retained lipoproteins by either oxidative damage of enzyme digestion of some of the lipid components can liberate toxic by-products, which have been hypothesized to play a role in atherogenesis by facilitating local injury, generation of adhesion molecule and cytokine expression and inflammation [150]. Remnants of the TG-rich lipoproteins also can be taken up by macrophages leading to the formation of foam cells, an important

component of atherosclerotic plaques. HTG also is associated with a preponderance of small, dense LDL, particles, reduced levels of HDL-cholesterol, and in the metabolic syndrome, with abnormalities of HDL composition (see earlier). Small, dense LDL can traverse the endothelial barrier more easily than large, buoyant LDL particles [151], are retained more avidly than large, buoyant LDL [152], and also are more readily oxidized [153, 154], all of which may facilitate atherogenesis. HDL particles in some HTG states, e.g., in association with the metabolic syndrome, might be dysfunctional with respect to their cholesterol efflux, anti-inflammatory and anti-oxidant properties. Moreover, a hypercoagulable state has been reported in association with both HTG and the metabolic syndrome [119]. Thus, HTG might accelerate atherosclerosis by several mechanisms, all of which could increase CVD risk.

Genetics of TG and CVD

Recent human genetic studies have provided important insight into the contribution of TGs to CVD. Several genetic approaches, including candidate gene sequencing, GWAS of common DNA sequence variants and genetic analysis of TG phenotypes have unraveled new proteins and gene variants involved in plasma TG regulation [155]. Common genetic variants that influence TG levels appear to be associated with increased CVD risk even after adjusting for their effects on other lipid traits [156]. GWAS have identified common noncoding variants of the LPL gene locus associated with TG and CVD risk in individuals of European and non-European descent [157, 158]. A common gain-of-function mutation in the LPL gene, S447X (10% allele frequency), is associated with reduced TG levels and reduced risk of CVD [159]. Conversely, several loss-of-function LPL variants linked with elevated TG levels are associated with increased CVD risk [160]. Variants in the TRIB1 locus recently have been associated with LDL-C, HDL-C and TG levels [158], hepatic steatosis [161] and coronary artery disease [162]. Mutations that disrupt APOC3 gene function and reduce plasma apoC-III are associated with lower TG levels and decreased risk of clinical CVD [163, 164]. In contrast, carriers of rare mutations in APOA5 (encoding apoA-V, an activator of LPL) are associated with elevated TGs and with increased risk of myocardial infarction [165, 166].

Thus, exciting new human genetics findings have causally implicated TG and TG-rich lipoproteins in the development of cardiovascular risk. In particular, the LPL pathway and its reciprocal regulators apoC-III and apoA-V appear to have an important influence on atherosclerotic CVD risk.

Fatty liver and Non-alcoholic Steatohepatitis

Hepatic steatosis (fatty liver) and non-alcoholic steatohepatitis (NASH), collectively known as non-alcoholic fatty liver disease (NAFLD), is increasing in prevalence and predisposes to liver cirrhosis, liver failure and liver cancer [167]. NASH also is a risk factor for CVD [168, 169]. Patients with NASH, even mild cases, frequently have insulin resistance and the metabolic syndrome, and a near-universal association between NASH and

insulin resistance exists irrespective of obesity [170-172]. Consequently it has been suggested that NASH be considered a component of the metabolic syndrome [173]. This notion is further supported by evidence from multivariate analysis, which identified diabetes and HTG as independent predictors of NASH in a small group of patients [174]. HTG is present in about 80% of NAFLD patients, and TG levels correlate with histopathological subtypes of NAFLD [170]. Fatty liver also is common in association with very severe HTG, although it is less clear whether fatty liver that is unassociated with features of the metabolic syndrome actually progresses to NASH and cirrhosis to the same extent as in individuals with the metabolic syndrome.

Mechanisms

TG accumulation in the liver occurs despite increased secretion of VLDL in the metabolic syndrome (see earlier). Liver fat derives from several potential sources including increased flux of FFA, increased uptake by the liver of remnants of the TG-rich lipoproteins, and de novo lipogenesis, which contributes significantly to VLDL secretion in humans, and is increased in individuals with obesity and IR [111]. Studies in mice suggest that hepatic steatosis leads to hepatic insulin resistance by stimulating gluconeogenesis and interfering with tyrosine phosphorylation of IRS-1 and IRS-2, thereby impairing the ability of insulin to activate glycogen synthase [175]. Studies in both mice and humans have implicated various lipid species and have elucidated a key role for hepatic diacylglycerol activation of protein kinase Cε in triggering hepatic insulin resistance [176].

Pancreatitis in the chylomicronemia syndrome

FCS often presents in early childhood with severe colic or failure to thrive. However, the major complication of FCS is pancreatitis. The initial clinical presentation in MFCS often is acute abdominal pain. These patients almost always have relatives with common genetic forms of HTG, such as FCHL, FHTG, familial low HDL syndrome with HTG or remnant removal disease [78]. Pancreatitis due to very severe HTG may occur during infusion of lipid emulsions for parenteral feeding [177] or with use of the anesthetic agent propofol, which is infused in a 10% fat emulsion [178]. Finally, very severe HTG can result in pancreatitis in a subset of women with HTG during pregnancy, particularly the third trimester [179].

The pancreatitis that occurs in conditions of marked HTG often is recurrent. With long term multiple episodes of acute, recurrent pancreatitis, exocrine pancreatic insufficiency or insulin deficient secondary diabetes may occur. Abdominal pain also may be the result of rapid expansion of the liver by fat, since fatty liver occurs commonly in all forms of severe HTG [180]. In a prospective study of patients admitted with acute pancreatitis when plasma TG was measured at the peak of the pain the distribution of plasma triglyceride was bimodal [133, 134]. TG levels less than 880 mg/dL were associated with gall bladder disease and chronic alcoholism, while those above 2000 mg/dL were associated

with the simultaneous presence of familial and secondary forms of HTG. Although HTG-associated pancreatitis has been reported with TG levels lower than 2000 mg/dL[181, 182], in our experience this only occurs when patients with severe HTG stopped eating some time prior to the blood draw. Very severe HTG has been reported in 12-20% of patients with acute pancreatitis [183, 184]. Very severe HTG is the third most common cause of acute pancreatitis after alcohol and gall bladder disease. Moreover, the pancreatitis often is recurrent if HTG is not appreciated to be the cause and if TG levels are not adequately treated.

The diagnosis of HTG-associated pancreatitis can be made on the basis of severely elevated TG levels. Falsely low serum amylase levels can be encountered due to assay interference by the TG-rich lipoproteins [185]. Pseudohyponatremia due to the presence of large numbers of TG-rich lipoproteins in plasma can be seen with very severe HTG. Interference with liver transaminase assays may also occur, giving spuriously high values making it difficult to exclude alcoholic liver disease [185].

If the familial component of the HTG is believed to be FCHL, strategies to prevent CVD also need to be undertaken once the TGs have been lowered to a level where pancreatitis is unlikely to recur. A presumptive clinical diagnosis of FCHL can be made by the presence of premature CVD in multiple family members. In such cases, statin therapy and lifestyle changes aimed at reducing the risk of CVD should be undertaken in addition to strategies to maintain reduced TG levels.

Mechanism of Chylomicron-induced Pancreatitis

The mechanism by which very severe HTG leads to pancreatitis likely relates to liberation by pancreatic lipase of FFA from TGs and lysophosphatidylcholine from phosphatidycholine, when the enzyme encounters very high levels of TG-rich lipoproteins in the pancreatic capillaries [186]. High local concentrations of FFA overwhelm the binding capacity of albumin with resultant aggregation into micellar structures with detergent properties. Both FFA and lysophosphatidylcholine have been shown to cause chemical pancreatitis when infused into pancreatic arteries of dogs [187]. It also has been hypothesized that increased plasma viscosity due to the presence of increased numbers of chylomicrons in the pancreatic microcirculation contributes to the development of pancreatitis [188]. There also is recent evidence of gene associations in hypertriglyceridemic pancreatitis. In a Chinese cohort with HTG, a CFTR variant and TNF alpha promoter polymorphism were found to be independent risk factors for developing pancreatitis [189], while another study found an increased frequency of e-4 allele of the ApoE gene [190].

Other clinical features seen in individuals with hypertriglyceridemia

With chronic chylomicronemia, patients may also develop eruptive xanthomata (Figure 2). Xanthomas represent an inflammatory response to the deposition of chylomicron-

associated lipids in tissues and are yellow-red papules that usually appear on the buttocks, back and extensor surfaces of the upper limbs. Histologically, these lesions contain lipid laden foamy macrophages [191].

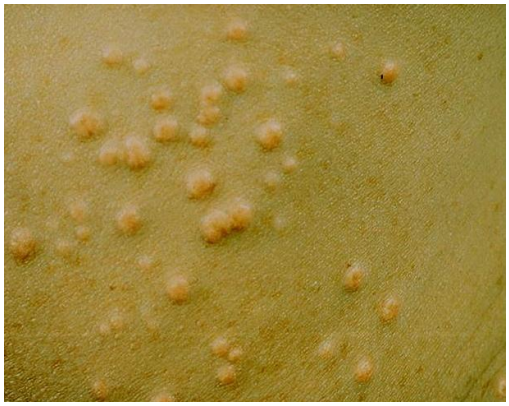

Figure 2. *Eruptive xanthomas. The commonest site is on the buttocks. The lesions are popular with an erythematous base. They often are itchy.*

Recognition of lipemia retinalis by an ophthalmologist, where the retinal vessels take on a whitish hue with pallor of the optic fundus and retina can be observed (Figure 3). There is no associated visual impairment.

Figure 3. *Lipemia retinalis. Note the pale color of the retinal vessels.*

Acute recent memory loss noted by the patient [124] can also occasionally be seen. Symptoms such as fatigue, blurred vision, dysesthesias and transient ischemic attacks have been suggested to be related to hyperviscosity resulting from high TG levels [192, 193]. Hepatosplenomegaly is frequently present in FCS due to macrophage infiltration in response to the chylomicron accumulation. Fatty liver is a common finding on imaging in both FCS and MFCS.

MANAGEMENT OF HYPERTRIGLYCERIDEMIA

Management of HTG by lifestyle and pharmacological means is discussed in detail in the chapters on Lifestyle Changes and Triglyceride Lowering and HDL Increasing Drugs. However, in this section we will make a few points specifically relevant to this chapter.

CVD Prevention

First, as is apparent from the aforegoing, not all familial forms of HTG confer the same degree of CVD risk. Therefore, different individuals might be treated differently despite equivalent TG levels. Factors that might mitigate against specific therapy aimed at using drugs to reduce CVD risk (either for primary or secondary prevention) include the absence of a positive family history of premature CVD (assuming sufficient family members are available to evaluate), normal apoB and apoA-I levels, absence of other features of the metabolic syndrome, and absence of other CVD risk factors. These individuals would be those described earlier as carrying a clinical diagnosis of FHTG. It is important to emphasize that these individuals are nonetheless susceptible to develop CVD later in life and to develop MFCS if they also acquire any of the secondary causes of HTG. The best clinical trial data currently available for the prevention of CVD in patients with HTG demonstrate that statins are likely to confer the most benefit, even though their primary mode of action is not to reduce plasma TGs, nor are they very effective in so doing [194]. The role of TG lowering by pharmacological means remains somewhat controversial and needs further study.

Management of NAFLD

The mainstay of treatment of patients with NAFLD is lifestyle modification. Weight reduction through a combination of diet, exercise and behavioral modification with a goal of 7-10% weight loss, results in histological improvement in liver inflammation [195]. Lesser degrees of weight loss (~5%) results in improvement of metabolic dysfunction without significant improvement in necroinflammation seen as part of NASH [196]. Pharmacological weight loss with orlistat has been shown to decrease liver fat and transaminase elevations in some studies only [197, 198]. Vitamin E therapy also has been shown to improve transaminase elevation and histological features of NASH [199]. However, since an increase in all-cause mortality with long-term vitamin E has been suggested [200], it is not routinely recommended. A meta-analysis suggests that therapy with thiazoledinediones such as pioglitazone improve hepatic steatosis, hepatocellular ballooning and inflammation, and reduce risk of progression of fibrosis [196]. Interestingly, these changes are reversed with discontinuation of therapy. A randomized control trial demonstrated that although prolonged treatment with pioglitazone resulted in metabolic improvement, it offered no additional histological benefit [199]. Although widely used for management of type 2 diabetes, metformin has not been shown to be beneficial in NAFLD [196]. Statins improve ALT in hyperlipidemic patients with NAFLD, but their effects on hepatic histology is unclear [201]. Ezetimibe has not been shown to reduce liver fat in NASH [202].

Prevention of Pancreatitis

Because of the low frequency of both FCS and MFCS, and because only some patients with these disorders develop pancreatitis, large random controlled clinical trials are difficult to perform and unlikely to be undertaken in the foreseeable future. Therefore, therapeutic decisions need to be based on less stringent criteria than might otherwise be desirable.

For infants with FCS presenting with abdominal pain or failure to thrive, discontinuation of breast feeding with replacement by very low fat formula feeding will cause a marked decrease in TG levels and symptoms. Later in childhood dietary fat calories should be severely restricted to the extent required to control the very severe HTG as much as possible and control abdominal pain (usually 5% to 15% of total daily calories). Long chain fatty acids may be replaced by medium-chain triglycerides (MCT), which are taken up directly by the liver after absorption and do not enter plasma as chylomicrons via the thoracic duct. While omega 3 fatty acids lower plasma TGs in MFCS, they may actually aggravate the severe HTG of FCS and are therefore contraindicated in LPL deficiency [203, 204]. Similarly, fibrates, which are very useful in MFCS, do not appear to be beneficial in LPL deficiency [180]. Use of oral contraceptives or alcohol can precipitate very severe HTG and acute pancreatitis in both conditions. Successful pregnancies in patients with FCS have become more common of late [205, 206].

For MFCS the primary goal is prevention of pancreatitis by maintaining TG levels below that at which pancreatitis occurs. From a practical standpoint, it is best to maintain levels <1000 mg/dL, ideally lower if possible. This requires reversal of any secondary cause of HTG, including switching beta-adrenergic blockers and diuretics to lipid neutral agents such as ACE inhibitors, ARBs, calcium channel inhibitors or alpha blockers for the management of hypertension. Although healthy lifestyle measure can help reduce TGs, particular attention should be paid to avoid the weight gain that commonly occurs after a period of successful weight loss [207]. Use of TG-lowering drugs, particularly fibrates, plays an important role in maintaining TGs at an acceptable level. The addition of niacin and/or omega 3 fatty acids sometimes is required.

Management of acute pancreatitis is similar to the management of non-TG induced pancreatitis, the major difference being avoidance of lipid emulsions for parenteral feeding, since their use will exacerbate the HTG. TGs fall rapidly with discontinuation of oral intake. The use of apheresis to acutely lower TGs is controversial. Although recommended by some [208, 209], the evidence for the benefit of its use is limited to small uncontrolled anecdotal series [210]. Therefore, we do not recommend its use in this situation. Heparin will liberate LPL into plasma from its endothelial binding sites and hence lower TGs rapidly [211]. However, it also can cause rebound HTG and increase the risk of hemorrhagic pancreatitis. Therefore its use should be avoided [212]. Intravenous (IV) infusion of regular insulin (in conjunction with IV glucose administration as needed) can be used with caution in the intensive care setting to decrease TG levels in patients with acute pancreatitis. Insulin stimulates LPL activity, thereby decreasing plasma TG levels [213]. The challenge is to determine both the primary and secondary causes of the

very severe HTG that preceded the acute pancreatitis, and to ensure continued management of the secondary form of HTG in an attempt to prevent recurrent pancreatitis. Particularly challenging are individuals with some forms of familial partial lipodystrophy, in whom glucose and TG control can be exceedingly difficult [102, 138], and for whom additional novel therapies might become available in the future (see below).

If fasting plasma TG levels remain above 1000 mg/dl after treating or removing the precipitating cause of the very severe HTG, fibrates or omega 3 fatty acids (3 to 4 grams per day) are indicated. It is not certain which patients with familial forms of mild to moderate HTG will develop very severe HTG and the MFCS. Therefore, life-long fibrate therapy might be considered. Limited evidence suggests that orlistat, a gastrointestinal lipase inhibitor that decreases absorption of ingested fat, thereby reducing intestinal chylomicron synthesis, may be of benefit in reducing TG levels when used in conjunction with fibrate therapy [214, 215].
A secondary goal of therapy is the prevention of cardiovascular disease (CVD) in some MFCS patients. This particularly pertains to those individuals in whom FCHL is the genetic disorder underlying the MFCS. Since individuals with FCHL have significantly increased risk of premature CVD, the mainstay of therapy for both primary and secondary prevention is with statins. Based on the results of the IMPROVE-IT trial [216], the addition of ezetimibe may be of additional benefit. Lowering plasma TG levels to reduce CVD risk remains unproven.

Emerging Therapies

Newer therapies are on the horizon for FCS. Drugs that block pancreatic lipase and cause fat malabsorption lower plasma TGs, but the gastrointestinal side effects associated with fat malabsorption often are not tolerated. Gene therapy for FCS due to LPL deficiency has been approved for adults in Europe, but not yet in the US. Alipogene tiparvovec is a recombinant adeno-associated viral vector of serotype 1 containing the coding sequence for the human gene variant LPL S447X, administered by intramuscular injection in conjunction with a low fat diet [217]. Administration of this drug is restricted to patients who are 18 years of age or older, with a known defect in LPL with some LPL protein present, and with unmanageable recurrent acute pancreatitis [218]. Drugs that inhibit apoC-III using either an anti-sense [219] or RNAi approach as well as those that inhibit ANGPTL3 [220] are in development for management of difficult to treat patients with very severe HTG. Inhibition of apoC-III can potentially reduce TG in FCS by possibly enhancing any residual LPL activity that may be present in these individuals, by stimulating non LPL mediated uptake of TG-rich lipoproteins, or by reducing the secretion of TG-rich lipoproteins into plasma [219]. The injectable antisense drug, mipomersen, which reduces the input of apoB-containing lipoproteins into plasma at the expense of increase fat deposition in the liver [221], may prove to be of value in reducing TG levels in some cases, although it currently is only approved in the US for management of homozygous familial hypercholesterolemia. The MTP inhibitor, lomitapide, also reduces the production of apoB-containing lipoproteins at the expense

of increased fatty liver [221]. It too is only approved in the US for use in homozygous familial hypercholesterolemia. Experimental drugs that block chylomicron synthesis in the gut are being explored, as are DGAT1 [222] and DGAT2 inhibitors [223], which block the final steps in TG synthesis. If successful, these emerging therapies might help manage the more resistant patients with very severe HTG.

REFERENCES

1. Fisher EA. The degradation of apolipoprotein B100: multiple opportunities to regulate VLDL triglyceride production by different proteolytic pathways. Biochim Biophys Acta. 2012;1821:778-81.

2. Sundaram M and Yao Z. Recent progress in understanding protein and lipid factors affecting hepatic VLDL assembly and secretion. Nutrition & metabolism. 2010;7:35.

3. Yao Z. Human apolipoprotein C-III - a new intrahepatic protein factor promoting assembly and secretion of very low density lipoproteins. Cardiovascular & hematological disorders drug targets. 2012;12:133-40.

4. Kindel T, Lee DM and Tso P. The mechanism of the formation and secretion of chylomicrons. Atheroscler Suppl. 2010;11:11-6.

5. Kersten S. Physiological regulation of lipoprotein lipase. Biochim Biophys Acta. 2014;1841:919-33.

6. Goldberg IJ, Scheraldi CA, Yacoub LK, Saxena U and Bisgaier CL. Lipoprotein ApoC-II activation of lipoprotein lipase. Modulation by apolipoprotein A-IV. J Biol Chem. 1990;265:4266-72.

7. Nilsson SK, Heeren J, Olivecrona G and Merkel M. Apolipoprotein A-V; a potent triglyceride reducer. Atherosclerosis. 2011;219:15-21.

8. Priore Oliva C, Pisciotta L, Li Volti G, Sambataro MP, Cantafora A, Bellocchio A, Catapano A, Tarugi P, Bertolini S and Calandra S. Inherited apolipoprotein A-V deficiency in severe hypertriglyceridemia. Arterioscler Thromb Vasc Biol. 2005;25:411-7.

9. Gonzales JC, Gordts PL, Foley EM and Esko JD. Apolipoproteins E and AV mediate lipoprotein clearance by hepatic proteoglycans. J Clin Invest. 2013;123:2742-51.

10. Kroupa O, Vorrsjo E, Stienstra R, Mattijssen F, Nilsson SK, Sukonina V, Kersten S, Olivecrona G and Olivecrona T. Linking nutritional regulation of Angptl4, Gpihbp1, and Lmf1 to lipoprotein lipase activity in rodent adipose tissue. BMC Physiol. 2012;12:13.

11. Lamiquiz-Moneo I, Bea AM, Mateo-Gallego R, Baila-Rueda L, Cenarro A, Pocovi M, Civeira F and de Castro-Oros I. [Identification of variants in LMF1 gene associated with primary hypertriglyceridemia]. Clin Investig Arterioscler. 2015.

12. Inukai K, Nakashima Y, Watanabe M, Kurihara S, Awata T, Katagiri H, Oka Y and Katayama S. ANGPTL3 is increased in both insulin-deficient and -resistant diabetic states. Biochem Biophys Res Commun. 2004;317:1075-9.

13. Shimamura M, Matsuda M, Ando Y, Koishi R, Yasumo H, Furukawa H and Shimomura I. Leptin and insulin down-regulate angiopoietin-like protein 3, a plasma triglyceride-increasing factor. Biochem Biophys Res Commun. 2004;322:1080-5.

14. Koster A, Chao YB, Mosior M, Ford A, Gonzalez-DeWhitt PA, Hale JE, Li D, Qiu Y, Fraser CC, Yang DD, Heuer JG, Jaskunas SR and Eacho P. Transgenic angiopoietin-like (angptl)4 overexpression and targeted disruption of angptl4 and angptl3: regulation of triglyceride metabolism. Endocrinology. 2005;146:4943-50.

15. Foley EM, Gordts PL, Stanford KI, Gonzales JC, Lawrence R, Stoddard N and Esko JD. Hepatic remnant lipoprotein clearance by heparan sulfate proteoglycans and low-density lipoprotein receptors depend on dietary conditions in mice. Arterioscler Thromb Vasc Biol. 2013;33:2065-74.

16. Crawford SE and Borensztajn J. Plasma clearance and liver uptake of chylomicron remnants generated by hepatic lipase lipolysis: evidence for a lactoferrin-sensitive and apolipoprotein E-independent pathway. J Lipid Res. 1999;40:797-805.

17. Dichek HL, Johnson SM, Akeefe H, Lo GT, Sage E, Yap CE and Mahley RW. Hepatic lipase overexpression lowers remnant and LDL levels by a noncatalytic mechanism in LDL receptor-deficient mice. J Lipid Res. 2001;42:201-10.

18. Greenfield MS, Kraemer F, Tobey T and Reaven G. Effect of age on plasma triglyceride concentrations in man. Metabolism. 1980;29:1095-9.

19. Hokanson JE and Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk. 1996;3:213-9.

20. Asplund-Carlson A and Carlson LA. Studies in hypertriglyceridaemia. 1. Serum triglyceride distribution and its correlates in randomly selected Swedish middle-aged men. J Intern Med. 1994;236:57-64.

21. Johansen CT, Kathiresan S and Hegele RA. Genetic determinants of plasma triglycerides. J Lipid Res. 2011;52:189-206.

22. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH and Stalenhoef AF. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:2969-89.

23. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, Boren J, Bruckert E, Catapano AL, Descamps OS, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A, Watts GF, Wiklund O and European Atherosclerosis Society Consensus P. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol. 2014;2:655-66.

24. Expert Panel on Detection E and Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection,

Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285:2486-97.

25. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S, American Heart Association Clinical Lipidology T, Prevention Committee of the Council on Nutrition PA, Metabolism, Council on Arteriosclerosis T, Vascular B, Council on Cardiovascular N and Council on the Kidney in Cardiovascular D. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2292-333.

26. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, McKenney JM, Grundy SM, Gill EA, Wild RA, Wilson DP and Brown WV. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol. 2014;8:473-88.

27. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF and Endocrine s. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:2969-89.

28. Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman M, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D, European Society of C and European Atherosclerosis S. ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis. 2011;217:3-46.

29. Brunzell JD. Clinical practice. Hypertriglyceridemia. N Engl J Med. 2007;357:1009-17.

30. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL and Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. J Clin Invest. 1973;52:1533-43.

31. Goldstein JL, Schrott HG, Hazzard WR, Bierman EL and Motulsky AG. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. J Clin Invest. 1973;52:1544-68.

32. Nikkila EA and Aro A. Family study of serum lipids and lipoproteins in coronary heart-disease. Lancet. 1973;1:954-9.

33. Brunzell JD, Schrott HG, Motulsky AG and Bierman EL. Myocardial infarction in the familial forms of hypertriglyceridemia. Metabolism. 1976;25:313-320.

34. Austin MA, McKnight B, Edwards KL, Bradley CM, McNeely MJ, Psaty BM, Brunzell JD and Motulsky AG. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: A 20-year prospective study. Circulation. 2000;101:2777-2782.

35. McNeely M, Edwards K, Marcovina S, Brunzell J, Motulsky A and Austin M. Lipoprotein and apolipoprotein abnormalities in familial combined hyperlipidemia: a 20-year prospective study. Atherosclerosis. 2001;159:417-481.

36. van Greevenbroek MM, Stalenhoef AF, de Graaf J and Brouwers MC. Familial combined hyperlipidemia: from molecular insights to tailored therapy. Curr Opin Lipidol. 2014;25:176-82.

37. Ayyobi AF and Brunzell JD. Lipoprotein distribution in the metabolic syndrome, type 2 diabetes mellitus, and familial combined hyperlipidemia. Am J Cardiol. 2003;92:27J-33J.

38. Reynisdottir S, Eriksson M, Angelin B and Arner P. Impaired activation of adipocyte lipolysis in familial combined hyperlipidemia. J Clin Invest. 1995;95:2161-9.

39. Reynisdottir S, Angelin B, Langin D, Lithell H, Eriksson M, Holm C and Arner P. Adipose tissue lipoprotein lipase and hormone-sensitive lipase. Contrasting findings in familial combined hyperlipidemia and insulin resistance syndrome. Arterioscler Thromb Vasc Biol. 1997;17:2287-92.

40. Venkatesan S, Cullen P, Pacy P, Halliday D and Scott J. Stable isotopes show a direct relation between VLDL apoB overproduction and serum triglyceride levels and indicate a metabolically and biochemically coherent basis for familial combined hyperlipidemia. Arterioscler Thromb. 1993;13:1110-1118.

41. Aitman T, Godsland I, Farren B, Crook D, Wong H and Scott J. Defects of insulin action on fatty acid and carbohydrate metabolism in familial combined hyperlipidemia. Arterioscler Thromb Vasc Biol. 1997;17:748-754.

42. Chait A, Albers JJ and Brunzell JD. Very low density lipoprotein overproduction in genetic forms of hypertriglyceridemia. Eur J Clin Invest. 1980;10:17-22.

43. Janus ED, Nicoll AM, Turner PR, Magill P and Lewis B. Kinetic bases of the primary hyperlipidemias: Studies of apolipoprotein B turnover in genetically defined subjects. Eur J Clin Invest. 1980;10:161-172.

44. Berneis KK and Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res. 2002;43:1363-79.

45. Cabezas MC, de Bruin TW, Jansen H, Kock LA, Kortlandt W and Erkelens DW. Impaired chylomicron remnant clearance in familial combined hyperlipidemia. Arterioscler Thromb. 1993;13:804-14.

46. Hokanson JE, Austin MA, Zambon A and Brunzell JD. Plasma triglyceride and LDL heterogeneity in familial combined hyperlipidemia. Arterioscler Thromb. 1993;13:427-434.

47. Hokanson JE, Krauss RM, Albers JJ, Austin MA and Brunzell JD. LDL physical and chemical properties in familial combined hyperlipidemia. Arterioscler Thromb Vasc Biol. 1995;15:452-459.

48. Purnell JQ, Kahn SE, Schwartz RS and Brunzell JD. Relationship of insulin sensitivity and ApoB levels to intra-abdominal fat in subjects with familial combined hyperlipidemia. Arterioscler Thromb Vasc Biol. 2001;21:567-72.

49. Ascaso J, Lorente R, Merchante A, Real J, Priego A and Carmena R. Insulin resistance in patients wtih familial combined hyperlipidemia and coronary artery disease. Am J Cardiol. 1997;80:1481-1487.

50. Castro Cabezas M, de Bruin T, de Valk H, Shoulders C, Jansen H and Willem Erkelens D. Impaired fatty acid metabolism in familial combined hyperlipidemia: a mechanism associating hepatic apolipoprotein B overproduction and insulin resistance. J Clin Invest. 1993;92:160-168.

51. van der Kallen C, Voors-Pette C, Bouwman F, Keizer H, Lu J, van de Hulst R, Bianchi R, Janssen M-J, Keulen E, Boeckx W, Rotter J and de Bruin T. Evidence of insulin resistant lipid metabolism in adipose tissue in familial combined hyperlipidemia, but not type 2 diabetes mellitus. Atherosclerosis. 2002;164:337-346.

52. Arner P, Bernard S, Salehpour M, Possnert G, Liebl J, Steier P, Buchholz BA, Eriksson M, Arner E, Hauner H, Skurk T, Ryden M, Frayn KN and Spalding KL. Dynamics of human adipose lipid turnover in health and metabolic disease. Nature. 2011;478:110-3.

53. Brouwers MC, Bilderbeek-Beckers MA, Georgieva AM, van der Kallen CJ, van Greevenbroek MM and de Bruin TW. Fatty liver is an integral feature of familial combined hyperlipidaemia: relationship with fat distribution and plasma lipids. Clin Sci (Lond). 2007;112:123-30.

54. Brouwers MC, Reesink KD, van Greevenbroek MM, Meinders JM, van der Kallen CJ, Schaper N, Hoeks AP and Stehouwer CD. Increased arterial stiffness in familial combined hyperlipidemia. J Hypertens. 2009;27:1009-16.

55. Keulen ET, Kruijshoop M, Schaper NC, Hoeks AP and de Bruin TW. Increased intima-media thickness in familial combined hyperlipidemia associated with apolipoprotein B. Arterioscler Thromb Vasc Biol. 2002;22:283-8.

56. Brouwers MC, van Greevenbroek MM, Stehouwer CD, de Graaf J and Stalenhoef AF. The genetics of familial combined hyperlipidaemia. Nat Rev Endocrinol. 2012;8:352-62.

57. Pajukanta P, Nuotio I, Terwilliger JD, Porkka KV, Ylitalo K, Pihlajamaki J, Suomalainen AJ, Syvanen AC, Lehtimaki T, Viikari JS, Laakso M, Taskinen MR, Ehnholm C and Peltonen L. Linkage of familial combined hyperlipidaemia to chromosome 1q21-q23. Nat Genet. 1998;18:369-73.

58. Mar R, Pajukanta P, Allayee H, Groenendijk M, Dallinga-Thie G, Krauss RM, Sinsheimer JS, Cantor RM, de Bruin TW and Lusis AJ. Association of the APOLIPOPROTEIN A1/C3/A4/A5 gene cluster with triglyceride levels and LDL particle size in familial combined hyperlipidemia. Circ Res. 2004;94:993-9.

59. Suviolahti E, Lilja HE and Pajukanta P. Unraveling the complex genetics of familial combined hyperlipidemia. Ann Med. 2006;38:337-51.

60. Pihlajamaki J, Valve R, Karjalainen L, Karhapaa P, Vauhkonen I and Laakso M. The hormone sensitive lipase gene in familial combined hyperlipidemia and insulin resistance. Eur J Clin Invest. 2001;31:302-8.

61. Pajukanta P, Porkka KV, Antikainen M, Taskinen MR, Perola M, Murtomaki-Repo S, Ehnholm S, Nuotio I, Suurinkeroinen L, Lahdenkari AT, Syvanen AC, Viikari JS, Ehnholm C and Peltonen L. No evidence of linkage between familial combined hyperlipidemia and genes encoding lipolytic enzymes in Finnish families. Arterioscler Thromb Vasc Biol. 1997;17:841-50.

62. Hoffer MJ, Snieder H, Bredie SJ, Demacker PN, Kastelein JJ, Frants RR and Stalenhoef AF. The V73M mutation in the hepatic lipase gene is associated with elevated cholesterol levels in four Dutch pedigrees with familial combined hyperlipidemia. Atherosclerosis. 2000;151:443-50.

63. Yang WS, Nevin DN, Peng R, Brunzell JD and Deeb SS. A mutation in the promoter of the lipoprotein lipase gene in a patient with familial combined hyperlipidemia and low LDL activity. Proc Natl Acad Sci USA. 1995;92:4462-4466.

64. Yang WS, Nevin DN, Iwasaki L, Peng R, Brown BG, Brunzell JD and Deeb SS. Regulatory mutations in the human lipoprotein lipase gene in patients with familial combined hyperlipidemia and coronary artery disease. J Lipid Res. 1996;37:2627-2637.

65. Reymer PW, Groenemeyer BE, Gagne E, Miao L, Appelman EE, Seidel JC, Kromhout D, Bijvoet SM, van de Oever K, Bruin T and et al. A frequently occurring mutation in the lipoprotein lipase gene (Asn291Ser) contributes to the expression of familial combined hyperlipidemia. Hum Mol Genet. 1995;4:1543-9.

66. Gagne E, Genest J, Jr., Zhang H, Clark LA and Hayden MR. Analysis of DNA changes in the LPL gene in patients with familial combined hyperlipidemia. Arterioscler Thromb. 1994;14:1250-1257.

67. Hoffer MJV, Bredie SJH, Boomsma D, Reymer PWA, Kastelein JJP, deKnijff P, Demacker PNM, Stalenhoef AFH, Havekes LM and Frants RR. The lipoprotein lipase (Asn291Ser) mutation is associated with elevated lipid levels in families with familial combined hyperlipidemia. Atherosclerosis. 1995;119:159-167.

68. Nevin DN, Brunzell JD and Deeb SS. The LPL gene in individuals with familial combined hyperlipidemia and decreased LPL activity. Arterioscler Thromb. 1994;14:869-873.

69. Nanni L, Quagliarini F, Megiorni F, Montali A, Minicocci I, Campagna F, Pizzuti A and Arca M. Genetic variants in adipose triglyceride lipase influence lipid levels in familial combined hyperlipidemia. Atherosclerosis. 2010;213:206-11.

70. Weissglas-Volkov D, Aguilar-Salinas CA, Sinsheimer JS, Riba L, Huertas-Vazquez A, Ordonez-Sanchez ML, Rodriguez-Guillen R, Cantor RM, Tusie-Luna T and Pajukanta P. Investigation of variants identified in caucasian genome-wide association studies for plasma high-density lipoprotein cholesterol and triglycerides levels in Mexican dyslipidemic study samples. Circ Cardiovasc Genet. 2010;3:31-8.

71. Ayyobi AF, McGladdery SH, McNeely MJ, Austin MA, Motulsky AG and Brunzell JD. Small, dense LDL and elevated apolipoprotein B are the common characteristics for the three major lipid phenotypes of familial combined hyperlipidemia. Arterioscler Thromb Vasc Biol. 2003;23:1289-94.

72. Sniderman A, Bailey SD and Engert JC. Familial combined hyperlipidaemia: how can genetic disorders be common, complex and comprehensible? Clin Sci (Lond). 2007;113:365-7.

73. Veerkamp MJ, de Graaf J, Hendriks JC, Demacker PN and Stalenhoef AF. Nomogram to diagnose familial combined hyperlipidemia on the basis of results of a 5-year follow-up study. Circulation. 2004;109:2980-5.

74. Zambon A, Brown BG, Deeb SS and Brunzell JD. Genetics of apolipoprotein B and apolipoprotein AI and premature coronary artery disease. J Intern Med. 2006;259:473-80.

75. Angelin B, Hershon KS and Brunzell JD. Bile acid metabolism in hereditary forms of hypertriglyceridemia: Evidence for an increased synthesis rate in monogenic familial hypertriglyceridemia. Proc Natl Acad Sci USA. 1987;84:5434-5438.

76. Hokanson JE and Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta- analysis of population-based prospective studies. J Cardiovasc Risk. 1996;3:213-9.

77. Hopkins PN, Heiss G, Ellison RC, Province MA, Pankow JS, Eckfeldt JH and Hunt SC. Coronary artery disease risk in familial combined hyperlipidemia and familial hypertriglyceridemia: a case-control comparison from the National Heart, Lung, and Blood Institute Family Heart Study. Circulation. 2003;108:519-23.

78. Chait A and Brunzell JD. Severe hypertriglyceridemia: Role of familial and acquired disorders. Metabolism. 1983;32:209-214.

79. Johansen CT, Wang J, Lanktree MB, McIntyre AD, Ban MR, Martins RA, Kennedy BA, Hassell RG, Visser ME, Schwartz SM, Voight BF, Elosua R, Salomaa V, O'Donnell CJ, Dallinga-Thie GM, Anand SS, Yusuf S, Huff MW, Kathiresan S, Cao H and Hegele RA. An increased burden of common and rare lipid-associated risk alleles contributes to the phenotypic spectrum of hypertriglyceridemia. Arterioscler Thromb Vasc Biol. 2011;31:1916-26.

80. Lewis GF, Xiao C and Hegele RA. Hypertriglyceridemia in the genomic era: a new paradigm. Endocr Rev. 2015;36:131-47.

81. Brunzell JD, Albers JJ, Chait A, Grundy SM, Groszek E and McDonald GB. Plasma lipoproteins in familial combined hyperlipidemia and monogenic familial hypertriglyceridemia. J Lipid Res. 1983;24:147-155.

82. Morganroth J, Levy RI and Fredrickson DS. The biochemical, clinical, and genetic features of type III hyperlipoproteinemia. Ann Intern Med. 1975;82:158-74.

83. Havel RJ and Kane JP. Primary dysbetalipoproteinemia: Predominancy of a specific apoprotein species in triglyceride-rich lipoproteins. Proc Natl Acad Sci USA. 1973;70:2015.

84. Mahley R and Rall S. Type III Hyperlipoproteinemia (Dysbetalipoproteinemia): The Role of Apolipoprotein E in Normal and Abnormal Lipoprotein Metabolism. In: C. Scriver, A. Beaudet, W. Sly and D. Valle, eds. The Metabolic & Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill; 2001(119): 2835-2862.

85. Siest G, Pillot T, Regis-Bailly A, Leininger-Muller B, Steinmetz J, Galteau MM and Visvikis S. Apolipoprotein E: an important gene and protein to follow in laboratory medicine. Clin Chem. 1995;41:1068-86.

86. Weisgraber KH, Rall SC, Jr. and Mahley RW. Human E apoprotein heterogeneity. Cysteine-arginine interchanges in the amino acid sequence of the apo-E isoforms. J Biol Chem. 1981;256:9077-83.

87. Smelt AH and de Beer F. Apolipoprotein E and familial dysbetalipoproteinemia: clinical, biochemical, and genetic aspects. Semin Vasc Med. 2004;4:249-57.

88. Mahley RW and Rall SC, Jr. Type III hyperlipoproteinemia (dysbetalipoproteinemia): The role of apolipoprotein E in normal and abnormal lipoprotein metabolism. In: C. R. Scriver, A. L. Beaudet, W. S. Sly and D. Valle, eds. The Metabolic Basis of Inherited Disease New York: McGraw-Hill; 1989: 1195.

89. Brummer D, Evans D, Berg D, Greten H, Beisiegel U and Mann WA. Expression of type III hyperlipoproteinemia in patients homozygous for apolipoprotein E-2 is modulated by lipoprotein lipase and postprandial hyperinsulinemia. J Mol Med (Berl). 1998;76:355-64.

90. Hopkins PN, Wu LL, Schumacher MC, Emi M, Hegele RM, Hunt SC, Lalouel JM and Williams RR. Type III dyslipoproteinemia in patients heterozygous for familial hypercholesterolemia and apolipoprotein E2. Evidence for a gene-gene interaction. Arterioscler Thromb. 1991;11:1137-46.

91. Feussner G and Ziegler R. Expression of type III hyperlipoproteinaemia in a subject with secondary hypothyroidism bearing the apolipoprotein E2/2 phenotype. J Intern Med. 1991;230:183-6.

92. Breslow JL, Zannis VI, SanGiacomo TR, Third JL, Tracy T and Glueck CJ. Studies of familial type III hyperlipoproteinemia using as a genetic marker the apoE phenotype E2/2. J Lipid Res. 1982;23:1224-35.

93. Chait A, Brunzell JD, Albers JJ and Hazzard WR. Type-III Hyperlipoproteinaemia ("remnant removal disease"). Insight into the pathogenetic mechanism. Lancet. 1977;1:1176-8.

94. Chait A, Hazzard WR, Albers JJ, Kushwaha RP and Brunzell JD. Impaired very low density lipoprotein and triglyceride removal in broad beta disease: comparison with endogenous hypertriglyceridemia. Metabolism. 1978;27:1055-66.

95. Dong LM, Innerarity TL, Arnold KS, Newhouse YM and Weisgraber KH. The carboxyl terminus in apolipoprotein E2 and the seven amino acid repeat in apolipoprotein E-Leiden: role in receptor-binding activity. J Lipid Res. 1998;39:1173-80.

96. Mahley RW, Huang Y and Rall SC, Jr. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia). Questions, quandaries, and paradoxes. J Lipid Res. 1999;40:1933-49.

97. Albers JJ, Warnick GR and Hazzard WR. Type III hyperlipoproteinemia: a comparative study of current diagnostic techniques. Clin Chim Acta. 1977;75:193-204.

98. Garg A. Clinical review#: Lipodystrophies: genetic and acquired body fat disorders. J Clin Endocrinol Metab. 2011;96:3313-25.

99. Simha V and Garg A. Inherited lipodystrophies and hypertriglyceridemia. Curr Opin Lipidol. 2009;20:300-8.

100. Agarwal AK and Garg A. A novel heterozygous mutation in peroxisome proliferator-activated receptor-gamma gene in a patient with familial partial lipodystrophy. J Clin Endocrinol Metab. 2002;87:408-11.

101. Garg A. Gender differences in the prevalence of metabolic complications in familial partial lipodystrophy (Dunnigan variety). J Clin Endocrinol Metab. 2000;85:1776-82.

102. Herbst KL, Tannock LR, Deeb SS, Purnell JQ, Brunzell JD and Chait A. Kobberling type of familial partial lipodystrophy: an underrecognized syndrome. Diabetes Care. 2003;26:1819-24.

103. Jacob KN, Baptista F, dos Santos HG, Oshima J, Agarwal AK and Garg A. Phenotypic heterogeneity in body fat distribution in patients with atypical Werner's syndrome due to heterozygous Arg133Leu lamin A/C mutation. J Clin Endocrinol Metab. 2005;90:6699-706.

104. Garg A, Subramanyam L, Agarwal AK, Simha V, Levine B, D'Apice MR, Novelli G and Crow Y. Atypical progeroid syndrome due to heterozygous missense LMNA mutations. J Clin Endocrinol Metab. 2009;94:4971-83.

105. Calvo M and Martinez E. Update on metabolic issues in HIV patients. Curr Opin HIV AIDS. 2014;9:332-9.

106. Eckel RH, Alberti KG, Grundy SM and Zimmet PZ. The metabolic syndrome. Lancet. 2010;375:181-3.

107. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A and Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation. 2004;109:42-6.

108. Sutherland JP, McKinley B and Eckel RH. The metabolic syndrome and inflammation. Metab Syndr Relat Disord. 2004;2:82-104.

109. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr., International Diabetes Federation Task Force on E, Prevention, Hational Heart L, Blood I, American Heart A, World Heart F, International Atherosclerosis S and International Association for the Study of O. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640-5.

110. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Almeras N, Bergeron J, Gaudet D, Tremblay G, Prud'homme D, Nadeau A and Despres JP. Hypertriglyceridemic waist: A marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? Circulation. 2000;102:179-84.

111. Choi SH and Ginsberg HN. Increased very low density lipoprotein (VLDL) secretion, hepatic steatosis, and insulin resistance. Trends Endocrinol Metab. 2011;22:353-63.

112. Ginsberg HN, Zhang YL and Hernandez-Ono A. Regulation of plasma triglycerides in insulin resistance and diabetes. Archives of medical research. 2005;36:232-40.

113. Adiels M, Westerbacka J, Soro-Paavonen A, Hakkinen AM, Vehkavaara S, Caslake MJ, Packard C, Olofsson SO, Yki-Jarvinen H, Taskinen MR and Boren J. Acute suppression of VLDL1 secretion rate by insulin is associated with hepatic fat content and insulin resistance. Diabetologia. 2007;50:2356-65.

114. Brunzell JD, Porte D, Jr. and Bierman EL. Abnormal lipoprotein lipase mediated plasma triglyceride removal in untreated diabetes mellitus associated with hypertriglyceridemia. Metabolism. 1979;28:897-903.

115. Ruderman NB, Schneider SH and Berchtold P. The "metabolically-obese," normal-weight individual. Am J Clin Nutr. 1981;34:1617-21.

116. Phillips CM. Metabolically healthy obesity: definitions, determinants and clinical implications. Rev Endocr Metab Disord. 2013;14:219-27.

117. Hamer M and Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J Clin Endocrinol Metab. 2012;97:2482-8.

118. Chahil TJ and Ginsberg HN. Diabetic dyslipidemia. Endocrinol Metab Clin North Am. 2006;35:491-510, vii-viii.

119. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H and Eckel RH. The metabolic syndrome. Endocr Rev. 2008;29:777-822.

120. Chait A. Secondary hyperlipidemia. J Clin Pathol. 1973;26:68-71.

121. Chait A and Brunzell JD. Acquired hyperlipidemia (secondary dyslipoproteinemia). Endocrinol Metab Clin North Am. 1990;19:259-278.

122. Fredrickson D, Levy R and Lees R. Fat transport and lipoproteins - an integrated approach to mechanisms and disorders. N Engl J Med. 1967;276:32,94,148,215,273.

123. Brunzell JD and Bierman EL. Chylomicronemia syndrome. Interaction of genetic and acquired hypertriglyceridemia. Med Clin North Am. 1982;66:455-468.

124. Chait A, Robertson HT and Brunzell JD. Chylomicronemia syndrome in diabetes mellitus. Diabetes Care. 1981;4:343-348.

125. Brahm AJ and Hegele RA. Chylomicronaemia-current diagnosis and future therapies. Nat Rev Endocrinol. 2015.

126. Brunzell J and Deeb S. Familial lipoprotein lipase deficiency, apo CII deficiency, and hepatic lipase deficiency. In: C. Scriver, A. Beaudet, W. Sly and D. Vale, eds. The Metabolic and Molecular Basis of Inherited Disease. 8th ed. New York: McGraw-Hill Book Co.; 2001(II): 2789-2816.

127. Rahalkar AR, Giffen F, Har B, Ho J, Morrison KM, Hill J, Wang J, Hegele RA and Joy T. Novel LPL mutations associated with lipoprotein lipase deficiency: two case reports and a literature review. Can J Physiol Pharmacol. 2009;87:151-60.

128. Peterson J, Ayyobi AF, Ma Y, Henderson H, Reina M, Deeb SS, Santamarina-Fojo S, Hayden MR and Brunzell JD. Structural and functional consequences of missense mutations in exon 5 of the lipoprotein lipase gene. J Lipid Res. 2002;43:398-406.

129. Nickerson DA, Taylor SL, Weiss KM, Clark AG, Hutchinson RG, Stengard J, Salomaa V, Vartiainen E, Boerwinkle E and Sing CF. DNA sequence diversity in a 9.7-kb region of the human lipoprotein lipase gene. Nat Genet. 1998;19:233-40.

130. Surendran RP, Visser ME, Heemelaar S, Wang J, Peter J, Defesche JC, Kuivenhoven JA, Hosseini M, Peterfy M, Kastelein JJ, Johansen CT, Hegele RA, Stroes ES and Dallinga-Thie GM. Mutations in LPL,

APOC2, APOA5, GPIHBP1 and LMF1 in patients with severe hypertriglyceridaemia. J Intern Med. 2012;272:185-96.

131. Calandra S, Priore Oliva C, Tarugi P and Bertolini S. APOA5 and triglyceride metabolism, lesson from human APOA5 deficiency. Curr Opin Lipidol. 2006;17:122-7.

132. Peterfy M. Lipase maturation factor 1: a lipase chaperone involved in lipid metabolism. Biochim Biophys Acta. 2012;1821:790-4.

133. Brunzell JD and Schrott HG. The interaction of familial and secondary causes of hypertriglyceridemia: Role in pancreatitis. Trans Assoc Am Physicians. 1973;86:245-254.

134. Brunzell JD and Schrott HG. The interaction of familial and secondary causes of hypertriglyceridemia: role in pancreatitis. J Clin Lipidol. 2012;6:409-12.

135. Parsons SK, Skapek SX, Neufeld EJ, Kuhlman C, Young ML, Donnelly M, Brunzell JD, Otvos JD, Sallan SE and Rifai N. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Blood. 1997;89:1886-95.

136. Tozuka M, Yamauchi K, Hidaka H, Nakabayashi T, Okumura N and Katsuyama T. Characterization of hypertriglyceridemia induced by L-asparaginase therapy for acute lymphoblastic leukemia and malignant lymphoma. Ann Clin Lab Sci. 1997;27:351-7.

137. Yadav D and Pitchumoni CS. Issues in hyperlipidemic pancreatitis. Journal of clinical gastroenterology. 2003;36:54-62.

138. Strickland LR, Guo F, Lok K and Garvey WT. Type 2 diabetes with partial lipodystrophy of the limbs: a new lipodystrophy phenotype. Diabetes Care. 2013;36:2247-53.

139. Johansen CT and Hegele RA. Allelic and phenotypic spectrum of plasma triglycerides. Biochim Biophys Acta. 2012;1821:833-42.

140. Rosenthal E RJ, Cosslin DR, Burt A, Brunzell JD, Motulsky AG, Nickerson DA Wijsman EM, Jarvik GP. Exome Sequencing Project NHLBI GO ESP. Joint linkage and association analysis with exome sequence data implicates SLC25A40 in hypertriglyceridemia. . Am J Hum Genet 2014:In press.

141. Castelli WP. The triglyceride issue: a view from Framingham. Am Heart J. 1986;112:432-7.

142. Harchaoui KE, Visser ME, Kastelein JJ, Stroes ES and Dallinga-Thie GM. Triglycerides and cardiovascular risk. Curr Cardiol Rev. 2009;5:216-22.

143. Langsted A, Freiberg JJ, Tybjaerg-Hansen A, Schnohr P, Jensen GB and Nordestgaard BG. Nonfasting cholesterol and triglycerides and association with risk of myocardial infarction and total mortality: the Copenhagen City Heart Study with 31 years of follow-up. J Intern Med. 2011;270:65-75.

144. Nordestgaard BG and Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384:626-35.

145. Zilversmit DB. Atherogenesis: A postprandial phenomenon. Circulation. 1979;60:473-485.

146. Zilversmit DB. Atherogenic nature of triglycerides, postprandial lipidemia, and triglyceride-rich remnant lipoproteins. Clin Chem. 1995;41:153-8.

147. Nordestgaard BG and Zilversmit DB. Large lipoproteins are excluded from the arterial wall in diabetic cholesterol-fed rabbits. J Lipid Res. 1988;29:1491-500.

148. Nordestgaard BG, Stender S and Kjeldsen K. Reduced atherogenesis in cholesterol-fed diabetic rabbits. Giant lipoproteins do not enter the arterial wall. Arteriosclerosis. 1988;8:421-8.

149. Williams KJ and Tabas I. The response-to-retention hypothesis of early atherogenesis. Arterioscler Thromb Vasc Biol. 1995;15:551-561.

150. Williams KJ and Tabas I. The response-to-retention hypothesis of atherogenesis reinforced. Curr Opin Lipidol. 1998;9:471-4.

151. Krauss RM. Dense low density lipoproteins and coronary artery disease. Am J Cardiol. 1995;75:53B-57B.

152. Olin-Lewis K, Krauss RM, La Belle M, Blanche PJ, Barrett PH, Wight TN and Chait A. ApoC-III content of apoB-containing lipoproteins is associated with binding to the vascular proteoglycan biglycan. J Lipid Res. 2002;43:1969-77.

153. Chait A, Brazg RL, Tribble DL and Krauss RM. Susceptibility of small, dense low density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. Am J Med. 1993;94:350-356.

154. Tribble DL, van den Berg J, Motchnik PA, Ames BN, Lewis DM, Chait A and Krauss RM. Oxidative susceptibility of LDL density subfractions is related to their ubiquinol-10 and à-tocopherol content. Proc Natl Acad Sci USA. 1994;91:1183-1187.

155. Rosenson RS, Davidson MH, Hirsh BJ, Kathiresan S and Gaudet D. Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2014;64:2525-40.

156. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkila K, Hypponen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikainen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Muller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Doring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimaki T, Lin SY, Lindstrom J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Muller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancakova A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N,

Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrieres J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Jarvelin MR, Jula A, Kahonen M, Kaprio J, Kesaniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, Marz W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Altshuler D, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Mohlke KL, Ingelsson E, Abecasis GR, Daly MJ, Neale BM and Kathiresan S. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat Genet. 2013;45:1345-52.

157. Waterworth DM, Ricketts SL, Song K, Chen L, Zhao JH, Ripatti S, Aulchenko YS, Zhang W, Yuan X, Lim N, Luan J, Ashford S, Wheeler E, Young EH, Hadley D, Thompson JR, Braund PS, Johnson T, Struchalin M, Surakka I, Luben R, Khaw KT, Rodwell SA, Loos RJ, Boekholdt SM, Inouye M, Deloukas P, Elliott P, Schlessinger D, Sanna S, Scuteri A, Jackson A, Mohlke KL, Tuomilehto J, Roberts R, Stewart A, Kesaniemi YA, Mahley RW, Grundy SM, Wellcome Trust Case Control C, McArdle W, Cardon L, Waeber G, Vollenweider P, Chambers JC, Boehnke M, Abecasis GR, Salomaa V, Jarvelin MR, Ruokonen A, Barroso I, Epstein SE, Hakonarson HH, Rader DJ, Reilly MP, Witteman JC, Hall AS, Samani NJ, Strachan DP, Barter P, van Duijn CM, Kooner JS, Peltonen L, Wareham NJ, McPherson R, Mooser V and Sandhu MS. Genetic variants influencing circulating lipid levels and risk of coronary artery disease. Arterioscler Thromb Vasc Biol. 2010;30:2264-76.

158. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA, Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, Konig IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Doring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL,

Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA, Jr., Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M and Kathiresan S. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010;466:707-13.

159. Rip J, Nierman MC, Ross CJ, Jukema JW, Hayden MR, Kastelein JJ, Stroes ES and Kuivenhoven JA. Lipoprotein lipase S447X: a naturally occurring gain-of-function mutation. Arterioscler Thromb Vasc Biol. 2006;26:1236-45.

160. Pimstone SN, Gagne SE, Gagne C, Lupien PJ, Gaudet D, Williams RR, Kotze M, Reymer PW, Defesche JC, Kastelein JJ and et al. Mutations in the gene for lipoprotein lipase. A cause for low HDL cholesterol levels in individuals heterozygous for familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 1995;15:1704-12.

161. Burkhardt R, Toh SA, Lagor WR, Birkeland A, Levin M, Li X, Robblee M, Fedorov VD, Yamamoto M, Satoh T, Akira S, Kathiresan S, Breslow JL and Rader DJ. Trib1 is a lipid- and myocardial infarction-associated gene that regulates hepatic lipogenesis and VLDL production in mice. J Clin Invest. 2010;120:4410-4.

162. Douvris A, Soubeyrand S, Naing T, Martinuk A, Nikpay M, Williams A, Buick J, Yauk C and McPherson R. Functional analysis of the TRIB1 associated locus linked to plasma triglycerides and coronary artery disease. J Am Heart Assoc. 2014;3:e000884.

163. Tg, Hdl Working Group of the Exome Sequencing Project NHL, Blood I, Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, Lu Y, Tang ZZ, Zhang H, Hindy G, Masca N, Stirrups K, Kanoni S, Do R, Jun G, Hu Y, Kang HM, Xue C, Goel A, Farrall M, Duga S, Merlini PA, Asselta R, Girelli D, Olivieri O, Martinelli N, Yin W, Reilly D, Speliotes E, Fox CS, Hveem K, Holmen OL, Nikpay M, Farlow DN, Assimes TL, Franceschini N, Robinson J, North KE, Martin LW, DePristo M, Gupta N, Escher SA, Jansson JH, Van Zuydam N, Palmer CN, Wareham N, Koch W, Meitinger T, Peters A, Lieb W, Erbel R, Konig IR, Kruppa J, Degenhardt F, Gottesman O, Bottinger EP, O'Donnell CJ, Psaty BM, Ballantyne CM, Abecasis G, Ordovas JM, Melander O, Watkins H, Orho-Melander M, Ardissino D, Loos RJ, McPherson R, Willer CJ, Erdmann J, Hall AS, Samani NJ, Deloukas P, Schunkert H, Wilson JG, Kooperberg C, Rich SS, Tracy RP, Lin DY, Altshuler D, Gabriel S, Nickerson DA, Jarvik GP, Cupples LA, Reiner AP, Boerwinkle E and Kathiresan S. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med. 2014;371:22-31.

164. Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG and Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. N Engl J Med. 2014;371:32-41.

165. Soufi M, Sattler AM, Kurt B and Schaefer JR. Mutation screening of the APOA5 gene in subjects with coronary artery disease. J Investig Med. 2012;60:1015-9.

166. Do R, Stitziel NO, Won HH, Jorgensen AB, Duga S, Angelica Merlini P, Kiezun A, Farrall M, Goel A, Zuk O, Guella I, Asselta R, Lange LA, Peloso GM, Auer PL, Project NES, Girelli D, Martinelli N, Farlow DN, DePristo MA, Roberts R, Stewart AF, Saleheen D, Danesh J, Epstein SE, Sivapalaratnam S, Hovingh GK, Kastelein JJ, Samani NJ, Schunkert H, Erdmann J, Shah SH, Kraus WE, Davies R, Nikpay M, Johansen CT,

Wang J, Hegele RA, Hechter E, Marz W, Kleber ME, Huang J, Johnson AD, Li M, Burke GL, Gross M, Liu Y, Assimes TL, Heiss G, Lange EM, Folsom AR, Taylor HA, Olivieri O, Hamsten A, Clarke R, Reilly DF, Yin W, Rivas MA, Donnelly P, Rossouw JE, Psaty BM, Herrington DM, Wilson JG, Rich SS, Bamshad MJ, Tracy RP, Cupples LA, Rader DJ, Reilly MP, Spertus JA, Cresci S, Hartiala J, Tang WH, Hazen SL, Allayee H, Reiner AP, Carlson CS, Kooperberg C, Jackson RD, Boerwinkle E, Lander ES, Schwartz SM, Siscovick DS, McPherson R, Tybjaerg-Hansen A, Abecasis GR, Watkins H, Nickerson DA, Ardissino D, Sunyaev SR, O'Donnell CJ, Altshuler D, Gabriel S and Kathiresan S. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. Nature. 2015;518:102-6.

167. Yki-Jarvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol. 2014;2:901-10.

168. Targher G, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G and Arcaro G. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. Diabetes Care. 2007;30:2119-21.

169. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C and Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2007;30:1212-8.

170. Khurram M and Ashraf MM. A clinical and biochemical profile of biopsy-proven non-alcoholic Fatty liver disease subjects. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2007;17:531-4.

171. Luyckx FH, Lefebvre PJ and Scheen AJ. Non-alcoholic steatohepatitis: association with obesity and insulin resistance, and influence of weight loss. Diabetes & Metabolism. 2000;26:98-106.

172. Utzschneider KM and Kahn SE. Review: The role of insulin resistance in nonalcoholic fatty liver disease. J Clin Endocrinol Metab. 2006;91:4753-61.

173. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G and Melchionda N. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001;50:1844-50.

174. Ulitsky A, Ananthakrishnan AN, Komorowski R, Wallace J, Surapaneni SN, Franco J, Saeian K and Gawrieh S. A noninvasive clinical scoring model predicts risk of nonalcoholic steatohepatitis in morbidly obese patients. Obesity surgery. 2010;20:685-91.

175. Samuel VT, Liu ZX, Qu X, Elder BD, Bilz S, Befroy D, Romanelli AJ and Shulman GI. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. J Biol Chem. 2004;279:32345-53.

176. Perry RJ, Samuel VT, Petersen KF and Shulman GI. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. Nature. 2014;510:84-91.

177. Mirtallo JM, Dasta JF, Kleinschmidt KC and Varon J. State of the art review: Intravenous fat emulsions: Current applications, safety profile, and clinical implications. The Annals of pharmacotherapy. 2010;44:688-700.

178. Devaud JC, Berger MM, Pannatier A, Marques-Vidal P, Tappy L, Rodondi N, Chiolero R and Voirol P. Hypertriglyceridemia: a potential side effect of propofol sedation in critical illness. Intensive Care Med. 2012;38:1990-8.

179. Goldberg AS and Hegele RA. Severe hypertriglyceridemia in pregnancy. J Clin Endocrinol Metab. 2012;97:2589-96.

180. Brunzell JD DS. Familial lipoprotein lipase deficiency, apo CII deficiency and hepatic lipase deficiency. The Metabolic and Molecular Basis of Inherited Disease, 8th edition New York: McGraw-Hill Book Co.; 2001: 2789-2816.

181. Tremblay K, Methot J, Brisson D and Gaudet D. Etiology and risk of lactescent plasma and severe hypertriglyceridemia. J Clin Lipidol. 2011;5:37-44.

182. Lloret Linares C, Pelletier AL, Czernichow S, Vergnaud AC, Bonnefont-Rousselot D, Levy P, Ruszniewski P and Bruckert E. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. Pancreas. 2008;37:13-2.

183. Cameron JL, Capuzzi DM, Zuidema GD and Margolis S. Acute pancreatitis with hyperlipidemia: The incidence of lipid abnormalities in acute pancreatitis. Ann Surg. 1973;177:483-489.

184. Farmer RG, Winkelman EI, Brown HB and Lewis LA. Hyperlipoproteinemia and pancreatitis. Am J Med. 1973;54:161-165.

185. Durrington P. Dyslipidaemia. Lancet. 2003;362:717-31.

186. Havel RJ. Pathogenesis, differentiation and management of hypertriglyceridemia. Adv Intern Med. 1969;15:117-54.

187. Saharia P, Margolis S, Zuidema GD and Cameron JL. Acute pancreatitis with hyperlipemia: studies with an isolated perfused canine pancreas. Surgery. 1977;82:60-7.

188. Seplowitz AH, Chien S and Smith FR. Effects of lipoproteins on plasma viscosity. Atherosclerosis. 1981;38:89-95.

189. Chang YT, Chang MC, Su TC, Liang PC, Su YN, Kuo CH, Wei SC and Wong JM. Association of cystic fibrosis transmembrane conductance regulator (CFTR) mutation/variant/haplotype and tumor necrosis factor (TNF) promoter polymorphism in hyperlipidemic pancreatitis. Clin Chem. 2008;54:131-8.

190. Ivanova R, Puerta S, Garrido A, Cueto I, Ferro A, Ariza MJ, Cobos A, Gonzalez-Santos P and Valdivielso P. Triglyceride levels and apolipoprotein E polymorphism in patients with acute pancreatitis. Hepatobiliary Pancreat Dis Int. 2012;11:96-101.

191. Parker F, Bagdade JD, Odland GF and Bierman EL. Evidence for the chylomicron origin of lipids accumulating in diabetic eruptive xanthomas: A correlative lipid biochemical, histochemical and electron microscopic study. J Clin Invest. 1970;49:2172-2187.

192. Rosenson RS, Shott S, Lu L and Tangney CC. Hypertriglyceridemia and other factors associated with plasma viscosity. Am J Med. 2001;110:488-92.

193. Inokuchi R, Matsumoto A, Azihara R, Sato H, Kumada Y, Yokoyama H, Okada M, Ishida T, Nakamura K, Nakajima S, Yahagi N and Shinohara K. Hypertriglyceridemia as a possible cause of coma: a case report. J Med Case Rep. 2012;6:412.

194. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383-1389.

195. Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, Fava JL and Wing RR. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology. 2010;51:121-9.

196. Musso G, Cassader M, Rosina F and Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia. 2012;55:885-904.

197. Zelber-Sagi S, Kessler A, Brazowsky E, Webb M, Lurie Y, Santo M, Leshno M, Blendis L, Halpern Z and Oren R. A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2006;4:639-44.

198. Harrison SA, Fecht W, Brunt EM and Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. Hepatology. 2009;49:80-6.

199. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR and Nash CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362:1675-85.

200. Miller ER, 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ and Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142:37-46.

201. Nelson A, Torres DM, Morgan AE, Fincke C and Harrison SA. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis: A randomized placebo-controlled trial. Journal of clinical gastroenterology. 2009;43:990-4.

202. Loomba R, Sirlin CB, Ang B, Bettencourt R, Jain R, Salotti J, Soaft L, Hooker J, Kono Y, Bhatt A, Hernandez L, Nguyen P, Noureddin M, Haufe W, Hooker C, Yin M, Ehman R, Lin GY, Valasek MA, Brenner DA, Richards L and San Diego Integrated NRC. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). Hepatology. 2015;61:1239-50.

203. Rouis M, Dugi KA, Previato L, Patterson AP, Brunzell JD, Brewer HB and Santamarina-Fojo S. Therapeutic response to medium-chain triglycerides and omega-3 fatty acids in a patient with the familial chylomicronemia syndrome. Arterioscler Thromb Vasc Biol. 1997;17:1400-6.

204. Brunzell JD. Familial Lipoprotein Lipase Deficiency. GeneReviews at GeneTests: Medical Genetics Information Resource. 2011:1997-2010.

205. Tsai EC, Brown JA, Veldee MY, Anderson GJ, Chait A and Brunzell JD. Potential of essential fatty acid deficiency with extremely low fat diet in lipoprotein lipase deficiency during pregnancy: A case report. BMC pregnancy and childbirth. 2004;4:27.

206. Al-Shali K, Wang J, Fellows F, Huff MW, Wolfe BM and Hegele RA. Successful pregnancy outcome in a patient with severe chylomicronemia due to compound heterozygosity for mutant lipoprotein lipase. Clin Biochem. 2002;35:125-30.

207. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. Int J Obes (Lond). 2015.

208. Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, Sarode R, Schwartz J, Weinstein R, Shaz BH and Apheresis Applications Committee of the American Society for A. Guidelines on the use of therapeutic apheresis in clinical practice--evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. 2010;25:83-177.

209. Stefanutti C and Julius U. Treatment of primary hypertriglyceridemia states - General approach and the role of extracorporeal methods. Atheroscler Suppl. 2015;18:85-94.

210. Furuya T, Komatsu M, Takahashi K, Hashimoto N, Hashizume T, Wajima N, Kubota M, Itoh S, Soeno T, Suzuki K, Enzan K and Matsuo S. Plasma exchange for hypertriglyceridemic acute necrotizing pancreatitis: report of two cases. Ther Apher. 2002;6:454-8.

211. Whayne TF, Jr. and Felts JM. Activation of lipoprotein lipase. Effects of rat serum lipoprotein fractions and heparin. Circ Res. 1970;27:941-51.

212. Whayne TF, Jr. Concerns about heparin therapy for hypertriglyceridemia. Arch Intern Med. 2010;170:108-9; author reply 109.

213. Goldberg IJ. Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. J Lipid Res. 1996;37:693-707.

214. Wierzbicki AS, Reynolds TM and Crook MA. Usefulness of Orlistat in the treatment of severe hypertriglyceridemia. Am J Cardiol. 2002;89:229-31.

215. Tolentino MC, Ferenczi A, Ronen L and Poretsky L. Combination of gemfibrozil and orlistat for treatment of combined hyperlipidemia with predominant hypertriglyceridemia. Endocr Pract. 2002;8:208-12.

216. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM and Investigators I-I. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015.

217. Gaudet D, Methot J, Dery S, Brisson D, Essiembre C, Tremblay G, Tremblay K, de Wal J, Twisk J, van den Bulk N, Sier-Ferreira V and van Deventer S. Efficacy and long-term safety of alipogene tiparvovec (AAV1-LPLS447X) gene therapy for lipoprotein lipase deficiency: an open-label trial. Gene Ther. 2013;20:361-9.

218. Carpentier AC, Frisch F, Labbe SM, Gagnon R, de Wal J, Greentree S, Petry H, Twisk J, Brisson D and Gaudet D. Effect of alipogene tiparvovec (AAV1-LPL(S447X)) on postprandial chylomicron metabolism in lipoprotein lipase-deficient patients. J Clin Endocrinol Metab. 2012;97:1635-44.

219. Gaudet D, Brisson D, Tremblay K, Alexander VJ, Singleton W, Hughes SG, Geary RS, Baker BF, Graham MJ, Crooke RM and Witztum JL. Targeting APOC3 in the familial chylomicronemia syndrome. N Engl J Med. 2014;371:2200-6.

220. Sehgal A, Vaishnaw A and Fitzgerald K. Liver as a target for oligonucleotide therapeutics. J Hepatol. 2013;59:1354-9.

221. Rader DJ and Kastelein JJ. Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. Circulation. 2014;129:1022-32.

222. Meyers CD, Tremblay K, Amer A, Chen J, Jiang L and Gaudet D. Effect of the DGAT1 inhibitor pradigastat on triglyceride and apoB48 levels in patients with familial chylomicronemia syndrome. Lipids in health and disease. 2015;14:8.

223. Kim MO, Lee S, Choi K, Lee S, Kim H, Kang H, Choi M, Kwon EB, Kang MJ, Kim S, Lee HJ, Lee HS, Kwak YS and Cho S. Discovery of a novel class of diacylglycerol acyltransferase 2 inhibitors with a 1H-pyrrolo[2,3-b]pyridine core. Biol Pharm Bull. 2014;37:1655-60.