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THE CHYLOMICRONEMIA SYNDROME: AN UNCOMMON BUT POTENTIALLY LETHAL FORM OF HYPERTRIGLYCERIDEMIA

MEDICAL GRAND ROUNDS

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I. Introduction

The Chylomicronemia Syndrome is characterized by bouts of abdominal pain or pancreatitis, and one or more of the following: eruptive xanthomas, lipemia retinalis, memory loss or dementia, peripheral neuropathy and paresthesias (1). A patient should be considered at risk for developing this syndrome when the plasma triglyceride level approaches 1000 mg/dl, and especially when the triglyceride level approaches or exceeds 2000 mg/dl. This degree of hypertriglyceridemia is caused by an accumulation of chylomicron particles in the plasma, but very low density lipoproteins may also accumulate and contribute to the hypertriglyceridemia.

The Chylomicronemia Syndrome has several etiologies which vary from uncommon to rare. In this discussion, the various etiologies of the Chylomicronemia Syndrome will be described and a general approach to the treatment of patients with this syndrome will be outlined. It is important to be aware of the syndrome because the pancreatitis is often especially severe, and in some series produced a 15-20% mortality (2).

Selected Case #1:

A 59-year-old female was referred for evaluation of hypertriglyceridemia of 4000-5000 mg/dl. The problem was detected 4 years earlier during an evaluation for dizziness. The hypertriglyceridemia failed to respond to Mevacor 40 mg/day and Lopid 1200 mg/day given separately but in conjunction with a low cholesterol, low fat AHA diet. The dizzy spells persisted and the physician felt she had several episodes of cerebrovascular insufficiency which were not well defined. She denied abdominal pain or a skin rash. Her weight was 168 pounds and she was 65 inches tall. Her medications included Dyazide 1 capsule daily, Gemfibrozil 600 mg bid, Lovastatin 20 mg bid, and Premarin 2.5 mg daily which she took since age 47 when she had a hysterectomy. Presenting lipid levels included total cholesterol 669 mg/dl, triglyceride 4600 mg/dl, HDL 21 mg/dl, LDL 13 mg/dl, VLDL cholesterol 635 mg/dl. Her other blood chemistries were normal. Initial treatment was a reduction of the Premarin dose to 0.625 mg/day (the patient refused to stop this medication). Two months later, her total cholesterol was 193 mg/dl, triglycerides 464 mg/dl, HDL 45 mg/dl, LDL 55 mg/dl. After reducing the Premarin dose to 0.3 mg/day, her total cholesterol was 179 mg/dl, triglycerides 309 mg/dl, HDL 47 mg/dl, LDL 54 mg/dl. She continued Gemfibrozil therapy but the Lovastatin was discontinued. She is following her diet but has not lost weight. She denies any alcohol consumption.

Selected Case #2:

A 30 year old female in the 36th week of pregnancy presented to the emergency room with abdominal pain. She was admitted with the diagnosis of premature labor. After several hours of unremitting pain, fetal distress was detected and a cesarean section was performed. A premature but otherwise healthy child was delivered. During surgery, the blood in the wound had a light appearance and a venous sample was obtained from the mother intraoperatively. Severe lipemia was noted and serum

triglycerides were 10,000 mg/dl. The clinical diagnosis of hemorrhagic pancreatitis was made and the patient survived after a prolonged post-operative course. Of note, she had no prior history of hyperlipidemia and had two prior uneventful pregnancies. A laboratory specimen drawn in the second trimester of this third pregnancy was noted to be lipemic but this clue to the syndrome went unnoticed.

Typically, the Chylomicronemia Syndrome is not detected until pancreatitis occurs and factors aggravating hypertriglyceridemia are often overlooked in the management of these patients.

II. Triglyceride Metabolism in Plasma (3)

Triglycerides are transported in plasma primarily as chylomicrons and very low density lipoprotein particles. The chemical composition of the lipoprotein particles is shown in table 1.

Table 1: Characteristics of Major Lipoproteins Found in Human Plasma

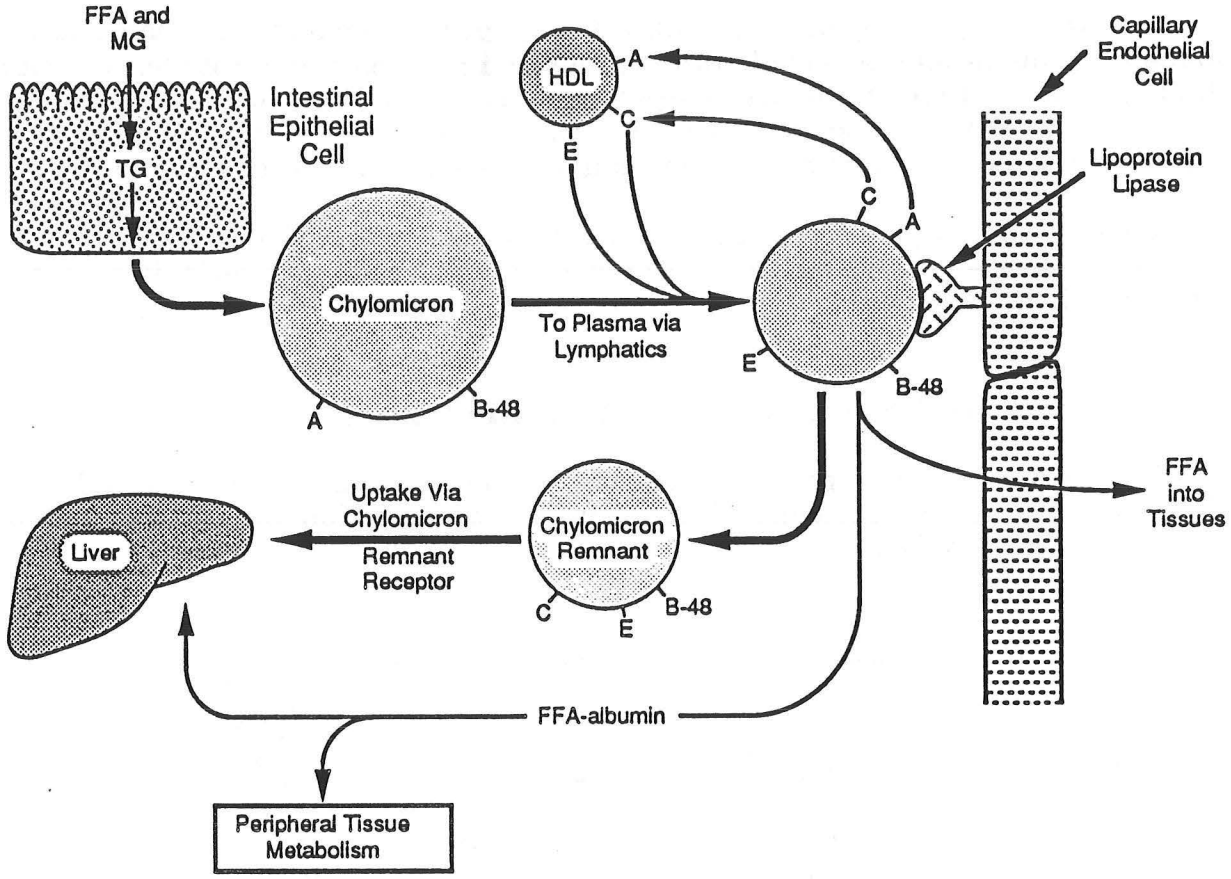
Lipoprotein	Density Range (g/ml)	Particle Size (nm)	Electrophoretic Mobility	Chemical Composition (% of dry mass)				
				Protein	*Triglycerides*	*Cholesteryl Esters*	*Cholesterol*	*Phospholipids*
Chylomicrons	0.93	75-1200	Remains at origin	2	86	3	2	7
VLDLs	0.93-1.006	30-80	pre-β	8	55	12	7	18
IDLs	1.006-1.019	25-35	slow pre-β	19	24	29	9	19
LDLs	1.019-1.063	18-25	β	22	6	42	8	22
HDL_2	1.063-1.125	9-12	α	40	5	17	5	33
HDL_3	1.125-1.210	5-9	α	55	3	13	4	25
Lp(a)*	1.050-1.120	25	pre-β	33	3	33	9	22

* Lp(a) is also termed "sinking pre-β lipoprotein". It is usually a minor lipoprotein but can reach substantial concentrations in some cases. The concentration is directly correlated with risk for atherosclerotic heart disease. The apoprotein in Lp(a) is B-100 linked by disulfide bonds to a plasminogen-like protein.

Fatty acids are obtained from dietary sources and by biosynthesis from intermediate molecules derived from the catabolism of sugars, certain amino acids and other fatty acids. For transport through plasma and lymph, they are converted to triglycerides (triacylglycerols) which become the major core lipids of chylomicrons and VLDL.

Chylomicrons are synthesized in intestinal epithelial cells in response to the ingestion of dietary fat (Figure 1). The longer chain fatty acids (those with >12-14 carbons) are converted to triglyceride for incorporation into chylomicrons while the shorter chain fatty acids are absorbed directly into the portal circulation. In the intestinal epithelial cells, the longer chain fatty acids are re-esterified to triglycerides which then combine with apoB-48, apoAI and apoAII for secretion into the lymph as chylomicrons. Cholesterol absorbed from the intestinal lumen is also incorporated into chylomicrons; although it contributes only 5% to the mass of the particle (Table 1), chylomicrons represent the major route by which dietary cholesterol is taken into

Figure 1. Chylomicron Metabolism in Plasma



the body. Freshly secreted chylomicrons contain primarily apoB-48, apoAI and ApoAII but as they traverse the lymphatics and enter plasma, they acquire CI, CII, CIII, and E by simple exchange, primarily from HDLs. As chylomicrons enter capillaries, they attach to lipoprotein lipase anchored to capillary endothelial cells (figure 2) (4). Lipoprotein lipase is activated by CII on the chylomicron surface to hydrolyze the core triglyceride to Free Fatty Acids (FFA) which are taken into tissues for oxidation (e.g. muscle) or storage for future use (e.g. adipose tissue). Some of the

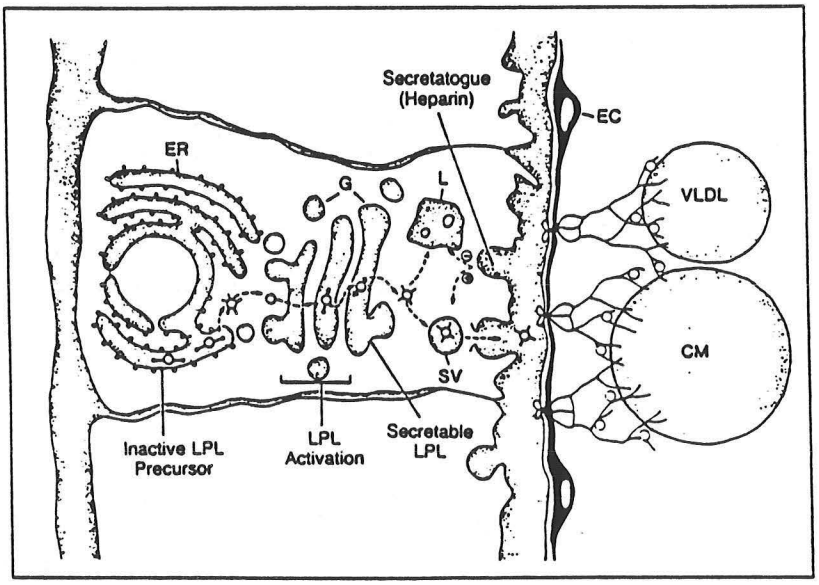
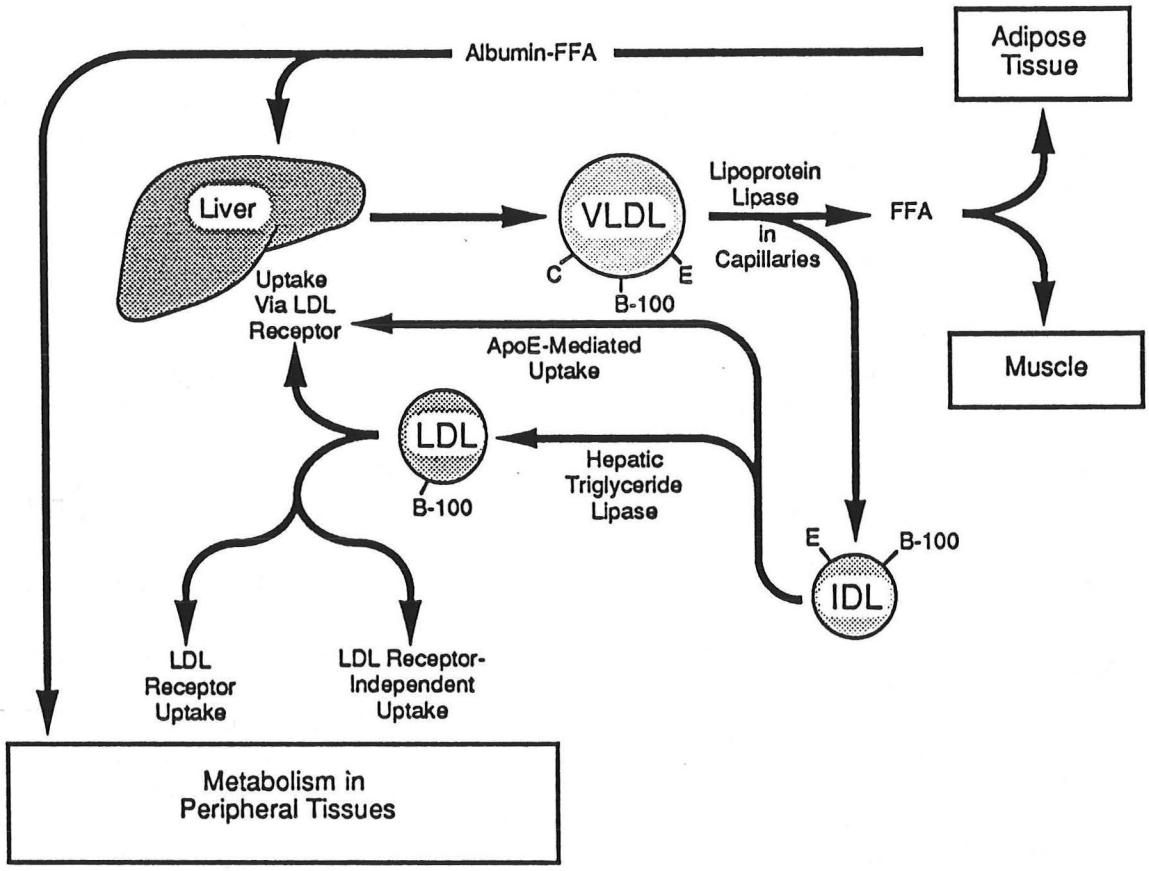


Figure 2. Cell Biology of Lipoprotein Lipase.

Lipoprotein lipase is synthesized as an inactive precursor in the endoplasmic reticulum (ER). After high mannose units are trimmed, the lipase is activated in the Golgi apparatus (G), where progressive *N*-linked glycosylation occurs. A secretable pool of lipase is then packaged into secretory vesicles (SV). In the presence of factors such as heparin, the active enzyme can be secreted and transported to the endothelial surface. Otherwise, degradation can take place in lysosomes (L). After transport, lipoprotein lipase is placed at the luminal extent of the glycocalyx, which is anchored in the basement membrane of the endothelial cell (EC). Here the lipase can hydrolyze circulating triglyceride-rich lipoproteins, chylomicrons (CM), and VLDLs. Modified from Olivecrona et al.[16] and Ailhaud et al.,[17] with the permission of the publishers.

FFA not assimilated by the tissues bind to plasma albumin and are distributed throughout the body or returned to the liver for oxidation or re-esterification to triglyceride for subsequent secretion in VLDL (Figure 3).

Figure 3. VLDL Metabolism in Plasma



After most of the chylomicron-triglyceride core is hydrolyzed, the particle disassociates from lipoprotein lipase as a chylomicron remnant. These remnants are depleted of triglyceride and apoC peptides, but retain apoB-48, apoE and most of the cholesterol originally incorporated from the intestinal lumen. The remnant particles are rapidly removed from the circulation by an hepatic chylomicron remnant receptor that binds with apoE on the remnant particle surface.

Chylomicrons enter the plasma whenever a meal containing fat is consumed and they are removed from the plasma with a half-life of about 30 minutes. Therefore the plasma concentration of chylomicrons undergoes wide fluctuation during the day but chylomicrons are normally not found in plasma in the post-absorptive state (following a 9 to 15 hour fast). The amount of triglyceride transported each day as chylomicrons varies with the amount of fat in the diet. The greater the load of dietary fat, the greater the amount of chylomicrons produced by the intestine. However, in the post-absorptive state, and during periods when high carbohydrate, low fat diets are consumed, chylomicron formation is markedly diminished and triglyceride transport takes place in VLDL particles originating from the liver.

Very low density lipoproteins are somewhat smaller in size and of higher density than chylomicrons. They are produced in the liver and secreted as triglyceride-rich particles containing apoB-100, apoE and the apoC peptides (Figure 3). VLDLs also acquire additional apoC and apoE by transfer from HDL. VLDLs interact with lipoprotein lipase in capillaries where the triglyceride core is hydrolyzed to yield FFA principally for adipose tissue and muscle, as described for chylomicrons.

When VLDL remnants disassociate from lipoprotein lipase, they are termed intermediate density lipoproteins (IDLs). IDL particles have two major metabolic fates: they may be taken up by LDL receptors on the liver or they may be converted to LDLs, the cholesterol-rich particles that supply cholesterol to cells via the LDL receptor pathway or by receptor-independent mechanisms. The conversion of IDL to LDL is thought to involve hepatic triglyceride lipase. It is estimated that about two-thirds of the clearance of LDLs from the plasma is mediated by LDL receptors and one-third by receptor-independent processes. LDL receptors are found in most tissues throughout the body. However, about 60 to 70% of total body LDL receptor activity is located in the liver which clears a major portion of LDLs from the plasma.

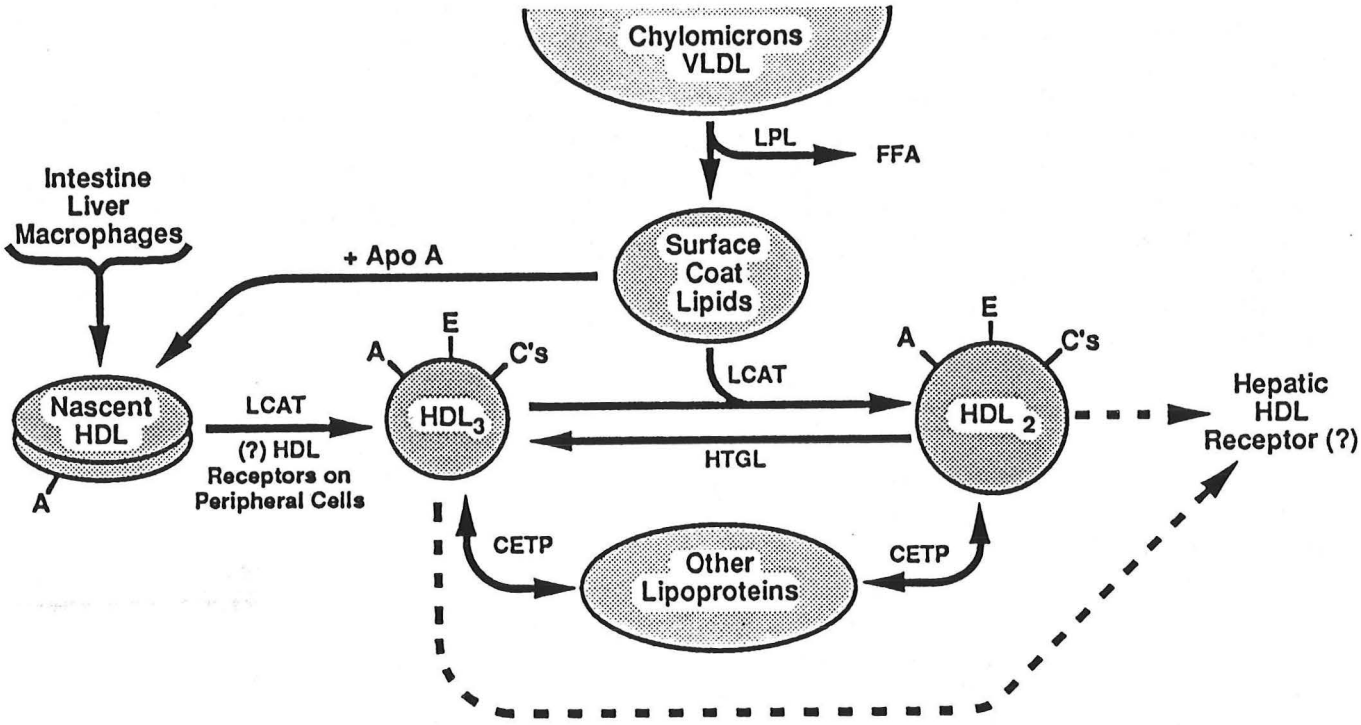
The half-lives of VLDL and IDL are approximately 9-12 hours, while that of LDL is about 2.5-3.5 days. Thus the concentration of VLDLs can vary significantly throughout the day, depending upon the quantity and type of calories consumed, while the level of LDL is relatively stable and less affected by the fasting or fed state.

VLDL particles supply triglycerides to tissues in the post-absorptive state and when high carbohydrate-low fat diets are consumed. In the post-absorptive state, adipose tissue releases stored triglyceride as free fatty acids which bind to plasma albumin for delivery to tissues including the liver. FFA returning to the liver are re-esterified to triglyceride for release in VLDL particles (Figure 3). If a high carbohydrate diet is consumed, the metabolic intermediates of carbohydrate catabolism are converted to fatty acids in the liver and these, too, are secreted as VLDL triglyceride.

HDL Metabolism in Plasma

To fulfill their apparent role in reverse cholesterol transport, HDL particles interact with several enzymes and lipid transfer proteins, and they also acquire excess surface coat material (including apoproteins and polar lipids) from chylomicrons and VLDL as the triglyceride core of these large particles is removed by the action of lipoprotein lipase. The concepts of HDL metabolism in plasma are summarized in Figure 4. As nascent HDL discs secreted from various tissues acquire more cholesteryl esters, they evolve into spherical HDL_3 particles which are the smallest of the HDL particle spectrum. HDL_3 particles enlarge to HDL_2 particles as they acquire surface coat material generated from the catabolism of chylomicrons and VLDL. This surface coat material consists primarily of apoproteins (C and E), phospholipids, and unesterified cholesterol which is esterified by LCAT to further contribute to the core lipids in HDL_2. Surface coat material can also lead to the formation of nascent HDL discs.

Figure 4. HDL Metabolism in Plasma



HDL_3 and HDL_2 also exchange lipid with other lipoproteins through the action of cholesteryl ester transfer protein (CETP). CETP transfers cholesteryl esters from HDL to chylomicrons, VLDL and IDL in the plasma. In this exchange process, HDL tends to acquire triglyceride. If the triglycerides and phospholipids in HDL_2 are hydrolyzed by hepatic triglyceride lipase, an enzyme with triglyceride lipase and phospholipase activity located on the sinusoidal surfaces of the liver and distinct from lipoprotein lipase, HDL_3 is generated. HDL_3 can then be reconverted to HDL_2 through the acquisition of more surface coat material from chylomicrons and VLDL. Eventually, HDL particles are removed from the circulation, perhaps by HDL receptors on the liver.

It is important to recognize that tissue cholesterol initially acquired by nascent HDL particles may eventually be transferred as cholesteryl ester to triglyceride-rich lipoproteins during their catabolism. If this transfer is to chylomicron remnants, the transferred cholesteryl esters are returned to the liver. If the transfer is to VLDL remnants and IDLs, the cholesteryl esters may return to the liver as IDLs or they may appear in LDLs. Thus "reverse cholesterol transport" does not involve a direct route from peripheral tissues to the liver, but depends upon the repeated transfer of cholesteryl esters among lipoproteins before final excretion occurs via the liver.

III. The Biology of Lipoprotein Lipase and Apolipoprotein C-II

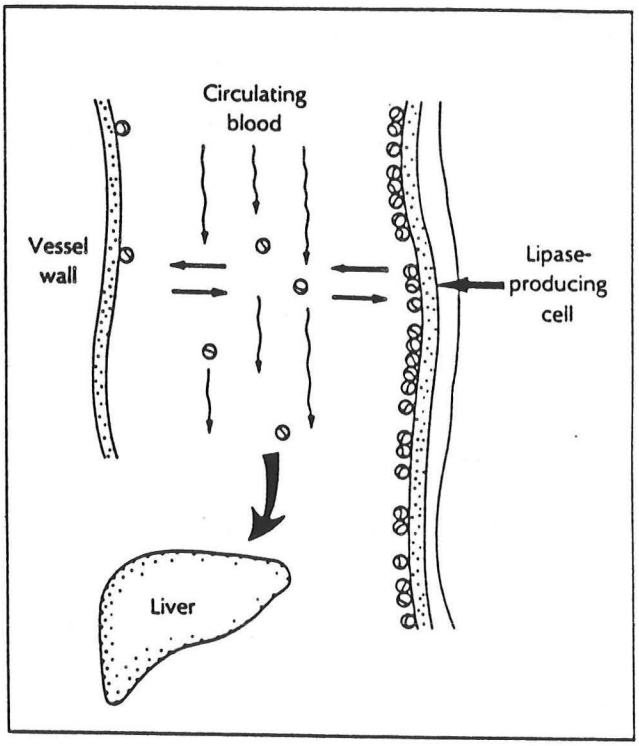
As indicated in figures 1 and 3, lipoprotein lipase (LPL) is important for the initial catabolism of both chylomicrons and VLDL. The enzyme is synthesized in adipose tissue and muscle, but it is also found in many other tissues, even in those where no mRNA for the enzyme can be detected. The most mRNA for LPL is in cardiac muscle, adipose tissue and lactating breast. Thus, it is believed that LPL "circulates" through the plasma, migrating from sites where it is synthesized to capillary beds throughout the body where it can function to effectively liberate free fatty acids (FFA) for cellular metabolism (figure 5) (5). It is assumed to be attached to the vascular endothelium by binding to glycan chains of heparan sulfate proteoglycans. It can be displaced from these binding sites by the intravenous injection of heparan and this reaction forms the basis for the post-heparin lipolytic activity (PHLA) used to check for the presence of LPL in vivo (2).

The enzyme primarily hydrolyzes triglycerides to monoglycerides and FFA, but it also is capable of slowly hydrolyzing monoglycerides and phospholipids (4). It is active as a dimer and loses activity when it dissociates. The activity of the enzyme is dependent on the presence of apolipoprotein C-II (apoC-II) which is found in HDLs, chylomicrons and VLDLs (table 2).

The activity of LPL varies with the metabolic state of the tissue. During a fast, LPL activity in adipose tissue declines, but it remains stable or increases in muscle. During insulin/glucose infusions in normal humans, adipose tissue LPL activity increases and skeletal muscle LPL activity decreases, a change that presumably directs lipoprotein triglyceride-derived FFA away from muscle and to adipose tissue for storage (6). Weight loss in very obese subjects leads to increases of activity and expression of LPL, thereby potentially enhancing lipid storage and making further weight loss more difficult (7).

In late pregnancy and after parturition, LPL activity in the mammary gland is increased through the action of prolactin to generate milk triglyceride (4).

Figure 5.



The transport of lipoprotein lipase (LPL). The enzyme is produced by parenchymal cells, illustrated here by a lipase-producing cell to the right. LPL is released from these cells and moves to binding sites at the luminal side of the endothelial cells in adjacent capillaries. The lipase then moves slowly along the endothelial surface from one binding site to the next, carried by blood. When it enters larger vessels and the general circulation it can spread to binding sites in other tissues, including those which do not produce LPL. This spreading is counteracted by avid uptake of LPL in the liver, Hence, the system is not in equilibrium but there is continuous supply of new LPL molecules from sites of synthesis, resulting in high concentration at these capillary segments. There is also continuous net uptake and degradation of LPL by the liver (Olivecrona and Bengtsson-Olivecrona. In *Lipoprotein Lipase* edited by Borensztajn. Evener, 1987, pp 15–58).

Table 2: Characteristics, Lipoprotein Distribution, Primary Tissue Source And Physiological Function Of The Major Apolipoproteins.

Apolipoproteins	Approximate Molecular Weight (daltons)	Primary Tissue Source	Lipoprotein Distribution	Physiological Function
A-I	28,016	Intestine,Liver	HDL, Chylomicrons	LCAT Cofactor.*
A-II	17,414	Intestine,Liver	HDL, Chylomicrons	Unknown
B-48	240,000	Intestine	Chylomicrons	Chylomicron synthesis and secretion.
B-100	510,000	Liver	VLDL, IDL, LDL	VLDL synthesis and secretion; LDL receptor binding.
C-I	6,630	Liver	Chylomicrons, VLDL,HDL	Inhibits binding to hepatic receptors.†
C-II	8,900	Liver	Chylomicrons, VLDL,HDL	Lipoprotein Lipase Cofactor.
C-III	8,800	Liver	Chylomicrons, VLDL, HDL	Inhibits binding to hepatic receptors.†
D	19,000	?	HDL	? Reverse cholesterol transport
E‡	34,145	Liver	Chylomicrons, VLDL, IDL, HDL	Receptor recognition.

* LCAT denotes Lecithin:cholesterol acyltransferase.
† Chylomicrons and VLDL containing C-I, C-II and C-III do not interact well with hepatic receptors; currently this function is attributed to all three C peptides.
‡ ApoE is polymorphic, a characteristic under genetic control; the major forms are E-II, E-III and E-IV, each the product of an allele at the apoE locus.

IV. Etiology of the Chylomicronemia Syndrome

The Chylomicronemia Syndrome may occur as a result of familial lipoprotein lipase deficiency or familial apolipoprotein C-II deficiency. A single kindred with familial lipoprotein lipase inhibitor has also been described.

The Chylomicronemia Syndrome may also occur in individuals with familial forms of hypertriglyceridemia (Familial Type 3 HLP; Familial Hypertriglyceridemia; Familial Multiple Lipoprotein Type HLP) when aggravating factors promote severe hypertriglyceridemia. Such factors include obesity, estrogen therapy, poorly controlled diabetes mellitus and excessive alcohol intake.

1. PRIMARY GENETIC DISORDERS CAUSING THE CHYLOMICRONEMIA SYNDROME

A. Familial lipoprotein lipase deficiency (table 3)

This is a rare autosomal recessive disorder characterized by the absence of lipoprotein lipase (LPL) in tissues and the massive accumulation of chylomicrons in plasma. The major clinical manifestations are eruptive xanthomas and recurrent episodes of pancreatitis (2).

Etiology and Pathogenesis

The hydrolysis of triglycerides in chylomicrons and VLDL *in vivo* requires the action of LPL in tissue capillary beds. LPL is activated by apolipoprotein C-II located in chylomicrons and VLDL. Patients with familial LPL deficiency produce adequate amounts of apoC-II but they are unable to produce lipoprotein lipase in their tissues. Consequently, when patients ingest long chain fats and generate chylomicrons, they are unable to catabolize the chylomicrons and develop massive hyperchylomicronemia. Since the hyperlipidemia is generated from dietary fat, these patients have exogenous hyperlipidemia.

Recently, substantial progress has been made in elucidating the genetic variants affecting human lipoprotein lipase (8, 9). Human lipoprotein lipase is a member of a family of proteins that includes hepatic lipase, mammalian pancreatic lipase and Drosophilia yolk proteins (vitellogenins) (10). The human LPL gene is on chromosome 8p22 and is about 35 kilobases in size with 10 exons that code for a 475-amino acid protein that includes a 27-amino-acid leader sequence. Numerous DNA sequences have now been described to cause the LPL deficiency. Most of these consist of missense and nonsense substitutions involving primarily the exons 4, 5 and 6. A list of the known mutations is given in table 4 and their location is depicted in Figure 6. (8). This information is providing important details about structure/function relationships of lipoprotein lipase. Some mutations alter the catalytic properties of LPL while others impair the ability of the enzyme to bind to heparin.

TABLE 3. PRIMARY HYPERLIPOPROTEINEMIAS ASSOCIATED WITH THE CHYLOMICRONEMIA SYNDROME CAUSED BY SINGLE-GENE MUTATIONS.

Genetic Disorder	Primary Biochemical Defect	Plasma Lipoproteins Elevated	Lipoprotein Type	Typical Clinical Findings	Genetic Transmission	Estimated Population Frequency
Familial lipoprotein lipase deficiency	Lipoprotein lipase deficiency	Chylomicrons	1	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	Autosomal recessive	Rare
Familial apolipoprotein CII deficiency	Apolipoprotein CII deficiency	Chylomicrons, VLDL	1 or 5	Pancreatitis	Autosomal recessive	Rare
Familial Type 3 hyperlipoproteinemia	Abnormal apolipoprotein E structure	Chylomicron and VLDL remnants	3, rarely 5	Xanthoma striata palmaris, tuberoeruptive xanthomas, premature atherosclerosis	Autosomal recessive	1/10,000
Familial hypertriglyceridemia	Unknown	VLDL, occasionally chylomicrons	4, occasionally 5	Premature atherosclerosis; eruptive xanthomas and pancreatitis occur with type 5 pattern	Autosomal dominant	2/1000
Familial multiple lipoprotein-type hyperlipoproteinemia	Unknown	VLDL and LDL; rarely chylomicrons	2a, 2b, 4, rarely 5	Premature atherosclerosis	Autosomal dominant	3-5/1000

(Adapted and modified from M. S. Brown and J. L. Goldstein. The Hyperlipoproteinemias and other disorders of lipid metabolism. In: Harrison's Principles of Internal Medicine, 11th ed. E. Braunwald et al (eds.). New York: McGraw-Hill, 1987, pp 1650-1661.)

Table 4.

A list of the mutations described in the lipoprotein lipase gene.

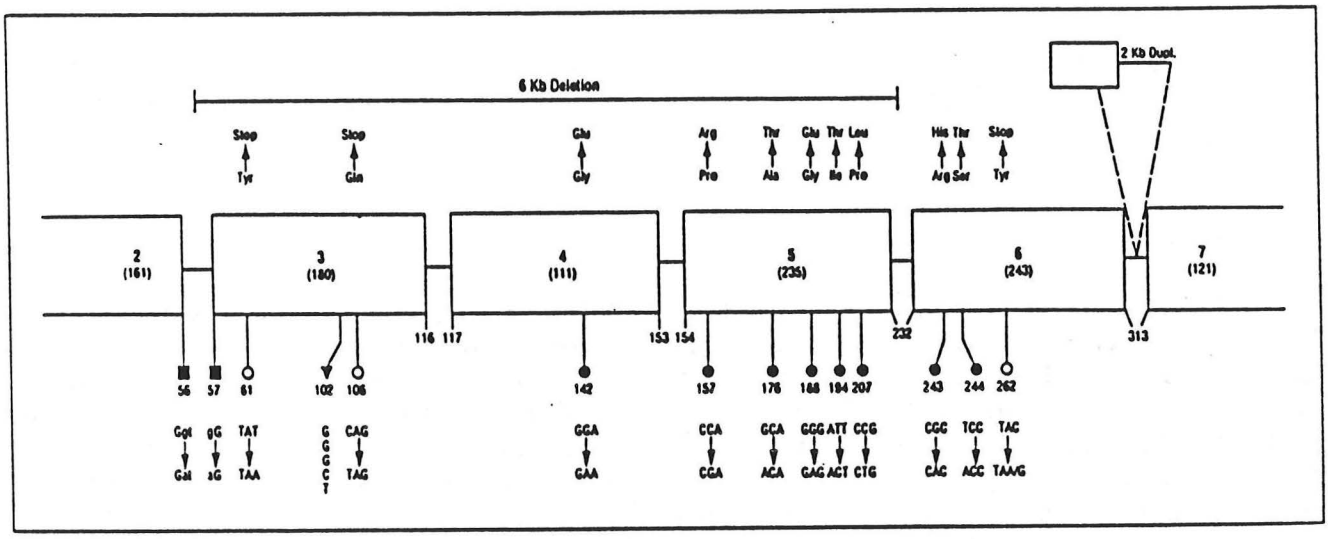
Mutation	Amino acid substitution	Exon	Mutagenesis	Ancestral background	Mutant alleles	Reference
Null allele						
G→A	First nucleotide of intron 2	–	No	Japanese	2	Gotoda *et al.* [16•]
G→A	Last nucleotide of intron 2	–	No	French	1	Hata *et al.* [17•]
Duplication		6	No	English	1	Devlin *et al.* [15•]
				Irish	1	
				German	1	
				Polish	1	
Deletion		3, 4, 5	No	English	1	Langlois *et al.* [14]
Missense						
G→A	Gly^{142}→Glu	4	Yes	Northern-European	2	Ameis *et al.* [19••]
C→G	Pro^{157}→Arg	5	No	Dutch	2	Bruin *et al.* [20•]
G→A	Ala^{176}→Thr	5	Yes	Black-American	2	Beg *et al.* [21•]
G→A	Gly^{188}→Glu	5	Yes	French-Canadian	11	Monsalve *et al.* [23•]
				Polish	2	
				German	1	
				Dutch	2	
				Indian	2	
				English	3	Emi *et al.* [22••]
				Northern-European	2	
T→C	Ile^{194}→Thr	5	Yes	Dutch-French	5	Henderson *et al.* [25••]
				Caucasian	1	Dichek *et al.* [24••]
C→T	Pro^{207}→Leu	5	Yes	French-Canadian	54	Ma *et al.* [26••]
G→A	Arg^{243}→His	6	Yes	Caucasian	1	Dichek *et al.* [24••]
				Japanese	2	Gotoda *et al.* [16•]
T→A	Ser^{244}→Thr	6	Yes	French	1	Hata *et al.* [17•]
Nonsense						
T→A	Tyr^{61}→Stop	3	No	Japanese	1	Gotoda *et al.* [16•]
C→T	Gln^{106}→Stop	3	No	German	1	Emi *et al.* [18•]
				Polish	1	
C→(A/G)	Tyr^{262}→Stop	6	No	German	1	Funke *et al.* [28•]
Frameshift						
GGGCT	102	3	No	Malay	2	Henderson *et al.* [27•]

Clinical Manifestations

Patients develop severe hyperlipidemia from birth. The hyperchylomicronemia produces creamy or lactescent plasma and the chylomicron layer is especially evident following overnight refrigeration of the plasma. Triglyceride levels may reach 10,000-20,000 mg/dl and cholesterol levels are mildly to moderately increased from the cholesterol contained in the chylomicrons. The severe hypertriglyceridemia and its attendant turbidity will render some other laboratory tests inaccurate (11). Lipemia retinalis, which gives a white or pale appearance to the retinal vessels and a pallor to the fundus, is due to the lactescent plasma. This finding becomes increasingly evident when triglyceride levels exceed 3000-4000 mg/dl.

Macrophages may ingest chylomicrons to produce foam cells, a process that may lead to hepatosplenomegaly. The most prominent feature of the disorder is

Figure 6.



The location of the known mutations in the human lipoprotein lipase gene. ■, Splice site substitution; ▼, frameshift insertion; ●, missense; ○, nonsense. Exons 1, 8, 9 and 10 are not shown. Diagram is not drawn to scale.

recurrent attacks of abdominal pain and pancreatitis associated with the severe hypertriglyceridemia. In infants, these attacks appear as abdominal colic. The severe hypertriglyceridemia has also been associated with recent memory loss, depression and objective dyspnea. These symptoms resolve when the hypertriglyceridemia improves. Assay of amylase levels during bouts of abdominal pain may be erroneously low due to interference of the hypertriglyceridemia with the enzyme assay (11). Since chylomicrons displace water volume in plasma, severe hypertriglyceridemia is associated with artifactual decreases in plasma components due to dilution (12). For example, serum sodium levels decrease 2-4 mEq for each 1000 mg/dl of plasma triglyceride (pseudohyponatremia). Premature atherosclerosis is not a feature of this disease (13).

Diagnosis

The diagnosis is suggested by the presence of turbid plasma or an obvious cream layer in the plasma obtained from a child or adult after an 8-12 hr fast. Triglyceride levels vary widely, depending on the degree of dietary fat consumption prior to the test. Lipoprotein electrophoresis will demonstrate a type I pattern. If lipoprotein levels are measured, LDL- and HDL-cholesterol concentrations are typically low. Special centers will provide LPL assays following intravenous heparin injection (post-heparin lipolytic activity or PHLA). The heparin releases LPL from its capillary binding sites into the plasma where it can be assayed. LPL can also be measured directly in adipose tissue obtained by needle biopsy. Patients with familial LPL deficiency have little or no LPL present in their tissues or in the plasma following a heparin injection.

Assay of apolipoprotein C-II by radioimmunoassay or gel electrophoresis is also required to exclude the diagnosis of apolipoprotein C-II deficiency.

Heterozygotes have a 50 percent reduction in PHLA; they may be normolipidemic but they may also exhibit mild hypertriglyceridemia or combined hyperlipidemia (14, 15, 16).

Treatment

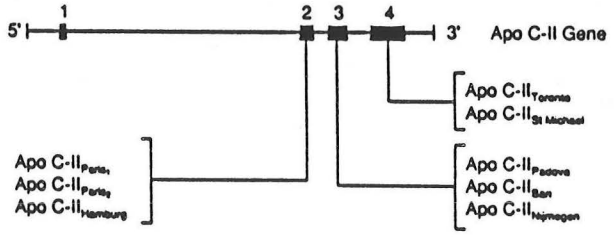
Lifelong restriction of dietary fat is required to control the hypertriglyceridemia. The goal of therapy is to maintain the triglyceride level below 1000 mg/dl to reduce the attacks of pancreatitis and abdominal pain. This usually requires a reduction in total dietary fat intake (including both saturated and unsaturated fats) to 10-20% of calories. Caloric supplementation with medium chain triglycerides, which do not promote chylomicron formation but are absorbed directly into the portal vein, is useful (14). Since these diets are rich in carbohydrate and plant protein, it may be necessary to provide vitamin supplementation. Currently available lipid-lowering drugs are not effective in these patients.

B. Familial Apolipoprotein C-II Deficiency (table 3)

This rare autosomal recessive disorder is caused by the absence of apolipoprotein C-II, the cofactor essential for the function of lipoprotein lipase in vivo (2, 9, 17, 18). Several gene defects can account for the dysfunction or absence of the apo C-II in plasma (9) (Figure 7). The result is a functional deficiency of lipoprotein

Figure 7.

A



B

Family	Mutation/Residue	RFLP	Reference
Hamburg	G→C/Intron 2 Donor Splice Defect	*Dde I*/*Hph* I	16
Nijmegen	G Deletion/Frameshift/ Val_{16}→Stop	*Hph* I	12
Padova	C→A/Tyr_{37}→Stop	*Rsa* I	13
Bari	C→G/Tyr_{37}→Stop	*Rsa* I	11
$Paris_1$	A→G/Met_{-22}→Val	...	9
$Paris_2$	C→T/Arg_{-10}→Stop	*Nla* III	10
Toronto	T Deletion/Frameshift/ Leu_{75}→Stop	NR	15, 17
St Michael	NR/Frameshift With Extension to 96 aa	NR	6

.. —A, Schematic representation of the apoliprotein (apo) C-II gene with the location of the mutations. B, Identifies the nature and position of the defects and indicates the presence of any restriction fragment length polymorphisms (RFLPs) generated by the mutation. NR indicates not reported; aa, amino acids.

lipase and the accumulation of chylomicrons and VLDL in plasma to produce severe hypertriglyceridemia. Of note, the hypertriglyceridemia is ameliorated by infusion of one or more units of normal plasma which contains sufficient apoC-II to activate the endogenous lipoprotein lipase (17). The clinical picture is similar to that of familial lipoprotein lipase deficiency but pancreatitis is less common in children and eruptive xanthomas are usually not observed. The reasons for these clinical differences are not known. The condition has been described in a neonate (19). Patients come to medical attention because they develop pancreatitis or because they have pronounced hypertriglyceridemia and lipemic plasma in a casual blood sample. An increased incidence of atherosclerosis is not apparent in most patients, but one kindred with premature atherosclerosis has been described (20).

The diagnosis requires the demonstration of apoC-II deficiency on gel electrophoresis of VLDL from the patient and the demonstration that post-heparin lipolytic activity (PHLA) is present in the plasma following addition of apoC-II from a normal source. Treatment is similar to that for familial lipoprotein lipase deficiency and lifelong adherence to the low-fat diet is required to avoid recurrent attacks of abdominal pain and pancreatitis. It is possible to relieve the severe hypertriglyceridemia during attacks of pancreatitis by infusing one or more units of normal plasma which provides enough apoC-II to activate the endogenous lipoprotein lipase. Current lipid-lowering drugs are not effective.

C. Familial Lipoprotein Lipase Inhibitor

Hyperchylomicronemia was noted in a mother and her son (21). Lipoprotein lipase levels were above normal in adipose tissue and apolipoprotein C-II was present in the plasma of both patients. The plasma from each patient contained an inhibitor of lipoprotein lipase. This inhibitor was non-dialyzable, heat-stable, sensitive to freeze-thawing, and was present in the non-lipoprotein fraction of plasma. The chylomicronemia was documented in three successive generations, indicating a dominant mode of inheritance. Specific therapy has not been developed but dietary fat restriction is recommended (2).

2. CHYLOMICRONEMIA SECONDARY TO A RELATED LIPOPROTEIN DISORDER WHICH ALONE DOES NOT TYPICALLY CAUSE CHYLOMICRONEMIA

The original pheonotypic classification scheme for hyperlipidemia proposed by D.S. Fredrickson and colleagues included a "disorder" called type V hyperlipoproteinemia. This phenotype was defined by the presence of severe hypertriglyceridemic and mild-to-moderate hypercholesterolemia, which was explained by the accumulation of both chylomicrons and VLDLs in the plasma. Clinical features of this phenotype included abdominal pain and pancreatitis; eruptive xanthomas; hepatosplenomegaly; abnormal glucose tolerance; hyperuricemia; ischemic heart disease; and peripheral neuropathy (22, 23, 24, 25, 26, 27). This phenotype was considered distinct from type I hyperlipoproteinemia due to lipoprotein lipase deficiency because the type I phenotype did not include VLDLs (a

distinction no longer considered valid). Furthermore, patients with the type V phenotype had lipoprotein lipase in their plasma following a bolus injection of heparin. Although some studies suggest that patients with the type V phenotype do have reduced tissue LPL levels (28), this reduction in LPL level alone is not sufficient to explain the marked hypertriglyceridemia.

Another feature of the pedigrees of type V patients was that the relatives often displayed other types of hyperlipidemia (especially type IV, but also type IIa and IIb) (22, 23). Patients with the type V phenotype, when treated, often reverted to a type IV pattern.

These observations led Chait and Brunzell (29) to re-evaluate patients with severe hypertriglyceridemia. The index patients they studied had a mean triglyceride level of 6391 mg/dl, whereas the mean triglyceride level in hypertriglyceridemic relatives was 467 mg/dl (table 5). In the patients with adequate family members to study, 31% of the patients came from families with familial hypertriglyceridemia and 17% came from families with familial combined hyperlipidemia (table 6). None of the 54 index cases had relatives without hypertriglyceridemia.

When the families were evaluated for secondary causes of hyperlipidemia, the causes that emerged included diabetes mellitus, alcohol consumption, and estrogen use (table 7). Diabetes accounted for the largest number of cases with type V hyperlipidemia and evidence has been presented that the diabetes and genetic forms of hypertriglyceridemia are independent entities (30, 31, 32). In these cases, the diabetes is NIDDM. In patients with IDDM and severe ketosis, severe hypertriglyceridemia that may occur frequently clears completely, indicating that a familial form of hypertriglyceridemia is not present in many of these patient (33). Thus, it is not clear that the type V lipoprotein phenotype constitutes a distinct entity. The data collectively indicate that the type V phenotype is usually the result of an acquired disorder acting on the genetic background of familial hypertriglyceridemia, familial combined hyperlipidemia or some other familial form of hypertriglyceridemia, such as the

Table 5.

Plasma Triglyceride Concentrations (mg/dl)

	$\bar{x}$ ± SD	Range
Index patients-initial value*	6391 ± 3787	2064-17,780
on treatment	717 ± 516	114-1784
Level in hypertriglyceridemic relatives	467 + 267	229-1052

*Values in index patients were measured on several occasions. Since in many instances lipid lowering treatment was commenced immediately, the initial value represents the single value obtained at initial presentation. No specific dietary precautions were taken other than that patients were required to fast for at least 12-14 hr prior to the blood sampling.

Table 6.

Familial Forms of Hypertriglyceridemia in the 54 Index Patients with Relatives to Study

	Number	Percentage
Familial hypertriglyceridemia	17	31
Familial combined hyperlipidemia	9	17
Both parents affected	5	9
Family positive	23	43
No hyperlipidemic relatives	0	0
	54	100

heterozygous form of LPL deficiency. Additional disorders associated with the Chylomicronemia Syndrome are listed in table 8. (34).

Table 7.

Secondary Causes of Hypertriglyceridemia

	Diabetes Mellitus	Ethanol	Estrogen	Glucocorticoids	Renal Failure	Hypothyroidism	Other	No Secondary Cause	More Than One Secondary Cause
Familial hypertriglyceridemia	12	4	1	1	1	1	0	0	2
Familial combined hyperlipidemia	8	0	0	0	0	0	0	1	0
Both parents affected	1	0	0	0	0	0	0	4	0
Family positive	13	2	5	1	0	0	2	2	2
	34	6	6	2	1	1	2	7	4

3. THE CHYLOMICRONEMIA SYNDROME IN PREGNANCY - A SPECIAL CLINICAL CHALLENGE

Pregnancy is associated with a progressive rise in plasma lipoprotein levels which is usually modest and generally requires no treatment (35). Triglycerides increase progressively until term, whereas LDL-cholesterol reaches maximum levels at week 36 of gestation. HDL increases initially and then falls slightly through week 32, and then it remains stable until delivery (35). An occasional patient, however, develops progressive and severe hypertriglyceridemia as the pregnancy continues (36, 37, 38, 39, 40, 41, 42, 43). If this condition goes undetected and the hypertriglyceridemia is allowed to progress, severe pancreatitis results, threatening the life of the mother and the fetus. Patients who develop this complication may have LPL deficiency or apo C-II deficiency. Another contributing cause is Familial Hypertriglyceridemia. In some cases the precise nature of the underlying lipid disorder cannot be defined. Particularly puzzling are the patients who experience one or two uncomplicated pregnancies, only to develop the Chylomicronemia Syndrome with pancreatitis in the third. The mechanism for the hyperlipidemia is complex. As the estrogen level increases during pregnancy, hepatic VLDL production increases and this partially explains the progressive rise in triglycerides (43). Human placental lactogen stimulates lipolysis and may therefore contribute to VLDL overproduction by increasing available substrate (43). In addition, increasing estrogen levels may cause a reduction in adipose tissue LPL activity while stimulating mammary gland LPL for milk production. Prolactin has a similar effect on LPL (43). all of these changes may contribute to the marked hypertriglyceridemia in susceptible patients. Serial lipids in one patient during pregnancy and in the post-partum period and their response to therapy are shown in Figure 8. (42).

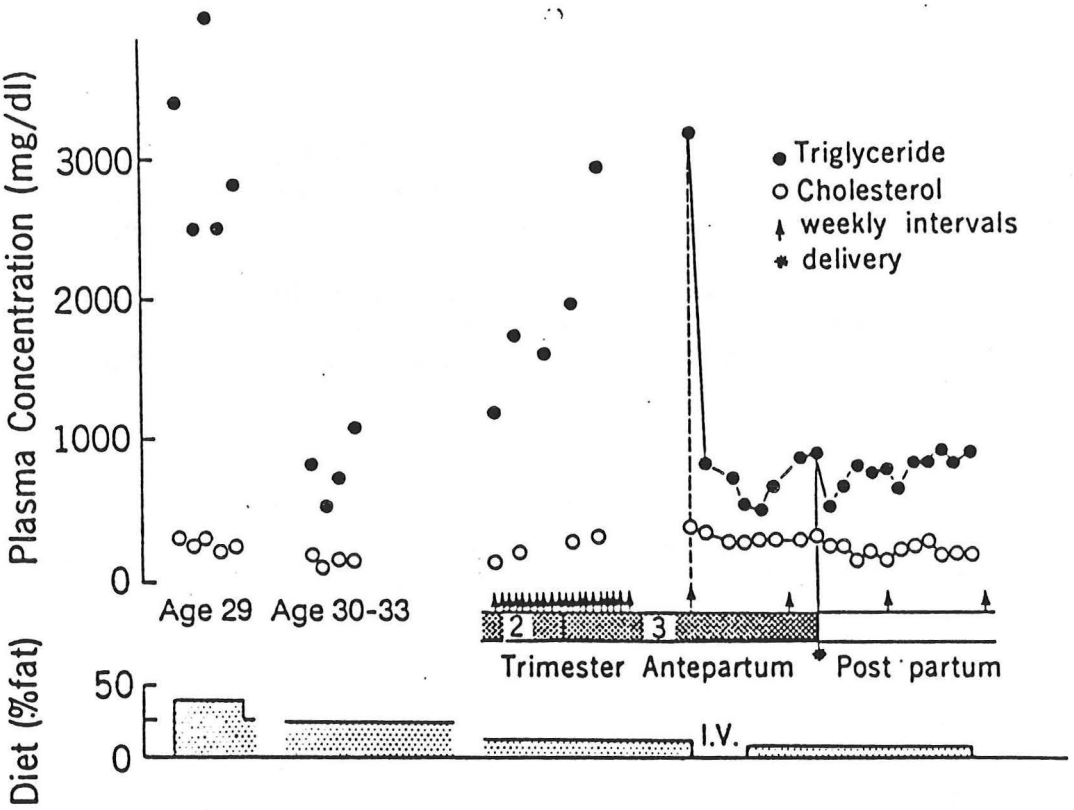
The most important first step is to recognize the presence of the condition and its potential seriousness. High-risk patients include women who have a primary form of hypertriglyceridemia prior to pregnancy, women who come from families where other members have hyperlipidemia, women who display lipemic plasma

TABLE 8. DISORDERS ASSOCIATED WITH THE CHYLOMICRONEMIA SYNDROME

Disorder	Chylomicrons	VLDLs	IDLs	LDLs	Lipoprotein Phenotype	Proposed Mechanism
Endocrine/Metabolic						
Diabetes Mellitus						
Severe, untreated	+	+			4 or 5	↓ VLDL and chylomircon metabolism due to decreased lipoprotein lipase activity
Estrogen or oral contraceptive therapy	+	+			4 or 5	↑ VLDL secretion in those predisposed to hypertriglyceridemia
Lipodystrophy (congenital or acquired)	+	+			4 or 5	↑ VLDL secretion
Glycogen Storage Disease Type I	+	+			4 or 5	↑ VLDL production and ↓ lipoprotein lipase activity.
Immunologic						
Dysglobulinemia (multiple myeloma, macroglobulinemia)	+	+			3 or 4	Immunoglobulin binds to chylomicron remnants and VLDL to impair lipoprotein catabolism.
Systemic lupus Erythematosus	+				1	Immunoglobulin binds to heparin, a cofactor for lipoprotein lipase, causing decreased activity of this enzyme.
Drug-related						
Isotretinoin and etretinate	+	+		+	4, occasionally 2b or 5	Unknown

(Adapted and modified from M. S. Brown and J. L. Goldstein. The Hyperlipoproteinemias and other disorders of lipid metabolism. In: Harrison's Principles of Internal Medicine, 11th ed. E. Braunwald et al (eds.). New York: McGraw-Hill, 1987, pp 1650-1661.)

Figure 8.



Plasma triglyceride and cholesterol levels before (age 29–33 years), during and after pregnancy (age 33 years). The fat content of the patient's diet is recorded as a percent of the total calories consumed. During the period IV the patient received nothing by mouth.

during a routine blood test, and women who have a history of developing hyperlipidemia while taking birth control pills. A prior uneventful pregnancy does not help in ruling out the problem.

If hyperlipidemia is detected, the patient should be monitored with fasting cholesterol and triglyceride tests on a weekly basis. In a recently published successful protocol, the patients were admitted to the hospital whenever the triglyceride level exceeded 2000 mg/dl. At that point the patient was made NPO and was given IV fluids (5% D-glucose in 0.45% sodium chloride, 2520 k J/d) (43). When the lipids dropped clearly below 2000 mg/dl, the patient was discharged to consume a very low fat diet (10% of total calories) to reduce chylomicron formation. This approach reduces the progressive rise in triglycerides which leads to saturation of clearing mechanisms and ultimately to massive hypertriglyceridemia and pancreatitis (44). None of the drugs currently available for treating hypertriglyceridemia has been tested adequately for safety in pregnancy and experience with drug treatment in such women is minimal or non-existent. The approach of giving a very low fat diet, and only IV fluids when hypertriglyceridemia is severe, appears to be beneficial and is associated with low risk to the mother and fetus, although clinical experience remains limited due to the low incidence of the problem.

4. GENERAL APPROACH TO TREATMENT

When the Hyperchylomicronemia Syndrome results in pancreatitis, the therapy is the same as that for pancreatitis resulting from any other cause. If the hyperlipidemia is especially severe, plasmapheresis to remove triglyceride may be performed but clear benefits from this therapy have not been established.

Maintenance care is focused on control of the hyperchylomicronemia. Even if the precise cause is not known, certain general measures can be applied to alleviate the hypertriglyceridemia and reduce the risk for pancreatitis (table 9). (45).

Table 9. Control of Hyperchylomicronemia

- Restrict dietary fat as required to 10-20% of calories
- Weight loss in obese subjects
- Control of Diabetes Mellitus, when present
- Exercise as tolerated
- Avoid alcohol
- Avoid drugs that aggravate the hypertriglyceridemia (estrogens, birth control tablets, Vitamin A, beta blockers, thiazides, Isotretinoin)
- Lipid-lowering drug therapy
  - Gemfibrozil
  - Nicotinic Acid (avoid in diabetic patients)
  - Fish oil supplements

Weight loss may not be successful over the long term. In some patients weight loss, followed by prompt weight gain, may actually provoke an attack of pancreatitis (2). Bulimia was detected in 5 of 21 patients who survived attacks of pancreatitis and were diagnosed as having primary hyperlipidemia (46). Gradual, sustained weight loss is clearly ideal but often not possible to achieve.

Gemfibrozil is well tolerated and is generally prescribed to control the hypertriglyceridemia. It may not lower the triglycerides signficantly below 1000 mg/dl in severe cases, but there is a general clincial sense that the incidence of pancreatitis is reduced as a result of Gemfibrozil therapy (1). Nicotinic acid is an effective agent for lowering triglycerides but it aggrevates glucose tolerance and is not recommended for use in patients with diabetes (47, 48). Fish oil supplements in doses of 4.5 g of n-3 fatty acids, or greater, reduce triglycerides and are helpful in selected patients (49, 50). When using fish oils, it is necessary to make caloric adjustments to avoid weight gain in the patient. Fish oils appear to reduce VLDL production by the liver; they exert no effect on LPL activity (50). It must be

emphasized that drug therapy is of no benefit in patients with familial lipoprotein lipase deficiency or familial apolipoprotein C-II deficiency.

In difficult cases, anabolic steroids, androgens and progestational agents have been used to treat severe hypertriglyceridemia (51, 52, 53, 54). The therapy often lowers the HDL-cholesterol dramatically and the long term safety of these drugs is not established. These therapies are therefore not recommended for general use.

References

1. Brunzell, JD and Bierman, EL. Chylomicronemia syndrome. Interaction of genetic and acquired hypertriglyceridemia. Med. Clinics of NA. 66:455-468, 1982.

2. Brunzell, JD. Familial lipoprotein lipase deficiency and other causes of the chylomicronemia syndrome. In: The Metabolic Basis of Inherited Disease. 1. Scriver, CR, Beaudet, AL, Sly, WS and Valle, D. ed. McGraw-Hill. New York, 1989, 1165-80.

3. Bilheimer, DW. Lipid Metabolism. In: Textbook of Internal Medicine. Kelley, W. ed. J. B. Lippincott Co. Philadelphia, 1989, 2139-44.

4. Eckel, RH. Lipoprotein lipase. A multifunctional enzyme relevant to common metabolic diseases. N. Engl. J. Med. 320:1060-1068, 1989.

5. Olivecrona, T and Bengtsson-Olivecrona, G. Lipoprotein lipase and hepatic lipase. Curr. Opin. Lipidol. 1:222-230, 1990.

6. Farese, RV, Jr., Yost, TJ and Eckel, RH. Tissue-specific regulation of lipoprotein lipase activity by insulin/glucose in normal-weight humans. Metabolism. 40:214-216, 1991.

7. Kern, PA, Ong, JM, Saffari, B and Carty, J. The effects of weight loss on the activity and expression of adipose-tissue lipoprotein lipase in very obese humans. N. Engl. J. Med. 322:1053-1059, 1990.

8. Hayden, MR, Ma, Y, Brunzell, J and Henderson, HE. Genetic variants affecting human lipoprotein and hepatic lipases. Curr. Opin. Lipidol. 2:104-109, 1991.

9. Santamarina-Fojo, S and Brewer, HB, Jr. The familial hyperchylomicronemia syndrome. New insights into underlying genetic defects. JAMA. 265:904-908, 1991.

10. Kirchgessner, TG, Chuat, J-C, Heinzmann, C, Etienne, J, Guilhot, S, Svenson, K, Ameis, D, Pilon, C, d'Auriol, L, Andalibi, A, Schotz, MC, Galibert, F and Lusis, AJ. Organization of the human lipoprotein lipase gene and evolution of the lipase gene family. Proc. Natl. Acad. Sci. USA. 86:9647-9651, 1989.

11. Steinberg, WM, Goldstein, SS, Davis, ND, Shamma'a, J and Anderson, K. Diagnostic assays in acute pancreatitis: a study of sensitivity and specificity. Ann. Intern. Med. 102:576-580, 1985.

12. Howard, JM and Reed, J. Pseudohyponatremia in acute hyperlipemic pancreatitis. A potential pitfall in therapy. Arch Surg. 120:1053-1055, 1985.

13. Malekzadeh, S, Dressler, FA, Hoeg, JM, Brewer, HB, Jr. and Roberts, WC. Left atrial endocardial lipid deposits and absent to minimal arterial lipid deposits in familial hyperchylomicronemia. Amer. J. Cardiol. 67:1431-1434, 1991.

14. Wilson, DE, Edwards, CQ and Chan, I-F. Phenotypic heterogeneity in the extended pedigree of a proband with lipoprotein lipase deficiency. Metabolism. 32:1107-1114, 1983.

15. Babirak, SP, Iverius, P-H, Fujimoto, WY and Brunzell, JD. Detection and characterization of the heterozygote state for lipoprotein lipase deficiency. Arteriosclerosis. 9:326-334, 1989.

16. Wilson, DE, Emi, M, Iverius, P-H, Hata, A, Wu, LL, Hillas, E, Williams, RR and Lalouel, J-M. Phenotypic expression of heterozygous lipoprotein lipase deficiency in the extended pedigree of a proband homozygous for a missense mutation. J. Clin. Invest. 86:735-750, 1990.

17. Breckenridge, WC, Little, JA, Steiner, G, Chow, A and Poapst, M. Hypertriglyceridemia associated with deficiency of apolipoprotein C-II. N.Engl. J. Med. 298:1265-1273, 1978.

18. Cox, DW, Breckenridge, WC and Little, JA. Inheritance of apolipoprotein C-II deficiency with hypertriglyceridemia and pancreatitis. N. Engl. J. Med. 299:1421-1424, 1978.

19. Ohno, M, Ishibashi, S, Nakao, K, Nozue, T, Nonomura, K, Yamada, N, Aburatani, H, Shimano, H and Murase, T. A neonatal case of apolipoprotein C-II deficiency. Eur. J. Pediatr. 148:550-552, 1989.

20. Connelly, PW, Maguire, GF and Little, JA. Apolipoprotien $CII_{St.\ Michael}$. Familial apolipoprotein CII deficiency associated with premature vascular disease. J. Clin. Invest. 80:1597-1606, 1987.

21. Brunzell, JD, Miller, NE, Alaupovic, P, St. Hilaire, RJ, Wang, CS, Sarson, DL, Bloom, SR and Lewis, B. Familial chylomicronemia due to a circulating inhibitor of lipoprotein lipase activity. J. Lipid Res. 24:12-19, 1983.

22. Greenberg, BH, Blackwelder, WC and Levy, RI. Primary type V hyperlipoproteinemia. A descriptive study in 32 families. Ann. Int. Med. 87:526-534, 1977.

23. Fallat, RW and Glueck, CJ. Familial and acquired type V hyperlipoproteinemia. Atherosclerosis. 23:41-62, 1976.

24. Borrie, P and Slack, J. A clinical syndrome characteristic of primary type IV-V hyperlipoproteinaemia. Brit. J. Dermatology. 90:245-253, 1974.

25. Kwiterovich, PO, Jr., Farah, JR, Brown, WV, Bachorik, PS, Baylin, SB and Neill, CA. The clinical, biochemical, and familial presentation of type V hyperlipoproteinemia in childhood. Pediatrics. 59:513-525, 1977.

26. Schlesinger, M, Jacotot, B, Beaumont, V and Buxtorf, J-C. Type V hyperlipemia. 54 cases. Nouv. Presse Méd. 8:833-837, 1979.

27. Simons, LA, Williams, PF and Turtle, JR. Type V hyperlipoproteinaemia re-visited: Findings in a Sydney population. Aust. N.Z. J. Med. 5:210-219, 1975.

28. Taskinen, M-R. Lipoprotein lipase in hypertriglyceridemias. In: Lipoprotein Lipase. Borensztajn, J. ed. Evener Publishers, Inc. Chicago, 1987, 201-28.

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

30. Brunzell, JD, Hazzard, WR, Motulsky, AG and Bierman, EL. Evidence for diabetes mellitus and genetic forms of hypertriglyceridemia as independent entities. Metabolism. 24:1115-1121, 1975.

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

32. Abbate, SL and Brunzell, JD. Pathophysiology of hyperlipidemia in diabetes mellitus. J. Cardio. Pharm. 16(Suppl. 9):S1-S7, 1990.

33. Fulop, M and Eder, H. Severe hypertriglyceridemia in diabetic ketosis. Am. J. Med. Sci. 300:361-365, 1990.

34. Chait, A and Brunzell, JD. Acquired hyperlipidemia (secondary dyslipoproteinemias). Endocrin. and Metabol. Clinics N.A. 19:259-278, 1990.

35. Desoye, G, Schweditsch, MO, Pfeiffer, KP, Zechner, R and Kostner, GM. Correlation of hormones with lipid and lipoprotein levels during normal pregnancy and postpartum. J. Clin. Endocrinol. Metab. 64:704-712, 1987.

36. Glueck, CJ, Christopher, C, Mishkel, MA, Tsang, RC and Mellies, MJ. Pancreatitis, familial hypertriglyceridemia, and pregnancy. Am. J. Obstet. Gynecol. 136:755-761, 1980.

37. Bartelink, AKM, Gimbrere, JSF, Schoots, F and Dony, JMJ. Maternal survival after acute haemorrhagic pancreatitis complicating late pregnancy. Eur. J. Obst. Gynecol. & Reproductive Biol. 29:41-50, 1988.

38. De Chalain, TMB, Michell, WL and Berger, GMB. Hyperlipidemia, pregnancy and pancreatitis. Surg. Gynecol. & Obstet. 167:470-473, 1988.

39. Nies, BM and Dreiss, RJ. Hyperlipidemic pancreatitis in pregnancy: A case report and review of the literature. Am. J. Perinatology. 7:166-169, 1990.

40. Potter, JM and Michael, CA. Type I hyperlipoproteinaemia and pregnancy. Aust. N.Z. J. Obstet. Gynaec. 22:155-158, 1982.

41. Weinberg, RB, Sitrin, MD, Adkins, GM and Lin, CC. Treatment of hyperlipidemic pancreatitis in pregnancy with total parenteral nutrition. Gastroenterology. 83:1300-1305, 1982.

42. Steiner, G, Myher, JJ and Kuksis, A. Milk and plasma lipid composition in lactating patient with type I hyperlipoproteinemia. Am. J. Clin. Nutr. 41:121-128, 1985.

43. Sanderson, SL, Iverius, P-H and Wilson, DE. Successful hyperlipemic pregnancy. JAMA. 265:1858-1860, 1991.

44. Brunzell, JD, Hazzard, WR, Porte, D, Jr. and Bierman, EL. Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. J. Clin. Invest. 52:1578-1585, 1973.

45. Toskes, PP. Hyperlipidemic pancreatitis. Gastro. Clinics of N.A. 19:783-791, 1990.

46. Gavish, D, Eisenberg, S, Berry, EM, Kleinman, Y, Witztum, E, Norman, J and Leitersdorf, E. Bulimia. An underlying behavorial disorder in hyperlipidemic pancreatitis: A prospective multidisciplinary approach. Ar. Intern. Med. 147:705-708, 1987.

47. Miettinen, TA, Taskinen, M-R, Pelkonen, R and Nikkilä, EA. Glucose tolerance and plasma insulin in man during acute and chronic administration of nicotinic acid. Acta Med. Scand. 186:247-253, 1969.

48. Garg, A and Grundy, SM. Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. JAMA. 264:723-726, 1990.

49. Harris, WS, Rothrock, DW, Fanning, A, Inkeles, SB, Goodnight, SH, Jr., Illingworth, DR and Connor, WE. Fish oils in hypertriglyceridemia: A dose-response study. Am. J. Clin. Nutr. 51:399-406, 1990.

50. Nozaki, S, Garg, A, Vega, GL and Grundy, SM. Postheparin lipolytic activity and plasma lipoprotein response to ω–3 polyunsaturated fatty acids in patients with primary hypertriglyceridemia. Am. J. Clin. Nutr. 53:638-642, 1991.

51. Glueck, CJ, Brown, WV, Levy, RI, Greten, H and Fredrickson, DS. Amelioration of hypertriglyceridaemia by progestational drugs in familial type-V hyperlipoproteinaemia. Lancet. 1:1290-1291, 1969.

52. Hazzard, WR, Kushwaha, RS, Applebaum-Bowden, D, Haffner, SM, Steinmetz, A and Foster, DM. Chylomicron and very low-density lipoprotein apolipoprotein B metabolism: Mechanism of the response to stanozolol in in a patient with severe hypertriglyceridemia. Metabolism. 33:873-881, 1984.

53. Glueck, CJ, Ford, S, Jr., Steiner, P and Fallat, R. Triglyceride removal efficiency and lipoprotein lipases: Effects of oxandrolone. Metabolism. 22:807-814, 1973.

54. Olsson, AG, Orö, L and Rössner, S. Effects of oxandrolone on plasma lipoproteins and the intravenous fat tolerance in man. Atherosclerosis. 19:337-346, 1974.